Considerations of treatment standardization from the procession of NCCN guideline of esophageal cancer

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[Abstract] Esophageal carcinoma is one of the most common malignant tumors, especially in China which is the high incidence area. As a result of mild symptoms of early-stage esophageal cancer, the majority of patients cannot be diagnosed until they develop to advanced cancer, and the treatment outcome of surgery or chemoradiotherapy is still unsatisfactory at present. The guidelines of esophageal cancer issued by National Comprehensive Cancer Network (NCCN) are regarded as important reference tools by clinical oncologists, and provide uniform criteria for the diagnosis and treatment of esophageal carcinoma. However, the guidelines are not always suitable for Chinese patients because the data come from European and American population which have significant ethnical difference from Chinese. We retrospectively analyzed the changes of treatment strategy of esophageal cancer in NCCN guidelines and the advance of treatment for esophageal carcinoma in China, aiming to provide our oncologists with new research ideas. We also hope to set up clinical cancer cooperation organizations, and release our own cancer guidelines to serve Chinese patients and oncologists.

Key words: Esophageal cancer, National Comprehensive Cancer Network (NCCN), standardized treatment

Esophageal carcinoma is one of the most common malignant tumors, and is prevalent in many countries and regions on a global scale. Great differences of incidence of esophageal carcinoma exist among various regions, which could be as high as ten times or even dozens of times between areas with high and low incidence. It is estimated that there would be 16 470 newly diagnosed cases of esophageal cancer and 14 280 cases of death in America in 2008 [1]. China is the area with relatively high incidence of esophageal cancer. The majority of patients are centered in the city of Linzhou, Henan province and Cixian county, Hebei province, with sporadic cases found in Jiangsu and Sichuan province and the area of Mountain Taihang range such as Hebei, Henan, and Shanxi province [2]. Regional difference exists among various pathology types of esophageal cancer. Squamous cell carcinoma is commonly seen in areas with high incidence such as China, whereas adenocarcinoma is commonly seen in areas without high incidence such as Europe and America. As a result of mild symptoms of early-stage esophageal cancer, the majority of patients cannot be diagnosed until they become advanced. As diagnosis, nearly 50% of the patients have tumor which are beyond local primary disease, more than 60% of the patients have local disease which could not be totally resected, and 70%–80% of the patients have regional lymph node metastasis in their surgical specimens. Surgery, radiotherapy, and chemotherapy are major treatment methods for esophageal carcinoma, and the combined therapy based on chemoradiotherapy is playing an increasingly important role in nonoperative therapy for esophageal carcinoma. It has been clearly defined in the treatment guidelines of America and Japan for esophageal carcinoma that for patients with operable esophageal carcinoma, concurrent chemoradiotherapy is one of the first-line treatment modalities together with surgery. What’s more, it’s regarded as the first-line treatment for patients with inoperable esophageal carcinoma.

National Comprehensive Cancer Network (NCCN) of America is a non-profit cooperation organization which consists of numbers of top American medical institutes and cancer centers. It is primarily oriented towards the great majority of clinical oncologists, and guides and standardizes the clinical diagnosis and treatment procedure of cancer. NCCN issues clinical treatment guidelines for each type of cancer every year ever since 1995. Clinical practice guidelines are defined as “systematically developed statements to assist practitioner and patient in making
decisions about appropriate health care for specific clinical circumstances”. Clinical practice guidelines could increase the efficiency of clinical determination, and could provide more information for oncologists and patients when assessing the balance between the sum of the benefits and the sum of the risks. What’s more, NCCN clinical practice guidelines are continuously and quickly updated to reflect newest clinical research results. Therefore, NCCN clinical practice guidelines are important reference materials for doctors with high or low seniority during their clinical practice. Using a decision tree, NCCN guidelines not only instruct in principle the diagnosis, staging, treatment modality selection and follow-up of cancer, but also give relatively detailed explanation. They help either clinical doctors or patients to make treatment judgments clearly.

One of the bright characteristics of NCCN guidelines is that they provide reliable basis for their users by the way of evidence and consensus. In NCCN guidelines, these evidence and consensus are divided into three categories. Category 1 recommendation is based on high-level evidence from randomized controlled clinical trials, and the NCCN Guidelines Panel has reached uniform consensus. Category 2 recommendation is based on lower level evidence, and there is uniform consensus from NCCN Guidelines Panel or non-uniform consensus which does not represent a major disagreement. Category 3 recommendation has engendered a major disagreement among the NCCN Guidelines Panel Members, and the level of evidence is not pertinent in this category. Clinical doctors and patients could evaluate disease benefit and risk and decide appropriate treatment strategy basing on different evidence categories. NCCN updates the clinical practice guidelines on a nonscheduled basis, and timely reflect clinical research results to guarantee the advance of guidelines. Another characteristic of NCCN guidelines is that new content is listed in detail in each update, which could help their readers to know the updated content quickly and realize the orientation of development consequently. NCCN guidelines have become important reference tools for clinical oncologists in China during their clinical practice.

From the comprehensive survey of the change of treatment strategy of esophageal cancer in NCCN guidelines, what are impressive include the following:

(1) NCCN guidelines are more detailed, ranging from the simple to the complicated and focusing on evidence.

The guidelines of esophageal cancer issued recently by NCCN in 2010 have increased from 22 pages in 2003 to 51 pages, and the content has more than doubled. The updated contents ever since 2007 are listed in detail after the catalogue. So that the readers could realize the each specific updated content faster and more conveniently and get to know the clinical research events of esophageal cancer. In addition, guiding principles of surgery, radiotherapy and chemotherapy have been added ever since 2007, clearly defining the operative methods selection, number of dissected lymph nodes, dose and method of radiotherapy, and chemotherapy regimen. Their contents are more and more abundant, not only including some fundamental concept and overall guiding principle, but also including concrete delivery method, which shows the trend of further detailed guidelines and is more beneficial to reference for clinical doctors and delivery of standard treatment. NCCN guidelines give relatively more detailed explanation on the hot spots in recent researches, and point out current focus of dispute, existing clinical results of researches and future research interests. References are attached to each conclusion from clinical scientific researches. This is not only convincing, but also convenient for readers in their further researches.

(2) Concurrent chemoradiotherapy has played a more and more important role in the combined modality treatment of esophageal cancer and the status of surgery should need a new review.

Surgery has always played a leading role in the treatment of esophageal cancer, and radiotherapy or chemotherapy is usually used as postoperative adjuvant therapy or for inoperable patients. However, although patients with esophageal cancer receiving surgery alone were selected elaborately, the treatment outcome was unsatisfactory. Liu et al. summarized the treatment results of surgery in esophageal cancer in the past 20 years, and found that the 5-year survival lingered about 20%. The results of radiotherapy or chemotherapy alone was also disappointing, the 5-year overall survival was only about 10%. As a result, researchers have begun the exploration of combined therapy. When it comes to concurrent chemoradiotherapy of esophageal cancer, two landmark clinical researches have to be addressed. Results of RTOG85-01 research were reported in the New England Journal of Medicine by Herskovic et al. in 1992 and in the JAMA by Cooper et al. in 1999, respectively. It was indicated that for patients with squamous cell carcinoma, compared with radiotherapy alone, four courses of chemotherapy of 5-fluorouracil (S-FU) and cisplatin combined with concurrent radiotherapy of 50 Gy (2 Gy/d) significantly improved median survival time (14 months vs. 9 months) and 5-year survival (26% vs. 0), and the treatment outcome of concurrent chemoradiotherapy was already close to the results of surgery, which was exhilarating. Although the subsequent INT 0123 clinical trial compared the treatment outcome of two groups using high and low dose of concurrent chemoradiotherapy, its results were similar to those of concurrent chemoradiotherapy group in the RTOG 85-01 trial, and thus confirmed the results of the RTOG 85-01 trial indirectly. From this time on, these two clinical trials have established the status of...
concurrent chemoradiotherapy in nonoperative therapy of esophageal cancer. Since the results of these two clinical trials were published, American NCCN and Japanese guidelines of esophageal cancer have listed concurrent chemoradiotherapy as the standard treatment strategy for non-operative therapy of esophageal cancer in succession. For operable esophageal cancer, results of numbers of clinical trials and meta-analysis have shown the trend that preoperative concurrent chemoradiotherapy combined with surgery was more beneficial than surgery alone. However, there is still no definite conclusion on whether radical concurrent chemoradiotherapy is better than surgery alone. Stahl et al. [7-8] have studied the treatment effect of surgery after chemoradiotherapy for patients with locally advanced esophageal cancer. Totally there were 172 patients enrolled. They received induction chemotherapy followed by concurrent chemoradiotherapy, and surgery or concurrent chemoradiotherapy was given randomly. The results showed that although the 2-year disease-free survival time of patients was better in surgery group than in chemoradiotherapy group (64.3% vs. 40.7%), there was no difference in overall survival between the two groups. Treatment-related mortality of surgery group was significantly higher than that of chemoradiotherapy group (12.8% vs. 3.5%), but the observation of long-term follow-up (median follow-up time: 10 years) also showed that there was no difference in overall survival between the two groups. Results of the research by Bedenne et al. [9] (FFCD9102 trial) also showed that there was no benefit when concurrent chemoradiotherapy followed by surgery compared with chemoradiotherapy alone, especially for patients with esophageal squamous cell carcinoma who have got remission after concurrent chemoradiotherapy. Because of the publication of the results of these two clinical trials, it is pointed out in the NCCN guidelines that for patients with operable esophageal cancer, there is radical chemoradiotherapy or preoperative chemoradiotherapy to choose, and following surgery or salvage surgery could be delivered according to the results of chemoradiotherapy. In this way, some of the patients who responded better to concurrent chemoradiotherapy could avoid operation, risk of surgery was brought down, and the aim of radical treatment was achieved. For patients with relapse or residual diseases after concurrent chemoradiotherapy, re-operation could also achieve excellent effects. Hence we could realize that concurrent chemoradiotherapy has play a more and more important role in the treatment of esophageal cancer, and the indication and timing of intervention of surgery should be reevaluate.

(3) The effect of positron emission tomography-computed tomography (PET/CT) in preoperative staging and treatment outcome assessment of esophageal cancer is accepted.

PET/CT scan plays an important role in detecting distant metastasis in lymph nodes and peripheral blood. Studies have shown that this kind of method could improve N staging and help to define whether a certain patient is with stage IV esophageal cancer [10-11]. Different stage could impact on the choice of treatment strategies, and distant metastasis is an independent prognostic factor influencing the overall survival of patients with esophageal cancer [12]. As a result, PET/CT is playing an important role on the staging and treatment strategy selection of esophageal cancer, and its application has become increasingly wider no matter at home or abroad in recent years. PET/CT has some effect on the location of tumor during target contouring in radiotherapy for esophageal cancer. However, because of the false positives of PET, results of other examine such as esophageal endoluminal sonography, barium meal radiography and CT scan should be referred. In addition, a more thorough understanding of PET/CT on assessing the treatment effect of concurrent chemoradiotherapy for esophageal cancer has been gained. It is pointed out in the NCCN guidelines of esophageal cancer that for patients with operable esophageal cancer, either radical chemoradiotherapy or preoperative concurrent chemoradiotherapy could be selected. So, the important issues we face are which patients would respond to chemoradiotherapy, which patients would be resistant to chemoradiotherapy and suitable to receive surgery, and how to evaluate the reaction of esophageal cancer to chemoradiotherapy earlier. PET/CT could solve these problems to a certain extent [13-17]. One recent clinical study indicated that PET/CT scan is more accurate than esophageal endoluminal sonography needle biopsy and CT scan in assessing whether esophageal cancer has got complete remission to neoadjuvant chemoradiotherapy, and plays an important role on monitoring tumor reaction to primary treatment [18]. In recent years, NCCN guidelines have classified PET/CT results as category 2B evidence for assessing the treatment effect of concurrent chemoradiotherapy for patients with operable esophageal cancer, and deciding whether surgery or continued concurrent chemoradiotherapy should be given according to remission status. Nevertheless, because of the false positives and false negatives of the results of PET/CT, more clinical studies are still needed to determine its value in combined treatment of esophageal cancer.

Most of the referenced evidence of NCCN guidelines is from the results of European and American clinical trials, and significant ethnical difference from Chinese existed, so its results do not altogether apply to Chinese. For example, defining 5 cm superior and inferior to gross tumor volume (GTV) and GTV plus a 1.5–2 cm margin as planning target volume (PTV) in radiotherapy for esophageal cancer is
generally adopted by European and American countries. The target volume is obviously too large, and many patients fail to complete expected treatment plan in practical clinical use. Gao et al. [9] from China have studied 34 cases of subclinical disease of esophageal squamous cell carcinoma by serial pathology section technique. The results showed that 94% of the subclinical disease was located within 30 mm to primary tumor. So they considered 30 mm superior and inferior to GTV would be a relatively more reasonable range for clinical target volume (CTV). At present, this is most commonly used in China. Similarly, difference existed when choosing the chemotherapy dosage in concurrent chemoradiotherapy. The chemotherapy regimen adopted by both classical RTOG85-01 and 94-05 trial was 5-FU combined with cisplatin, in which 5-FU was given at 1000 mg/(m²·d), d1–4, and cisplatin was given at 75 mg/m²·d, d1. Their results showed that about 32% of the patients failed to complete the entire treatment, and treatment related mortality significantly increased. Lin et al. [20] have studied the maximum tolerance dose for Chinese in FP regimen by dose escalating trial. The results showed that the maximum tolerance dose was 5-FU at 700 mg/(m²·d), d1–5, and cisplatin at 52.5 mg/m²·d, d1. These dosages were significantly lower than those adopted in the two clinical trials by RTOG. What’s more, China has carried out relatively deeper research on late course accelerated hyper-fractionation fraction, and attained relatively satisfactory effect [21,22]. Hence we could conclude that Chinese patients with esophageal cancer have unique characteristics no matter in epidemiologic pathology features or personal constitution. China is the high incidence area of esophageal cancer and has abundant clinical resources. However, it is a pity that no uniform treatment standard for esophageal cancer has formed yet, and obvious difference exists among each clinical institution on the adopted treatment method, indication, treatment modality and treatment effect. As a result, no effective evidence based medicine data could be made. When using corresponding NCCN clinical practice guidelines in Chinese population, the result of its implementation should be fully observed at the same time, and Chinese characteristics should be considered comprehensively.

We hope to set up clinical cancer cooperation organizations, release our own cancer guidelines for diagnosis and treatment to serve Chinese population, and provide authoritative reference for Chinese tumor diagnosis and treatment. After years of research and discussion, Chinese esophageal cancer treatment standard (draft) has been written by Esophageal Cancer Research Group, Society of Radiation Oncology, Chinese Medical Association (see the current issue “Treatment guideline of radiotherapy for Chinese esophageal carcinoma (draft)” on pages 855–859). We hope that the general clinical physicians will use it during clinical work and give us valuable criticisms and suggestions, hence constantly advance the process of standardization of esophageal cancer treatment in China.

References


