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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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EDITORIAL

Present situation and prospect of immunotherapy for unresectable locally advanced esophageal cancer during peri-radiotherapy

Feng-Mei Wang, Peng Mo, Xue Yan, Xin-Yue Lin, Zhi-Chao Fu

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Abstract

Four major studies (Checkmate577, Keynote-590, Checkmate649 and Attraction-4) of locally advanced esophageal cancer published in 2020 have established the importance of immunotherapy, represented by anti-programmed death protein (PD)-1 in postoperative adjuvant treatment and advanced first-line treatment of locally advanced or advanced esophageal cancer and esophagogastric junction cancer, from the aspects of proof of concept, long-term survival, overall survival rate and progression-free survival. For unresectable or inoperable nonmetastatic esophageal cancer, concurrent radiotherapy and chemotherapy is the standard treatment recommended by various guidelines. Because its curative effect is still not ideal, it is necessary to explore radical radiotherapy and chemotherapy in the future, and it is considered to be promising to combine them with immunotherapeutic drugs such as anti-PD-1. This paper mainly discusses how to combine radical concurrent radiotherapy and chemotherapy with immunotherapy for unresectable local advanced esophageal cancer.

Key Words: Esophageal carcinoma; Locally advanced; Radiotherapy; Immunotherapy

Core Tip: For unresectable or inoperable non-metastatic esophageal cancer, concurrent radiotherapy and chemotherapy is the standard treatment recommended by various guidelines. Because its curative effect is still not ideal, it is still necessary to explore radical radiotherapy and chemotherapy in the future, and it is considered to be very promising to combine with immune drugs represented by anti-programmed death protein-1. This paper mainly discusses how to combine radical concurrent radiotherapy and chemotherapy with immunotherapy for unresectable local late esophageal cancer.

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INTRODUCTION

In 2020, esophageal cancer ranked as the seventh most prevalent cancer globally and the sixth leading cause of cancer-related deaths[1]. The predominant subtype of esophageal cancer in the Asian region is esophageal squamous cell carcinoma (ESCC)[2]. ESCC accounts for > 84% of newly diagnosed cases of esophageal cancer each year[3,4]. As one of the four cancer types with the lowest survival rates, the overall 5-year survival rate is 20%[1]. Local advanced esophageal cancer refers to tumors that invade local structures or show regional lymph node metastasis without distant metastasis (*i.e.*, American Joint Committee on Cancer stage ≥ T2 or N+, M0)[5], representing the majority of clinical cases.

The feasibility of radical resection can be divided into resectable and unresectable groups. For the resectable group, simple surgery alone may not achieve satisfactory results. Currently, the main treatment approach for this group involves a combination of surgery and radiotherapy and/or chemotherapy[6,7]. Unresectable locally advanced ESCC is diagnosed in cases such as T4 stage (tumor invasion into other adjacent organs, such as the aorta and trachea) or metastasis beyond regional lymph nodes, such as supraclavicular and abdominal lymph nodes. Due to the invasion of vital organs, unresectable locally advanced ESCC is sometimes accompanied by esophageal fistula (10%-22%), leading to a decrease in quality of life and increased risk of sudden death[8].

Since the approval of immune checkpoint inhibitors (ICIs), immunotherapy has made an indelible mark in the field of cancer treatment[9]. With the widespread application of programmed death protein (PD)-1/PD ligand (PD-L)1 and cytotoxic lymphocyte-associated antigen-4 inhibitors in various indications, these ICI drugs have brought about transformative responses in advanced solid tumors over the past decade[10]. Immunotherapy, as an emerging treatment modality, has demonstrated significant clinical efficacy in the treatment of locally advanced or metastatic ESCC. Importantly, increasing evidence suggests that traditional radiotherapy serves as a potent adjunct to immunotherapy by enhancing systemic antitumor immune function. This combination has shown to reduce the risk of recurrence and improve patient survival rates.

NEOADJUVANT CHEMOTHERAPY BEFORE CONCURRENT RADIOTHERAPY AND CHEMOTHERAPY

The distant metastasis rate of locally advanced esophageal cancer after radical concurrent radiotherapy and chemotherapy can reach > 25%[11,12]. In theory, as a systemic treatment, inductive chemotherapy has the potential to reduce the rate of distant metastasis to a certain extent. However, such studies are mainly conducted in potentially resectable patients, and only two studies included patients with stage T4 cancer. One compared the efficacy of induction chemotherapy + concurrent chemoradiotherapy + surgery with induction chemotherapy + radical concurrent chemoradiotherapy. The overall survival (OS) of the two groups of patients was similar, and the progression-free survival (PFS) of patients in the surgical group was longer, but this study did not investigate the advantages and disadvantages of chemotherapy before chemoradiotherapy[13]. Another radiation therapy oncology group (RTOG) phase II randomized controlled trial[12], which focused on adenocarcinoma, compared the advantages and disadvantages of induction chemotherapy based on cisplatin + fluorouracil regimen and paclitaxel + cisplatin regimen + concurrent radiotherapy and chemotherapy. The toxic reactions in patients in both groups were large, and the incidence of G4 toxicity was 27% and 40%, respectively. The 1-year survival rate did not reach the expected 77.5%, and the 2-year survival rates of the two groups were 56% and 37%, respectively, which had no obvious advantage compared with the 40% 2-year survival rate in the INT 0123 study[14]. Therefore, no research has shown that induction chemotherapy before concurrent chemoradiotherapy + concurrent chemoradiotherapy is superior to direct concurrent chemoradiotherapy.

NEOADJUVANT CHEMOTHERAPY COMBINED WITH IMMUNOTHERAPY BEFORE CONCURRENT RADIOTHERAPY AND CHEMOTHERAPY

Research of neoadjuvant chemotherapy combined with immunotherapy for resectable esophageal cancer has made some progress[15], which shows that neoadjuvant chemotherapy combined with immunotherapy has a high pathological

complete response (pCR) rate, which gives a new option for the treatment of locally advanced esophageal cancer. Most clinical studies of neoadjuvant chemotherapy combined with immunotherapy are phase I/II studies, among which the typical one was the National Institute for Health and Care Excellence (NICE) study reported at the European Society for Medical Oncology conference in 2020[16]. This evaluated the efficacy of karelizumab combined with albumin-bound paclitaxel and carboplatin in patients with locally advanced thoracic ESCC. The patients received two courses of karelizumab combined with carboplatin and albumin paclitaxel, and underwent surgery 4 wk after the end of treatment. The results were pCR 45.5% (5/11) and pT0 54.5% (6/11). The NICE study data[17] updated at the American Society of Clinical Oncology meeting in 2021 included 60 patients: 55 (91.7%) received two cycles of neoadjuvant therapy, and 47 patients underwent surgery. Seven of the surgical patients delayed surgery due to treatment-related adverse events (AEs) (TRAEs), and 20 patients (42.6%) achieved pCR. The incidence of grade 3-5 TRAE was 53.3%, including lymphocytopenia (50%), thrombocytopenia (10%), pneumonia (5%) and thyroid dysfunction (3.3%). Neoadjuvant chemotherapy combined with immunotherapy needs Phase III clinical trials and longer follow-up time.

Compared with neoadjuvant radiotherapy and chemotherapy, the radiotherapy dose and target intensity of radical radiotherapy and chemotherapy are significantly increased to achieve better local control. Whether neoadjuvant chemotherapy and immunotherapy are beneficial for unresectable locally advanced esophageal cancer is still in the exploratory phase[18]. However, this treatment strategy is theoretically feasible. Unresectable local advanced esophageal cancer has a large tumor load, and after radical concurrent radiotherapy and chemotherapy, it has a high rate of local recurrence and distant metastasis, and has high treatment-related toxic and adverse effects. For example, radiotherapy-related radiation pneumonia, esophageal fistula, upper gastrointestinal bleeding and other clinical-related fatal causes are difficult to be accepted clinically[19]. Neoadjuvant chemotherapy combined with immunotherapy has good effectiveness and safety, which has been verified in the first-line chemotherapy combined with immunotherapy for advanced esophageal cancer[20]. Therefore, the advantages of neoadjuvant chemotherapy combined with immunotherapy are as follows. Neoadjuvant chemotherapy combined with immunotherapy can effectively reduce the tumor load during radical radiotherapy and chemotherapy for unresectable locally advanced esophageal cancer. As a result, it improves the safety of radical radiotherapy and chemotherapy while ensuring the successful completion of radical radiotherapy and chemotherapy. Neoadjuvant chemotherapy combined with immunotherapy can theoretically reduce the tumor load and further reduce the risk of distant metastasis through the treatment of subclinical lesions. The high lymph node metastasis rate of esophageal cancer is also an important factor for poor prognosis, and the probability of distant metastasis of locally advanced esophageal cancer also increases significantly. In clinical trials, the negative value of traditional neoadjuvant chemotherapy in radical radiotherapy and chemotherapy for local late esophageal cancer should be mainly due to the poor effectiveness and tolerance of neoadjuvant chemotherapy, while neoadjuvant chemotherapy combined with immunotherapy can overcome the above shortcomings and provide a new treatment plan for radical radiotherapy and chemotherapy[21]. A phase II clinical study of tirelizumab combined with chemotherapy in the treatment of locally unresectable ESCC (NCT05515315) aims to explore the efficacy and safety of adjuvant chemotherapy combined with immunotherapy in the treatment of locally unresectable esophageal cancer, and provide experimental data for this model.

IMMUNE MAINTENANCE THERAPY AFTER RADICAL RADIOTHERAPY AND CHEMOTHEROPY

Immunotherapy has been successful in the treatment of resectable locally advanced esophageal cancer[22-24] and gastroesophageal junction cancer[25,26]. CheckMate-577 was a randomized, double-blind, phase III trial[27]. A total of 794 patients with phase II or III esophageal or gastroesophageal junction cancer who had residual lesions after neoadjuvant radiotherapy and chemotherapy and underwent R0 resection were randomly treated with navuliuzumab (240 mg/2 wk for 16 wk, followed by 480 mg/4 wk) or placebo at a ratio of 2:1. Adjuvant therapy lasted for up to 1 year, and the main end point was disease-free survival (DFS). The median DFS of 532 patients treated with navuliuzumab was 22.4 mo, and the median DFS of 262 patients treated with placebo was 11.0 mo. Therefore, immune maintenance therapy for patients who did not reach pCR after neoadjuvant radiotherapy and chemotherapy sequential surgery is the standard treatment plan recommended by grade I of the guidelines at present.

However, the effective treatment of unresectable locally advanced esophageal cancer after radical radiotherapy and chemotherapy is still unclear[28-30]. After radical radiotherapy and chemotherapy for non-small cell lung cancer (NSCLC)[31,32], PACIFIC[33] study established the therapeutic position of immune maintenance therapy in unresectable locally advanced NSCLC, and the PACIFIC phase III clinical study[34] compared the clinical efficacy of dulvalizumab consolidation therapy with placebo for patients with unresectable phase III NSCLC without disease progression after concurrent radiotherapy and chemotherapy. The results showed that compared with placebo treatment, dulvalizumab consolidation treatment reduced the risk of death by 28% (stratified hazard ratio = 0.72; 95% confidence interval, 0.59-0.89). The median OS was 47.5 mo and 29.1 mo in the dulvalizumab consolidation group and the 5-year OS rates were 42.9% and 33.4% in the placebo group. Dulvalizumab consolidation therapy can significantly improve the OS and PFS of patients, and the safety is controllable. The LUN 14-179 carried out by papolizumab[35] also reached the same conclusion.

The TENERGY study evaluated the efficacy of 1-year consolidation of atezolizumab after concurrent chemoradiotherapy in the treatment of unresectable locally advanced ESCC, and the midterm analysis demonstrated a clinical complete remission rate of 42.1%, a median PFS of 3.2 mo, and median OS of 31.0 mo, in addition to the 12-mo PFS and OS rates of 29.6% and 65.8%, respectively[36].

Radical concurrent chemoradiotherapy is the standard treatment for unresectable esophageal cancer[5,37], based mainly on the RTOG 8501[38] and INT 0123[14] trials, but the median survival time of the chemoradiotherapy group was significantly longer than that of the radiotherapy alone group (14 *vs*. 9 mo), and the 5-year survival rate was also

significantly improved (27% *vs* 9.3%). The curative effect still does not meet the clinical and patient needs. By referring to the PACIFIC model, after radical radiotherapy and chemotherapy, giving PD-L1 inhibitor, immunotherapy combined with targeted therapy and double immune target therapy for maintenance therapy may become a new plan of peri-radiotherapy for esophageal cancer. Radiotherapy can be used as an immune ignition agent, which can improve the curative effect of immunotherapy after radiotherapy and chemotherapy for unresectable esophageal cancer by reshaping the tumor microenvironment and activating the immune system[24]. It can avoid adverse reactions related to immunotherapy and radical radiotherapy and chemotherapy, thus becoming one of the new modes of immunotherapy during peri-radiotherapy. The SKYSCRAPER-07 Phase III clinical trial comparing atezolizumab ± tiragolumab for treatment of unresectable locally advanced ESCC (NCT04543617) is being enrolled, which is hoped to establish whether this model has survival benefits.

CONCRRENT RADIOTHERAPY AND CHEMOTHERAPY COMINED WITH IMMUNOTHERAPY

Most previous studies have found that induction chemotherapy before radiotherapy and chemotherapy for unresectable locally advanced ESCC does not benefit survival[29,39,40], so the exploration and consideration of neoadjuvant therapy in radical concurrent radiotherapy and chemotherapy is not the preferred clinical consideration. Based on the standard treatment, combined immunotherapy may achieve more positive results[41,42], which has become the clinical trial plan of most clinical studies at present.

In 2020, the American Society for Radiation Oncology[42] published the results of a one-arm exploratory study on the treatment of locally advanced ESCC with karelizumab. Twenty patients were enrolled, and immunotherapy continued for the whole process of concurrent radiotherapy and chemotherapy for 6 wk. After radiotherapy, they continued to receive immune maintenance therapy for a period of time and took apatinib from week 11. The overall response rate was 65% (2 complete response, 11 partial response). By the median follow-up time of 17 mo, only five patients had disease progression, with a 1-year PFS rate of 80% and a 1-year OS rate of 86.4%. The incidence of grade ≥ 3 adverse reactions was 35%, and no grade 4 or 5 adverse reactions occurred. The most common adverse reaction was radiation esophagitis (80%), and esophageal fistula occurred in two patients (10%), which was equivalent to the previously reported adverse reaction rate. This small sample study pioneered the introduction of immunotherapy into concurrent radiotherapy and chemotherapy for locally advanced esophageal cancer, and its curative effect reached a new high in the field. This lays a foundation for future research on large-sample immunotherapy combined with concurrent radiotherapy and chemotherapy. In a Korean single-arm phase II clinical study of durvalumab and tremelimumab with definitive chemoradiotherapy for locally advanced ESCC[43], the median follow-up duration was 27.5 mo, 2-year PFS 57.5%, and OS was 75%. The study showed the lowest in-field failure rate (17.5%) of all studies published to date. Pruritus, rash, hypothyroidism, and hyperthyroidism were the most common immune-related AEs, and the incidence of immune-related pneumonia was 7.5%. However, another trial involving nivolumab ± ipilimumab plus radiotherapy had to be terminated due to the accumulation of AEs. Despite this problem, the favorable prognosis of dual immunotherapy significantly exceeds the historical data and does not show a significant increase in toxicity, therefore, immunotherapy of esophageal cancer merits further in-depth study.

To improve the survival rate of these patients, several multicenter phase III clinical studies are currently in progress. KEYNOTE-975[44], KUNLUN, RATIONALE 311[45] and ESCORT-CRT[46] were all phase III randomized trials to evaluate the safety and effectiveness of immunotherapy combined with radical radiotherapy and chemotherapy in patients with locally advanced esophageal cancer. Other immunotherapy which has different mechanisms also showed benefits in esophageal cancer patients. A Japanese randomized trial[47] indicated that protein-bound polysaccharide may have a beneficial effect on esophageal carcinoma when given in combination with radiotherapy and chemoradiotherapy. A Chinese study[48] showed that dendritic-cell–cytokine-induced immunotherapy plus intensity-modulated radiotherapy in older patients with esophageal carcinoma may lengthen survival time. Combined immunotherapy may lead to immunotherapy-related AEs and radical radiotherapy-chemotherapy-related AEs, which brings new safety problems, especially the overlap of immune pneumonia and radiation pneumonia, which may lead to fatality. It is believed that the results of these trials will clarify the safety and effectiveness of immunotherapy in the treatment of unresectable locally advanced esophageal cancer.

CONCLUSION

The clinical trial results listed above can answer some questions about the treatment of unresectable locally advanced esophageal cancer in the immunotherapy age, but there are still many problems to be resolved. Firstly, immunotherapy always has a dilemma; it is not effective for all patients, and the effectiveness of single drug treatment is not high in esophageal cancer. We emphasize that immunotherapy combined with radiotherapy and chemotherapy is necessary for patients with advanced esophageal cancer, but even if it is combined with radiotherapy and chemotherapy, treatment is only effective in about half of the patients, so how to select patients accurately needs further research. Secondly, how to combine immunotherapy with radiotherapy and chemotherapy, including optimization of surgery, chemotherapy and radiotherapy dose and range, still needs further exploration.

FOOTNOTES

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