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Advances in Neoadjuvant Immunotherapy for Locally Advanced Esophageal Cancer

Xue Ji, Lixia Tian, Fengjuan Tao, Xue Tian, Beibei Zhang, Sheqing Liu, Xianshu Song, Huaqiang Chen, Zhong Dai*

Cancer Hospital of Huanxing ChaoYang District Beijing, Beijing 100122, China

***Corresponding author:** Zhong Dai, daizhong1102@sohu.com

Abstract: Esophageal cancer is one of the common malignant tumors in China with a high mortality rate. Neoadjuvant chemoradiotherapy (nRCT) is currently the primary treatment method for locally advanced esophageal cancer. However, nRCT has not been not widely applied in China due to several reasons. First, the radiotherapy equipment and technology vary in different regions, and the learning curve for these technologies is steep, making rapid implementation difficult. Furthermore, the combined toxicity of radiotherapy and chemotherapy can counteract the survival benefits of preoperative treatment. In recent years, a promising approach involves combining neoadjuvant chemotherapy with immunotherapy for patients with locally advanced esophageal cancer. This article offers an overview of the progress in neoadjuvant therapy for this condition.

Keywords: Locally advanced esophageal cancer; Neoadjuvant chemoradiotherapy; Immunotherapy; Neoadjuvant chemotherapy

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1. Introduction

Esophageal cancer is one of the most common digestive tract malignancies in the world. Data from collaborative research by various cancer research centers indicates that, in 2020, there were 604,000 new cases of esophageal cancer globally, which resulted in 544,000 deaths. More men than women were diagnosed with esophageal cancer (age-standardized incidence rate 9.3 vs 3.6/100,000) [1]. There are also differences in the distribution of global incidence rates. In China, the incidence rate of esophageal cancer accounts for 53.7%, with a mortality rate of 55.3%. The main histological type of esophageal cancer in our country is squamous cell carcinoma [2]. Squamous cell carcinoma is strongly associated with lifestyle and dietary habits, such as the consumption of hot foods, hot tea, alcohol, and smoking. Additionally, factors like food spoilage, charcoal, and certain cooking methods like roasting or smoking, as well as water quality, soil composition, and environmental microbial flora, contribute to its development. [3].

The choice of treatment for esophageal cancer mainly depends on the type of case and the stage of the disease. Early esophageal cancer often lacks noticeable clinical symptoms, making it challenging to detect.

As a result, most esophageal cancer patients are diagnosed when the disease has already reached an advanced stage or has metastasized to distant sites. Locally advanced esophageal cancer (locally advanced esophageal carcinoma) refers to esophageal tumors that have locally invaded the adventitia of the esophagus (T3) or adjacent organs (T4), or have local lymph node metastasis (N+) without distant metastasis. The results of Worldwide Esophageal Cancer Collaboration in 2021 show that most of the patients with esophageal cancer are locally advanced esophageal cancer.

Surgical resection is considered the most effective approach for achieving local control in esophageal squamous cell carcinoma. However, for patients with stage IIA to III disease, undergoing surgery alone yields a 5-year survival rate ranging from 20.64% to 34.00%. Unfortunately, many of these patients experience metastasis or local recurrence shortly after surgery, leading to unsatisfactory treatment outcomes [4]. The 3-year and 5-year survival of esophageal cancer patients has increased to 61.6% and 52.9% in primary specialist hospitals. However, the postoperative recurrence rate of locally advanced esophageal cancer is still as high as 33.7% [5]. In recent years, the emergence and advancement of molecular targeted therapy and novel immunotherapy drugs have significantly enhanced the role of systemic drug therapy in managing esophageal cancer and controlling its spread.

2. Literature review

Neoadjuvant chemoradiotherapy (nRCT) is the standard treatment for locally advanced esophageal cancer. The CROSS study established the therapeutic status of NCRT in locally advanced esophageal cancer. A total of 366 patients with locally advanced esophageal cancer were included in the study, and a total of 161 cases received carboplatin + paclitaxel along with radiotherapy (41.4 Gy) before surgery, while the control group underwent surgery alone. The results showed a significant difference in the R0 resection rate (92.00% in the nRCT group vs. 69.00% in the control group, $P < 0.001$). Additionally, the postoperative lymph node positivity rate in the nRCT group was notably lower at 31.00% compared to the control group. Patients who received nCRT had a median OS (overall survival) of 49.4 months compared to surgery alone, compared with 24 months in the control group (HR = 0.657; 95% CI = 0.495–0.871, $P = 0.003$). The absolute benefit in overall survival at 10-year follow-up in 2021 was 13% (38% vs 25%). However, the nCRT group did not lead to a higher incidence of postoperative complications and early mortality, only a few high-grade toxic and side effects, and the difference was not statistically significant ($P > 0.05$). Among the patients in the nRCT group, 47 cases (29%) achieved pathological complete response (pCR). In a subgroup analysis, it was observed that the pCR rates for adenocarcinoma and squamous cell carcinoma were 23.00% and 49.00%, respectively ($P = 0.008$). This suggests that patients with squamous cell carcinoma had better pCR rates compared to those with adenocarcinoma [6].

NEOCRTEC 5010 study [7] included 451 patients with esophageal squamous cell carcinoma with locally advanced esophageal cancer could be surgically resected. Among them, 224 cases in the NCRT group received cisplatin combined with vinorelbine regimen, concurrent radiotherapy (40 Gy/20 times) followed by surgery, and the control group received surgery alone. The R0 resection rate in the nRCT group was 98.40% vs. 91.20% ($P = 0.002$), with a pCR rate of 43.20%. In the updated 2021 results, compared to the operation-only group, patients in the nRCT group showed significantly improved overall survival (HR = 0.74; 95% CI = 0.57–0.97; $P = 0.03$) and disease-free survival time (DFS) (HR = 0.60; 95% CI = 0.45–0.80; $P < 0.001$). The 5-year survival rates were 59.9% (95% CI = 52.9%–66.1%) and 49.1% (95% CI: 42.3%–55.6%) for the two groups, respectively.

3. Current status of treatment for locally advanced esophageal cancer in China

Although nRCT is the standard treatment for locally advanced esophageal cancer, a comprehensive analysis of surgical treatment for esophageal cancer in our country indicates that the utilization rate of nRCT remains low. In the many countries, most patients receive neoadjuvant therapy. The most commonly used with neoadjuvant chemotherapy (nCT) program at home and abroad is platinum combined with fluorouracil or paclitaxel. It is mainly based on clinical research results such as OEO2 and JCOG9907. Researchers believe that administering chemotherapy before surgery can enhance patients' tolerance to treatment, lead to tumor shrinkage, increase the rate of complete tumor removal (R0 resection), eliminate micrometastases, and extend survival. Numerous studies have demonstrated improvements in the short-term response rate and rate of achieving pCR with nCT (35.7%:3.8% [8]; 38.9%:5.6% [9]; 27.6%:4.8% [10]) are lower than nRCT, but whether there is a difference in the overall survival is still debated. Moreover, there are certain difficulties in promoting preoperative radiotherapy and chemotherapy.

The complexity of preoperative radiotherapy and chemotherapy arises from the demands it places on the diagnostic and treatment capabilities of the medical center. It requires a high level of expertise in pre-treatment evaluation, radiotherapy, surgery, nutrition, perioperative care, and pathology. Such a comprehensive approach necessitates close collaboration among various departments, functioning as a multidisciplinary platform. The extensive learning curve involved makes it challenging to rapidly implement these procedures in a short timeframe. Secondly, the combined toxicity of radiotherapy and chemotherapy should be taken in to account. Excessive toxicity not only raises the risk of acute adverse reactions during radiotherapy and chemotherapy but also diminishes a patient's tolerance and necessitates lower dosages of these treatments, potentially affecting their compliance. Furthermore, heightened toxicity can lead to increased perioperative complications and, in severe cases, higher perioperative mortality rates. These adverse outcomes may counteract the survival benefits offered by preoperative chemoradiotherapy.

4. Neoadjuvant immunotherapy

4.1. Immune checkpoint inhibitors

Tumor cells are in a highly immunosuppressive microenvironment, in which programmed death protein 1 (PD-1) and programmed death protein ligand 1 (PD-L1) are important immune checkpoint molecules involved in tumor immune escape. PD-1 is a co-inhibitory receptor induced and expressed on the surface of T cells, B cells, monocytes, and NK cells. It is involved in antigen recognition and is one of the signs of immune cell activation. There are two ligands for PD-1, PD-L1 and PD-L2. PD-L1 is widely expressed on the surface of various cells, including tumor cells, and is the main ligand of PD-1. After PD-1/PD-L1 is combined, it induces the generation of regulatory T cells and maintains their function by down-regulating the activity of the PI3K/Akt pathway, thereby playing an immunosuppressive role. PD-L2 is only expressed on antigen-presenting cells and Th2 cells, and can inhibit the activation of T cells after binding to PD-1. By highly expressing immune checkpoint molecules, tumor cells inhibit the proliferation and activation of T cells, evade the monitoring and elimination of the immune system, and cause immune escape of tumor cells. Therefore, blocking the activation of PD-L1-related pathways can suppress tumors, and this procedure is known as immune checkpoint blockade therapy. By detecting 428 surgically resected esophageal squamous cell carcinoma tissues, it was found that the positive rate of PD-L1 was 79.7%, and the positive rate was closely related to the postoperative disease-free survival and overall survival of patients. Another group of experiments found that PD-L1 was highly expressed in 101 cases of esophageal cancer that did not undergo preoperative chemotherapy or radiotherapy This elevated expression

was linked to unfavorable prognosis, implying that PD-L1 plays a significant role in esophageal cancer progression. Therefore, inhibiting PD-L1's activity could potentially be employed as a treatment approach for esophageal cancer.

4.2. Neoadjuvant concurrent chemoradiotherapy combined with immunotherapy for esophageal cancer

In 2019, the Netherlands conducted the PERFECT study, a phase II single-arm single-center clinical trial [11]. This study recruited 33 patients diagnosed with esophageal adenocarcinoma. The treatment regimen included atezolizumab (1200 mg/kg q3w) in combination with the standard CROSS regimen: paclitaxel (50 mg/m^2 qw) + carboplatin (AUC 2 qw), along with concurrent radiotherapy at a dose of PTV 41.4 Gy/23 f. The study yielded several key findings: a pCR rate of 30% (10 out of 33 patients), a 100% R0 resection rate (all 33 patients achieved complete resection), and zero mortality rates at both the 30-day and 90-day perioperative periods. Common adverse reactions observed in the study included fatigue (95%), mucositis (60%), nausea (53%), and anorexia (43%). Notably, the pCR rate of 30% in this trial represents a significant improvement compared to the standard CROSS regimen. It is important to note that the trial is ongoing, and more comprehensive results are anticipated in the future.

A study by Kelly *et al.* enrolled 10 patients with esophageal adenocarcinoma [12]. The dose of concurrent radiotherapy was PTV 41.4 Gy/23 f. The chemotherapy regimen was paclitaxel (50 mg/m^2 qw) + carboplatin (AUC 2 qw) combined with sodium Vulumab 240 mg or 1 mg/kg q2w ± LAG-3 targeted drug (relatimab 80 mg q2w). The results of the study showed that the overall pCR rate was 40% (4/10); the main adverse reactions were dermatitis (6.3%) and hepatitis (6.3%).

Lee *et al.* from South Korea carried out a phase II single-arm single-center clinical study [13]. In this study, 26 patients with esophageal squamous cell carcinoma were enrolled, and they were treated with paclitaxel (45 mg/m^2 qw) + carboplatin (AUC 2 qw) combined immunotherapy. Pembrolizumab was administered at a dose of 2 mg/kg every 3 weeks, along with concurrent radiotherapy with a dose of PTV 44.1 Gy delivered in 21 fractions. This neoadjuvant therapy was initiated 6 to 8 weeks after surgery. Postoperatively, pembrolizumab at the same dose and schedule was used as adjuvant therapy for up to 2 years, with potential adjustments based on disease progression. The results indicated a promising pCR rate for the primary tumor, which was 46.1% (95% CI = 28.8%–64.6%). However, there was a postoperative mortality rate of 7.7% (2 out of 26 patients), primarily due to acute lung injury. Common adverse reactions included neutrophil cytopenia (50.0%), and liver damage (30.8%). The overall survival rates at 6, 12, and 18 months were 89.3%, 80.8%, and 73.1%, respectively. These findings suggest the potential efficacy of this treatment approach in esophageal cancer patients. Based on the PALACE1 study in China in 2020 [14], 18 patients with esophageal squamous cell carcinoma received a radiotherapy dose of PTV 41.4 Gy/23 f; the concurrent chemotherapy regimen was paclitaxel (50 mg/m^2 qw) combined with carboplatin (AUC 2 qw), and immunotherapy with pembrolizumab (2 mg/kg q3w) was given. Surgery was performed 4 to 6 weeks after the end of neoadjuvant therapy. The overall pCR rate was 56% (10/18), and post-surgery pathology revealed that the major pathologic response MPR rate of the primary tumor was 89% (16/18), while the R0 resection rate was 94% (17/18). The incidence of adverse reactions above grade 3 was 65%. These studies indicate an increased pCR rate with concurrent chemoradiotherapy and immunotherapy, although the difference varies. The combination therapy led to a higher incidence of adverse reactions, but these were generally manageable. Future research should focus on long-term survival outcomes and the development of phase III clinical trials.

4.3. Neoadjuvant chemotherapy combined with immunotherapy for esophageal cancer

Concurrent chemoradiotherapy is relatively unpopular in China. Researchers have been exploring new perioperative treatment methods for esophageal cancer. There has been some research output in the past 3 years. For example, the CheckMate 577 study confirmed that postoperative adjuvant nivolumab can significantly prolong the DFS of patients with locally advanced esophageal cancer and esophagogastric junction cancer after neoadjuvant chemoradiotherapy [15]. The famous KEYNOTE-590 study proved the first-line treatment of pembrolizumab combined with chemotherapy (PF regimen) significantly extends the Combined Positive Score CPS of PD-L1, to ≥ 10 in patients with advanced esophageal squamous cell carcinoma [16], so our country's National Medical Products Administration (NMPA) approved pembrolizumab combined with platinum and fluorouracil chemotherapy drugs in September 2021 as the first-line treatment of locally advanced unresectable or metastatic esophagus or gastroesophageal junction cancer. These studies all suggest the important role of immunotherapy in esophageal cancer.

4.3.1. Nivolumab combined with chemotherapy

The FRONTiER study is a multi-center study conducted by Japanese scholars [17] that involved patients with esophageal squamous cell carcinoma were enrolled, The treatment regimens included fluorouracil (800 mg/m2 on days 1-5 every 3 weeks) + cisplatin (80 mg/m^2 every 3 weeks) in combination with sodium Vulumab (360 mg every 3 weeks for group A; 240 mg every 3 weeks for group B); and docetaxel (70 mg/m^2 every 3 weeks) + fluorouracil (750 mg/m^2 on days 1–5 every 3 weeks) + cisplatin (80 mg/m^2 every 3 weeks) + nivolumab (group C: 360 mg every 3 weeks; group D: 240 mg every 3 weeks). The reported results indicated a pCR rate of 33.3% (2/6) in group A and a 92.3% R0 resection rate, with no dose-limiting adverse reactions observed.

4.3.2. Toripalimab combined with chemotherapy

The phase II study carried out by Li *et al.* [18] used toripalimab 240 mg q3w combined with chemotherapy: nab-paclitaxel (260 mg/m^2 q3w) + carboplatin (AUC 5 q3w), and surgery was performed after 4 weeks of treatment. The overall pCR rate was 16.7% (2/12) and the MPR rate of the primary tumor was 58.3% (7/12) after re-administration of the same drug; the incidence of serious adverse reactions was 11.8%.

4.3.3. Sintilimab combined with chemotherapy

The KEEP-G 03 study came from a Phase Ib/II single-arm multicenter study in China [19], using paclitaxel liposome (135 mg/m2 q3w) + cisplatin (75 mg/m2 q3w) + tegafur (40 mg bid d1-d14 q3w) three-drug combination immunotherapy sintilimab (200 mg q3w), the overall pCR rate was 26.7% (4/15), and the primary tumor MPR rate was 53.3% (8/15). 15); R0 resection rate was 100% 15/15); adverse reactions above grade 3 included lymphopenia (29.4%) and neutropenia (11.8%).

4.3.4. Camrelizumab combined with chemotherapy

The NICE study conducted in China [20] utilized camrelizumab (200 mg every 3 weeks) in combination with chemotherapy: nab-paclitaxel (100 mg/m2 every week) + carboplatin (AUC 5 every 3 weeks), followed by surgery 4 weeks after treatment. In the 2020 ESMO conference report, it was revealed that the overall pCR rate was 45% (5/11), with a primary tumor pCR rate of 54.5% (6/11) and a 100% R0 resection rate (11/11). Grade 3 or higher adverse reactions included neutropenia (72.7%) and thrombocytopenia (18.2%). According to the 2021 ASCO meeting report, with an increased number of participants, updated data indicated that out of 60 patients who underwent surgery, 20 of them (42.5%) achieved pCR. Subsequent Phase II and Phase III studies will be conducted to further validate the survival improvement.

Another study [21] in 2021 used camrelizumab (200 mg q3w) combined with docetaxel (75 mg/m2 q3w) + nedaplatin (75 mg/m^2 q3w). Surgery was performed 4 to 6 weeks after treatment. The results reported at the ASCO GI meeting showed that the R0 resection rate was 100%, 22 of the 33 patients underwent surgery, the overall pCR rate was 31.8% (7/22), 15 cases reached the primary goal, and the MPR rate was 68.2 Notably, there were no immune-related adverse reactions above grade 3, and serious adverse reactions were limited to anemia (3%), with no perioperative deaths reported. These findings suggest that combining immunotherapy with chemotherapy yields favorable results, including effective downstaging, a high MPR rate, and overall efficacy and safety. While some studies have shown pCR rates close to those seen in classic CROSS studies, the long-term survival outcomes after surgery still require further accumulation and validation.

5. Conclusion

Esophageal cancer is a life-threatening disease, and it has burden China greatly. Most patients with esophageal cancer are at the locally advanced stage when they are diagnosed. Therefore, it is important to reduce the perioperative period of patients with locally advanced esophageal cancer so that the patients are able to undergo surgery. Immunotherapy has been the primary option in esophageal cancer treatment, and has been recommended as a guideline for second-line and first-line treatment of advanced esophageal cancer. At present, the research data of neoadjuvant immunotherapy conducted at home and abroad have shown good curative effect, and it also brings us more thoughts. The first is the selection of the treatment population. Not all patients can benefit from immunotherapy, and there are cases of progression and relapse. The current predictive indicators for immunotherapy include PD-L1, TMB, mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H), among which dMMR/MSI-H is more sensitive, and other indicators or new markers need to continue to be explored. A review of several important immunotherapy studies for advanced esophageal cancer, including KN590, CheckMate649, KEYNOTE-181, ATTRACTION-3, and ESCORT, showed that patients with high expression levels of PD-L1 assessed by CPS may benefit from immunotherapy. Additionally, the timing of combining immunotherapy with chemotherapy is a critical consideration, whether it's synchronous or sequential. Theoretically, pretreatment with chemotherapy drugs to induce an inflammatory tumor environment may benefit immunotherapy. An ongoing study is investigating the effect of the sequence of chemotherapy and toripalimab treatment on the rate and safety of pCR in patients with locally advanced esophageal cancer. As of now, the primary endpoint has not been reached, and a phase III study is underway (NCT04280822). Other aspects that require exploration include the time interval between neoadjuvant therapy and surgery, the initiation of postoperative adjuvant therapy, the impact of neoadjuvant therapy on surgical and postoperative complications, how to evaluate patients with complete clinical response (cCR), and whether a watch-and-wait approach without surgery is a viable option. These areas require further investigation.

Disclosure statement

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