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Review

Expert consensus on radiotherapy combined with immunotherapy for esophageal cancer (2024 edition)

Professional Committee of Radiation Oncology, China Anti-Cancer Association[1], Branch of Radiation Oncology, Chinese Medical Association, Branch of Radiation Oncology Treatment Physician, Chinese Medical Doctor Association

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ABSTRACT

Radiotherapy represents an essential treatment approach for esophageal cancer. Over recent years, immunotherapy combined with chemotherapy has become the first-line standard treatment for patients with advanced esophageal cancer. Several phase III studies on immunotherapy combined with radiotherapy for locally advanced esophageal cancer are currently underway. Sufficient evidence-based medical data are urgently needed to support the integration of immunotherapy and chemoradiotherapy as a new treatment strategy for patients with locally advanced esophageal cancer. This consensus, formulated based on the latest study results, in-depth research, and thorough discussions, provides a comprehensive set of recommendations. The document extensively covers treatment strategies and evaluation methods for radiotherapy combined with immunotherapy across patients with operable esophageal cancer, inoperable locally advanced esophageal cancer, and advanced esophageal cancer. Moreover, common complications and radiation-related issues associated with radiotherapy combined with immunotherapy are discussed, serving as clinical guidance. Our expert group comprised members from the Professional Committee of Radiation Oncology, China Anti-Cancer Association, the Branch of Radiation Oncology, Chinese Medical Association, and the Branch of Radiation Oncology Treatment Physician, Chinese Medical Doctor Association.

1. Introduction

Esophageal cancer is one of the most prevalent malignancies worldwide. In 2020, and ranked No.7 among leading cancer types, with approximately 604,000 new cases and 544,000 fatalities globally in 2020.[1] Esophageal cancer can be broadly classified into two subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Asia and Africa are associated with the highest morbidity of esophageal cancer, with ESCC being the predominant subtype.[1–3] Notably, >50% of global ESCC cases are reported in China.[4]

The early clinical symptoms of esophageal cancer are often subtle, leading to challenges in detection. Consequently, most patients are diagnosed at an advanced stage or with distant metastases. The primary treatment for advanced ESCC involves chemotherapy with platinum-containing drugs,[2] but survival outcomes remain suboptimal, with a median overall survival (OS) time of 7–13 months.[5–7] Monotherapy with immune checkpoint inhibitors (ICIs) has demonstrated significant antitumor efficacy as second-line therapy, and effectiveness has also been reported for unresectable or advanced esophageal cancer.[8–11] The combination of immunotherapy and chemotherapy has become the standard first-line treatment for advanced ESCC.

Emerging studies indicate promising synergistic effects and clinical efficacy when combining immunotherapy with radiotherapy, presenting a novel treatment avenue for patients with ESCC. Radiotherapy not only eliminates tumor cells but also stimulates the release of tumor-specific antigens, activating dendritic cells with antigen-presenting abilities, priming and activating T cells, and inducing acquired antitumor immune responses. The combination of radiotherapy with immunotherapy (e.g., ICIs) sustains the activation of acquired antitumor immune responses, resulting in synergistic antitumor effects.[12–15] Several clinical studies have reported that this combination enhances systemic immune function.[14,15] To offer guidance for the clinical practice of radiotherapy combined with immunotherapy, we organized a multidisciplinary expert committee to develop a consensus. This consensus, based on recent

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clinical practice and research reports on immunotherapy combined with radiotherapy for esophageal cancer, was established after meticulous discussion and multiple revisions.

2. Current status and progress in chemoradiotherapy for esophageal cancer

2.1. Current status of chemoradiotherapy for esophageal cancer

Radiotherapy plays a crucial role in the treatment of esophageal cancer, encompassing neoadjuvant, adjuvant postoperative, curative, and palliative therapies. The 2023 Chinese Society of Clinical Oncology (CSCO) guidelines, the Chinese guidelines for esophageal cancer radiotherapy, and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Esophageal and Esophagogastric Junction Cancers (2023.v2) collectively recommend preoperative neoadjuvant chemoradiotherapy for operable patients (cT1B-cT2 or cT3-cT4A, any N). Concurrent chemoradiotherapy is suggested for inoperable patients or those refusing surgery, while radiotherapy alone is advised for patients with palliative disease or those medically unfit for concurrent chemoradiotherapy.[2] Intensity-modulated radiation therapy (IMRT) is the preferred technique.[16]

The recommended radiation dose is 40–45 Gy for preoperative radiotherapy, 50–56 Gy for postoperative radiotherapy, and 50–60 Gy for definitive chemoradiotherapy, respectively. Fractionation is advised at 1.8–2.0 Gy per day, five fractions a week.[2] At present, no randomized trials have demonstrated a survival benefit for higher radiation doses.

The gross tumor volume includes primary tumor and metastatic lymph nodes. The clinical target volume (CTV) extends 3 cm above and below the primary tumor and 0.6 cm radially, encompassing lymph node areas with metastatic nodes. However, consensus is lacking on whether the clinical target volume should include elective lymph node areas, contingent on the location of the primary esophageal tumor. The planning target volume (PTV) extends 0.5–1.0 cm in three dimensions from CTV.[2]

The 2023 CSCO guideline for esophageal cancer treatment recommends various concurrent chemotherapy regimens, including paclitaxel + carboplatin (class 1A), cisplatin + 5-fluorouracil or capecitabine (class 1A) or tegafur (class 2B), irinotecan + cisplatin (class 1A), paclitaxel + cisplatin, oxaliplatin + 5-fluorouracil or capecitabine or tegafur (class 2B, recommended for adenocarcinoma), and paclitaxel + 5-fluorouracil or capecitabine or tegafur (class 2B).[16]

2.2. Advancements in immunotherapy for esophageal cancer and guideline recommendations

Based on the findings reported by the KEYNOTE-180, KEYNOTE-181, and ATTRACTION-3 studies, the U.S. Food and Drug Administration (FDA) granted approval for pembrolizumab in 2019 as a second-line treatment of ESCC with a PD-L1 combined positive score (CPS) of $\geq$10. Nivolumab received approval in 2020 for the treatment of patients with unresectable, advanced, recurrent, or metastatic ESCC who progressed after fluoropyrimidine and platinum-based chemotherapy.[8,10,11] In addition, based on the results from the ESCORT and RATIONALE-302 studies, the National Medical Products Administration (NMPA) of China approved camrelizumab and tislelizumab in 2020 and 2022, respectively, for the second-line treatment of advanced or metastatic ESCC.[9,17]

Subsequent studies, including KEYNOTE-590, CheckMate-648, ESCORT-1st, ORIENT-15, and JUPITER-06, further explored the effects of first-line immunotherapy for patients with advanced esophageal cancer.[18–22] Between 2021 and 2022, the FDA approved the combination of pembrolizumab or nivolumab with chemotherapy (including fluorouracil and platinum-based drugs) as the first-line treatment for patients with advanced or metastatic esophageal or esophagogastric junction cancers. Subsequently, the NMPA approved camrelizumab, tislelizumab, and sintilimab combined with chemotherapy for the first-line treatment of advanced ESCC. At present, immunotherapy combined with chemotherapy stands as the standard first-line treatment for advanced esophageal cancer.

2.3. Overview and controversies related to clinical studies of radiotherapy combined with immunotherapy for esophageal cancer

Preliminary studies with limited samples have indicated that combining durvalumab and tremelimumab with concurrent chemoradiotherapy can significantly prolong progression-free survival (PFS) and OS in patients with unresectable locally advanced ESCC, particularly those with PD-L1 positivity.[23] Similar survival benefits were observed in these patients when combining camrelizumab with concurrent chemoradiotherapy.[24] Furthermore, the PALACE-1 study demonstrated that neoadjuvant chemoradiotherapy combined with pembrolizumab achieved a 55.6% pathological complete response (pCR) rate in ESCC.[25] Several phase III studies on immunotherapy combined with radiotherapy, such as ESCORT-CRT, KEYNOTE-975, RATIONALE-311, KUNLUN, SKYSCRAPER-07, are ongoing. Consequently, a lack of evidence-based medical data currently exists. It is thus imperative to convene experts for discussions and consensus formation to guide the clinical practice of combing immunotherapy and chemoradiotherapy for esophageal cancer based on the latest research data.

3. Method of consensus formation and evidence levels

3.1. Method of consensus formation

The consensus was developed by experts from the Professional Committee of Radiation Oncology, China Anti-Cancer Association; the Branch of Radiation Oncology, Chinese Medical Association; and the Branch of Radiation Oncology Treatment Physician, Chinese Medical Doctor Association. The group leader organized drafting experts responsible for literature search, evidence sorting, drafting consensus items, and preparing the initial draft. The draft was then distributed to all committee members for feedback, followed by intensive discussions to ultimately reach a consensus.

3.2. Purpose and target audience of the consensus

The consensus aims to assist clinicians participating in esophageal cancer diagnosis and treatment, helping them comprehend the effects, indications, and specific challenges that might arise during the treatment process of immunotherapy combined with chemoradiotherapy or radiotherapy. The consensus also furnishes information on the current development of relevant clinical research and evidence levels.

3.3. Literature search

The references cited in the consensus were retrieved through PubMed and conferences using these keywords: “esophageal cancer” or “esophageal squamous cell carcinoma (ESCC)” or “esophageal adenocarcinoma (EAC)” and “immunotherapy” or “immune checkpoint inhibitors (ICIs)” or “programmed death receptor 1 (PD-1)” or “programmed death ligand 1 (PD-L1)” and “radiotherapy” or “chemoradiotherapy (CRT).” The search included papers published up to March 2023 (including those published online).

4. Expert consensus

4.1. Resectable esophageal tumors

Expert consensus I: For patients with resectable locally advanced esophageal tumors, neoadjuvant chemoradiotherapy combined with immunotherapy can achieve higher pCR rates. Treatment-related adverse

effects are similar to those of preoperative chemoradiotherapy. Clinical trials are recommended (evidence quality: medium; consensus level: 96%).

According to the 2022 CSCO guidelines for esophageal cancer, resectable locally advanced esophageal tumors is defined as stages cT1B-CT2N + or cT3-4AN by the eighth edition of the American Joint Committee on Cancer.[26] The decision for surgery in patients with multiple or multi-station lymph node metastases should be based on patient age and physical conditions.[16]

In the CROSS study, patients with locally advanced esophageal cancer undergoing neoadjuvant chemoradiotherapy with paclitaxel and carboplatin (the CROSS regimen) achieved a postoperative pCR rate of 29% (49/171), with a median OS of 81.6 months.[27] The NEOCRTEC5010 study applied a neoadjuvant regimen of irinotecan combined with cisplatin chemotherapy concurrent with 40 Gy radiotherapy in patients with locally advanced esophageal cancer, achieving a median OS of 100.1 months.[28] Since then, neoadjuvant concurrent chemoradiotherapy is recommended as the standard treatment for resectable locally advanced esophageal tumors in various guidelines, including the NCCN and CSCO guidelines. Despite its widespread clinical application, many patients still have a poor prognosis. A retrospective cohort study involving 6,354 Korean patients with esophageal cancer reported that after neoadjuvant concurrent chemoradiotherapy, the postoperative recurrence rate was 34.1% and as high as 47.2% for patients with stage II and III esophageal cancer, respectively.[29] This underscores the need to explore more effective antitumor neoadjuvant treatments clinically.

Immunotherapy with concurrent chemoradiotherapy might exert stronger antitumor effects. Several small-sample single-arm trials have studied the effects of neoadjuvant concurrent chemoradiotherapy combined with immunotherapy on locally advanced esophageal cancer. In the PALACE-1 study, which enrolled 20 patients with ESCC, neoadjuvant treatment with the CROSS regimen concurrent with pembrolizumab achieved a postoperative pCR rate of 55.6% (10/18), major pathologic response (MPR) rate of 89% (16/18), and R0 resection rate of 94% (17/18), with a 65% incidence of grade ≥3 treatment-related adverse effects.[25] Furthermore, the PERFECT study enrolled 40 patients with EAC treated with the CROSS regimen concurrently or sequentially with atezolizumab. Postoperative results showed a pCR rate of 25% (10/40), with no statistically significant difference in pCR rates or postoperative survival in comparison to the group receiving standard neoadjuvant concurrent chemoradiotherapy.[30] A single-arm phase II clinical trial (NCT02844075), which enrolled 28 patients with ESCC treated with neoadjuvant concurrent chemoradiotherapy (paclitaxel + cisplatin) combined with pembrolizumab, indicated a postoperative pCR rate of 46.1% in the primary lesion, with a 1-year survival rate of 89.3% after continuing pembrolizumab postoperatively.[31] Based on existing data, neoadjuvant concurrent radiotherapy or chemoradiotherapy combined with immunotherapy for ESCC seems capable of achieving higher pCR rates for patients undergoing surgery. However, long-term survival data are lacking, and this combination treatment strategy needs validation in future phase III clinical trials.

The exploration of adding immunotherapy to neoadjuvant chemotherapy is ongoing, with several phase II studies providing valuable insights. In the NICE study, locally advanced ESCC patients ($n = 60$) with multi-station lymph node metastases received preoperative treatment with albumin-bound paclitaxel and carboplatin chemotherapy combined with camrelizumab. Among those who underwent surgery, 39.2% (20/51) achieved a pCR.[32] Furthermore, in the HCHTOG1909 study (NCT04177797), 16 patients with esophageal squamous carcinoma received neoadjuvant chemotherapy with paclitaxel and carboplatin combined with tislelizumab, with the pCR rate of 18.8% and the MPR rate 43.8%.[33] These studies suggest the potential efficacy of combining neoadjuvant immunotherapy with chemotherapy in resectable locally advanced esophageal tumors. However, due to the lack of long-term survival data and confirmatory results from phase III studies, no definitive conclusions can be drawn regarding its efficacy compared to neoadjuvant concurrent chemoradiotherapy combined with immunotherapy.

In comparison to neoadjuvant chemotherapy combined with immunotherapy, neoadjuvant concurrent chemoradiotherapy combined with immunotherapy may achieve higher pCR rates and maintain generally controllable safety; however, careful attention is required for treatment-related adverse events (AEs) during therapy. A meta-analysis indicated that the pCR rate for neoadjuvant immunotherapy combined with chemoradiotherapy or chemotherapy was 38% and 28% ($P = 0.078$), respectively, and that the MPR rate was 67% and 57% ($P = 0.181$), respectively. The incidence of grade ≥3 treatment-related adverse reactions was 58% and 18% ($P < 0.001$), respectively.[34] Therefore, for patients with a high tumor burden, difficulty in surgical resection, or multiple lymph node metastases, neoadjuvant chemoradiotherapy combined with immunotherapy may offer advantages in reducing local tumor size, lower tumor stage, increase the possibility of R0 resection, and even provide surgical opportunities for those previously deemed inoperable. Optimization is needed for the timing and sequence of combining radiotherapy and immunotherapy, radiation doses, and scope of radiotherapy targets. In cases where patients are contraindicated for radiotherapy or their physical condition prohibits concurrent chemoradiotherapy and when there is a risk of adverse reactions, neoadjuvant chemotherapy with or without immunotherapy can be considered.

Expert consensus II: For patients with resectable locally advanced esophageal tumors who have undergone neoadjuvant chemoradiotherapy without achieving a pCR, postoperative maintenance therapy with anti-PD-1 monoclonal antibodies is recommended for 1 year (evidence quality: high; consensus level: 98%).

A phase III multicenter randomized clinical trial (CheckMate-577 study) enrolled 794 patients with esophageal or esophagogastric junction cancer who underwent neoadjuvant concurrent chemoradiotherapy and R0 resection without achieving a pCR. Among the 532 patients who received postoperative nivolumab therapy, the median disease-free survival (DFS) was 22.4 months, twice that of the placebo group (median DFS = 11.0 months).[35] Consequently, both the NCCN and CSCO guidelines recommend postoperative nivolumab adjuvant therapy for patients who have undergone preoperative chemoradiotherapy and R0 resection but did not achieve pCR in their postoperative pathology. However, another phase II randomized double-blind study, involving 86 patients with esophageal squamous carcinoma who received neoadjuvant concurrent chemoradiotherapy and complete resection followed by durvalumab or placebo treatment, showed no statistically significant differences in DFS and OS between the durvalumab adjuvant therapy and placebo groups.[36] Further exploration is needed to assess the potential of different immunotherapy drugs for adjuvant treatment after neoadjuvant chemoradiotherapy, identify the most beneficial patient groups, and validate efficacy in real-world settings.

For patients with locally advanced esophageal cancer who did not receive neoadjuvant therapy preoperatively, the CSCO guidelines suggest considering adjuvant radiotherapy, chemotherapy, or chemoradiotherapy based on the postoperative achievement of R0 resection, though extensive evidence-based data are lacking. In cases with postoperative R1/R2 resection, adjuvant concurrent chemoradiotherapy can be considered.[16] The feasibility of adding immunotherapy to adjuvant treatment remains unclear due to a lack of clinical trial data, and thus, further exploration is warranted.

4.2. Inoperable locally advanced esophageal cancer

Expert consensus III: For patients with inoperable locally advanced esophageal cancer, concurrent chemoradiotherapy is the standard treatment modality. Based on current single-arm phase I/II clinical trials, chemoradiotherapy combined with immunotherapy shows efficacy and acceptable tolerance. Chemoradiotherapy combined with immunotherapy is recommended for clinical trials or selective patient treatment

(evidence quality: medium; consensus level: 98%).

The 2023 CSCO guidelines for esophageal cancer define patients with clinical stages cT1B-4BN0M0/cT1-4BN + M0 (including those deemed inoperable, contraindicated for surgery, or refusing surgery) as those with inoperable locally advanced esophageal cancer.[16] Concurrent chemoradiotherapy remains the standard treatment method for them, although the efficacy of curative concurrent chemoradiotherapy remains an area for improvement.

Combining chemoradiotherapy with immunotherapy may further enhance treatment efficacy. Several phase I/II single-arm clinical studies with small sample sizes have explored the combination of immunotherapy with chemoradiotherapy or radiotherapy in patients with inoperable locally advanced esophageal cancer.[23,24,37–42] Zhang et al.[24] treated 20 patients with locally advanced ESCC using camrelizumab in conjunction with concurrent chemoradiotherapy. They reported 2-year OS and PFS rates of 69.6% and 65.0%, respectively, along with a 45% incidence of grade ≥3 treatment-related adverse reactions, 20% incidence of grade ≥3 radiation esophagitis, and 10% incidence of grade ≥3 esophageal fistula, without any grade ≥3 radiation pneumonitis. Furthermore, Zhu et al.[42] reported on 42 patients with untreated, inoperable stage II-IVA ESCC who received tislelizumab combined with curative chemoradiotherapy. The 1-year OS and PFS rates were 78.4% and 54.5%, respectively. Current evidence from small-sample single-arm phase I/II clinical trials suggests that in comparison with traditional chemoradiotherapy, concurrent immunotherapy with chemoradiotherapy improves efficacy in locally advanced esophageal cancer, with acceptable tolerance and controllable adverse reactions (Table 1). Few phase III randomized controlled studies, such as ESCORT-CRT, KEYNOTE-975, RATIONALE-311, and KUNLUN, are ongoing.[43–45]

For patients with inoperable locally advanced esophageal cancer, the optimization of the combination of chemoradiotherapy and immunotherapy, including radiation dose, radiation scheme, and chemotherapy regimen, warrants further investigation. Regarding the selection of the most responsive patient population for chemoradiotherapy combined with immunotherapy, current studies suggest that patients with PD-L1-positive expression in tumor tissues exhibit better survival outcomes, indicating a potential predictive value of PD-L1 expression in the studied population.

Expert consensus IV: The recommended method to assessing the efficacy of chemoradiotherapy combined with immunotherapy in locally advanced esophageal cancer is the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. This assessment should be complemented by endoscopic ultrasound, endoscopic biopsy, and upper gastrointestinal radiography to enhance accuracy (evidence quality: medium; consensus level: 92%).

The evaluation of the effects of neoadjuvant concurrent chemoradiotherapy combined with immunotherapy in locally advanced esophageal cancer mainly relies on postoperative pathology. Esophageal cancer pathology reports should include all information related to patient treatment and prognosis, specifying the degree of remission after neoadjuvant treatment and the post-neoadjuvant therapy pathological stage (ypTNM). The assessment of the response to neoadjuvant therapy often employs the standards of the College of American Pathologists, referencing residual tumor cell proportions using grading systems (e.g., the Mandard and Becker systems) and tumor regression grading following the definitions proposed by the Japan Esophageal Society (JES). While phase I and II clinical studies of neoadjuvant therapy commonly use pCR or MPR as study endpoints, their ability to predict long-term survival remains inconclusive due to limited prospective data. Endpoints for neoadjuvant immunotherapy, such as OS and DFS, require extended follow-up periods.

While conventional RECIST provides some reflection of the effects of neoadjuvant concurrent chemoradiotherapy combined with immunotherapy, discrepancies between radiological and pathological assessments tend to exist. Therefore, pathological assessment should take precedence when surgical pathology results are available, with radiological assessment serving as an auxiliary method to evaluate the effects of neoadjuvant therapy.

The 2022 guidelines by the National Health Commission (NHC) of China recommend efficacy assessment 1 month after the completion of neoadjuvant radiotherapy, including enhanced CT scans (neck, chest, and abdomen) and routine laboratory tests. Invasive examinations, such as repeat biopsies under esophagoscopy, endobronchial ultrasound-guided transbronchial needle aspiration or endoscopic ultrasound-guided fine-needle aspiration, and biopsies of enlarged regional lymph nodes, can assist in precise clinical restaging preoperatively.[46] The combination of multiple detection methods and application of artificial intelligence (AI) may significantly improve the accuracy of predicting and evaluating treatment efficacy.[47]

RECIST v1.1 remains widely adopted for the assessment of chemoradiotherapy combined with immunotherapy in inoperable locally advanced esophageal cancer. However, the effectiveness of the evaluation criteria for solid tumor immunotherapy, including the immune-related response criteria and modified RECIST v1.1 for immune-based therapeutics, has not been specifically validated in the context of inoperable locally advanced esophageal cancer.

Multimodal assessment methods are needed to accurately assess the effects of chemoradiotherapy combined with immunotherapy in such cases. For example, for lymph nodes suspected of metastasis, fine-needle aspiration biopsy under endoscopic ultrasonography guidance or

Table 1
Clinical trials of radiotherapy or chemoradiotherapy combined with immunotherapy for locally advanced unresectable esophageal cancer.

Treatment regimen	Registration no.	Number of cases	Efficacy	Adverse events
Camrelizumab + radiotherapy[37]	NCT03222440	20 (19 evaluable)	ORR: 73.7%; median OS: 16.7 months; median PFS: 11.7 months	Capillary hemangioma: 89%; grade 3 AE: 47%; grade 4 AE: 5%
Camrelizumab + radiotherapy[40]	–	16 (14 evaluable)	CR: 7.1%; PR: 92.9%	Grade 1–2 AE: 42.9%
Camrelizumab + concurrent chemoradiotherapy[24]	NCT03671265	20	ORR: 65%; 1, 2-year OS rate: 85.0%, 69.6%; 1, 2-year PFS rate: 80.0%, 65.0%	Grade ≥3 TRAE: 45%; grade ≥3 radiation esophagitis: 20%; grade ≥3 esophageal fistula: 10%; severe TRAE: 40%
Teriprizumab + concurrent chemoradiotherapy[42]	NCT04005170	42	clinical complete response rate: 62.0%; 1-year OS rate: 78.4%; 1-year PFS rate: 54.5%	grade ≥3 AE: 86%; esophageal fistula: 14%
Durvalumab + tislelizumab + concurrent chemoradiotherapy[23]	NCT03377400	40 (25 initial treatment, 15 relapse)	2-year PFS rate: 57.5%; 2-year OS rate: 75.0%; PD-L1-positive patients had higher PFS and OS than PD-L1-negative patients	8 patients discontinued due to treatment-related adverse reactions, 1 case of grade 4 lipase increase, 1 case of grade 3 colitis, 1 case of grade 3 interstitial pneumonitis.
Radical concurrent chemoradiotherapy, followed by camrelizumab[38]	NCT04286958	11	SD: 8/9; PD: 1/9; DCR: 88.9%	Reactive skin capillary endothelial proliferation: 6/11; pneumonitis: 4/11; hypothyroidism: 1/11; hyperthyroidism: 1/11

Note: ORR. objective response rate; OS. overall survival; PFS. progression-free survival; AE. adverse event; TRAE. treatment-related adverse event; CR. complete response; PR. partial response.

through-wall biopsy under endobronchial ultrasound guidance is recommended to obtain more accurate N staging.[48] Wang and Li[41] reported preliminary results of a phase II clinical study on locally advanced inoperable ESCC treated with envafolimab combined with endostar and concurrent chemoradiotherapy. Among the 10 enrolled patients, the objective response rate was 100% based on enhanced CT evaluation 4 weeks after chemoradiotherapy and the pCR rate was 88.9%, as assessed by endoscopic ultrasonography-guided biopsy.

Comprehensive approaches are recommended considering the limitations of each diagnostic method, including neck, chest, and abdominal CT with enhancement scanning combined with three-dimensional reconstruction, PET-CT, and esophageal endoscopic ultrasonography, which assist in the accurate evaluation of clinical staging pre- and post-treatment of inoperable locally advanced esophageal cancer.[2] MRI can also be utilized to provide supplementary information if necessary.

4.3. Advanced esophageal cancer

Expert consensus V: For advanced esophageal cancer, the standard treatment strategy is chemotherapy combined with immunotherapy. Although high-level evidence-based medical data are lacking, radiotherapy may further improve survival in patients with oligometastatic disease. For patients with multiple metastatic esophageal cancers, radiotherapy can alleviate symptoms. There is a need for clinical studies to determine the significance and timing of adding radiotherapy to chemotherapy combined with immunotherapy in advanced esophageal cancer (evidence quality: low; consensus level: 96%).

According to the 2022 Chinese guidelines for esophageal cancer radiotherapy, radiotherapy should be considered as part of the treatment strategy for advanced esophageal cancer. This includes patients whose metastatic lesions have either diminished or stabilized following chemotherapy, those experiencing recurrence at the primary site after curative treatment, or those with obstructive symptoms and difficulty in eating due to a sizeable primary tumor. In cases where distant metastases occur after curative treatment or when distant metastases cause clinical symptoms, radiotherapy may be a viable option for these metastatic lesions. For patients with extensive multi-station lymph node metastases, palliative radiotherapy targeting both primary and metastatic lesions is recommended.[49] Academic communities have been exploring the potential benefits of incorporating immunotherapy into radiotherapy for these patients.

Immunotherapy combined with chemotherapy has become the standard treatment approach for advanced esophageal cancer.[18,20] However, resistance and tumor progression can still occur in some patients during clinical practice. Patients with a poor prognosis often exhibit oligometastases, characterized by a limited number of recurrent, progressive, or refractory metastatic lesions as observed in radiological examinations.[50] The investigation into combining radiotherapy to manage local tumors or oligometastases with the standard systemic treatment strategies of immunotherapy and chemotherapy represents a crucial research direction for metastatic esophageal cancer.

In a retrospective study encompassing 127 patients with recurrent/metastatic ESCC who had received immunotherapy, no statistically significant differences were found in OS between those who received radiotherapy and those who did not. However, in case of those experiencing local regional recurrence and subsequently undergoing radiotherapy after a combination of immunotherapy and chemotherapy, OS was significantly prolonged, indicating that radiotherapy may play a more critical role in the treatment of locally recurrent advanced esophageal cancer.[51] Zhao et al.[52] prospectively enrolled 49 patients with advanced ESCC oligometastases who had previously failed immunotherapy and chemotherapy. These patients received the second-line camrelizumab combined with chemoradiotherapy, with the disease control rate 75.5%, and the objective response rate was 40.8%. The median PFS was 6.9 months (95% *CI*: 4.6–9.3), and the median OS was 12.85 months (95% *CI*: 10.1–15.5). Ongoing prospective randomized controlled studies are currently investigating the potential of incorporating radiotherapy into the first-line chemotherapy and immunotherapy combined treatment to enhance survival outcomes for advanced esophageal cancer. The findings of such studies are expected to provide new evidence for advanced esophageal cancer treatment.

4.4. Safety considerations for radiotherapy combined with immunotherapy

Expert consensus VI: At present, there is insufficient evidence-based medical evidence supporting that radiotherapy combined with immunotherapy induces additional or more severe safety events. Nevertheless, to mitigate AEs, it is essential to assess patient risk factors before and during treatment to predict or reduce the risk of complications. In addition, radiotherapy planning should prioritize minimizing damage to normal tissues, with stricter limits for normal tissues compared to concurrent chemoradiotherapy (evidence quality: low; consensus level: 100%).

As radiotherapy can induce systemic immune effects and the mechanisms of adverse reactions induced by ICIs and radiotherapy may overlap,[13,53] combining immunotherapy with radiotherapy might enhance adverse reactions. Therefore, a careful assessment of the risk of complications is necessary before treatment initiation, and the selection of patients suitable for combined radiotherapy and immunotherapy is equally important. Special attention should be given to patients with poor physical condition, cachexia, compromised cardiopulmonary function, or severe diseases in vital organs. In specific scenarios, such as significant esophageal bleeding, severe infection complications from esophageal fistulas, or evident signs of perforation in esophageal fistulas, radiotherapy should be avoided, if possible.[49]

Common treatment complications of radiotherapy and immunotherapy for esophageal cancer include the following:

4.4.1. Esophageal fistula

The incidence of esophageal fistula is closely related to the extent of tumor invasion. The risk increases with evidence such as tumor invasion into the trachea and large blood vessels and significant tumor necrosis.[54–56] The median survival of patients with advanced esophageal cancer with esophageal fistula is only 3.63 months, with a mortality rate of 65% within 2 months. The median time to the development of esophageal fistulas is 3–4 months after radiotherapy starts. Small-sample prospective studies of chemoradiotherapy combined with immunotherapy have reported esophageal fistula rates of 10%–14%.[24,42] For risk reduction, patients assessed as high risk before radiotherapy can be managed with reduced intensity of treatment, close monitoring of tumor changes, and improved nutrition. In case of those who develop esophageal fistulas, prompt management and appropriate treatment, such as gastrostomy, enteral nutrition tube placement, esophageal covered stent insertion, and intravenous nutrition support, should be considered.

4.4.2. Major hemorrhage

Major hemorrhage is another serious complication of radiotherapy for esophageal cancer. Although the incidence is low, it is life-threatening. Patients whose tumors invade major blood vessels or even the thoracic aorta may experience massive bleeding after thoracic radiotherapy; they thus require careful monitoring.[57] To prevent major hemorrhage, it is essential to assess the extent of esophageal cancer lesion invasion and related risk factors before radiotherapy.

4.4.3. Lung injury

Radiation-induced lung injury (RILI) is the most common complication of thoracic tumor radiotherapy and a major dose-limiting adverse reaction that occurs in 5%–15% cases. ICI-related pneumonitis (ICI-P) is the most common cause of immunotherapy-related death, accounting for 10% of deaths from immune-related AEs. During anti-PD-1/PD-L1 treatment, pneumonitis reportedly accounts for 35% deaths.[58] The combination of immunotherapy and radiotherapy might increase the

incidence of pneumonitis.[59] RILI and ICI-P share similar clinical symptoms, such as difficulty breathing, cough, shortness of breath, chest pain, and fever. RILI can progress to pulmonary fibrosis, while ICI-P can be accompanied by other immune-related AEs and, in severe cases, lead to acute interstitial pneumonitis.[60] Distinguishing the cause of pneumonitis during combined radiotherapy and immunotherapy is challenging. Radiographic manifestations can serve as a reference: RILI often presents as ground-glass opacities or consolidation within the irradiated lung,[61] while ICI–P lesions can be located anywhere. Both these conditions are primarily treated with corticosteroids, supplemented, as needed, with oxygen, bronchodilators, and antibiotics. ICI-P treatment usually involves discontinuation or reduction of immunotherapy, and even immunosuppressants in severe cases.[62] Prevention is critical for RILI, primarily through accurate target delineation and optimization of radiotherapy plans to minimize the dose and volume of normal lung tissue irradiated.[49]

4.4.4. Cardiac injury

Radiation-induced cardiac injury, including arrhythmias, pericarditis, and myocardial infarction, is one of the most common complications of chemoradiotherapy and radiotherapy. Cardiovascular AEs induced by immunotherapy are rare, constituting <1% cases. The primarily cardiovascular AE is myocarditis, which may also affect the pericardium and coronary arteries.[63] Radiation-induced cardiac injury typically remains confined to the radiotherapy area and manifests months or even years after radiotherapy. In contrast, immunotherapy-related cardiac injuries lack a specific occurrence location. Hence, the prevention of radiation-induced cardiac injuries is paramount, and treatment plans for patients with risk factors need to be optimized. In the event of cardiac injury, symptomatic cardiovascular drugs become essential.[64] Cardiac AEs caused by immunotherapy necessitate the discontinuation of immunotherapy and administration of corticosteroids. If there is no significant improvement following steroid treatment, alternative therapies such as infliximab, mycophenolate mofetil, or intravenous immunoglobulin may be considered.[62]

4.5. Clinical considerations for radiotherapy combined with immunotherapy

Expert consensus VII: With the growing application of chemoradiotherapy combined with immunotherapy in clinical settings, there is an imperative need for further optimization of treatment regimens. This optimization encompasses considerations such as the timing of adding immunotherapy, delineation of radiotherapy target areas, dosage adjustments, concurrent chemotherapy regimens, identification of patient populations that would derive maximum benefit, and mitigation of severe adverse reactions (evidence quality: low; consensus level: 100%).

4.5.1. Radiotherapy target area

Involved-field irradiation is recommended when combining chemoradiotherapy with immunotherapy (evidence quality: medium; consensus level: 97%).

Determining the gross tumor volume (GTV) range for esophageal cancer involves utilizing multimodal imaging techniques, such as PET-CT, enhanced CT, MRI, endoscopic ultrasound, and upper gastrointestinal radiography.[65–67] The CTV range for esophageal cancer exhibits variability across studies. In case of esophageal cancer, although extending the radiation range along the longitudinal 5 cm boundary of the esophagus in conventional radiotherapy poses a risk of recurrence beyond the irradiated field,[68,69] involved-field irradiation, as supported by randomized studies, lowers the probability of out-of-field recurrence.[70,71] In the context of chemoradiotherapy combined with immunotherapy, involved-field irradiation does not evidently increase out-of-field recurrence; however, if the target area is too large, peripheral blood lymphocyte count might reduce, negatively impacting survival. Animal studies suggest that preventing irradiation of lymph nodes may kill lymphocytes in the lymph nodes near the tumor, alleviating treatment efficiency.[72] Therefore, involved-field irradiation is recommended when combining chemoradiotherapy with immunotherapy.

4.5.2. Dose recommendation in curative chemoradiotherapy combined with immunotherapy

In curative chemoradiotherapy combined with immunotherapy, it is recommended to administer a dose of 95% PTV 50–50.4 Gy at 1.8–2.0 Gy per fraction, while for preoperative chemoradiotherapy combined with immunotherapy, the recommended dose is 95% PTV 40–41.4 Gy at 1.8–2.0 Gy per fraction (evidence quality: high; consensus level: 98%).

Considering the radiation dose and fractionation for combining radiotherapy with immunotherapy is essential. Larger fractions are suggested to have a stronger effect on immune activation; however, as the esophagus is a hollow organ, the risk of bleeding and esophageal fistula increases with increased fraction size. Hence, a fractionation of 1.8–2.0 Gy per session is recommended in curative chemoradiotherapy. According to the NCCN and CSCO guidelines, the recommended dose is 95% PTV 40–41.4 Gy at 1.8–2.0 Gy per fraction for preoperative radiotherapy and 95% PTV 50–50.4 Gy at 1.8–2.0 Gy per fraction for curative radiotherapy. Several phase III multicenter studies have shown that increasing the radiation dose to ≥60 Gy does not improve patient survival.[73,74] As per previous small-sample phase I/II clinical studies of chemoradiotherapy combined with immunotherapy for esophageal cancer, the recommended dose is 95% PTV 50.0–50.4 Gy at 1.8–2.0 Gy per fraction for curative chemoradiotherapy combined with immunotherapy and 95% PTV 40–41.4 Gy at 1.8–2.0 Gy per fraction for preoperative chemoradiotherapy combined with immunotherapy.[23–25,30] Future research should investigate the effects of different radiotherapy doses and fractionation when radiotherapy is combined with immunotherapy to optimize radiotherapy regimens.

4.5.3. Timing of immunotherapy intervention

The timing of adding immunotherapy in curative chemoradiotherapy for esophageal cancer lacks specific recommendations, necessitating further research (evidence quality: high; consensus level: 98%).

Immunotherapy can be administered before, during, or after radiotherapy when added to chemoradiotherapy. While there are no studies specifically on the timing of adding immunotherapy to curative chemoradiotherapy for esophageal cancer, preclinical animal experiments[75] and small-sample phase I/II clinical studies have reported favorable outcomes with concurrent immunotherapy with radiotherapy or a short interval between them. Sequential immunotherapy after chemoradiotherapy is associated with lower proportionate benefits. Ongoing clinical trials (concurrent immunotherapy with curative chemoradiotherapy: NCT04210115 [KEYNOTE-975], NCT04426955, NCT03957590 [RATIONALE-311], and NCT04595149 [TAPESTRY]; immunotherapy as consolidation therapy after curative concurrent chemoradiotherapy: NCT04543617, UMIN000034373, NCT04514835, NCT03817658, and NCT04054518) are expected to provide valuable insights into the optimal timing of chemoradiotherapy combined with immunotherapy for esophageal cancer.

4.5.4. Selection of beneficiary populations

Patients exhibiting high PD-L1 expression in tumor tissues may benefit from immunotherapy or combined immunotherapy for esophageal cancer (evidence quality: medium; consensus level: 98%).

In the realm of ICI-based treatment for patients with ESCC, the studied biomarkers include PD-L1 expression, tumor mutation burden, and microsatellite instability/deficient mismatch repair. PD-L1 expression has been the most extensively studied. In a meta-analysis involving 1,350 patients with ESCC from China and Japan, 559 (41.4%) exhibited

PD-L1 overexpression, which indicates that PD-L1 might be a biomarker of poor prognosis.[76] At present, PD-L1 expression can be assessed using two systems: CPS and tumor proportion score. The KEYNOTE-590 study reported that in the subgroup analysis of CPS ≥10, the group receiving pembrolizumab combined with chemotherapy experienced greater survival benefits than that receiving chemotherapy alone, demonstrating a 3.4-month improvement in survival compared to the CPS <10 subgroup.[77] Similarly, the ESCORT study indicated clinical benefits for patients with positive PD-L1 expression in the camrelizumab group, with longer survival observed in those with PD-L1-positive expression tumor proportion score ≥10% in comparison with those in the low expression group.[9] Phase IB clinical trials investigating radiotherapy or chemoradiotherapy combined with immunotherapy have also highlighted the predictive value of PD-L1 expression in tumor tissues for the efficacy of this combined approach. Altogether, these findings indicate that patients with esophageal cancer exhibiting high PD-L1 expression in tumor tissues may potentially benefit from immunotherapy or combined immunotherapy.

4.5.5. Prediction and avoidance of severe adverse reactions in combined immunotherapy

The combination of radiotherapy with immunotherapy does not significantly increase the risks of radiation pneumonitis, esophageal fistula, or major hemorrhage; pretreatment patient screening can reduce the occurrence of adverse reactions (evidence quality: medium; consensus level: 98%).

A recent study by the FDA examining whether patients receiving immunotherapy combined with radiotherapy experience an increased risk of adverse reactions revealed that administering ICIs within 90 d after radiotherapy did not amplify the risk of severe adverse reactions. Their results suggested that undergoing immunotherapy within 90 d of radiotherapy does not affect the occurrence of immune-related AEs.[78] Comprehensive findings from existing small-sample phase I/II single-arm clinical studies have reported that radiotherapy combined with immunotherapy for patients with esophageal cancer does not significantly increase the risks of radiation pneumonitis, esophageal fistula, or major esophageal hemorrhage. In general, patients show good tolerance, and adverse reactions are controllable. Despite the favorable tolerability observed in clinical studies on immunotherapy combined with chemoradiotherapy for esophageal cancer, attention should still be directed toward adverse reactions caused by immunotherapy. Screening patients before treatment can reduce the occurrence of adverse reactions. For those at a high risk of esophageal fistula or major bleeding, high-intensity chemoradiotherapy combined with immunotherapy should be avoided. Patients with compromised lung function or a history of chronic lung disease are not recommended for chemoradiotherapy combined with immunotherapy. Furthermore, additional screening for biomarkers associated with immune-related severe adverse reactions can help reduce the occurrence of serious AEs.

5. Summary

Drawing from the available clinical data, this expert consensus clarifies the role of chemoradiotherapy combined with immunotherapy in the perioperative period of esophageal cancer, definitive chemoradiotherapy combined with immunotherapy for locally advanced esophageal cancer, and radiotherapy combined with immunotherapy for advanced esophageal cancer. The consensus extends valuable recommendations pertaining to radiotherapy dose, target area range, and the integration of varied treatment modalities. Anticipating the forthcoming results of phase III clinical trials investigating chemoradiotherapy combined with immunotherapy, there is a potential paradigm shift in the treatment landscape for locally advanced esophageal cancer. Future studies should focus on the meticulous selection of beneficiary populations, targeted screening of cohorts prone to severe adverse reactions, and further development of combined treatment modalities.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The consensus level was derived through the collaborative efforts of experts from the radiation therapy, oncology, and oncology surgery departments. This also involved dedicated participation from both the consensus writing and approval groups. In total, 130 experts worked on the consensus: 77% were from the radiation therapy department, 16% from the oncology department, and 7% from the oncology surgery department. The consensus level, quantified as a percentage of expert opinions, reflects the culmination of insights and expertise from a diverse array of medical professionals.

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