Expert consensus on the whole-process management of the clinical application of immune checkpoint inhibitors for esophageal cancer

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Abstract:
With the rapid development in the field of tumor immunotherapy, immune checkpoint inhibitors (ICIs) centered on programmed death ligand-1 (PD-Ll) have made significant progress in the centered on programmed death-1(PD-1) and PD-L1 have made significant progress in the treatment of esophageal cancer. Several studies have confirmed the effectiveness and safety of ICIs in the treatment of esophageal cancer, and have gradually changed the landscape for treating advanced esophageal cancer. At present, ICls have been widely used in the clinical treatment of esophagal cancer in China. To better guide the whole-process management of esophageal cancer ICIs application, and improve the scientificity and standardization of esophageal cancer ICIs application, the China Anti-cancer Association Esophageal Tumor Integration Rehabilitation Professional Committee organized domestic experts in related fields to systematically sort out the latest domestic and foreign guidelines and evidence-based medical evidence through multiple rounds of discussions and revisions, and reach a consensus among expert in this review by fully considered the specific situation of clinical practice in China.

Key words: Esophageal cancer; Immune checkpoint inhibitor; Whole-process management; Expert consensus

1 Introduction

Esophageal cancer is one of the most common malignant tumors in the world. In 2020, there will be more than 600 000 new esophageal cancer patients worldwide. 53% of new esophageal cases and 55.3% of esophageal deaths occurred in China[1]. According to the disease burden of malignancy in China released by the National Cancer Center in 2022, the incidence rate and mortality rate of esophagus ranked 7th and 5th respectively among malignancies in China[2]. According to the different histological types, esophageal cancer mainly includes esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) two subtypes. ESCC is the main pathological type in China, accounting for more than 90%. Therefore, esophageal cancer mentioned in this consensus is ESCC. Immunotherapy of esophageal adenocarcinoma can refer to Expert Consensus on Gastric Cancer Immunotherapy Based on PD-L1 Protein Expression Level (2023 Edition) issued by Gastric Cancer Professional Committee of China Anti-Cancer Association[3].

Due to the lack of obvious clinical symptoms in the early stage of esophageal cancer, most patients are diagnosed with locally advanced or distant metastasis[4]. Platinum-based chemotherapy regimens have been the mainstay of first-line treatment for advanced esophageal cancer for the past 40 years, but they have shown minimal improvement in overall survival.

Tumor immunity is closely related to the occurrence and development of cancer. With the development of immunotherapy, tumor immunotherapy is changing the research direction and treatment pattern ofthe tumor field at home and abroad. In recent years, ICIs represented by PD-1/ PD-L1 have been comprehensively distributed in the field of esophageal cancer, from second line to first line, from single drug to combination, immunotherapy has completely changed the treatment pattern of advanced esophageal cancer. Based on the excellent results achieved in advanced esophageal cancer, the exploration of immunotherapy in the field of esophageal cancer has been further advanced to the perioperative period.

2 Principles and methods for consensus formulation

The formulation of the consensus followed the principles and methods of the WHO《Guidelines Development Manual》[5] and Chinese Medical Association《Guidelines for Developing/Revising Clinical Diagnosis and Treatment Guidelines in China (2022 Edition)》[6], and conforms to the requirements of Appraisal of Guidelines for Research Evaluation II (AGREE II)[7]. Methodological construction and writing are carried out.

2.1 Grading of evidence quality

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system is used to grade evidence-based medicine evidence, and the initial evidence quality is divided into 1 ~ 3 categories (Table 1).

Table 1 Definition of Consensus Levels of Evidence

class	Description of evidence
Class 1	Meta-analysis with a narrow confidence interval, or double-blind randomized controlled trial with multiple placebo/positive drug controls and sample size greater than 30 in each group
Class 2	Meta-analysis with a wide confidence interval, or double-blind randomized controlled trials with single placebo/positive drug control and sample size greater than 30 in each group; double-blind randomized controlled trials with at least 1 placebo/positive drug control and sample size between 10 and 29 in each group, inclusive, or administrative data from health systems
Class 3	uncontrolled trial, case report or case system, or expert opinion

2.2 Form recommendations

For each clinical question, the evidence evaluation team develops recommendations and evidence decision tables based on current evidence. Consensus development team members form initial recommendations based on the quality of evidence, patient preferences and values, health economics analysis, and trade-offs, and determine the strength of recommendations. Con-

sensus on recommendations and their strength through 1 – 2 rounds of Delphi and 1 – 2 rounds of online or offline discussion.

The rules are as follows: if more than 75% of the experts participating in the consensus vote agree with the recommendation, consensus will be reached; for recommendations that do not reach consensus, a second round of Delphi consensus or discussion will be conducted after revision according to expert opinions until consensus is reached or deleted from consensus. After consensus is reached on the recommendations, they will be submitted to the Steering Committee for approval. With the consent of 75% of the members of the consensus formulation group, the steering committee can revise and improve the important problems existing in the recommendations, and the secretary group shall truthfully record the whole revision process (Table 2).

Table 2 Definition of consensus evidence recommendation level

Grade of recommendation	standard
Grade I recommendation	Demonstrate that interventions do more good than harm or harm than good; support application with high-quality evidence; benefit or no impact on resource allocation.
Grade II recommendation	Interventions do more good or harm than good, although the evidence is not clear; evidence exists to support application, although the quality of evidence is not high enough; they have a positive, negative, or small impact on resource allocation.

ICIs not marketed in China are not included in this consensus recommendation.

3 ICIs Introduction

3.1 Types of ICIs

Immune checkpoint molecules include cytotoxic T lymphocyte antigen-4 (CTLA – 4), PD – 1, PD – L1, and other novel immune checkpoint molecules. As of May 2024, National Medical Products administration (NMPA) has approved the marketing of 19 ICIs, including 1 CT – LA – 4 inhibitor and 1 ipilimumab; 10 PD – 1 inhibitors, including nivolumab, pembrolizumab, toripalimab, sintilimab, camrelizumab, tislelizumab, penpulimab, zimberelimab, serplulimab and pucotenlimab; There are 7 PD – L1 inhibitors, namely durvalumab, atezolizumab, envafolimab, sugemalimab, adebrelimab, socazolimab and benmelstobart; 1 PD – 1/CTLA – 4 bispecific antibody, cadonilimab.

In the field of esophageal cancer, ICIs have been approved for indications as shown in Table 3.

3.2 The biomarker

Recommendation 1: For esophageal cancer patients scheduled for PD – 1 inhibitor therapy, it is recommended to assess PD – L1 protein expression in cancer tissue. Specific detection indicators can be CPS and tumor positive score (TPS) (evidence level: Class 1; recommendation level: Class I recommendation; expert consensus: 100%).

Recommendation 2: Microsatellite instability (MSI), tumor mutational burden (TMB) and novel molecular markers for predicting efficacy can be considered if conditions permit (evidence level: Class 2; recommendation level: Class II recommendation; expert consensus: 100%).

3.2.1 PD – L1 protein expression detection

The results of multiple studies and meta-analyses show that PD – L1 protein expression level is closely related to the efficacy of PD – 1 inhibitors and the survival benefit of patients [Refs]. PD – L1 protein expression detection is an effective indicator to guide clinical screening of the immunotherapy benefit population. KEYNOTE – 181 study [11] showed that pembrolizumab significantly prolonged overall survival (OS) compared with chemotherapy in patients with PD – L1 CPS≥10, especially in ESCC patients. Checkmate – 648 study[9] showed that in patients with advanced ESCC with PD – L1TPS≥1%, nivolumab combined with chemotherapy was more beneficial than nivolumab combined with ipilimumab and chemotherapy alone. However, PD – L1 expression was highly heterogeneous in esophageal carcinoma, with the expression rate ranging from 15% to 83% in ESCC cells and from 13% to 31% in immune cells. A pooled analysis published by JAMA Oncology[20] found that combination immuno-

Table 3 Indications for esophageal cancer of ICIs approved for marketing by NMPA (as of March 2024)

Generic name	Cancer types	Lines of therapy	Approved indications in China	Study	Approval time
Nivolumab	esophageal or gastric junction cancer squamous cell carcinoma of the esophagus	Adjuvant therapy First-line therapy	It can be used as adjuvant therapy for esophageal cancer or gastroesophageal junction cancer patients with pathological residue after neoadjuvant CRT and complete surgical resection Combinationfluoropyrimidine and platinum-based chemotherapy for first-line treatment of advanced or metastatic esophageal squamous cell carcinoma	CheckMate - 577 study[8] CheckMate - 648 study[9]	June 2022 June 2022
Pembrolizumab	esophageal cancer	First-line therapy Second-line therapy	Combination platinum and fluorouracil chemotherapy for first-line treatment of patients with locally advanced unresectable or metastatic esophageal or gastroesophageal junction cancer Single-agent use in patients with locally advanced or metastatic ESCC who have failed prior first-line systemic therapy and whose tumor expression PD - L1 is CPS≥10	KEYNOTE - 590 study[10] KEYNOTE - 181 study[11]	September 2021 June 2020
Toripalimab	esophageal cancer	first-line treatment	In combination with paclitaxel and cisplatin for the first-line treatment of patients with unresectable locally advanced/recurrent or distant metastatic esophageal squamous cell carcinoma	JUPITER-06study[12]	May 2022
Sintilimab	esophageal cancer	first-line treatment	Combination of paclitaxel and cisplatin or fluorouracil and cisplatin for the first-line treatment of unresectable locally advanced, recurrent, or metastatic squamous cell carcinoma of the esophagus	ORIENT - 15Study[13]	June 2022
Camrelizumab	esophageal squamous cell carcinoma	First-line therapy Second-line therapy	Combination of paclitaxel and cisplatin for first-line treatment of patients with unresectable locally advanced/recurrent or metastatic squamous cell carcinoma of the esophagus For the treatment of locally advanced or metastatic squamous cell carcinoma of the esophagus in patients whose disease has progressed or is intolerable after prior first-line chemotherapy	ESCORT - 1ststudy[14] ESCORT Research[15]	December 2021 June 2020
Tislelizumab	esophageal squamous cell carcinoma	First-line therapy Second-line therapy	Combination chemotherapy for first-line treatment of esophageal squamous cell carcinoma For the treatment of patients with locally advanced or metastatic squamous cell carcinoma of the esophagus who are not tolerated after prior first-line standard chemotherapy	RATIONALE 306study[16] RATIONALE 302study[17]	May 2023 April 2022
Serplulimab	esophageal squamous cell carcinoma	first-line treatment	First-line treatment of unresectable locally advanced/recurrent or metastatic esophageal squamous cell carcinoma with PD - L1-positive(CPS≥1) in combination with fluorouracil and platinum	ASTRUM - 007 study[18]	September 2023
Sugemalimab	esophageal squamous cell carcinoma	first-line treatment	Combination with fluorouracil and platinum-based chemotherapy for the first-line treatment of unresectable locally advanced, recurrent, or metastatic esophageal squamous cell carcinoma	GEMSTONE - 304study[19]	December 2023

Note: NMPA, National Medical Products administration; ICIs, immune checkpoint inhibitors; CRT, chemoradiotherapy; PD - L1, programmed death protein ligand - 1; CPS, combined positive score; ESCC, esophageal squamous cell carcinoma.

therapy did not improve survival in the TPS < 1% population, but helped to improve OS in the CPS < 10 population, indicating that different PD - L1 detection platforms and cut-offs may have different predictive effects. Sun Yat-sen University Cancer Center conducted a comprehensive analysis of five clinical studies and performed a meta-analysis[21], finding that patients with low PD - L1 expression can still benefit from com-

bined immunotherapy. Therefore, the predictive role of PD - L1 expression in combination immunotherapy should be further explored.

3.2.2 Microsatellite instability/mismatch repair defects

MSI - H phenotype is a specific tumor subtype that is highly sensitive to immunotherapy. MSI refers to an increase or decrease in the number of short tandem repeats in the genome, reflecting DNA replication errors due to mismatch repair (MMR) gene abnormalities. These tumors tend to have higher TMB and higher PD - L1 expression levels and respond better to PD - 1 therapy[22]. MSI is widely present in a variety of malignancies, MSI - H incidence in gastric cancer is 7%, esophagogastric junction adenocarcinoma is 4%, and esophageal adenocarcinoma is 0.4%[23].

3.2.3 TMB

TMB has been a promising predictor of immunotherapy efficacy in recent years. In a phase II clinical trial of pembrolizumab in refractory esophageal cancer[24], 39 patients with esophageal adenocarcinoma and 10 patients with esophageal squamous cell carcinoma were included. Among 27 patients evaluable for TMB, 7 patients had TMB ≥ 10 mut/Mb, and OS tended to improve when TMB was 10mut/Mb or higher (P = 0.086). Overall, TMB appears to be a predictor of response to immunotherapy for esophageal cancer, but large phase III trials are needed to confirm it.

3.2.4 Novel molecular markers for predicting efficacy

Circulating tumor DNA

Qualitative and quantitative analysis of circulating tumor DNA (ctDNA) is helpful for early diagnosis, curative effect evaluation, prognosis judgment, and monitoring tumor metastasis and recurrence of esophageal cancer. Sun Yat-sen University Cancer Center has demonstrated for the first time that ctDNA and blood tumor mutation burden (bTMB) can predict the efficacy and survival of patients receiving PD - 1 inhibitors combined with radical radiotherapy and chemotherapy in locally advanced ESCC[25]. ctDNA detection methods include PCR-based first-generation sequencing methods and next-generation sequencing (NGS) technology. NGS has been more and more widely used in clinical practice due to its advantages of non-invasive or minimally invasive, short detection time, ability to reflect heterogeneity of tumor and metastasis, and dynamic monitoring of treatment efficacy [26]. With the continuous exploration of ctNDA and optimization of detection methods, ctDNA can make better progress in the field of accurate diagnosis and treatment of esophageal cancer.

Tumor microenvironment

The tumor microenvironment (TME) is a dynamic whole, including the immune microenvironment, interstitial microenvironment, hypoxic microenvironment, angiogenesis, and so on. Myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) in TME promote the immune escape of cancer cells by secreting cytokines and activating pro-inflammatory pathways, thus promoting the malignant progression of esophageal cancer. Other immune cells, such as cancer-associated fibroblasts (CAFs), secrete growth factors that alter the extracellular matrix (ECM) to form tumor niches and promote tumor cell migration and invasion. Tumor-associated macrophages (TAMs) also have other tumor-promoting functions, including inducing angiogenesis and tumor cell invasion [27]. However, a single biomarker is difficult to fully reflect the status of TME, and a multi-dimensional accurate assessment of esophageal cancer TME is needed to predict treatment effects.

Esophageal microecology

In 2015, two papers published in *Science* first clarified the relationship between intestinal flora and immunotherapy[28-29]. Microbes are emerging as potential biomarkers for predicting the efficacy of immunotherapy. Gao et al.[30] found that Porphyromonas gingivalis, a specific bacterium that can cause oral squamous cell carcinoma, may be related to the occurrence of squamous cell carcinoma when studying the pathogenesis of squamous cell carcinoma, and once again proposed the similarity between these two tumors, and this bacterium will selectively infect squamous cell carcinoma and surrounding mucosa, but will not infect healthy esophageal mucosa. Even this bacterium is related to the progression degree and prognosis of esophageal carcinoma, which can be considered as a tumor marker of squamous cell carcinoma. Diakowska et

al.[31] found that H. pylori infection increases the production of interleukin - 18 (IL - 18), an inducer of interferon-c that stimulates the development of innate and reactive immune responses (Th1 and Th2 cells), activates NK cells to induce apoptosis and inappropriate IL - 18 release is associated with clinical stage of squamous cell carcinoma.

4 Clinical application of immune checkpoint inhibitors for esophageal cancer

4.1 Principles of first-line treatment for advanced esophageal cancer

Recommendation 3: ICIs combined with chemotherapy are recommended for patients with advanced ESCC (Level of Evidence: Class 1; Level of Recommendation: Class I; Expert Consensus: 100%).

Treatment options include: Nivolumab + fluorouracil + cisplatin (FP); pembrolizumab + FP; toripalimab + paclitaxel + cisplatin (TP); sintilimab + TP/FP; camrelizumab + TP; Tislelizumab + TP/FP; serplulimab + FP (PD - L1 expression CPS ≥ 1 point); sugemalimab + FP.

Recommendation 4: If mismatch repair defects/MSI - H are detected, ICIs can be recommended regardless of PD - L1 expression. envafolimab, pembrolizumab, serplulimab, tislelizumab, and toripalimab are currently approved for use in adult patients with unresectable or metastatic MSI - H/dMMR with advanced solid tumors (Level of Evidence: Class 1; Level of Recommendation: Class I; Expert Consensus: 97.2%).

Recommendation 5: For patients with advanced ESCC who have chemotherapy contraindications or refuse chemotherapy and PD - L1 CPS ≥ 1, it is recommended to choose a combination treatment regimen of dual-target ICIs (evidence level: Class 1; recommendation level: Class II recommendation; expert consensus: 94.4%).

Treatment regimen: nivolumab + ipilimumab.

Recommendation 6: Bispecific antibodies may be considered for patients with advanced esophageal squamous cell carcinoma (evidence level: Class 3; recommendation level: Class II recommendation; expert consensus: 88.9%).

Treatment regimen: cadonilimab.

Recommendation 7: PD - 1 combined with antiangiogenic drugs can be considered (evidence level: Class 2; recommendation level: Class II; expert consensus: 94.4%).

A total of 8 phase III clinical studies in the first-line treatment of advanced esophageal cancer confirmed each other, confirming that the efficacy of immunotherapy combined with chemotherapy was superior to chemotherapy alone, the overall objective response rate (ORR) of patients increased by nearly 20%, OS time prolonged by 2 ~ 6 months, and immunotherapy combined with chemotherapy became the standard of first-line treatment for advanced esophageal cancer. However, the median OS time for patients with advanced esophageal cancer is only 15 to 18 months. To further improve the short-term efficacy and prolong the long-term survival of advanced esophageal cancer, it is necessary to optimize the current treatment regimen.

Checkmate - 648[9, 32-33] is a Phase III clinical trial evaluating the efficacy and safety of immune-immune combination and immune-chemotherapy combination as first-line treatment for advanced ESCC. Results presented at the 2021 and 2022 annual meetings of the American Society of Clinical Oncology showed that nivolumab in combination with chemotherapy or nivolumab in combination with ipilimumab significantly prolonged OS compared with chemotherapy in patients with advanced ESCC who had previously been untreated with PD-L1 expression ≥1% and in all randomized populations. At 13 months of follow-up, the median OS (mOS) for nivolumab plus chemotherapy was 15.4 months (95% *CI*: 11.9 to 19.5) and 9.1 months (95% *CI*: 7.7 to 10.0), respectively, and the 12-month OS rates were 58% and 37%, respectively, in patients with PD - L1 expression ≥1%. Time to median OS was 13.7 months (95% *CI*: 11.2 - 17.0) in the nivolumab plus ipilimumab group and 9.1 months (95% *CI*: 7.7 - 10.0) in the chemotherapy group, with OS rates at 12 months of 57% and 37%, respectively. In the overall population, mOS was 13.2 months (95% *CI*: 11.1 to 15.7) for nivolumab plus

chemotherapy and 10.7 months (95% *CI*: 9.4 to 11.9) for chemotherapy. Time to mOS was 12.7 months (95% *CI*: 11.3 to 15.5) in the nivolumab plus ipilimumab arm and 10.7 months (95% *CI*: 9.4 to 11.9) in the chemotherapy arm. At 29 months of long-term follow-up, the 24-month OS rate for patients with PD-L1 expression ≥1% was 31% in the nivolumab plus chemotherapy arm (12% in the chemotherapy arm) and 29% in the nivolumab plus chemotherapy arm (19% in the chemotherapy arm) of all randomized patients. Longer follow-up data suggest that nivolumab + chemotherapy and nivolumab + ipilimumab continue to demonstrate clinically meaningful survival benefits, durable objective responses, and acceptable safety profiles compared to chemotherapy. Further support immunotherapy combination regimens as a first-line treatment option for advanced ESCC.

Keynote-590 study[10, 34] enrollment criteria were locally advanced or metastatic EAC or ESCC, or Siewert type I gastroesophageal junction adenocarcinoma; RECIST v1.1 measurable disease; Eastern Cooperative Oncology Group (ECOG) PS0 or 1. Patients were randomized 1∶1 to receive pembrolizumab (pembro) 200mg or placebo (pbo) intravenously every 3 weeks for ≤35 cycles in combination with chemotherapy (≤35 cycles of 5-fluorouracil; ≤6 cycles of cisplatin). The primary endpoints were OS in patients with ESCC and patients with PD-L1CPS≥10 points, and progression-free survival (PFS) time and OS assessed by the investigator according to RECIST v1.1 in all patients, PFS and OS in patients with ESCC regardless of PD-L1 expression, and PFS and OS in the intention-to-treat (ITT) population with CPS≥10 points. Secondary endpoints included investigator assessment of ORR and duration of response (DOR) according to RECISTv1.1, and safety. The data cut-off was on July 10, 2023. A total of 749 patients were randomly assigned to receive pembro + chemotherapy (373 cases) or pbo + chemotherapy (376 cases). The median time from randomization to data cutoff was 58.8 months (range, 49.2 to 70.6 months), with 701 of 740 patients (94.7%) discontinuing treatment, the most common reason being disease progression (449 patients, 60.7%). In the ITT population, mOS time was 12.3 months in the pembro + chemotherapy arm and 9.8 months in the pbo + chemotherapy arm (*HR* = 0.72, 95% *CI*: 0.62 to 0.84); 5-year OS rates were 10.6% and 3.0%, respectively. Median PFS times were 6.3 months and 5.8 months, respectively (*HR* = 0.64, 95% *CI*: 0.54 to 0.75); 5-year PFS rates were 5.5% and 0, respectively. Treatment-related adverse events (TRAE) of grade 3-5 occurred in 266 patients (71.3%) and 250 patients (66.5%), respectively. There were 9 deaths (2.4%) due to TRAEs in the respective groups and 5 deaths (1.3%) in the other group. Therefore, after 5 years of follow-up, in patients with previously untreated advanced esophageal cancer, compared to pbo plus chemotherapy, pembro plus chemotherapy demonstrated sustained efficacy with no new safety signals. The long-term outcomes continue to support pembro plus chemotherapy as a first-line treatment for advanced esophageal cancer.

JUPITER-06 study[12] is a domestic multicenter randomized controlled study to compare the efficacy of toripalimab combined with chemotherapy versus placebo combined with chemotherapy for first-line treatment of advanced ESCC, including 514 patients. In the interim analysis, OS and PFS were significantly better in the toripalimab combination chemotherapy population than in chemotherapy (OS 17 months vs 11 months, *HR* = 0.58, 95% *CI*: 0.43 to 0.78, *P* = 0.000 4; PFS 5.7 months vs 5.5 months, *HR* = 0.58, 95% *CI*: 0.46 to 0.74, *P* 0.000 01). JUPITER-06 study focused on the Chinese population. Paclitaxel combined with a cisplatin regimen with stronger immune synergy showed better OS and PFS, further supporting the role of chemotherapy combined with immunotherapy in the first-line treatment of advanced esophageal cancer.

ORIENT-15 Study[13, 35] is an international multicenter, randomized, double-blind Phase III trial evaluating sintilimab in combination with placebo chemotherapy as first-line treatment for unresectable locally advanced, relapsed, or metastatic ESCC. Participants were given either sintilimab or placebo in combination with chemotherapy (the chemotherapy regimen was chosen by the investigator between TP and FP). As of 28 August 2022, a total of 690 subjects have been ran-

domized into the study with a median follow-up of 32.2 months. In the overall population, the time to mOS was significantly longer in the sintilimab plus chemotherapy arm than in the placebo plus chemotherapy arm (17.4 months versus 12.8 months, *HR* = 0.661, *P* 0.000 1). In the PD - L1-positive (CPS≥10) population, the mOS time was 18.4 months in the sintilimab combination chemotherapy arm versus 14.5 months in the placebo combination chemotherapy arm, *HR* = 0.635, *P* = 0.000 1. The 1-year OS rate and 2-year OS rate in the sintilimab group versus the placebo group were 64.0% vs 53.5% and 41.4% vs 22.9% respectively. The safety profile was generally consistent with the findings reported in the interim analysis, with no new safety signals.

ESCORT - 1ststudy[14] is a randomized, double-blind, multicenter Phase III clinical trial evaluating camrelizumab in combination with TP for the first-line treatment of advanced esophageal cancer. 596 patients with esophageal squamous cell carcinoma were randomly assigned 1∶1 to camrelizumab + TP or placebo + TP. The primary endpoints were PFS and OS assessed by an independent imaging assessment committee. The trial group achieved a significant improvement in mOS time compared with the control group (15.3 months vs. 12.0 months, *P* = 0.001), reducing the risk of death by 30%, and a significant benefit in mPFS time for the co-primary endpoint (6.9 months vs. 5.6 months, *HR* = 0.56, *P* = 0.001). In terms of safety, the incidence of TRAE was similar between the two groups except for reactive cutaneous telangiosis, which mostly disappeared spontaneously; however, the incidence of TRAE in the camrelizumab plus TP group was lower on grade ≥3 TRAE (63.4% vs 67.7%).

The ESCORT - RWS study[36] was a prospective real-world study of 624 patients with advanced esophageal cancer treated with camrelizumab, including 305 first-line patients, 238 second-line patients, and 81 third-line patients and above. No new safety signal was found in this study. In terms of drug treatment mode, camrelizumab combined with chemotherapy accounted for the most (91.8%), among which paclitaxel combined with platinum was the main chemotherapy regimen (82.1%). ORR, mPFS time, and mOS time were 54.2%, 10.1 months, and 17.5 months for first-line therapy, 31.4%, 7.9 months and 14.0 months for second-line therapy, and 28.1%, 7.9 months and 12.8 months for third-line therapy and above, respectively. The results of the analysis showed that the efficacy and safety of camrelizumab in patients with advanced esophageal cancer in the real world were generally consistent with those observed in the pivotal phase 3 clinical trials (ESCORT and ESCORT-1st).

RATIONALE 306[16] is a global, multicenter, randomized, controlled phase III clinical trial evaluating the efficacy and safety of tislelizumab in combination with chemotherapy versus placebo in combination with chemotherapy as first-line treatment for advanced or metastatic ESCC. Tislelizumab plus chemotherapy significantly improved mOS compared with control (17.2 months vs 10.6 months, *HR* = 0.66, *P* < 0.000 1) and benefited patients regardless of PD - L1 score (PD - L1 score ≥10%: OS time 16.6 months vs 10.0 months, *HR* = 0.62; PD - L1 score < 10%: OS time 15.8 months vs 10.4 months, *HR* = 0.77). PFS was also significantly improved in the tislelizumab plus chemotherapy arm compared with the control arm (7.3 months vs 5.6 months, *HR* = 0.62, *P* 0.000 1), and ORR was higher and more durable (ORR 63.5% and DOR 7.1 months in the test arm versus ORR 42.4% and DOR 5.7 months in the control arm).

ASTRUM - 007 study[18] was a randomized, double-blind, multicenter phase III trial comparing serplulimab or placebo in combination with chemotherapy (cisplatin + 5-fluorouracil) as first-line treatment in patients with unresectable locally advanced/relapsed or metastatic PD - L1-positive (CPS≥1) ESCC, with primary endpoints of PFS and OS. Between 19 June 2019 and 17 December 2021, a total of 976 patients were screened, of whom 551 were randomized to serplulimab plus chemotherapy (368) and chemotherapy (183). At a median follow-up of 24.2 months, mOS was significantly longer in the serplulimab plus chemotherapy arm than in the chemotherapy arm, 14.6 months versus 11.2 months (*HR* = 0.70, 95% *CI*: 0.57 to 0.86; *P* = 0.000 6). Independent Radiology Review Committee (IRRC) mPFS time was 6.5 months vs. 5.3 months (*HR* = 0.58, 95% *CI*: 0.47 to

0.72). Improvement in efficacy was observed in the serplulimab combination chemotherapy arm in time to confirm ORR and DOR assessed by IRRC, 58.7% versus 42.1% and 7.1 months versus 4.6 months, respectively. The incidence of ≥ grade 3 TRAE was 53.1% and 48.8%, respectively. Grade ≥3 immune-related adverse events occurred more frequently in the serplulimab plus chemotherapy arm (9.2% vs 3.0%, respectively). Fifteen death events possibly related to study treatment were reported, 3.1% in the serplulimab plus chemotherapy arm and 1.8% in the chemotherapy arm.

GEMSTONE-304[19] is a randomized, double-blind, Phase 3 study of sugemalimab or placebo in combination with FP as first-line treatment for advanced ESCC. Eligible patients were randomized 2:1 to sugemalimab plus FP or placebo plus FP, stratified by PD-L1 expression status, ECOG score, and distant metastases. The data cut-off date for the final PFS and interim OS is 07 October 2022. A total of 540 patients were randomly assigned to sugemalimab plus FP (358 patients) or placebo plus FP (182 patients). Sugemalimab plus FP had an advantage in OS (mOS time: 15.3 months vs. 11.5 months; *HR* = 0.70, 95% *CI*: 0.55 to 0.90, *P* = 0.007 6). PFS and OS benefits were observed across all prespecified subgroups, including different PD-L1 expression levels. Sugemalimab in combination with FP showed higher ORR (60.1% vs. 45.2%) and longer DOR (time to mDOR: 6.0 months vs. 4.5 months) per blinded independent central review (BICR). The incidence of grade 3 and above TRAE was 51.3% and 48.4% in the two groups, and serious TRAE was 21.5% and 13.2% in the two groups, respectively. Discontinuations due to AEs were 13.3% and 10.4%, respectively, and mortality due to TRAE was 1.7% and 0.5%, respectively.

The exploration of immunotherapy combined with targeted therapy, immunotherapy combined with immunotherapy, and PD-1/CTLA-4 bispecific antibody combined with chemotherapy as first-line treatment for advanced esophageal cancer.

The LEAP-014 study[37] is an ongoing phase III clinical trial of targeted therapy combined with immunotherapy, aimed at evaluating the efficacy and safety of pembrolizumab plus lenvatinib plus chemotherapy versus pembrolizumab plus chemotherapy as first-line treatment for advanced ESCC. At present, 13 patients have been treated. Part I (safety trial) shows that pembrolizumab plus lenvatinib plus chemotherapy has acceptable safety and tolerability in previously untreated patients with metastatic ESCC, and the second part of the trial can be initiated.

SKYSCRAPER-08 (NCT04540211) study[38] was a randomized, double-blind, placebo-controlled Phase III clinical trial conducted primarily in China. The study included 461 patients with locally advanced unresectable or metastatic ESCC who had not previously received systemic therapy and aimed to compare the efficacy and safety of tiragolumab plus atezolizumab plus chemotherapy versus placebo plus chemotherapy for newly diagnosed esophageal squamous cell carcinoma using dual primary endpoints of PFS and OS. For the primary endpoint, OS, as of February 13, 2023, with a minimum survival follow-up of 14.5 months, the median OS was 15.7 months in the tiragolumab + atezolizumab arm and 11.1 months in the placebo arm (*HR* = 0.70, 95% *CI*: 0.55 to 0.88, *P* = 0.002 4). For PFS, the median PFS time was 6.2 months in the tiraglomab + atezolizumab arm and 5.4 months in the placebo arm (*HR* = 0.56, 95% *CI*: 0.45 to 0.70, *P* < 0.000 1). For secondary endpoints, 59.7% and 45.5% of patients responded in the tiragolumab + atezolizumab and placebo arms, respectively. The complete response (CR) rates were 11.5% and 3.2% respectively, and the partial response (PR) rates were 48.2% and 42.3% respectively. The median DOR was 7.1 months and 4.3 months in the two groups, respectively. In terms of safety, 98.2% of patients in both groups experienced TRAE of any grade. Grade 3-4 TRAE occurred in 59.6% and 56.4% of patients in the tiraglomab puls atezolizumab and placebo arms, respectively, and Grade 5 TRAE occurred in 2.6% and 0.9% of patients, respectively.

The latest results of the clinical study of first-line treatment of advanced ESCC with anlotinib plus benmelstobart[39] included 46 patients with metastatic or

locally advanced ESCC who had not received prior systemic treatment. All patients received anlotinib plus benmelstobart. The primary endpoint ORR was 69.6%. The disease control rate (DCR) was 93.5%, and the median PFS time was 9.92 months. The preliminary study results showed that anlotinib combined with benmelstobart had good efficacy and controllable toxicity in the first-line treatment of advanced ESCC, but further verification was needed.

A single-center parallel open-label phase II clinical trial[40] to evaluate the efficacy and safety of paclitaxel/albumin-bound paclitaxel plus carboplatin (TC) in combination with anlotinib and PD-1 inhibitor in the treatment of advanced esophageal cancer was divided into three groups: group A received anlotinib + PD-1 inhibitor + TC; group B received PD-1 inhibitor + TC; and group C received TC only. As of 20 September 2022, a total of 90 patients have been enrolled in the study and 88 patients are evaluable for efficacy. Twenty-five of the 28 patients in Arm A achieved PR, 13 of the 30 patients in Arm B achieved PR, and 7 of the 30 patients in Arm C achieved PR. ORR was 89.3% in Arm A, 43.3% in Arm B, and 23.3% in Arm C; DCR was 100% in Arm A, 96.7% in Arm B, and 83.3% in Arm C; median PFS was not reached. In all three groups, the incidence of TRAEs of any grade was 100%, and the incidence of TRAEs of grade 3 was 23.3%, 16.7%, and 13.3%, respectively; the most common TRAEs of grade 3 were thrombocytopenia (6.7%), leukopenia (5.6%), and neutropenia (5.6%); no TRAEs of grade 4 or 5 occurred. The study results showed that a combination of anlotinib as first-line treatment for ESCC patients based on immunotherapy showed a high ORR (89.3%) and controllable safety.

Cadonilimab in combination with paclitaxel and cisplatin as first-line treatment for ESCC was a multicenter open-label clinical trial[41] designed to evaluate the efficacy and safety of cadonilimab (10 mg/kg, IV, every 3 weeks on Day 1) in combination with paclitaxel and cisplatin as first-line treatment for advanced ESCC, with cadonilimab monotherapy continued for up to 24 months after 6 cycles of combination therapy. The primary endpoint was ORR, and secondary endpoints included PFS, OS, DCR, and safety. The results showed that as of September 21, 2023, a total of 22 patients were included, with a median age of 61 years and 50.0% of PD-L1 CPS <10 patients. Of the 15 evaluable efficacy populations, 13 patients achieved PR, 2 patients were assessed as stable disease (SD), ORR was 86.7%, DCR was 100.0%, and median PFS and OS were not observed. Among evaluable patients with PD-L1CPS ≥10 and PD-L1CPS <10, ORR was 83.3% (5/6) and 88.9% (8/9), respectively. Seven patients (31.8%) had grade 3-4 TRAE, mainly including neutropenia (22.7%), leukopenia (9.1%), and hyponatremia (9.1%), of which 3 patients (13.6%) had immune-related adverse events, and no grade 5 TRAE occurred. Cadonilimab in combination with chemotherapy as first-line treatment for advanced ESCC showed good ORR and manageable safety regardless of PD-L1 expression.

4.2 Treatment principles for second-line and post-line treatment of advanced esophageal cancer

Recommendation 8: PD-1 inhibitor monotherapy is recommended for second-line immunotherapy for squamous cell carcinoma patients who have progressed on first-line therapy and have not received ICIs (Level of Evidence: Class 1; Level of Recommendation: Class I Recommendation; Expert Consensus: 100%). Or bispecific antibodies (Level of Evidence: Class 2; Level of Recommendation: Class I; Expert Consensus: 91.7%).

Treatment regimen: Camrelizumab; pembrolizumab (PD-L1CPS≥10 points); nivolumab; Tislelizumab.

Cadonilimab.

Recommendation 9: For patients who progress after immunotherapy, chemotherapy combined with bispecific antibodies based on PD-1 targets or ICIs combined with antiangiogenic drugs may be considered (Level of Evidence: Class 2; Level of Recommendation: Class I; Expert Consensus: 94.4%).

Cadonilimab (Level of Evidence: Class 3; Level of Recommendation: Class II; Expert Consensus: 94.4%).

Recommendation 10: For patients who progress

after immunotherapy, it is recommended to participate in relevant clinical studies (evidence level: Class 3; recommendation level: Class I recommendation; expert consensus: 100%).

KEYNOTE-181 study[11] was a global randomized, open-label Phase II clinical trial of 628 patients with recurrent, locally advanced, or metastatic esophageal cancer who progressed after first-line therapy. Among patients with PD-L1 CPS ≥ 10, mOS was 9.3 months in the pembrolizumab arm and 6.7 months in the chemotherapy arm (*HR* = 0.69; 95% *CI*: 0.52 to 0.93; *P* = 0.007 4), with 12-month OS rates of 43% and 20.4%, respectively. After a median follow-up of 7 months, pembrolizumab was not statistically different from chemotherapy in OS (*HR* = 0.89; 95% *CI*: 0.75 to 1.05; *P* = 0.056 0). In the CPS ≥ 10 PD-L1 subgroup (222 patients), mOS was 9.3 months in the pembrolizumab arm and 6.7 months in the chemotherapy arm, with 1-year survival rates of 43% vs 20%, respectively. There was a statistically significant difference in survival between the two groups (*HR* = 0.69, 95% *CI*: 0.52 - 0.93, *P* = 0.007 4). In the ESCC subgroup (401 patients), mOS was 8.2 months in the pembrolizumab arm and 7.1 months in the chemotherapy arm (*HR* = 0.78, 95% *CI*: 0.63 to 0.96, *P* = 0.009 5), but it did not reach statistical significance as expected in the study.

The ESCORT study[15] is a randomized, open-label Phase 3 clinical trial evaluating the efficacy and safety of camrelizumab as a second-line treatment for advanced or metastatic ESCC. 457 patients were enrolled in the study and randomized 1∶1 to receive camrelizumab or the investigator's choice chemotherapy regimen (docetaxel or irinotecan). Time to mOS was 8.3 months in the camrelizumab arm and 6.2 months in the chemotherapy arm (*HR* = 0.71, 95% *CI*: 0.57 to 0.87; *P* = 0.001 0). Kaplan-Meier-assessed OS rates at 6 and 12 months were 63% vs. 55% and 34% vs. 22% in the camrelizumab and chemotherapy arms, respectively. Subgroup analysis showed significant differences in survival advantage between camrelizumab and chemotherapy in all included subgroups. For patients with PD-L1 ≥ 1% at baseline, mOS was 9.2 months versus 6.3 months in the camrelizumab and chemotherapy arms, respectively (*HR* = 0.58, 95% *CI*: 0.42 to 0.81; *P* = 0.001 4). Median DOR was 7.4 months in the camrelizumab arm and 3.4 months in the chemotherapy arm (*HR* = 0.34, 95% *CI*: 0.14 to 0.92; *P* = 0.017).

RATIONALE302[34] is a global, multicenter, randomized, placebo-controlled, open-label Phase III clinical trial designed to explore the efficacy and safety of tislelizumab versus chemotherapy as a second-line treatment for advanced ESCC. Results showed that in the ITT population, OS was 8.6 months in the tislelizumab group and 6.3 months in the chemotherapy group, with a statistically significant difference (*HR* = 0.70, 95% *CI*: 0.57 to 0.85; *P* = 0.000 1). In the PD-L1 TAP ≥ 10% population, the OS time benefit was significantly greater in the tislelizumab arm at 10.3 months versus 6.8 months in the chemotherapy arm. In addition, in the ITT population, ORR was 20.3% and median DOR was 7.1 months in the tislelizumab arm versus 9.8% and 4.0 months in the chemotherapy arm.

ATTRACTION-03[42] was a randomized, multicenter, open-label Phase III clinical trial of immune checkpoint inhibitors in ESCC patients, enrolling 419 patients, 210 of whom received nivolumab and 209 of whom received chemotherapy. The primary endpoint was OS. Secondary endpoints included objective response rate (ORR), best overall response (BOR), DCR, PFS, duration of response (DOR), and safety. Compared with chemotherapy, nivolumab significantly improved OS, with median OS of 10.9 months (95% *CI*: 9.2 - 13.3) and 8.4 months (95% *CI*: 7.2 - 9.9), respectively (*HR* = 0.77, 95% *CI* 0.62 - 0.96; *P* = 0.019). In terms of safety, there were relatively few Grade 3 or 4 treatment-related adverse events in the nivolumab arm. The ATTRACTION-3 study suggests that nivolumab provides a new standard second-line treatment regimen for patients with advanced esophageal squamous cell carcinoma.

Exploration of immunotherapy combined with targeted therapy, and PD-1/CTLA-4 bispecific antibody combined with chemotherapy as second-line treatment for advanced esophageal cancer.

The AdvanTIG-203 study[43] is a randomized

phase II clinical trial of the TIGIT inhibitor ociperlimab in combination with tislelizumab for the second-line treatment of advanced ESCC patients with PD - L1 TAP≥10% who have progressed on first-line chemotherapy. A total of 125 patients were enrolled and randomly assigned to the ociperlimab + tislelizumab combination arm and placebo + tislelizumab control arm, with the primary endpoint of ORR. The results showed that the ORR value of the test group was improved compared with the control group (30.6% vs 20.6%), but the difference did not reach statistical significance (P=0.211 4). There were no significant differences in mOS (10.1 months vs. 9.3 months) and median PFS(3.4 months vs. 3.5 months), but OS data were not yet mature. The safety profiles of the two groups were comparable. These results suggest that TIGIT inhibitors combined with PD - 1 inhibitors have some potential to improve efficacy, but efficacy predictors still need to be explored to further enrich the benefit population.

ALTER - E - 006 study[44] was a multicenter retrospective real-world study of patients with advanced esophageal cancer who had previously received immunotherapy. This study included patients with advanced ESCC who had previously received an anti - PD - 1/PD - L1/CTLA - 4 agent (single agent or combination) but had not received antivascular drug therapy and received immunotherapy combination rechallenge therapy with anlotinib and ICIs. From September 2019 to November 2022, a total of 96 patients were enrolled in this trial. The results showed that ORR was 21.9% (95% *CI*: 14.1% ~ 31.5%), DCR was 67.7% (95% *CI*: 57.4% ~ 76.9%), median OS time was 10.97 months (95% *CI*: 8.83 ~ 13.11), OS rates at 12 months and 24 months were 45.78% and 27.55%, respectively, and median PFS was 6.31 months (95% *CI*: 5.10 ~ 7.52). The results preliminarily indicate that anlotinib combined with PD - 1 inhibitor has good efficacy and safety in the treatment of previously immune-treated patients with advanced ESCC.

COMPASSION - 03 (AK104 - 201) study[45] evaluated the efficacy and safety of PD - 1/CTLA - 4 bispecific antibodies in the treatment of advanced solid tumors and in combination with chemotherapy in the treatment of advanced unresectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction. Among them, 22 ESCC patients who had previously failed no more than first-line systemic therapy were included. As of January 8, 2022, 22 ESCC patients were enrolled. (17 patients were treated with second-line monotherapy), investigator-assessed ORR was 18.2% (4/22), DCR was 50% (11/22), mPFS time was 3.48 months, mOS time was 9.4 months, 6-month OS rate was 60.6%, 12-month OS rate was 39.8%, median PFS time was 3.5 months, 6-month PFS rate was 30.4%, 12-month PFS rate was 15.2%, Preliminary efficacy of PD - 1/CTLA - 4 bispecific antibody was shown.

4.3 Principles of treatment for locally advanced esophageal cancer

4.3.1 Perioperative neoadjuvant/adjuvant therapy for resectable esophageal cancer

Recommendation 11 Resectable patients with high-risk factors such as lymph node metastasis, poor differentiation, and high T stage should be regarded as the first choice population for neoadjuvant immunotherapy, and it is recommended to carry out the treatment after full informed consent of patients within the scope of clinical study (evidence level: Class 2; recommendation level: Class II recommendation; expert consensus: 100%).

Recommendation 12 Before neoadjuvant immunotherapy, Multidisciplinary Team (MDT) should comprehensively evaluate the patient's medical history and overall condition, and screen for contraindications related to immunotherapy (evidence level: Class 2; recommendation level: Class II recommendation; expert consensus: 97.2%).

Recommendation 13 Neoadjuvant immunotherapy regimen should be selected independently in combination with drug accessibility and medical insurance policy of each hospital, and comprehensive consideration should be given to treatment effect, operation timing, economy, and patient compliance; ICIs combined with chemotherapy regimen is recommended for 2 ~ 4 cycles, and paclitaxel/platinum-based treatment regimen is recommended for chemotherapy regimen (evidence level: Class 2; recommendation level: Class II

recommendation; expert consensus: 97.2%).

Recommendation 14 Whether ICIs should be used in postoperative adjuvant therapy should be determined after a comprehensive evaluation by the MDT team (evidence level: Class 2; recommendation level: Class II; expert consensus: 100%).

Among them, patients with locally advanced esophageal or esophagogastric junction cancer who were not pathologically complete response after neoadjuvant concurrent chemoradiotherapy combined with R0 resection were assisted with nivolumab (evidence level: Class 1; recommendation level: Class I recommendation; expert consensus: 97.2%).

For patients with locally advanced resectable esophageal cancer, the goal of neoadjuvant therapy is to improve the resection rate, including R0 resection rate, and reduce local and systemic recurrence, thus improving OS of the disease, but the current neoadjuvant chemotherapy regimen for esophageal cancer has limited efficacy[46]. In recent years, ICIs combined with chemotherapy have been explored in the field of neoadjuvant therapy for locally advanced esophageal cancer [46-63] (Table 4). From the series of study results, it can be seen that the pathological complete response (pCR) rate of neoadjuvant immunotherapy is 20.0% ~ 50.0%, and the Major Pathological Response (MPR) rate is 24.0% ~72.4%, which is improved compared with neoadjuvant chemotherapy, but it still needs further verification in phase III clinical trials.

The ESCORT - NEO/NCCES01 study[47] is a multicenter, randomized, three-arm, parallel-controlled Phase III clinical trial. It enrolled 391 patients with locally advanced resectable esophageal squamous cell carcinoma (T1b - 3N1 - 3M0 or T3N0M0) and randomly (1:1:1) divided them into three groups for two cycles of neoadjuvant therapy. Group A: camrelizumab plus paclitaxel and cisplatin (cam + nab-TP); Group B: camrelizumab plus paclitaxel and cisplatin (cam + TP); Group C: paclitaxel and cisplatin (TP). The primary study endpoints were BIRC-assessed pCR rate and investigator-assessed event-free survival (EFS). Secondary endpoints included MPR rate, R0 resection rate, disease-free survival (DFS), OS, and safety. In the ITT population, the BIRC assessed pCR rates were significantly better in Arm A (28.0%) and Arm B (15.4%) than Arm C (4.7%) ($P < 0.000\,1$, $P = 0.003\,4$), and both Arm A and Arm B met the primary endpoint. This study initially confirmed that the pCR rate of neoadjuvant immunotherapy was superior to neoadjuvant chemotherapy, and further updates of survival data are expected in the future.

The REVO study[46] is a multicenter, randomized, open-label phase II clinical trial comparing neoadjuvant immunochemotherapy with neoadjuvant immunochemoradiotherapy, using a non-inferiority trial design. Patients aged 18 to 75 years with resectable locally advanced thoracic esophageal cancer were enrolled in the study. Clinical stage was T1b ~4a, N1 ~ 3, M0 ~ 1 (supraclavicular metastasis only) or T3 ~ 4a, N0, M0 ~ 1 (suprasternal metastasis only). The performance status score was 0 or 1. A total of 85 patients were enrolled and randomly assigned to camrelizumab in combination with chemotherapy (ICT group, 41 patients) or concurrent chemoradiotherapy (CRT group, 44 patients). As of April 2023, 32 patients in the ICT group and 28 patients in the CRT group had undergone surgery. The pCR and MPR rates were 40.6% and 62.5% in the ICT group and 35.7% and 71.4% in the CRT group, respectively; ORR was 84.4% and 85.0% in the ICT and CRT groups, respectively. In terms of safety, the incidence of grade 3 or higher adverse events was 22.0% in the ICT group and 31.8% in the CRT group. From the data, the ICT group met the non-inferiority endpoint and was safer than the CRT group. Therefore, neoadjuvant camrelizumab combination chemotherapy is not inferior to concurrent CRT for patients with locally advanced esophageal squamous cell carcinoma, and the outcome and long-term survival outcomes are expected.

The CheckMate - 577 study[8] is a global randomized, double-blind, placebo-controlled phase III clinical trial exploring ICIs in adjuvant therapy. 794 patients with stage II/III R0 resection who had received prior neoadjuvant chemoradiotherapy and had residual pathology were randomly assigned 2:1 to receive nivolumab (240 mg, 14-day cycles, 8 cycles) followed by nivolumab (480 mg, 28-day cycles) or placebo.

Table 4 Clinical study on neoadjuvant immunochemotherapy for esophageal cancer

clinical test	Time (year)	stages	study population	Neoadjuvant therapy	number of treatment cycles	Number of cases included	primary endpoint	pCR (%)	MPR (%)	R0 resection rate
PD – 1 combined with chemotherapy										
ESCORT – NEO[46]	2024	Phase III	Stage Ⅱ – ⅣA	Camrelizumab + nab-TP Camrelizumab + TP	2	391	pCR Rate and EFS	28.0 15.4	59.1 36.2	99.1 95.7
NICE[49 – 50]	2024	Phase II	Stage III – IV	Camrelizumab + nab-TC	2	60	pCR	39.2	–	98.0
JS001 – ISS – CO143[51]	2023	Phase II	Stage Ⅱ – ⅣA	Toripalimab + Albumin Paclitaxel + S – 1	2	60	MPR	29.1	49.1	98.2
KEEP – G03[52]	2023	Phase II	Phase II – III	Sintilimab + paclitaxel liposomes + cisplatin + S – 1	2	30	Safety and surgical feasibility	20.0	50.0	100.0
TD – NICE[53]	2022	Phase II	Stage II – IVA	Tislelizumab + nab-TC	3	45	pCR	50.0	72.0	80.5
PEN – ICE[54]	2022	Phase II	Stage Ⅱ – ⅣA	Pembrolizumab + Paclitaxel + Nedaplatin	3	13	safety and effectiveness	46.2	69.2	84.6
Keystone-001[55]	2022	Phase II	Phase III	Pembrolizumab + TP	3	42	MPR and Safety	41.4	72.4	100.0
NIC – ES-CC2019[56]	2022	Phase II	Stage II – IVA	Camrelizumab + nab – TP	2	56	pCR	31.4	–	100.0
GASTO – 1056[57]	2022	Phase II	Stage Ⅱ – Ⅲ	Camrelizumab + Albumin Paclitaxel + Carboplatin	2	23	safety and feasibility	31.3	68.8	93.8
ESPRIT[58]	2021	Phase II	Stage IIA – III B	Camrelizumab + Paclitaxel + Nedaplatin	2 – 4	56	pCR	35.0	55.0	100.0
ChiCTR 1900026593[59]	2021	Phase II	Stage Ⅱ – ⅣA	Sintilimab + nab-TC	2	45	MPR	22.2	44.4	97.8
ESONICT – 1[60]	2021	Phase II	Stage III – IV A	Sintilimab + nab-TP	2	30	pCR and Safety	21.7	52.2	100.0
PD – L1 combination chemotherapy										
NCT04460066[61]	2023	Phase II	Stage Ⅰb – Ⅱ	Socazolimab + nab-TP	4	64	MPR	44.1	69.0	
immunotherapy										
NATION – 1907[62]	2023	stage IB	Stage Ⅱ – Ⅳ	Adebrelimab	2	30	safety and feasibility	8.0	24.0	92.0
PD – 1 combined with chemoradiotherapy										
NEOCRTEC 1901[63]	2023	Phase II	Stage Ⅱ – ⅣA	Toripalimab + TP + radiotherapy	2	44	pCR	50.0	–	98.0
REVO[47]	2023	Phase II	Stage Ⅱ – Ⅳ	Camrelizumab + nab-TP	2 – 4	41	pCR	40.6	62.5	100.0
				Camrelizumab + nab-TP + radiotherapy	2	44		35.7	71.4	100.0
PALACE – 1[64]	2021	Ⅰb	Stage Ⅱ – ⅣA	Pembrolizumab + TC + radiotherapy		20	security	56.0	89.0	94.0

Note: TP, paclitaxel + cisplatin; nab-TP, paclitaxel + cisplatin; TC, paclitaxel + carboplatin; nab-TC, paclitaxel + carboplatin; pCR, pathological complete response; MPR, major pathological response. 14 d is 1 cycle; " – " no data.

Adjuvant therapy lasted up to 1 year and the primary endpoint was DFS. At a median follow-up of 24.4 months, 532 patients received nivolumab versus 262 patients who received a placebo, and the median DFS was 22.4 months versus 11.0 months (*HR* = 0.69, *P* 0.001). Median distant metastasis-free survival was 28.3 months (95% *CI*: 21.3 ~ not estimable) and 17.6 months (95% *CI*: 12.5 ~ 25.4), respectively (*HR* = 0.74, 95% *CI*: 0.60 ~ 0.92). Grade 3 – 4 adverse reactions and serious adverse reactions were similar in both groups, and drug-related adverse reactions were more common in the nivolumab group.

4.3.2 Unresectable locally advanced esophageal cancer

Recommendation 15: For unresectable locally advanced esophageal cancer, radical concurrent chemoradiotherapy is the standard treatment. ICIs lack sufficient evidence-based medical evidence and are recommended to be carried out within the scope of clinical studies (Level of Evidence: Category 2; Level of Recommendation: Level II; Expert Consensus: 97.2%).

EC – CRT – 001 study[65] is a single-arm, phase II clinical trial independently conducted in the Cancer Center of Sun Yat-sen University. A total of 49 inoperable and untreated patients with locally advanced ESCC were enrolled in the study. All patients received concurrent chemoradiotherapy combined with toripalimab monoclonal antibody immunotherapy. The primary endpoint of the study was the tumor regression rate 3 months after radiotherapy. The study results showed that the application of toripalimab monoclonal antibody combined with concurrent chemoradiotherapy in locally advanced ESCC patients led to a tumor regression rate of 62%, and the safety was acceptable. EC – CRT – 001 is the first study to demonstrate that immunotherapy combined with concurrent chemoradiotherapy is effective and safe for patients with unresectable locally advanced esophageal squamous cell carcinoma.

A domestic multicenter single-arm phase II clinical trial[66] (NCT03985046) enrolled patients with locally advanced esophageal cancer. During the induction phase, patients received 2 cycles of sintilimab, paclitaxel, and carboplatin every 21 days. The patient then received 5 cycles of carboplatin and paclitaxel once a week, with concurrent radiotherapy of 50.4 Gy divided into 28 fractions. The primary endpoint was the local control rate at 2 years. Immunofluorescence and perfusion CT were used to detect hypoxia and vascular normalization before and after induction. Between October 2019 and April 2021, a total of 75 patients with esophageal cancer participated in the study. The median follow-up time for surviving patients was 33.6 months (IQR = 29.3 ~ 35.7). The 2-year local control rate was 81.7% (95% *CI*: 72.7% ~ 90.7%), significantly higher than that of the concurrent radiochemotherapy group (71.3%). Biopsy specimens and perfusion CT both showed normalization of blood vessels and alleviation of hypoxia. The study confirmed that adding induction immunotherapy to standard concurrent radiochemotherapy can improve the radiosensitivity of locally advanced esophageal cancer as a non-surgical treatment by promoting vascular normalization and relieving hypoxia, thereby increasing the local control rate.

A multicenter phase II clinical trial exploring concurrent chemoradiotherapy followed byatezolizumab in patients with unresectable locally advanced ESCC showed[67] that the cCR rate of atezolizumab in curative chemoradiotherapy followed by atezolizumab could reach 42.1%, the median PFS time and OS time were 3.2 months and 31.0 months respectively, and the overall safety was controllable. The incidence of grade 3 ~ 5 pneumonia in the primary cohort was 5%.

The KEYNOTE975 study, RATIONALE – 311 study, ESCORT – CRT study, and KUNLUN study are currently underway, aiming to evaluate the efficacy and safety of pembrolizumab, tislelizumab, camrelizumab, and durvalumab combined with definitive chemoradiotherapy (dCRT) compared to placebo plus dCRT in the treatment of patients with locally advanced esophageal cancer.

5 Adverse reactions and management of esophageal cancer immunotherapy

Immune-related adverse events (irAEs) are a class of treatment-related adverse events specific to im-

munotherapy. After receiving ICIs, the immune system is overactivated, and normal tissues are attacked, resulting in various adverse reactions. IrAEs affect almost all organs and systems. Based on the mechanism of action of ICIs, irAEs could occur at any time during treatment or months after the end of treatment, thus requiring full management of patients treated with ICIs.

5.1 Monitoring and management of irAEs in advanced esophageal cancer

Recommendation 16: The management of irAEs of esophageal cancer should follow the whole process of "prevention-evaluation-diagnosis-treatment-follow-up", early identification, comprehensive evaluation, and timely and reasonable treatment. MDT team should be set up in qualified hospitals (evidence level: Class 2; recommendation level: Class II recommendation; expert consensus: 100%).

Recommendation 17: IrAEs usually occur weeks to months after the first treatment with ICIs; adverse reactions due to delayed toxicity may occur even after ICIs are discontinued. Patients treated with ICIs should be monitored and managed comprehensively, whole-person, and throughout the course (Level of Evidence: Category 2; Level of Recommendation: Level II; Expert Consensus: 100%).

Before starting ICIs, baseline examination and risk assessment should be improved. It is recommended to include baseline examination of cardiopulmonary function, liver and kidney function, thyroid gland, and other endocrine functions, exclude contraindications, and inform patients of irAEs. Patients with underlying diseases should additionally complete baseline examinations and dynamic monitoring of underlying diseases before ICIs are used.

During treatment, blood routine and biochemical tests should be performed before each treatment (or at least every 4 weeks); thyroid and other endocrine functions should be performed once every 3 to 6 weeks. After treatment, the above indicators should be reviewed every 6 to 12 weeks during follow-up.

When irAEs occur, the cause should be determined. If it is not caused by ICIs, corresponding symptomatic management shall be adopted; if it is judged to be caused by ICIs, the severity of irAEs shall be evaluated in time, and different management methods shall be selected according to the classification of irAEs.

Recommendation 18: It is recommended to use the management model of patient-reported outcomes to deal with unoccurred or occurred adverse reactions in a timely and effective manner (evidence level: Class 2; recommendation level: Class II; expert consensus: 100%).

KEYNOTE - 590 study[10] showed that the incidence of all-grade irAEs was 26% and grade 3 and higher adverse reactions was 7% in patients receiving pembrolizumab in combination with chemotherapy, compared with 12% and 2% in patients receiving chemotherapy alone; the most common irAEs in the combination chemotherapy arm included hypothyroidism, pneumonia, and hyperthyroidism[3]. In the ORIENT - 15 study[13], the incidence of all-grade irAEs was 47% after patients received sintilimab in combination with chemotherapy, with rash and thyroid dysfunction being the most common adverse reactions and grade 3 and higher adverse reactions occurring in 10%. In addition, when durvalumab was used in combination with chemoradiotherapy, results from a clinical trial[68] involving 33 patients with advanced esophageal adenocarcinoma showed irAEs in 17% of patients, with skin toxicity, gastrointestinal toxicity, and thyroid dysfunction being the most common adverse reactions; grade 3 and higher adverse reactions occurred in 12%. A meta-analysis of clinical trial data published in 2022 showed that the risk of adverse reactions in ESCC using ICIs in combination with chemotherapy was not significantly higher than chemotherapy alone[69-70].

A randomized controlled study involving 120 lung cancer patients showed[71] that the trial group, which adopted a WeChat platform nursing management model based on patient-reported outcomes, had significantly shorter durations of rash and itching compared to the control group ($P<0.05$), and significantly higher satisfaction levels ($P<0.05$). The durations of grade 1 and 2 maculopapular rash/rash, itching, gastrointestinal reactions, and other adverse reactions were also significantly shorter than those in the control group ($P<0.05$). There was no difference in the incidence of

adverse reactions between the two groups.

5.2 Monitoring and management of irAEs during the perioperative period

Recommendation 19: There is no conclusive evidence that neoadjuvant ICIs affect the procedure or safety (Level of Evidence: Category 2; Level of Recommendation: Level II; Expert Consensus: 100%).

Recommendation 20: After neoadjuvant ICIs treatment, thyroid and other endocrine functions should be reassessed before surgery (evidence level: Class 2; recommendation level: Class II; expert consensus: 100%).

In general, neoadjuvant immunotherapy combined with chemotherapy is relatively safe, whereas neoadjuvant immunotherapy combined with radiotherapy and chemotherapy has a higher incidence of adverse reactions. However, due to the different treatment modalities and various immunotherapy drugs among studies, there are differences in the adverse reactions observed.

A real-world multicenter retrospective study showed that in China esophageal cancer patients (41 cases) treated with ICIs alone as neoadjuvant therapy, the total incidence of irAEs was 19.5%, and no grade 3 or higher adverse reactions occurred; in patients (299 cases) treated with ICIs combined with chemotherapy, the total incidence of irAEs was 21.1%, the incidence of grade 3 – 4 adverse reactions was 2.3%, and 1.0% of patients died due to adverse reactions[72]; in patients (30 cases) treated with ICIs combined with radiotherapy and chemotherapy, the total incidence of irAEs was 23.3%, the incidence of grade 3 – 4 adverse reactions was 3.3%, and 3.3% of patients died due to adverse reactions. For the three treatment regimens, the most common irAEs included rash and pruritus, hepatitis, and thyroid dysfunction. The incidence of immune-associated pneumonia was 10% in patients treated with ICIs combined with chemoradiotherapy, significantly higher than ICIs alone (2.4%) or in combination with chemotherapy (1.7%). After the application of ICIs, the risk of irAEs should be predicted through monitoring including blood routine and blood biochemistry, and timely diagnosis and treatment should be made. Multidisciplinary consultation should be conducted if necessary.

Common complications after esophageal cancer surgery are anastomotic leakage, pulmonary complications, and cardiovascular complications[73]. A comprehensive evaluation was performed in combination with baseline condition, nutritional status, behavior status, organ function, and immune-related indicators after operation. Patients with low immunity and poor basic lung function had a relatively high risk of pneumonia; patients with poor cardiovascular history and cardiovascular function had a relatively high risk of cardiovascular complications; patients with poor nutrition should pay attention to perioperative nutritional support.

5.3 The most common irAEs and their management

5.3.1 Cutaneous adverse reactions

Skin adverse reactions are the most common irAEs, which usually appear early, within the first 2 cycles of treatment, and have a wide range of clinical manifestations, such as maculopapules on the trunk or limbs[74]. Common minor skin adverse reactions generally do not require hospitalization and can be symptomatic and relieved by oral or topically applied drugs. Most skin adverse reactions are low in severity and do not lead to discontinuation of immunotherapy, but a small number of skin irAEs caused by ICIs have been reported as fatal bullous dermatoses[75] requiring hospitalization and discontinuation of ICIs (Fig. 1)[76].

5.3.2 Key points for management of immunotherapy-related skin diseases

Before starting ICIs, a thorough examination of the patient's skin and mucous membranes should be performed; ask about a history of skin diseases such as psoriasis or autoimmune diseases with skin manifestations. If possible, the association of ICIs treatment with cutaneous AEs should be assessed and confirmed; the severity of cutaneous AEs should be assessed and whether expert advice or referral is required[77 – 78].

5.3.3 Endocrine adverse reaction

Immune-related endocrine adverse reactions can involve multiple organs, including the thyroid, pituitary, adrenal, and pancreas, and can manifest as hyperthyroidism, hypothyroidism, hypophysitis, type I diabetes, and primary adrenal insufficiency[79 – 80]. Previous studies have shown that the occurrence of endo-

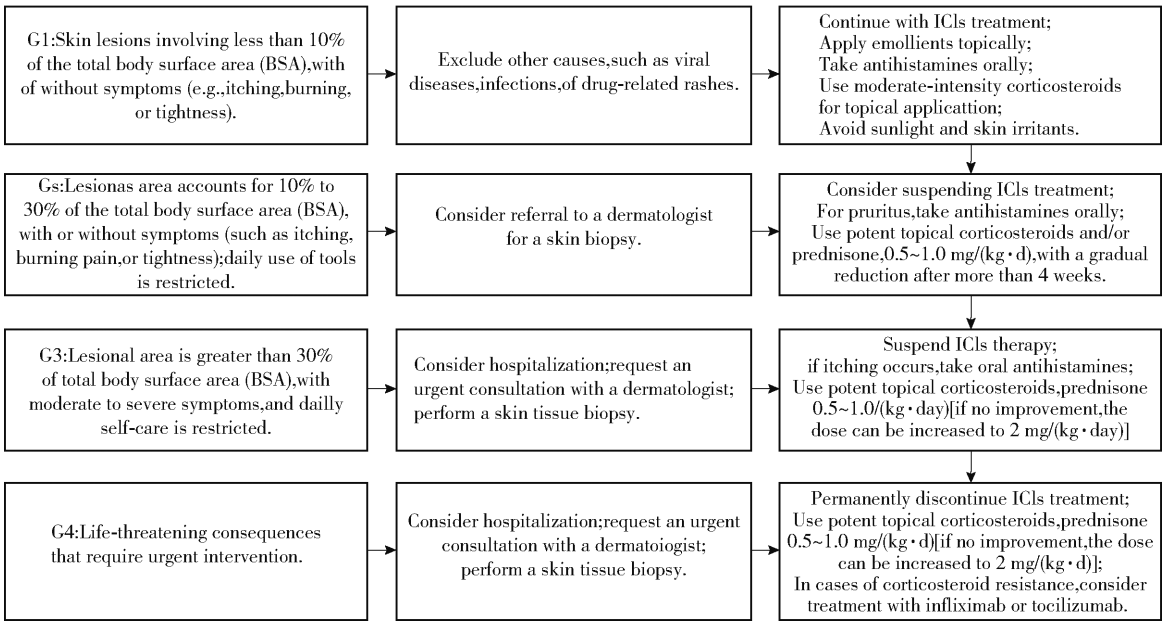

Fig. 1 Management of immunotherapy-related cutaneous adverse reactions[76-77]

Note: BSA, body surface area; ICIs, immune checkpoint inhibitors.

crine adverse reactions is related to treatment regimens. Thyroid dysfunction is more likely to occur with PD-1/PD-L1 inhibitors, hypophysitis is more likely to occur with CTLA-4 inhibitors, and the combination of CTLA-4 and PD-1 inhibitors increases the risk of adrenal dysfunction. Similar to other systems, drug combinations of CTLA-4 and PD-1 inhibitors increase the incidence of adverse reactions[81-82]. Immune-related endocrine toxicity is usually mild, but life-threatening conditions (thyroid crisis, diabetic ketoacidosis, etc.) can occur[83-84]. Adverse reactions mediated by ICIs often result in permanent damage to endocrine organs, and patients often require lifelong hormone supplementation. There is currently little evidence for the benefit of long-term use of glucocorticoids to treat immune-related endocrine adverse effects, but glucocorticoids may reduce symptoms of acute inflammation, such as hypophysitis and adrenalitis (Fig. 2)[85-86].

5.3.4 Key points in the management of thyroid diseases associated with immunotherapy

Hypothyroidism may be considered if the patient experiences unexplained fatigue, weight gain, hair loss, chills, constipation, depression, and other symp-

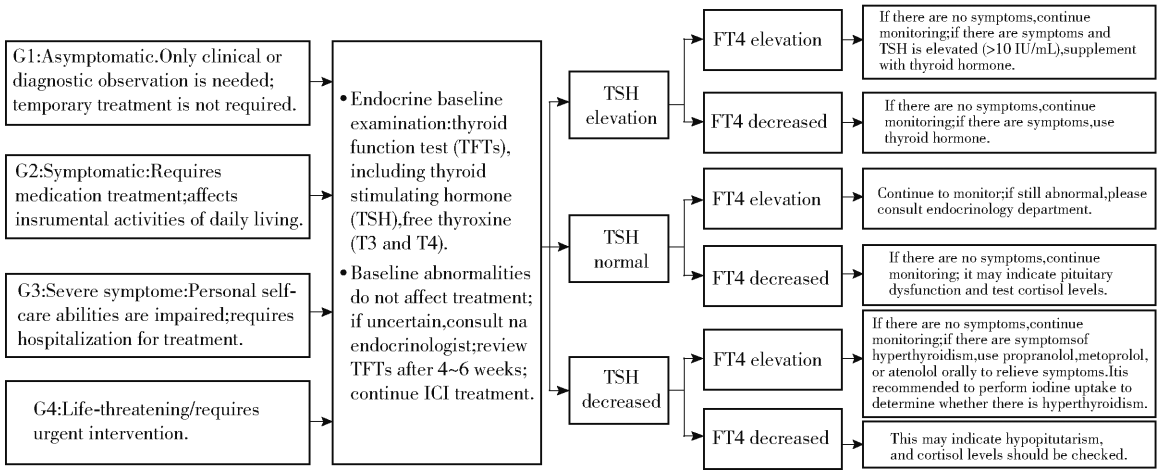

Fig. 2 Management of thyroid disease associated with immunotherapy[77-78]

Note: ICIs, immune checkpoint inhibitors; T3, triiodothyronine; T4, thyroid hormone.

toms during ICIs; hyperthyroidism may be considered if the patient experiences unexplained palpitations, sweating, increased eating and defecation, and weight loss[77-78].

In grade 2 or higher immune-related hypothyroidism, hormone replacement therapy (levothyroxine sodium, 50-100 μg/day) should be given to symptomatic patients and the dose should be increased over several weeks until thyroid-stimulating hormone levels return to normal. ICIs should only be interrupted if symptoms are severe (grade ≥3)[77-78].

For symptomatic hyperthyroidism (grade ≥2), ICIs should be interrupted and beta-blockers initiated. Short-term oral prednisolone acetate 0.5 ~ 1 mg/(kg·d) may be required if glandular inflammation or symptoms are severe. Asymptomatic patients should resume ICIs[77-78].

5.3.5 Gastrointestinal adverse reactions

The incidence of immune-related digestive tract adverse reactions is second only to skin adverse reactions. Clinically, diarrhea or colitis usually occurs 6 ~ 8 weeks after the initiation of immunotherapy[87-88]. Similar to skin adverse reactions, CTLA-4 inhibitors were associated with higher gastrointestinal adverse reactions, with diarrhea occurring in 30% to 40% of patients when CTLA-4 was used alone; the incidence of adverse reactions was significantly higher when CTLA-4 inhibitors were used in combination with PD-1/PD-L1 inhibitors[89-90]. Previous studies have shown no significant differences in the incidence of gastrointestinal adverse reactions among melanoma, NSCLC, and renal cell carcinoma[91]. Glucocorticoids are the first-line treatment for gastrointestinal adverse reactions, with symptoms resolved in 40% to 60% of patients and evidence of infliximab efficacy in severe colitis (Fig. 3)[92-93].

5.3.6 Key points in the management of immune-related diarrhea and enterocolitis

Patients with abdominal pain and diarrhea should be alert to the possibility of immune-related gastrointestinal toxicity. Sigmoidoscopy or colonoscopy is recommended for patients with severe diarrhea or persistent grade 2 or higher diarrhea to further confirm the diagnosis. For the re-administration of ICIs after gastrointestinal toxicity, a balance of risks should be considered based on the specific circumstances. The decision should be made based on individual patient conditions and discussed within a multidisciplinary team[77-78].

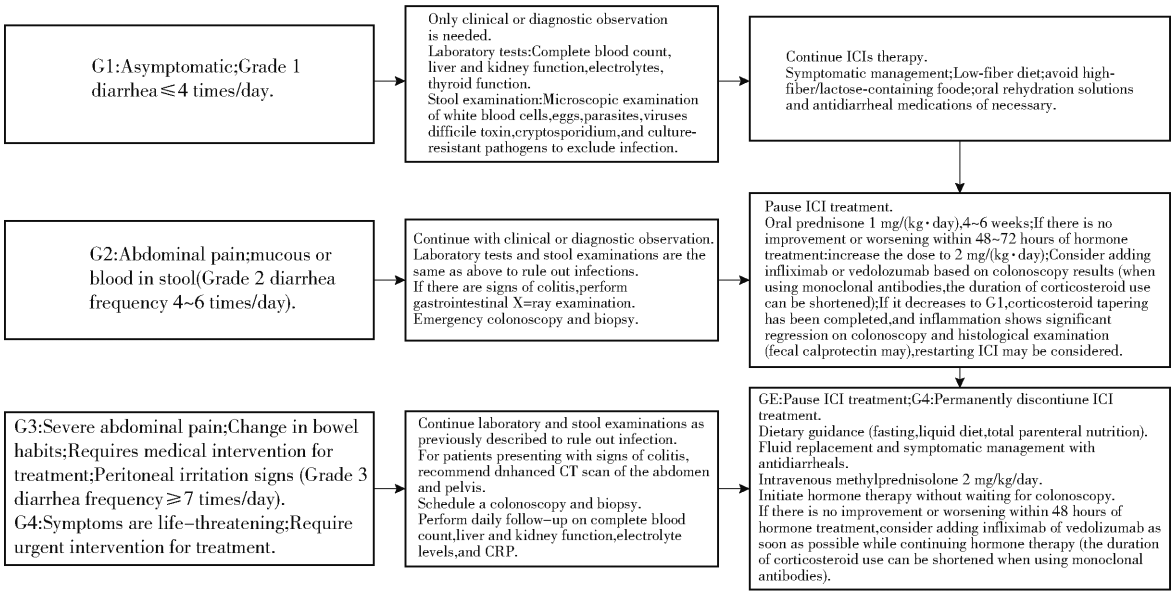

Fig. 3 Management of immune-related diarrhea and enterocolitis[76-77]

Note: ICIs, immune checkpoint inhibitors; CRP, C-reactive protein.

5.3.7 Liver adverse reactions

Immune-related hepatotoxicity occurs less frequently than gastrointestinal adverse reactions and is usually mild. The most common liver adverse reactions

are elevated aspartate aminotransferase and alanine aminotransferase, but in rare cases, it may rapidly develop into serious adverse reactions and even life-threatening[94-95]. Previous studies have reported that the incidence of immune-related liver adverse reactions with CTLA-4 inhibitors is estimated to be 5% ~ 10%, and the incidence of PD-1/PD-L1 inhibitors is only about 1%. However, when CTLA-4 inhibitors are combined with PD-1/PD-L1, the incidence of adverse reactions is significantly increased, the incidence of all-grade liver adverse reactions is about 30%, and the incidence of high-grade liver adverse reactions is about 20%[96-97]. Glucocorticoids remain the first-line treatment for liver adverse reactions, and some severe hepatitis can be treated with mycophenolate mofetil[93, 98].

5.3.8 Respiratory adverse reactions

Although the incidence ofcheck point inhibitor pneumonitis (CIP) is not high in the course of immunotherapy for esophageal cancer, its potential risk and severity cannot be ignored, so it has been paid great attention in clinical practice.

The PALACE-1 study[64] showed that the incidence of pneumonitis in patients receiving neoadjuvant immunotherapy combined with radiotherapy and chemotherapy reached as high as 20%. Due to the lack of typical clinical symptoms and imaging features in CIP, patients treated with ICIs who develop new respiratory symptoms such as cough, wheezing, and dyspnea should be given attention and carefully evaluated, and chest CT imaging is preferred[77-78].

5.3.9 Other adverse reactions

Adverse effects in other systems or organs, including cardiotoxicity and neurotoxicity, were previously considered severe in clinical symptoms, but the incidence was low. The latest evidence suggests that the incidence of these adverse reactions is likely to be higher than is generally recognized. Cardiovascular toxicity, for example, has been underreported in the past, but recent studies have confirmed that major cardiovascular adverse events occur in 10% of patients treated with ICIs at a median follow-up of 13 months. Clinically, these cardiovascular adverse events are likely to be associated with poor prognosis[99-100].

Neurotoxicity also requires clinician attention, as these adverse events are clinically complex to diagnose, but often present at a higher grade and require prompt treatment.

The diagnosis and management of rare irAEs requires the collaboration of multidisciplinary teams[101-102].

5.4 Integrated therapy during esophageal cancer immunotherapy

5.4.1 Nutritional status assessment and management

Recommendation 21: When esophageal cancer patients suffer from malnutrition or are at risk of malnutrition, nutrition specialists should be invited for evaluation, personalized nutrition intervention should be carried out early, and the effect of nutrition intervention should be monitored regularly (evidence level: Class 2; recommendation level: Class II recommendation; expert consensus: 100%).

Malnutrition has adverse effects on malignant tumor patients throughout the whole course of the disease. A nutritional status survey of common malignant tumor patients in China shows that the incidence of moderate and severe malnutrition in tumor patients is 58.2%, especially upper digestive tract tumors (pancreatic cancer, gastric cancer, and esophageal cancer are the three most serious tumors of malnutrition)[103]. The high incidence of malnutrition is due to multiple factors such as tumor location (causing stenosis with partial or complete esophageal or gastric obstruction), surgical trauma, perioperative dietary control, caloric restriction, and side effects of systemic therapy[104-105]. Malnutrition reduces OS, PFS, and treatment tolerability, and increases the frequency and severity of postoperative complications and TRAE[106-107], which may lead to treatment discontinuation and poor outcomes[108-109]. Therefore, personalized nutritional interventions should be carried out early in clinical practice[110].

NutritionalRisk Screening 2002 (NRS2002) was selected as a nutritional risk screening tool for nutritional risk screening, and the patient-generated subjective global assessment (PG-SGA) scale was selected as a nutritional status assessment tool for nutritional status assessment. The nutritional status of patients was

divided into four grades: normal, suspicious malnutrition, moderate malnutrition, and severe malnutrition. Nutritional interventions include nutritional supplementation, metabolic regulation, and treatment for disease reduction [111].

Dietary guidance or nutritional education, fortification of special medical use formulas, tube feeding supplements, and intravenous nutrition infusion were selected according to the patient's eating ability. For patients with chewing and swallowing difficulties, esophago-bronchial fistula, and severe gastric reflux, naso-intestinal tube feeding gastrostomy or combined parenteral nutrition support should be adopted.

Deglutition disorder caused by edema of local mucosa surface of esophageal occupation, a delicious mixture containing lidocaine and dexamethasone, 5 ~ 10 times/day. Nasojejunal catheterization is needed to determine patients with esophagotracheal fistula, severe gastric reflux, or choking after drinking water and eating. Patients with severe food choking and radiation esophagitis were given intravenous methylprednisolone 40mg/d and megestrol to stimulate appetite. For specific nutritional treatment methods for esophageal cancer patients, please refer to the Guidelines for Nutritional Treatment of Esophageal Cancer Patients formulated by the Cancer Nutrition Professional Committee of China Anti-Cancer Association[112]. In case of malignant intestinal obstruction, please refer to China Expert Consensus on Treatment of Malignant Intestinal Obstruction (2023) formulated by the China Anti-Cancer Association[113].

5.4.2 Physical recovery and lifestyle improvement during immunotherapy

During immunotherapy, esophageal cancer patients should be encouraged to participate in moderate cultural and recreational activities and physical exercise, such as light walking, swimming, Tai Chi Chuan, and other low-intensity exercise to promote physical and mental health. It is recommended that patients maintain a regular lifestyle, go to bed early and get up early, avoid overwork, and maintain a balance between body and spirit. At the same time, pay attention to emotional management, release negative emotions reasonably, and maintain stability and optimism of mentality. A positive mindset helps boost immune function. In terms of diet, attention should be paid to balanced nutrition and reasonable adjustment of diet structure[114]. For specific exercise therapy scheme, please refer to《China Expert Consensus on Exercise Therapy for Malignant Tumor Patients》[115] organized by Tumor Nutrition Professional Committee of China Anti-Cancer Association; for psychological intervention mode, please refer to China Technical Guidelines for《Integrated Diagnosis and Treatment of Tumor (CACA) Psychotherapy》[116]. For the management of cancer pain, please refer to《Expert Consensus on Patient-controlled Analgesia for Cancer Pain》prepared by Cancer Rehabilitation and Palliative Care Professional Committee of China Anti-Cancer Association[117].

6 Summary and outlook

Immunotherapy has achieved remarkable results in the field of esophageal cancer, and related research is changing the practice of esophageal cancer treatment and the outcomes for patients. However, clinical practice also faces many challenges, such as the selection of neoadjuvant treatment modalities, the optimal treatment strategy for locally advanced patients who cannot undergo surgery, the screening of immunotherapy benefit populations, immunotherapy resistance, and organ preservation strategies after neoadjuvant treatment. In addition, clinical research on the combination of ICIs and immunomodulators such as thymosin has made progress, but due to the limited evidence-based medical evidence, it has not been described in this consensus. In the future, it is necessary to carry out translational and clinical research around related issues, promote precision treatment and multidisciplinary integrated treatment of esophageal cancer, and bring more survival benefits to patients with esophageal cancer.

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