REVIEW

Perioperative immunotherapy for esophageal squamous cell carcinoma: Now and future

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Abstract

Esophageal cancer (EC) ranks among the most prevalent malignant tumors affecting the digestive tract. Esophageal squamous cell carcinoma (ESCC) stands as the prevailing pathological subtype, encompassing approximately 90% of all EC patients. In clinical stage II-IVA locally advanced ESCC cases, the primary approach to treatment involves a combination of neoadjuvant therapy and surgical resection. Despite concerted efforts, the long-term outcomes for ESCC patients remain unsatisfactory, with dismal prognoses. However, recent years have witnessed remarkable strides in immunotherapy, particularly in the second- and first-line treatment of advanced or metastatic ESCC, with the development of monoclonal antibodies that inhibit programmed death 1 or programmed death ligand 1 demonstrating encouraging responses and perioperative clinical benefits for various malignancies, including ESCC. This comprehensive review aims to present the current landscape of perioperative immunotherapy for resectable ESCC, focusing specifically on the role of immune checkpoint inhibitors during the perioperative period. Additionally, the review will explore promising biomarkers and offer insights into future prospects.

Key Words: Esophageal squamous cell carcinoma; Immune checkpoint inhibitors; Immunotherapy; Neoadjuvant; Randomized clinical trial

Core Tip: Esophageal cancer ranks among the most prevalent malignant tumors affecting the digestive tract. In locally advanced esophageal squamous cell carcinoma (ESCC), the mainstay of treatment involves neoadjuvant therapy in conjunction with surgical resection. Notably, immunotherapy has achieved significant breakthroughs in the second- and first-line treatment of advanced or metastatic ESCC. This review focuses on the current landscape of perioperative immunotherapy for resectable ESCC and discusses promising biomarkers and future perspectives.

INTRODUCTION

Esophageal cancer (EC), one of the most prevalent malignancies affecting the digestive tract, originates from the epithelial lining of the esophagus. According to the International Agency for Research on Cancer's latest update on the global cancer burden, based on the GLOBOCAN 2020 projections of cancer incidence and mortality, EC ranks seventh in terms of cancer incidence worldwide and sixth in cancer-related mortality[1]. The incidence of EC varies significantly across countries and regions, with East Asia having the highest disease occurrence, being twice the global average (12.2/1000). EC can be classified into two histological subtypes: Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). EAC is the predominant pathological type in relatively low-incidence areas such as Europe and America. However, globally, ESCC accounts for approximately 90% of all EC cases[2], and more than half of the ESCC cases occur in China[3].

For many years, surgery has served as the primary treatment for early-stage ESCC. High-grade dysplasia and very early-stage tumors are amenable to local therapies such as endoscopic resection, ablation, or surgery. Surgery can improve the 5-year survival rate to 60%-85% in patients with early-stage disease[4]. However, due to the subtle nature of early symptoms, many patients present with advanced or metastatic disease at the time of diagnosis. For locally advanced disease, surgery alone has not yielded satisfactory results, with a median survival time of 12 to 18 mo and a 5-year survival rate of 15%-39%[5,6]. Furthermore, local or systemic recurrence is common, with recurrence reported in 35%-50% of patients who had underwent surgery alone[7].

Neoadjuvant therapy combined with surgery stands as a cornerstone in the treatment of locally advanced ESCC, typically encompassing clinical stages II to IVA[8]. The medical community widely acknowledges the value of neoadjuvant therapy due to its efficiency compared to postoperative adjuvant therapy. Moreover, it leads to reductions in tumor and lymph node (LN) volumes, improves the R0 resection rate, and enhances long-term survival rates[9-11]. Additionally, neoadjuvant therapy allows for the evaluation of patient response using resected specimens[12]. Numerous randomized controlled trials (RCTs) have indicated that preoperative or neoadjuvant chemoradiotherapy (nCRT) may result in longer overall survival (OS) compared to surgery alone[13-15]. The CROSS trial established nCRT as the first-line therapeutic choice for resectable locally advanced ESCC, combining radiotherapy with a chemotherapy regimen containing carboplatin and paclitaxel[16]. The NEOCRTEC5010 phase III, multi-center, open-label RCT confirmed the findings of the CROSS trial for ESCC[9]. However, the optimal neoadjuvant therapy for resectable locally advanced ESCC remains a topic of debate. Neoadjuvant chemotherapy showed improved OS over surgery alone only for EAC, whereas nCRT demonstrated considerably better OS than surgery alone for both EAC and ESCC, according to the NewEC study [17]. Several subsequent meta-analyses also supported the utility of preoperative nCRT, showing improved OS compared to other treatment modalities, including surgery alone, neoadjuvant chemotherapy, and neoadjuvant radiotherapy, albeit with increased postoperative mortality[18,19]. Postoperative morbidity was similar between the nCRT and S (surgery) groups (55.6% *vs* 52.8%; *P* = 0.720), while in-hospital postoperative mortality was significantly higher in the CRT group (11.1% *vs* 3.4%; *P* = 0.049)[20]. A Japanese study[21] examined late complications, revealing grade 2 anastomotic stricture as the most common event, occurring in 30% of the 33 patients. A total of 12 events of grade 3 or worse complications were observed in ten patients, including gastric tube ulcer, cardiac complications, and pulmonary complications. The 5-year incidence rate was 22%, and three patients succumbed to the late complications. A clear advantage of nCRT over neoadjuvant chemotherapy was not established.

Presently, both the National Comprehensive Cancer Network and the Chinese Society of Clinical Oncology guidelines recommend chemoradiotherapy (CRT) as the standard approach for locally advanced ESCC[22-24]. Despite significant efforts made by the medical community, the expected long-term outcomes for ESCC patients have seen limited improvement, remaining poor. The 5-year OS in patients undergoing nCRT and surgery is approximately 50%, and the incidence of local recurrence or distant metastasis remains high[25]. Relapse after nCRT is common and constitutes a major hurdle to overcome[26].

Immunotherapy is a therapeutic approach that involves the use of substances to stimulate or suppress the immune system, aiding the body in combating cancer, infections, and other diseases. It encompasses biologic/targeted agents that aim to enhance and restore the immune system's ability to recognize and eliminate cancer cells by modifying and/or blocking costimulatory signals[27,28]. Over the past few years, immunotherapy has achieved remarkable progress in cancer treatment, particularly with the advent of immune checkpoint inhibitors (ICIs)[29]. The development of ICIs,

which inhibit programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1), has shown convincing responses and clinical benefits across various malignancies, including ESCC[30,31].

In the study "KEYNOTE-181", Pembrolizumab demonstrated superior OS, a higher objective response rate, and a lower incidence of grades 3-5 treatment-related adverse events (trAEs) compared to chemotherapy in the second-line setting [32]. Grades 3-5 trAEs occurred in 18.2% of patients treated with Pembrolizumab *vs* 40.9% in the chemotherapy group. Other trials such as "RATIONALE-302"[33], "ATTRACTION-3"[34], and "ESCORT"[35] have also reported positive outcomes. In these trials, immunotherapy showed lower rates of grades 3-5 trAEs compared to chemotherapy, with percentages of 18.8% *vs* 55.8% in "RATIONALE-302"[33], 18% *vs* 63% in "ATTRACTION-3"[34], and 19% *vs* 39% in "ESCORT"[35].

It is important to note that in studies like "JUPITER-06"[36], "CheckMate-648"[37], "ORIENT-15"[38], "ESCORT-1st"[39], and "KEYNOTE-590"[40], treating patients with advanced EC using PD-1 inhibitors in combination with chemotherapy as first-line therapy resulted in significantly longer OS and progression-free survival (PFS) compared to chemotherapy alone. The occurrence rates of grades 3-5 trAEs in these trials were relatively comparable.

Neoadjuvant immunotherapy has been explored in various other malignancies, such as lung cancer[41,42], melanoma [43], bladder cancer[44], colon cancer[45], and glioblastoma[46]. In a clinical trial (NCT02259621) investigating neoadjuvant Nivolumab, surgery was not delayed, and 45% of resected tumors showed a major pathological response (MPR). In the NADIM trial[42], patients were treated with a neoadjuvant regimen consisting of paclitaxel and carboplatin in combination with Nivolumab. Out of the initial 51 patients deemed eligible, 46 patients received neoadjuvant treatment and subsequently underwent surgery. At the 24-mo mark, the PFS rate was observed to be 77.1%. Among the 27 patients who had melanoma, eight experienced either a complete response or an MPR after receiving a single dose of the anti-PD-1 drug, Pembrolizumab. Importantly, all eight of these patients remained free from the disease[43]. In a single-arm phase II study exploring Atezolizumab before cystectomy in 95 patients with muscle-invasive urothelial cancer (NCT02662309), the pathological complete response (pCR) rate was 31%[44]. In the exploratory NICHE study (NCT03026140)[45], patients with early-stage colon cancers, categorized as mismatch repair-deficient (dMMR) or mismatch repair-proficient (pMMR) tumors, received a single dose of Ipilimumab and two doses of Nivolumab before surgery. Among dMMR tumors, 20 out of 20 displayed a pathological response, with 19 cases of MPR and 12 cases of pCR. In pMMR tumors, 4 out of 15 showed pathological responses, with three cases of MPR and one case of partial response. In a single-arm phase II clinical trial (NCT02550249)[46], a presurgical dose of Nivolumab followed by postsurgical Nivolumab until disease progression or unacceptable toxicity was tested in 30 patients. However, no significant clinical benefit was observed following salvage surgery, although two out of the three patients treated with Nivolumab before and after primary surgery remained alive 33 and 28 mo later.

Based on this background, this review aims to depict the current scenario in the field of perioperative immunotherapy for resectable ESCC, focusing in particular on an overview of the role of ICIs in this field, alongside a discussion of the promising biomarkers and forecast of future perspectives.

PERIOPERATIVE IMMUNOTHERAPY OF ESCC

Drugs for immunotherapy of ESCC

Cancer cells have the ability to evade immune surveillance by disrupting the balance of the tumor microenvironment (TME). This disruption can lead to tumor development by blocking apoptosis, promoting angiogenesis, proliferation, and distant metastasis, and evading immune detection[47]. CD8(+) T cells, also known as cytotoxic T lymphocytes, play a crucial role in killing tumor cells, and their presence in the TME is associated with improved cancer prognosis[48]. For CD8(+) T cells to effectively kill tumor cells, two signals are essential: The recognition of antigens presented by major histocompatibility complexes[49] and the stimulation or suppression of T cell activation. The second signal, acting as a co-stimulatory or co-inhibitory signal, is often referred to as an "immune checkpoint" for CD8(+) T cell function. Immune checkpoints help maintain the balance of T-cell activation, immune tolerance, and immune-mediated tissue damage[50]. Both co-stimulatory and co-inhibitory ligands and their receptors are present on T cells and antigen-presenting cells. Inhibitory checkpoint molecules displayed by CD8(+) T cells can respond to and aid the tumor in evading the immune system[51].

There are four main ICIs named after the corresponding Food and Drug Administration (FDA)-approved monoclonal antibody therapies: Cytotoxic T lymphocyte antigen-4 (CTLA-4), PD-1, PD-L1/L2, and lymphocyte activation gene-3 (LAG-3)[52]. CTLA-4 and PD-1 are members of the CD28 receptor family expressed on T-cells, which bind to their corresponding targets of the B7 family[53]. CTLA-4 is an intracellular protein often found on regulatory T cells, inhibiting CD8(+) T cell activity. Ipilimumab, approved by the FDA in 2011, targets CTLA-4[54]. PD-1 is a transmembrane protein upregulated by repeated stimulation of T cells. PD-1 has two ligands, PD-L1 and PD-L2, which are cell surface proteins expressed on tumor cells and some immune cells within the TME. When PD-1 binds to these ligands, T cell function is inhibited. Overexpression of PD-L1 is associated with tumor progression, as cancer cells exploit the PD-1/PD-L1 and PD-1/PD-L2 pathways to create an immunosuppressive environment[55]. Nivolumab and Pembrolizumab are ICIs that target the PD-1 molecule, both FDA-approved in 2014. In 2018 and 2021, Cemiplimab and Dostarlimab were also approved, respectively[56,57]. Atezolizumab, Avelumab, and Durvalumab are FDA-approved PD-L1 inhibitors[58-60]. LAG-3 is a transmembrane receptor expressed on CD8(+) T cells, further upregulated by T cell activation. Relatlimab is the only FDA-approved LAG-3 inhibitor[61].

In recent years, several domestic anti-PD-1 monoclonal antibodies have been approved as drugs for various tumors by the China National Medical Product Administration. Notably, Camrelizumab, Sintilimab, Toripalimab, and Tislelizumab are representative drugs that are currently undergoing in-depth research. Camrelizumab, a humanized anti-PD-1 monoclonal antibody developed in China, has shown promising activity and manageable toxicity when combined with Apatinib, an anti-angiogenic drug. This combination may serve as a potential second-line treatment option for patients with advanced ESCC[62] or patients with recurrent or metastatic ESCC[63].

Neoadjuvant immunotherapy of ESCC

As previously mentioned, ICI immunotherapy has demonstrated improved outcomes in terms of OS and disease-free survival (DFS) for both second-line and first-line treatments of ESCC. In the context of resectable locally advanced ESCC, there has been a growing interest in perioperative immunotherapy combined with chemotherapy or radiotherapy, representing a key research direction for this disease. Preoperative neoadjuvant immunotherapy aims to activate the patient's immune system, leading to the formation of immune memory cells, thereby enabling the immune system to assume an immune surveillance role[64,65]. This review will summarize the current status of neoadjuvant immunotherapy as a treatment for ESCC.

Completed and reported clinical studies of neoadjuvant immunotherapy

Numerous clinical studies have investigated the efficacy and safety of immunotherapy for resectable ESCC in the neoadjuvant setting, as detailed in Table 1. Most neoadjuvant immunotherapy trials are conducted in conjunction with chemotherapy or CRT. Given the high incidence of this disease in China, numerous clinical trials on this subject are carried out in the country. Specifically, six ICIs targeting PD-1/PD-L1, namely, Pembrolizumab (4 studies), Camrelizumab (10 studies), Sintilimab (4 studies), Toripalimab (5 studies), and Tislelizumab (1 study), have been studied as neoadjuvant therapy. Additionally, there is an ongoing drug-based neoadjuvant therapy RCT involving Nivolumab, the first ICI used in adjuvant immunotherapy in the CheckMate-577 study[66]. The results of this trial, known as the FRONTiER study (NCT03914443), are eagerly anticipated[67]. In Table 1, four reports were retrospective in nature, while the other 21 reports were prospective, with 20 of them being single-arm trials. Only three studies employed neoadjuvant immunotherapy in combination with concurrent CRT as an intervention. In studies involving neoadjuvant immunotherapy combined with chemotherapy, the chemotherapy drugs used included 5-fluorouracil (5-FU), cisplatin (DDP), carboplatin (CBP), nedaplatin (NDP), paclitaxel (PTX), docetaxel (DTX), albumin-bound paclitaxel (nab-PTX), and PTX liposomes. Over the past few years, the use and dosages of these chemotherapy drugs have demonstrated efficacy for ESCC treatment in clinical settings. Most surgeons have chosen an interval time of 4-6 wk from the end of neoadjuvant therapy to surgery. The primary outcomes of utmost concern to doctors are safety, feasibility, and pCR, while MPR and R0 resection rate are commonly selected as primary or secondary outcomes.

Ensuring the safety of participants is of utmost importance in clinical trials, and the occurrence of trAEs is a key indicator in assessing the safety of neoadjuvant immunotherapy[68]. When ICIs are combined with other anti-cancer therapies, such as chemotherapy, immunotherapy, targeted therapy, or radiotherapy, the incidence of trAEs is significantly higher compared to the use of ICIs alone[69]. These trAEs can affect various organs, with the most common being endocrine (hypothyroidism and hyperthyroidism), gastrointestinal (diarrhea and colitis), pulmonary (pneumonitis), dermatological (rash and pruritus), and hepatic (elevated liver enzymes) complications[70,71]. The majority of trAEs (grades 1-2) are self-limiting or can be managed with immunosuppressive therapy, such as corticosteroids. However, persistent trAEs that do not respond to corticosteroids require close monitoring and appropriate treatment. Fatal trAEs are extremely rare for anti-PD-1 antibodies, with an incidence of less than 0.5% in a meta-analysis of ICI monotherapy studies across various cancer types, most commonly associated with pneumonitis[71]. The incidence of serious trAEs (grade ≥ 3) in neoadjuvant ICI plus chemotherapy ranged from 0% to 36.7% in the studies presented in Table 1. Notably, the combination of chemotherapy with Camrelizumab and Apatinib resulted in the highest incidence of patients experiencing serious trAEs (36.7%). In another meta-analysis comparing the efficacy and safety of various ICIs for patients with advanced or metastatic ESCC, Camrelizumab and Nivolumab were found to have a lower incidence of serious trAEs in the first-line and refractory settings, respectively[72]. Close monitoring and early recognition of relevant symptoms and signs are essential to ensure appropriate management.

Feasibility can be assessed by comparing the completion rate of the trial. In a pooled analysis, the rates of completion of neoadjuvant therapy and surgery ranged from 49.4% (Camrelizumab + nab-PTX + NDP) to 100% (Sintilimab + PTX liposome, DDP, and S-1). Failures in the study were mainly attributed to trAEs[73,74], patient decisions[75-77], or disease progression[78]. As most trials achieved a treatment completion rate of over 60%, interpreting the data in the conference abstract (ChiCTR2000039170) is challenging.

The definition of pCR is the absence of any signs of cancer on a histological resection specimen. The pCR rate is a crucial efficacy-related parameter reported in all studies, with some studies choosing it as a secondary outcome. In a meta-analysis of seven clinical trials involving 815 patients, the pooled pCR rate was 32.4% (95% confidence interval [CI]: 28.2%-36.8%)[79]. Data from Table 1 shows that the pCR rate ranges from 6.7% to 46.1%. The definition of MPR is the presence of less than 10% of the remaining viable tumor cells in the resected primary tumor. In the aforementioned meta-analysis, the pooled MPR rate was 49.4% (95%CI: 42.1%-56.7%)[79]. MPR rate was chosen as the primary outcome in four studies and seemed to be a second primary outcome in the main studies verified in Table 1, with reported rates ranging from 42% to 72.3%[73,76,77,80-83]. The R0 resection rate is defined as a complete resection of the tumor with a negative microscopic edge, indicating no residual tumor. It is another crucial indicator to evaluate the effectiveness of neoadjuvant therapy. The R0 resection rate in Table 1 ranges from 80.4% to 100%, which indicates positive outcomes.

Table 1 Reported clinical results of neoadjuvant immunotherapy for resectable esophageal squamous cell carcinoma

Drug & Ref.	Trial No.	Phase	Number of enrollments	Clinical stage	Design	Chemotherapy drugs	Chemotherapy cycles	Radiotherapy	Interval time to surgery	Primary outcome	Safety (rate of grade ≥ 3 trAEs)	Feasibility (therapy completion rate)	pCR	MPR	Surgical outcome (R0 rate)
Pembrolizumab [111]	Park et al[111] (NR)	NA	38	IA-IVA	Retrospective	5-FU + DDP/PTX + CBP	NA	41.4 Gy/23 f	6-8 wk	Operative risk	18.75% (3/16)	100% (16/16)	NA	NA	100%
Pembrolizumab [112]	Huang et al[112] (NR)	NA	54	II–IVA	Retrospective	DTX + NDP	2, Q3W		4-6 wk	pCR	13.04% (4/23)	NA	30.4% (7/23)	NA	100%
Pembrolizumab [113]	NCT02844075	II	28	IB-III	Single-arm	PTX + CBP	5, Q1W	41.4 Gy/23 f	5 wk	pCR	NA	92.9% (26/28)	46.1% (12/26)	NA	NA
Pembrolizumab [80]	Keystone-001/NCT04389177	II	50	IIIA-IIIB	Single-arm	PTX + DDP	3, Q3W		4-6 wk	pCR, MPR, safety	0	69.0% (29/42)	41.4% (12/29)	72.4% (21/29)	100%
Camrelizumab [114]	Qiao et al[114] (NR)	NA	254	IA-IVA	Retrospective	PTX, nab-PTX/DTX	2, Q3W		NA	pCR	6.25% (3/48)	NA	41.7% (20/48)	60.4 (29/48)	NA
Camrelizumab [74]	ChiCTR1900026240	II	60	IIIA-IVA	Single-arm	nab-PTX + CBP	2, Q3W		4-6 wk	pCR	56.7% (34/60)	85.0% (51/60)	39.2% (20/51)	NA	98.0%
Camrelizumab [115]	NCT04506138	I-II	46	II-IVA	Single-arm	nab-PTX + CBP			4-6 wk	pCR	15.2% (7/46)	82.6% (38/46)	21.6% (8/37)	48.6% (18/37)	80.4%
Camrelizumab [82]	GASTO1056/ChiCTR2000028900	II	23	II-III	Single-arm	nab-PTX + CBP	2, Q3W		3-6 wk	Safety	47.8%	87.0% (20/23)	25% (5/20)	50% (10/20)	100%
Camrelizumab [116]	Yang et al[116] (NR)	II	12	II-III	Single-arm	nab-PTX + S1	3, Q3W		3-6 wk	pCR	0	75.0% (9/12)	33.3% (4/12)	41.7% (5/12)	100%
Camrelizumab [75]	NIC-ESCC2019/NCT04225364	II	56	II-IVA	Single-arm	nab-PTX + DDP	2, Q3W		6 wk	pCR	10.7% (6/51)	91.1% (51/56)	35.3% (18/51)	23.5% (12/21)	100%
Camrelizumab [117]	ChiCTR1900023880	Ib	30	IC-IIIB	Single-arm	nab-PTX + NDP + Apatinib	2-4, Q3W		4-8 wk	Safety, feasibility	36.7% (11/30)	96.7% (29/30)	24.1% (7/29)	51.7% (15/29)	NA
Camrelizumab [118]	ESPRIT/ChiCTR2000033761	II	48	IIA-IIIB	Single-arm	PTX + NDP	2-4, Q3W		NA	pCR	4.2%	62.5% (30/48)	35.0% (7/20)	NA	NA
Camrelizumab [119]	NCT 03917966	II	40	IC-IVA	Single-arm	DTX + NDP	2, Q3W		4-6 wk	MPR	3%	70.6% (12/17)	25.0% (3/12)	41.6% (5/12)	100%
Camrelizumab [120]	ChiCTR2000039170	II	166	Locally advanced	Single-arm	nab-PTX + NDP	NA		NA	Safety	7.8% (13/166)	49.4% (82/166)	18.5% (15/81)	63.0% (51/81)	97.5% (79/82)
Sintilimab[121]	ChiCTR1900026593	II	47	II-IVA	Single-arm	PTX liposome +	2, Q3W		3-6 wk	pCR	29.8%	95.7%	22.2%	44.4%	97.8%

						CBP					(14/47)	(45/47)	(10/45)	(20/45)	(44/45)
Sintilimab[81]	SIN-ICE study/ChiCTR2100048917	II	23	IC-IVA	Single-arm	Platinum	3, Q3W		4-6 wk	pCR, safety	30.4% (7/23)	73.9% (17/23)	35.3%, (6/17)	52.9% (9/17)	94.1% (16/17)
Sintilimab[73]	ESONICT-1/ChiCTR2100045659	II	30	IIB-IVA	Single-arm	DDP + nab-PTX	2, Q3W		4-6 wk	pCR, safety	3.3% (1/30)	76.6% (23/30)	21.7% (5/23)	52.2% (12/23)	100%
Sintilimab[88]	KEEP-G03/NCT03946969	II	30	IB-IVA	Single-arm	PTX liposom + DDP + S1	2, Q3W		Within 6 wk	Safety, feasibility	36.7%	100.0% (30/30)	20% (6/30)	50% (15/30)	100%
Toripalimab [122,123]	NCT03985670	II	30	II-IVA	Two-arm	PTX + DDP	2, Q3-4W		4-6 wk	pCR	8.33% (2/24)	80.0% (24/30)	20.8% (5/24)	NA	100%
Toripalimab [124]	ChiCTR1900025318	II	23	IIB-IVA	Single-arm	PTX + DDP	2, Q3W		4-6 wk	pCR, R0 rate	8.70% (2/23)	78.3% (18/23)	33.3% (6/18)	NA	100%
Toripalimab [77]	NCT04177797	II	20	IIIA-IVA	Single-arm	PTX + CBP	2, Q3W		4-6 wk	Safety, feasibility, MPR, pCR	20.0% (4/20)	80.0% (16/20)	18.8% (3/16)	43.8% (7/16)	87.5% (14/16)
Toripalimab [125]	ESONICT-2/ChiCTR2100052784	II	20	IIB-IVA	Single-arm	DTX + DDP	2, Q3W		4-6 wk	pCR, safety	15.0% (3/20)	60.0% (12/20)	16.7% (2/12)	41.7% (5/12)	100%
Toripalimab [126]	SCALE-1/ChiCTR2100045104	Ib	20	IIB-IVA	Single-arm	PTX + CBP	2, Q3W	30 Gy/12 f	4-7 wk	Safety	NA	87.0% (20/23)	55% (11/20)	80% (16/20)	
Tislelizumab [76]	TD-NICE/ChiCTR2000037488	II	45	IIIA-IVA	Single-arm	CBP + nab-PTX	2, Q3W		3-6 wk	MPR	33.3% (15/45)	80.0% (36/45)	50% (18/36)	72% (26/36)	97.2% (35/36)
Multiple[127]	CHICTR2100045659		27	IC-IVA	Retrospectively, two-arm	Platinum+ PTX or platinum + 5-Fu	2, Q3w		4–8 wk	30-d major complications	11.1% (3/27)	NA	NA	NA	100%

NR: Not registered; NA: Not available; 5-FU: 5-fluorouracil; DDP: Cisplatin; PTX: Paclitaxel; DTX: Docetaxel; CBP: Carboplatin; NDP: Nedaplatin; nab-PTX: Albumin bound paclitaxel; S1: Tegafur (Gimeracil and Oteracil Potassium Capsules); pCR: Pathological complete response; MPR: Major pathological response; trAEs: Treatment-related adverse events.

Ongoing clinical trials in neoadjuvant immunotherapy

This period marks a surge in clinical trials focused on neoadjuvant immunotherapy, particularly for perioperative treatment of ESCC, with a significant number of ongoing RCTs, especially led by Chinese investigators (Table 2). Eight ICIs are currently under investigation, with dozens of trials in progress. PD-1 is the primary target in seven of these trials, while Adebrelimab targets PD-L1. Camrelizumab is the most extensively studied ICI, involved in ten clinical trials, followed by Toripalimab with seven trials. Among these trials, there are 23 single-arm studies, 11 two-arm studies, two three-arm studies, and one four-arm study.

An array of combinations of new adjuvant therapies for ESCC are constantly emerging. Most ICIs are being utilized as neoadjuvant adjuncts, combined with chemotherapy in 13 trials or CRT in 18 trials. Adebrelimab, a PD-L1-targeting ICI, is used alone in one trial (NCT04215471), as is Nivolumab in another (NCT03987815). Camrelizumab, on the other hand, is being combined with radiotherapy (NCT05176002 and NCT03200691), or paired with multitargeted small molecule inhibitors and CRT or chemotherapy (NCT04666090), or further combined with both CRT and an anti-EGFR antibody

Table 2 Ongoing clinical trials of neoadjuvant immunotherapy for resectable esophageal squamous cell carcinoma

Drug & target	Trial name/No./Ref.	Phase	Sample size	Clinical stage	Design	Chemotherapy drugs	Chemotherapy cycles	Radiotherapy	Interval to surgery	Primary endpoint	Start date
Nivolumab	FRONTiER/NCT03914443[67]	I	36	IC-IVA	Two-arm	5-FU + DDP	2, Q3W		12 wk	Incidence of dose-limiting toxicities	07-May-19
	NCT03987815	II	20	NA	Single-arm	NA				MPR	01-Aug-19
	NCT05213312	II-III	90	II-III	Two-arm	PTX/5-FU + DDP	2, Q3W		4-6 wk	pCR	01-Jun-22
Pembrolizumab	PALACE-1/NCT03792347[85]	I	20	IC-IVA	Single-arm	CBP + PTX	5, Q1W	41.4 Gy/23 f	4-6 wk	Safety	21-Jan-19
	PALACE-2/NCT04435197[84]	II	143	IC-IVA	Single-arm	CBP + PTX	5, Q1 W	41.4 Gy/23 f	4-6 wk	pCR	11-Aug-20
	NCT05302011	II	30	IIB/IIIB/IVA	Single-arm	CBP/DDP + DTX	4, Q3W			Tumor response, pCR	01-Jun-20
	NCT05281003	II	128	IC-IVA	Single-arm	PTX + DDP	4, Q4W			pCR	20-Feb-23
Camrelizumab	NCT04520035	II	60	IIB-IVA	Single-arm	PTX + DDP	2, Q3W			pCR	01-Aug-20
	NCT04767295	II	28	IA-IVA	Single-arm	nab-PTX + CBP	2, Q3W		5-8 wk	pCR	01-Mar-21
	NICE-2 Study/NCT 05043688 [128]	II	204	Locally advanced	Three-arm	nab-PTX, CBP, PTX	2, Q3W	41.4 Gy/23 f	4-12 wk	pCR	14-Sep-21
	NCT05476380	II	39	IIIB-IVA	Single-arm	PTX + DDP	3, Q3W			pCR	19-Feb-21
	NCT05182944	II	130	IIB-IVA	Four-arm	nab-PTX + DDP	2, Q3W			pCR, 3-yr DFS	15-Jan-22
	NCT04937673	II	40	IIB-IVA	Two-arm	PTX/nab-PTX + DDP	3, Q3W		NA	Biomarkers related to pCR	01-Jul-21
	NCT05176002	I-II	26	II-IVA	Single-arm	NA	NA	Radiotherapy, NA	NA	Efficacy Safety	23-Sep-21
	NCT04666090	II	42	IIA-IVA	Single-arm	nab-PTX + NDP + Apatinib	2-3, Q2W		4-6wk	pCR	23-Nov-20
	NCT05355168	I-II	57	IC-IVA	Single-arm	Nimotuzumab + CRT	NA			pCR, MPR	01-Nov-21
	NCT03200691	II	21	IIA-III	Single-			40 Gy/20 f	2-4 wk	pCR	10-Aug-

Drug	Trial/NCT	Phase	N	Stage	Arm	Chemotherapy	Cycles	Radiotherapy	Interval	Outcome	Date
				arm							17
Sintilimab	NCT03940001	I	20	IIB-IVA	Single-arm	PTX + CBP	2, Q3W	41.4 Gy/23 f	NA	Unacceptable toxicity; pCR; MPR	01-May-19
	(NICCE)NCT05028231	NA	46	IIB-IVA	Single-arm	nab-PTX + DDP	2, Q3W			pCR	05-Jun-21
	NCT05357846	III	422	IIB-IVA	Two-arm	PTX + DDP	4, Q1W	40 or 45 Gy / 20 f	6-8 wk	OS	01-Nov-22
	NCT05244798	III	420	IC-IVA	Three-arm	nab-PTX + CBP	2, Q3	41.4 Gy/23 f	6-8 wk	pCR	01-Nov-22
Toripalimab	NCT04280822	III	400	IC-IVA	Two-arm	DDP + PTX	2, Q3W		2-3 wk	3 yr EFS; 5 yr EFS	21-Apr-20
	NCT04804696	II	53	NA	Single-arm	PTX + DDP	NA		NA	pCR	10-Feb-21
	NCT04177875	II	44	IC-IIIB	Single-arm	DTX/PTX + DDP	2, Q3W	40 Gy/20 f	NA	MPR; ORR	01-May-19
	NCT04888403	II	45	IIB-IVA	Single-arm	nab-PTX + NDP	5, Q1W	41.4 Gy/23 f	Within 7 wk	pCR	31-Dec-21
	NCT04644250	II	32	IIB-IVA	Single-arm	CBP + PTX liposome	5, Q1W	41.4 Gy/23 f	2-4 wk	pCR	01-Sep-20
	NCT04848753	III	632	IC-IVA	Two-arm	DDP + PTX	NA		NA	EFS	18-Jun-21
	NCT04006041	II	44	IIB-IVA	Single-arm	PTX + DDP	4, Q1W	44 Gy/20 f	6-8 wk	pCR	25-Jun-19
Tislelizumab	iCROSS/NCT04973306	II-III	176	II-III	Two-arm	CBP + PTX	5, Q1W	41.4 Gy/23 f	NA	pCR; OS	02-Mar-22
	NCT05323890	II	15	IIB-IVA	Single-arm	nab-PTX + DDP	5, Q1W	41.4 Gy/23 f	NA	MPR, pCR	20-Apr-22
	NCT04974047	II	70	IIB-IVA	Two-arm	PTX/5-FU + DDP	2, NA	40 or 45 Gy/20 fractions	NA	pCR	17-Aug-21
	NCT05189730	II	80	II-III	Single-arm	PTX + CBP	2, Q3W	40 Gy/20 f	4-6 wk	pCR, incidence of adverse events	01-Jul-21
Adebrelimab (PD-L1)	NATION1907II/NCT04215471	II	30	Resectable	Single-arm					ORR	01-Feb-20
Durvalumab	NCT04568200	II	60	IIB-IVA	Two-arm	CBP + PTX	4, Q3W	41.4 Gy/23 f		pCR	19-Jun-20
Pembrolizumab (+ Adjuvant)	KEYSTONE-002/NCT04807673 [86]	III	342	IC-IIIB	Two-arm	PTX + DDP	3, Q3W	41.4 Gy/23 f	4-6 wk	EFS	01-Dec-21

| PD-1 Inhibitor | REVO/NCT05007145 | II | 92 | IB-IVA | Two-arm | nab-PTX + DDP | 2-4, Q3W | 40 Gy/20 f | | pCR | 15-Aug-21 |
| Toripalimab (+ Adjuvant) | NCT 04437212 | II | 20 | IIB-IVA | Single-arm | PTX/DDP | 5, Q3W | 41.4 Gy/23 f | 6-8 wk | MPR | 01-Jul-20 |

EFS: Events-free survival; DFS: Disease-free survival; OS: Overall survival; ORR: Objective response rate; NA: Not available; 5-FU: 5-fluorouracil; DDP: Cisplatin; PTX: Paclitaxel; DTX: Docetaxel; CBP: Carboplatin; NDP: Nedaplatin; nab-PTX: Paclitaxel for injection (albumin bound); pCR: Pathological complete response; MPR: Major pathological response.

(NCT05355168).

Several large medical centers are now conducting phases II and III clinical studies based on promising results from phases I and II studies. Examples include PALACE-2 (NCT04435197)[84], an advancement of PALACE-1 (NCT03792347) [85], and KEYSTONE-002 (NCT04807673)[86], another advancement based on Keystone-001 (NCT04389177)[80]. Although Pembrolizumab is the ICI being studied in both series of trials, the PALACE trial was designed as neoadjuvant immunotherapy combined with chemotherapy, while the Keystone trial was designed as neoadjuvant combined with chemotherapy and adjuvant immunotherapy. Most chemotherapy regimens include taxols and platinum, with 5-FU being chosen in only two trials. The mainstream radiotherapy method utilizes 41.4 GY divided into 23 fractions, and the interval between neoadjuvant therapy and surgery ranges from 2 to 12 wk, with 4-6 wk being the most common choice. The primary outcome sought by most ongoing trials is pCR.

Ongoing clinical trials of adjuvant immunotherapy

Despite the benefits of neoadjuvant chemoradiation in improving survival compared to surgery alone, achieving a pCR remains challenging, with persistent disease in LNs leading to decreased survival[66]. An RCT involving 346 patients with ESCC compared preoperative and perioperative chemotherapy. Both groups received two cycles of paclitaxel, cisplatin, and 5-fluorouracil before surgery, but only half received two cycles after surgery. The group receiving adjuvant chemotherapy showed an estimated 16% improvement in 5-year survival[87].

In contrast to neoadjuvant methods, adjuvant immunotherapy has received relatively little attention. The global CheckMate-577 trial, a randomized, double-blind, placebo-controlled phase III trial, demonstrated the DFS benefit of Nivolumab for ESCC (29.7 *vs* 11.0 mo)[66]. Despite the promising results of CheckMate-577 for adjuvant immunotherapy after surgery, there are currently only three ongoing trials in this area. One trial is investigating the effectiveness of Toripalimab (NCT04437212) in both neoadjuvant and adjuvant settings. The other two RCTs are assessing postoperative adjuvant therapy with Tislelizumab, with one in phase II as a single-arm study and the other in phase III with two-arm trials. The phase II trial involves adjuvant immunotherapy combined with CRT, while the phase III trial is adjuvant immunotherapy combined with chemotherapy (Table 3). Further details and results from these ongoing trials are eagerly awaited.

ISSUES SHOULD BE CONCERNED IN FUTURE

The majority of neoadjuvant immunotherapy trials in ESCC are currently single-arm, phase II clinical trials. These trials explore various combinations of different drugs and different methods of other therapies, leading to a continuous emergence of new clinical trials in this field. However, it is important to acknowledge that progress in some cases has

Table 3 Clinical trials of adjuvant immunotherapy for resectable esophageal squamous cell carcinoma

Drug	Trial name/No.	Phase	Sample size	Clinical stage	Design	Chemotherapy drugs	Chemotherapy cycles	Radiotherapy	Interval time to surgery	Primary endpoint	Start date	Outcome
Nivolumab	CheckMate-577/NCT02743494	III	784 (ESCC29%)	NA	Two-arm	NA				DFS	Completed	22.1:11.0 mo
Toripalimab (+ Neoadjuvant)	NCT 04437212	II	20	IIB-IVA	Single-arm	PTX + DDP	5, Q3W	41.4 Gy/23 f	6-8 wk	MPR	Jul 1, 2020	
Tislelizumab	AIRE/ChiCTR2100045651	III	110	High-risk resected locally advanced	Two-arm	Platinum-based doublets	2, Q3W			DFS	May 1, 2021	
Tislelizumab	CRISEC/NCT04776590	II	30	NA	Single-arm	PTX + CBP	5, Q1W	41.4 Gy/23 f		pCR	Jan 28, 2021	

DFS: Disease-free survival; NA: Not available; DDP: Cisplatin; PTX: Paclitaxel; CBP: Carboplatin; pCR: Pathological complete response; MPR: Major pathological response.

been slow or stagnant.

Ethical conduct should be a primary concern in the development of new therapies. As the development of immunotherapy is often driven by related industries, methodological, legal, and ethical frameworks can sometimes be overlooked. Currently, a significant portion of scientific research in immunotherapy is industry-driven, with various pharmaceutical companies involved in registering RCTs. Despite the existence of international research registries aimed at improving the transparency of medical research, there are still uncertainties and "not applicable" rules and regulations. Consequently, there may be a lack of control over data mining and publication bias. Even if there are significant differences between the research protocol and the reported results, most trial outcomes are still published. To ensure the reliability, quality, and expected clinical benefits of ongoing and future trials in this field, the medical community and relevant stakeholders should focus on curbing the significant increase in "feasibility" trials with unclear expected benefits. Emphasizing a few multi-center phase III trials, conducted by leading centers in ESCC research, could be a crucial approach to prevent unclear or contradictory results and uphold the integrity of the research.

The second issue of concern in clinical trials is safety, which should be carefully considered throughout the perioperative treatment of ESCC. One of the major safety risks is the occurrence of trAEs, especially immune-related adverse events. Perioperative immunotherapy trials for ESCC typically consist of three parts: Preoperative neoadjuvant therapy, surgery, and postoperative adjuvant therapy. Different immunotherapy drugs are administered at varying intervals: Pembrolizumab, Tislelizumab, Atilizumab, Toripalimab, and Sintilimab are usually given at 3-wk intervals, while Nivolumab, Camrelizumab, and Durvalumab are given at 2-wk intervals. The treatment cycles generally involve 2-4 cycles, and multiple factors such as treatment efficacy, surgical timing, economic considerations, and patient compliance are taken into account. Since most RCTs in this field are single-arm or two-arm studies within phase I or II, the safety data obtained may be limited and not fully comprehensive. This might result in an underestimation of the occurrence and severity of trAEs, especially those of grade 3 or above. Additionally, the introduction of new emerging drugs into clinical trials adds uncertain factors that could impact the results. Therefore, researchers should be attentive to the incidence and severity of trAEs, even when they are below grade 2. In cases where the trAEs are grade 3 or higher in severity, special attention should be given to the subjects to avoid fatal consequences. Furthermore, if three or more anti-cancer therapies, including immunotherapy, are administered to a subject simultaneously, researchers should exercise caution due to the

higher risk of trAEs for the patient. Vigilance and thorough monitoring are essential to ensure the safety of subjects throughout the course of treatment.

Neoadjuvant immunotherapy presents a dual challenge, aiming to achieve better treatment outcomes while minimizing harm to normal organs caused by immunotherapy. The impact of trAEs during preoperative therapy on surgery must be carefully considered. In the trial "KEEP-G 03"[88], 36.7% (11/30) of patients experienced grades 3-4 TRAEs, but fortunately, these did not result in any surgical delays. However, in another multicenter, single-arm, phase II trial using Camrelizumab and chemotherapy as neoadjuvant treatment for locally advanced ESCC[74], 34 patients (56.7%) experienced adverse events of grade 3 or worse, with one patient (1.7%) experiencing a fatal grade 5 adverse event due to pneumonia and acute respiratory failure. The risk of increased surgical complications after immunotherapy is a concern, emphasizing the importance of forming a multidisciplinary team to address trAEs and conduct comprehensive evaluations during immunotherapy. Early detection and management of trAEs can minimize the impact on subsequent treatment and related complications. Additionally, exploring biomarkers related to trAEs is crucial in the research field.

Surgery itself poses another safety concern. ESCC radical resection is a complex procedure with a high incidence of complications, and surgical team experience significantly influences the rate of complications. Patients undergoing neoadjuvant treatment may face unexpected surgical challenges. High-volume medical units with stable and mature treatment processes, including neoadjuvant therapy and operations, generally have lower complication and mortality rates[89]. Therefore, RCTs involving neoadjuvant treatment should preferably be conducted in high-volume centers to reduce surgical risks and avoid any adverse impacts. Even in multi-center clinical trials, it is advisable to select larger surgical units or include surgeons with significant experience in performing over 100 operations on ESCC, both open and minimally invasive surgeries. Such measures ensure optimal surgical outcomes and minimize potential complications.

The third issue pertains to how we can accurately assess the efficacy of chosen drugs or treatments. Imaging is a crucial tool for preoperative efficacy assessment. Circulating tumor DNA (ct-DNA) has shown promise as an effective predictive method[90]. Positron emission tomography (PET) also has reference value as an assessment method[91,92]. Typically, pCR and MPR rates are used to predict efficacy, based on the examination of residual tumor cells in postoperative pathology. However, this method has certain limitations[93,94]. First, accurately assessing the pathological conditions of ESCC before immunotherapy, especially in cases of LN metastasis, is challenging. Detection can only be done in resected specimens after neoadjuvant immunotherapy, leading to an inability to make accurate comparisons with pathological specimens before surgery. Second, there is currently no universal standard for evaluating pathological response in ESCC after neoadjuvant immunotherapy. Pathologists are relied upon for positioning, measuring, sampling, slicing, and labeling, introducing variability. The different patterns of resection after neoadjuvant treatment, involving thoracic surgeons and pathologists, may also impact ESCC prognosis[95]. Thus, there is a need for a highly sensitive, specific, and preferably repeatable, simple, and feasible biomarker to predict efficacy in clinical practice.

PET is an integral part of the standard staging for ESCC. Its utility and acceptance in initial staging and recurrence detection have led to the hypothesis that PET could be used to differentiate responders from non-responders during neoadjuvant treatment. However, the precise PET parameters with the best predictive values are still a subject of debate. Several traditional PET parameters, such as the maximum and mean standardized uptake value (SUVmax and SUVmean), metabolic tumor volume (MTV), and total lesion glycolysis (TLG)[96], have been studied to correlate with pathological response. In a study of 31 patients with resectable ESCC or EAC, PET was used prospectively during treatment with trimodality therapy, and it was found that baseline TLG and post-chemoradiotherapy TLG were associated with OS[97]. More recently, efforts have been made to develop radiomic signatures and more robust predictive models. Simoni *et al*[98] investigated multiple traditional PET parameters and identified several radiomic features, as well as tumor regression grade, which correlated with pathological response in a retrospective analysis[98]. However, further research is necessary to develop more reliable predictive models and to validate them in prospective randomized trials. The credibility of PET evaluations in the era of immunotherapy remains largely unknown. Although PET has shown promise in predicting efficacy, especially with regard to OS, its applicability to immunotherapy response assessment is not fully understood. If sufficient high-quality CT or PET data, correlating with pathological response in ESCC, can be obtained, machine learning and artificial intelligence (AI) may emerge as new methods for evaluating neoadjuvant immunotherapy in ESCC. Such advancements could potentially enhance our ability to predict treatment outcomes and optimize patient care.

As of the current writing, specific biomarkers that can precisely determine the efficacy or predict perioperative surgery outcomes of ESCC have not been identified. However, several biomarkers have been explored mainly based on immuno-logical and genetic criteria, including PD-L1 expression, intertumoral lymphoid infiltrates, dMMR/microsatellite instable (MSI), tumor mutation burden (TMB)/tumor neoantigen burden (TNB), and human leukocyte antigen (HLA)[99]. Among these biomarkers, PD-L1 expression is one of the best characterized for anti-PD-1/PD-L1 therapy. It is assessed using immunohistochemistry (IHC) staining and evaluated by the combined positive score (CPS) or tumor proportional score (TPS). CPS is determined by dividing the number of PD-L1-positive cells (tumor cells and other lymphocytes) by the total number of tumor cells[100], while TPS is calculated by dividing the number of PD-L1-positive tumor cells by the total number of tumor cells. In general, high PD-L1 expression usually correlates with an improved objective response to anti-PD-1/PD-L1 therapy[101]. However, some clinical studies have failed to consistently demonstrate this correlation, showing that patients with tumors showing high PD-L1 expression do not always respond to PD-1/PD-L1 blockade [102]. The relationship between PD-L1 expression and clinical outcome in ESCC remains a topic of controversy[103]. While some studies have shown that PD-L1 overexpression is associated with poor clinical outcomes[104], others have indicated a favorable prognosis[105].

Studies have also shown that circulating tumor cells (CTCs) and ct-DNA have a predictive role in evaluating the treatment efficacy of PD-1/PD-L1 inhibition[106,107]. CTCs have been found to be associated with a poor response to PD-L1 inhibitors in non-small cell lung cancer (NSCLC)[106]. Similarly, ct-DNA minimal residual disease (ct-DNA MRD) is

an important indicator for monitoring the efficacy of treating NSCLC[108]. Therefore, it is worth exploring whether CTCs and ct-DNA can be introduced into the long-term follow-up of ESCC to help assess treatment response and predict patient outcomes. However, further research is needed to validate the predictive value of these biomarkers in ESCC and determine their potential role in guiding treatment decisions for patients undergoing perioperative immunotherapy.

The fourth issue pertains to the long-term benefits of perioperative immunotherapy. Many clinical trials on perioperative immunotherapy have focused on short-term or mid-term outcomes, such as safety, feasibility, and pCR. However, the true primary outcomes that need to be concerned with are long-term OS and PFS, regardless of the type of immunological drugs selected or the combination with other anti-cancer therapies. For neoadjuvant anti-PD-1 therapy in resectable NSCLC, a trial with a median follow-up of 63 mo (NCT02259621) reported promising long-term outcomes. The 5-year recurrence-free survival (RFS) and OS rates were 60% and 80%, respectively[109]. Similarly, a study evaluating neoadjuvant anti-PD-1 treatment for localized dMMR colorectal cancer (CRC) also reported positive long-term follow-up data. Among patients who underwent surgery or achieved complete response, the 2-year tumor-specific disease-free and OS rates were both 100%[110].

In the context of resectable locally advanced ESCC, neoadjuvant chemotherapy and nCRT remain the standard treatments before surgery. While immune checkpoint-based therapy shows promise, it currently benefits only a small proportion of ESCC patients. Therefore, perioperative immunotherapy should be strictly monitored with ethical confirmation and preferably conducted within clinical trials. Patients must be fully informed about the potential benefits and risks and give informed consent before participating. Accurate screening of target populations and appropriate choice of combination therapy will be crucial for future research in this field. The importance of monitoring and managing trAEs, especially when combining immunotherapies with other anti-cancer therapies, cannot be ignored. Robust predictive and prognostic biomarkers or comprehensive biomarkers need to be identified to optimize treatment strategies and ensure the most effective therapy for patients. The development of clinical consensus or guidelines based on research findings will also be necessary to ensure that patients receive the most applicable and effective immunotherapy treatments.

CONCLUSION

The utilization of immunotherapy is progressively transitioning from a second-line approach for advanced or metastatic cases to a perioperative strategy for resectable locally advanced ESCC. Despite the current results lacking comprehensiveness and robustness, substantial advancements in perioperative immunotherapy for ESCC are evident. With the assurance derived from existing outcomes, numerous EC centers are now engaged in conducting multicenter, multi-arm RCTs. These RCTs hold the promise of providing further insights into the value of perioperative immunotherapy. It is plausible that in the near future, perioperative immunotherapy will emerge as a pivotal component of comprehensive treatment for resectable locally advanced ESCC. However, the determination of the optimal drug or the most effective combination of therapies, as well as the potential role of AI as an assistant, will require further observation and investigation.

FOOTNOTES

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