Advances in the treatment of unresectable locally advanced esophageal squamous carcinoma (Review)

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Abstract. Treatment options for unresectable locally advanced esophageal squamous cell carcinoma (ESCC) are limited. Currently, radical concurrent chemoradiotherapy is recommended as the standard treatment at home and abroad, but its local control rate and overall survival are not satisfactory. Previously, the expected therapeutic effect was not achieved by optimizing radiotherapy and chemotherapy regimens. Significant progress has been made in the efficacy of immune checkpoint inhibitors (ICIs) in treating patients with advanced and resectable locally advanced ESCC, and clinical trials of ICIs for unresectable locally advanced ESCC are underway. Based on the existing literature, the present review discusses the current status and prospects of treating unresectable locally advanced ESCC.

Contents

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1. Introduction

In China, esophageal cancer is a primary thoracic malignant tumor with high morbidity and mortality. Histologically, it is divided into esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). According to statistics, the site of esophageal cancer is usually in the middle and upper part of the esophagus, and >90% of patients have the pathologic type of squamous carcinoma (1). The incidence of EAC has been rising rapidly in some regions, particularly in Western countries, partly due to lifestyle factors such as obesity, gastroesophageal reflux disease and Barrett's esophagus. Pathologically, it is a multidimensional process in which normal squamous epithelium transforms into basal cell hyperplasia and then undergoes a series of evolutions from low-grade intraepithelial neoplasia to high-grade intraepithelial neoplasia to invasive carcinoma. Genome-wide association studies in Chinese, European and Japanese patients have shown that multiple susceptibility loci can contribute to the development of ESCC. Some of these loci have been associated with alcohol consumption, including genes encoding alcohol dehydrogenase family proteins; Barrett's esophagus, a precursor of EAC, arises at the gastroesophageal junction as an adaptive response to prolonged exposure to noxious acidic gastroduodenal reflux products enriched with bile salts. Recent evidence from chromatin and single-cell transcriptome analyses suggests that c-MYC- and HNF4A-driven transcriptional programs lead to the development of Barrett's esophagus in cells within the gastric cardia, underscoring that intestinal metaplasia is a specific precursor of adenocarcinoma (2).

Early ESCC is clinically latent; >50% of patients cannot be directly resected at diagnosis (3). Although radical concurrent radiotherapy (CRT) is currently the best treatment option, 40% of patients remain insensitive to treatment, with a local recurrence rate of up to 50% and a 5-year survival rate of less than 26% (4,5). More regrettably, the SCOPE1 study added cetuximab-targeted therapy to concurrent chemoradiotherapy (CCRT) and showed worse overall survival (OS) and increased toxicity in the targeted therapy group (6). In conclusion, the treatment of esophageal cancer still faces serious challenges. Immunotherapy has become an important part of antitumor therapy, especially the application of programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1)

immune checkpoint inhibitors (ICIs), which can effectively improve the prognosis of numerous malignant tumors (7). Fortunately, the clinical finding that ESCC also exhibits PD-L1 expression and high tumor mutation load provides a theoretical basis for immunotherapy. Genomic analyses have shown that ESCC is similar to head and neck squamous cell carcinoma, whereas EAC has a higher molecular similarity to gastric adenocarcinoma (especially the CIN subtype). The success of immunotherapy depends on a deep understanding of the tumor immune microenvironment (TIME). In ESCC, TIME is characterized by inflammation and immunosuppression. In EAC, immunosuppression is more severe compared with ESCC. This immunosuppression leads to decreased efficacy of immunotherapies such as checkpoint inhibitors against EAC (8). Currently, several studies, including KEYNOTE-181, ESCORT-1st, KEYNOTE-590 and CheckMate648, have demonstrated that PD-1/PD-L1 inhibitors significantly prolonged the survival of patients with advanced esophageal cancer and transitioned them from second- to first-line therapy. In addition, subgroup analyses have shown that immunotherapy is more effective in treating patients with ESCC than patients with EAC. In this context, it is important to integrate current treatment modalities and explore therapeutic strategies that may improve patient survival and prognosis.

2. Current status of treatment of unresectable ESCC

Differences in radiation therapy (RT) dose in CRT. In the RTOG85-01 study, high-dose (HD) radical chemoradiotherapy (dCRT) improved the 5-year OS of unresectable locally advanced esophageal cancer from 0-26%. However, most patients with ESCC had a local recurrence rate of >50%, with a recurrence rate of up to 90% within the RT target area (gross tumor volume). The subsequent INT0123 study suggested that in the 2D era, most patients could not tolerate the radiotoxicity associated with radiation dose escalation, leading to treatment interruption (9,10). However, ESCC exhibits genomic features more reminiscent of the efficacy of other SCC tumors, such as the local failure rate of HD CCRT in locally advanced squamous carcinoma of the head and neck, which is ~10-20% (11) and locally advanced non-small cell lung cancer, which is ~30% (12-14). Moreover, ESCC has a higher local recurrence rate than EAC. With the increasing understanding of the biology of esophageal cancer in clinical practice and the continuous improvement of RT techniques, the issue of dose escalation needs to be revisited (15,16) (Table I). Ren *et al* (17) retrospectively analyzed 380 patients with ESCC. They used a propensity score-matched cohort to compare the efficacy of HD and standard-dose (SD) CRT in the treatment of ESCC. The results revealed that 60 Gy of HD dCRT resulted in more favorable local control and survival outcomes for patients with ESCC than 50.4 to 54 Gy of SD dCRT. However, patients had significantly more grade 2-3 acute esophagitis toxicity (17). Chang *et al* (18) suggested that under modern RT techniques such as intensity modulated RT (IMRT), HD dCRT could provide patients with advanced thoracic ESCC with more favorable survival benefit, and multivariate Cox regression analysis showed that AJCC stage (≥IIIA), alcohol consumption, and smoking were significant adverse independent predictors. A meta-analysis by Song *et al* (19) demonstrated that ≥60 Gy dCRT improved the clinical outcome of patients, especially the prognosis of patients with ESCC, compared with the standard group. However, previous retrospective studies showed some differences in tumor load, tumor stage, tumor cell sensitivity to RT, RT technique and chemotherapy regimen, which reduced the value of the conclusions. Therefore, the efficacy and safety of dCRT need to be validated in prospective randomized controlled trials (RCT).

A recent multicenter phase III RCT (ARTDECO) in the Netherlands enrolled 260 patients with locally advanced esophageal cancer (61% of whom were squamous). The results showed that there was no significant difference in 3-year OS and localized progression-free survival (LRPFS) between the two groups (HD group vs. SD group: 39 vs. 42%, P=0.22; 59 vs. 52%, P=0.08) (20). Xu *et al* (21) included 331 patients with stage IIA-IVA ESCC. The results demonstrated that the 3-year LRPFS rate, PFS and OS efficacy were similar between the 60 and 50 Gy groups. The incidence of toxicity was similar in both groups, but the incidence of severe pneumonia was higher in the HD group (7.4 vs. 2.4%) (21). Zhang *et al* (22) randomly assigned 588 patients with locally advanced squamous carcinoma in a ratio of 1:1:1:1 to the SD (50.4 Gy) + involved-field irradiation (IFI) group, SD + elective nodal irradiation (ENI) group, HD (59.4 Gy) + IFI group, and HD + ENI group. The results showed that the efficacy of IFI in dCRT for ESCC was similar to ENI's. HD irradiation improved PFS but did not significantly improve OS. Dose boosting based on IFI (HD + IFI) showed improved efficacy compared with the currently recommended dose boosting (SD + ENI), which deserves further validation (22). You *et al* (23) recruited 167 patients in 9 centers in China. The results showed that IMRT-based dCRT (radiation dose of 59.4 Gy) did not improve survival in patients with inoperable ESCC of the thoracic segment (23). Based on the aforementioned findings, a large proportion of patients with stage III ESCC with high heterogeneity were included, and 50.4 Gy did not increase the local recurrence rate or decrease the survival rate. However, in clinical practice, it remains necessary to screen patients who benefit most from dCRT based on the clinical response of their tumors during treatment or biomarkers of dCRT-sensitive tumors to provide more precise and effective treatment options.

Selection of RT target areas in dCRT. ESCC has a criss-crossing lymphatic system in the esophageal wall, and middle and advanced esophageal cancer is prone to lymph node metastasis, which is often manifested as 'jumping' metastasis. Nowadays, with the wide application of advanced RT technology, the clinical target area of radical RT for esophageal cancer remains the focus of research. Selective lymph node drainage area prophylactic irradiation (ENI) and IFI are currently mainstream CTV outlining modes. However, the specific beneficiaries of these two irradiation ranges have not yet reached a consensus.

Previous studies have found that selecting a HD IFI mode of 60 Gy for locally advanced esophageal cancer has the potential to increase the radiation dose to the regional lymph nodes to 40 Gy, which can help to eliminate localized subclinical foci. Wang *et al* (24) retrospectively analyzed the 8-year survival outcomes of 131 patients with ESCC who were treated with IFI and ENI. The results showed that the median

Table I. Summary of clinical trials of synchronized radiotherapy regimens.

First author, year	Study design	Number of patients	Treatment	LR rate (%)	Median PFS (months)	Year PFS (%)	Median overall survival (months)	(Refs.)
Ren *et al*, 2018	RA	380	dCRT-RT (50.4 to 54 Gy) - FP/TP	dCRT	NR	NR	NR	(17)
Chang *et al*, 2017	RA	2,061	i) RT (50.4 Gy) ii) RT (66.6 Gy) -chemotherapy (unknown)	NR	NR	NR	NR	(18)
Song *et al*, 2019	SA	4,344	i) SD 50-54 Gy ii) HD 60 Gy - chemotherapy (unknown)	i) 68.1% (DCR) ii) 86.2% (DCR)	i) 12.0 ii) 13.5	NR	i) 1 7.75 ii) 20.5	(19)
Hulshof *et al*, 2021	RCT	260	i) SD 50.4 Gy ii) HD 61.6 Gy -chemotherapy Carboplatin and paclitaxel, d1, once weekly, 6 weeks	i) 53% (3-year LRPFS) ii) 59% (3-year LRPFS) (P>0.05)	NR	i) 33.1% (3-year) ii) 25.4% (3-year) (P>0.05)	NR	(20)
Xu *et al*, 2022	RCT	331	i) SD 50 Gy ii) HD 60 Gy - chemotherapy docetaxel followed by cisplatin, d1, 5 weeks	i) 48.4% (3-year LRPFS) ii) 49.5% (3 year LRPFS) (P>0.05)	i) 25.5 ii) 27.7 (P>0.05)	i) 46.1% (3-year) ii) 46.4% (3-year) (P>0.05)	i) 41.2 ii) 45.3 (P>0.05)	(21)
Zhang *et al*, 2022	RCT	588	i) SD 50.4 Gy (IFI/ENI) ii) HD 59.4 Gy (IFI/ENI)-Tegafur/gimeracil/oteracil (S-1) and cisplatin, 2 cycles	NR	i) 20.0 ii) 29.1 (P=0.023)	NR	i) 28.3/33.9 (IFI/ENI) ii) 41.0/33.63 (IFI/ENI) (P>0.05)	(22)
You *et al*, 2023	RCT	167	i) SD 50.4 Gy ii) HD 59.4 Gy - paclitaxel and carboplatin, 1 per week, 6 cycles; Consolidation chemotherapy, 2-3 cycles	i) 46.8% (3-year LRPFS) ii) 54% (3-year LRPFS) (P>0.05)	NR	i) 32.2% (3-year) ii) 36.7% (3-year) (P>0.05)	i) 26.0 ii) 28.1 (P>0.05)	(23)

PFS, progression-free survival; RCT, randomized controlled trial; dCRT, high-dose radical chemoradiotherapy; NR, not reached; LRPFS, localized PFS; SD, standard dose; HD, high dose; DCR, disease control rate.

OS, 1-year, 3-year, 5-year and 8-year OS rates in the IFI group were 32 months, 83.7, 48.5, 38.5 and 31.1%, respectively. By contrast, those in the ENI group were 45.2 months, 89.8, 52.5, 37.5 and 26.1%, respectively, based on preservation of organ functions. Based on the preservation of organ function, the two groups had similar survival outcomes, but the IFI group had lower local control and myelosuppressive toxicity (24). The meta-analysis results also showed that IFI did not increase the risk of initial uninvolved or isolated lymph node failure or decrease OS while reducing adverse radiological effects compared with ENI (25). A recent prospective RCT comparing simultaneous radiochemistry at different doses (50.4 vs. 59.4 Gy) and in different targets (ENI vs. IFI) was performed by Zhang *et al* (22) for the survival benefit of simultaneous RT. It was revealed that IFI slightly decreased OS in SD patients (HR=1.18) compared with ENI, while IFI showed improved OS in HD patients (HR=0.83), suggesting that for patients subjected to SD radiation, IFI may be insufficient, and ENI can provide additional benefit; for patients subjected to HD radiation, the IFI should be sufficient and the increased radiation dose from ENI would provide additional harm rather than benefit. Among the four treatment regimens, the HD + IFI combination had the best prognosis (median OS of 46.3 months and median PFS of 30.8 months) (22). Although HD RT can improve tumor control, this improvement does not translate into significant OS prolongation. Previous studies have shown that ENI or IFI has a similar impact on survival in patients with stage T3 + 4/III + IV advanced ESCC treated with or without chemotherapy. Regardless of whether RT is administered with ENI or IFI, regional LN failure is not the predominant mode of recurrence in patients with advanced esophageal cancer, and the presence of significantly involved lymph nodes rather than the presence of micro-metastatic lymph nodes negatively affects the survival of patients with esophageal cancer. Intensive RT, chemotherapy, or immunotherapy to increase the complete response (CR) rate and reduce distant metastases may be the key to improving survival in patients with EC (26,27).

Most studies have shown that IFI does not sacrifice local control rate and OS and has significantly lower toxicity than ENI. Radiobiology suggests that the degree of lymphocyte depletion during RT is closely related to the radiation dose and has an important impact on prognosis. IFI adequately ensures that the regional lymph nodes are protected from the effects of HD RT and contributes to the enhancement of the antitumor efficacy of the immune system (28). In clinical application, IFI is usually better tolerated than ENI in patients with cervical ESCC and unresectable elderly ESCC (29). However, long-term survival outcomes need to be verified in clinical trials.

Selection of chemotherapeutic agents in CCRT. According to the RT Oncology Group (RTOG) 8501, dCRT combined with cisplatin and fluorouracil is the standard treatment for patients with unresectable locally advanced esophageal cancer. However, the treatment toxicity and survival outcomes were not satisfactory, with 42% grade 3 acute toxicity, 25% grade 3 late toxicity, and only 26% 5-year OS (9). The JCOG0303 trial, which compared the efficacy of RT combined with low-dose cisplatin and 5-fluorouracil with that of HD cisplatin and 5-fluorouracil in unresectable esophageal cancer, showed no significant difference in terms of toxicity. However, low-dose chemotherapy may lead to a poorer prognosis for patients (30). In recent years, several studies have investigated the use of paclitaxel analogs in combination with chemotherapy in ESCC, aiming to improve efficacy and reduce toxicities. The CROSS study suggested that patients treated with neoadjuvant RT in combination with Taxotere and Carboplatin regimen chemotherapy followed by surgery had a 34% reduction in the risk of death during the follow-up period (risk ratio, 0.657), with the most significant hematologic toxic effects being leukopenia (6%) and neutropenia (2%) (31). Chen *et al* (32) conducted a randomized, multicenter, phase III clinical trial to compare the efficacy of paclitaxel plus fluorouracil with that of cisplatin plus fluorouracil in CRT for locally advanced ESCC. Patients in both groups received 61.2 Gy of HD RT. The results showed that the efficacy of the paclitaxel plus fluorouracil group was not superior to that of the cisplatin plus fluorouracil group. However, the adverse events (AEs) characteristics of the two therapies were different. The incidence of severe leukopenia, radiation dermatitis and radiation pneumonitis was higher in the paclitaxel plus fluorouracil regimen. In comparison, the incidence of anemia, thrombocytopenia, gastrointestinal toxicity and fatigue was lower (32). Ai *et al* (33) enrolled 321 patients from multiple centers in a randomized phase III clinical trial comparing the efficacy of three paclitaxel-based RT regimens in patients with locally advanced ESCC. The results showed that in terms of treatment completion rates, 81 patients (75.7%) in the fluorouracil group, 94 patients (87.9%) in the cisplatin group, and 85 patients (79.4%) in the carboplatin group completed concurrent chemoradiation according to the regimen. However, fluorouracil showed no OS advantage in RT compared with cisplatin or carboplatin regimens. In terms of toxicity, the incidence of acute grade 3 or 4 hematologic toxicity was higher in the cisplatin group. By contrast, grade 2 or higher esophagitis incidence was significantly higher in the fluorouracil and carboplatin groups than in the cisplatin group (33). Owens *et al* (34) suggested that weekly regimens based on carboplatin plus paclitaxel were well-tolerated in elderly patients receiving dCRT, with survival outcomes comparable to cisplatin and fluorouracil. In addition, carboplatin + paclitaxel can be used as an alternative chemotherapy regimen for patients with cardiovascular complications and cardiotoxicity who cannot tolerate cisplatin + fluorouracil chemotherapy. Yada *et al* (35) suggested that CDDP is unsuitable for patients with cardiac and/or renal insufficiency. FOLFOX-RT is well-tolerated and could be a therapeutic option for patients with CDDP intolerance (35).

Based on *in vitro* experiments and mouse model studies of xenografted human tumors, docetaxel and cisplatin combined with fluorouracil exhibited significant enhancement of antitumor activity. Therefore, several studies have delved into the efficacy of dCRT with the combination of these three chemotherapeutic agents in locally advanced ESCC. Satake *et al* (36) suggested that in patients with ESCC with T4 stage tumors and/or M1 LYM, induction chemotherapy with the three-agent combination prior to dCRT resulted in treatment-related esophageal wall perforation in only two patients during dCRT. In terms of survival, the regimen achieved a clinical CR rate of 39.4%, a significant improvement over the previous rate of 15-33%. However, the DCF-RT (docetaxel, cisplatin

and fluorouracil in combination with RT) regimen was also associated with a higher incidence of neutropenic fever (grade 3 or higher, 38.1%) and an increased number of late toxic reactions (36). Another study showed that the DCF-RT regimen had higher CR and OS rates compared with cisplatin and 5-fluorouracil RT. However, the toxicity problem of the three-agent combination of dCRT should not be ignored as well (37).

In conclusion, fluorouracil plus cisplatin and paclitaxel-based regimens remain the mainstream chemotherapy regimen due to the varying levels of clinical trial evidence for different chemotherapy regimens. However, different chemotherapy regimens have different toxicities. The appropriate chemotherapy regimen can be selected in clinical practice according to the patient's condition.

3. Advances in immunotherapy for unresectable ESCC

Principles of action of immunotherapy and RT against tumors. The PD-1 pathway was an important inhibitory mechanism regulating T cell exhaustion. When PD-1 binds to tumor-expressed PD-L1, it transmits inhibitory signals to reduce the proliferation of $CD8^+$ T cells in lymph nodes while regulating the Bcl-2 gene, controlling the aggregation of antigen-specific T cells in lymph nodes, inhibiting T cell activation, and contributing to the achievement of immune escape by tumors (38). ICIs normalize the immune response by blocking PD-1/PD-L1 signaling. Data from phase III clinical trials in different cancers (for example, melanoma, non-small cell lung cancer and colorectal cancer) show that ICIs have satisfactory effects on inhibiting tumor growth, migration, invasion and other cancer characteristics (39). It was found that PD-L1 expression was observed in 80% of ESCC patients, suggesting that ESCC may benefit from it.

The combination of RT and immunotherapy has a synergistic effect, as demonstrated in mouse experiments and clinical studies, which confirmed that RT may convert cold tumors into hot tumors, remodel the tumor microenvironment, increase PD-L1 expression on tumor cells, and stimulate the immune system's re-recognition of tumor cells following the application of anti-PD-L1 agents, which can enhance cytotoxic T-cell-dependent mechanisms and influence antitumor efficacy (40). Meanwhile, RT-induced tumor cell death promotes the release of tumor-specific antigens for conversion into *in situ* vaccines, enhances antigen presentation, and leads to type I interferon responses, pro-inflammatory effects and T cell-mediated immunogenic elimination (41-43). In addition, there is increasing evidence that combining RT and immunotherapy enhances distant effects and increases local and systemic antitumor efficacy (43). In conclusion, mechanisms such as the creation of a new tumor microenvironment by RT and the upregulation of the expression of immune checkpoints provide a theoretical basis for combining immunological agents and RT.

Application of immunosuppressive agents combined with RT. Lian *et al* (44) conducted a propensity score-matched study that included 132 patients with unresectable locally advanced ESCC, 90% of whom were T3/4 or N+. The aim was to assess the efficacy and safety of CRT in patients with inoperable locally advanced ESCC after induction immunotherapy combined with chemotherapy (44). The results showed a significant increase in the overall objective remission rate in the induced immunotherapy (IC) group compared with the CCRT group (85.24 vs. 26.76%, P<0.001) and a significant improvement in PFS and OS in patients in the induced IC group [median PFS: not reached (NR) vs. 15.9 months; hazard ratio (HR)=0.412; 95% confidence interval (CI), 0.236-0.719], with P=0.0012; median OS: NR vs. 25.2 months (HR=0.526; 95% CI, 0.325-0.851; P=0.0077), with 2-year PFS rates of 67.6 and 42%, and 2-year OS rates of 74.6 and 52%, respectively. Multivariate analysis showed that lower tumor stage, concomitant use of two-agent synchronous chemotherapy, and CCRT-induced immunotherapy combined with chemotherapy were associated with an improved prognosis. In terms of toxicity, the aforementioned study reported that the utilization of a long-acting recombinant human granulocyte colony-stimulating factor and novel antiemetic-induced patients in the IC group exhibit a lower incidence of AEs, such as leukopenia, neutropenia, nausea and vomiting. Another study proposed that Camrelizumab is a well-tolerated potential treatment option for patients with ESCC who have received radical synchronized CRT (45).

Zhang *et al* (46) treated 20 patients with locally advanced ESCC with Carolizumab combined with dCRT (docetaxel + cisplatin + radiation dose of 60 Gy). The results showed a local failure rate of 15.0. Regarding survival, immunization combined with CCRT was slightly superior, with PFS rates of 80 and 65% at 1 and 2 years and OS rates of 85.0 and 69.6%, respectively. In terms of toxicity, combination therapy does not additionally increase dCRT-related toxicity. The most common most common immune-related AEs were grade 1 and grade 2 cutaneous capillary hemangiomas [17 patients (89%)]. Notably, 13 patients in the aforementioned study developed localized objective reactions at radiation doses up to 40 Gy. Reducing the radiation dose may be an important direction for future research to reduce the toxicity of esophageal and pulmonary RT. Meanwhile, high levels of IL-27 and IL-15 in peripheral blood were associated with improved survival, suggesting that the findings in peripheral blood indicate an important role of systemic immune response in antitumor therapy.

Park *et al* (47) reported the efficacy of durvalumab and tremelimumab in combination with CCRT for unresectable locally advanced ESCC. The treatment consisted of three main phases: first CCRT (radiation dose of 60 Gy and above) plus immunotherapy, then two cycles of consolidation therapy with durvalumab in combination with tremelimumab, and finally, maintenance therapy with durvalumab alone (47). The results demonstrated a median PFS and OS of 57.5% vs. 44.6% and 75% vs. 59.2%, respectively, at 2 years compared with the historical treatment group. In the subgroup analysis, patients with PD-L1-positive tumors had significantly longer PFS (HR, 0.2; 95% CI, 0.07-0.54; P<001) and OS (HR, 0.16; 95% CI, 0.05-0.56; P=001). This suggests that PD-L1 expression may have predictive value in ESCC and is associated with a favorable prognosis, but further studies are needed to confirm this. In terms of toxicity, the main non-immune-related AE in the aforementioned study was esophagitis, with an incidence of 80%, which is of concern. In addition, the study reported a local failure rate of 17.5% in the IC group, suggesting that

combination immunotherapy and HD RT may have additional benefits in affecting local control.

A phase II single-arm study conducted by Zhu *et al* (48) in China included 42 patients with unresectable ESCC, 39 of whom were staged as stage III or IVA and adopted sequential immune maintenance therapy after concurrent trenbolizumab treatment with radical CCRT (48,49). The results suggested that a CR rate was achieved in 62% of patients (95% CI, 46-76), which was higher than previously reported rates of 31-56% (20,33,50). 3-year OS and PFS rates were 44.8% (95% CI, 31.9-62.8) and 35.7% (95% CI, 23.8-53.6), which were higher than the 3-year OS and PFS rates in patients previously treated with radical CCRT involving esophageal cancer. This exceeds the rates reported in previous studies involving radical CRT for esophageal cancer, such as the RTOG 8501 (30%), PRODIGE5/ACCORD17 (27%), ARTDECO (39%), RTOG 9405 (40% at 2 years), RTOG 0436 (34%) and JCOG 0303 (26%) trials. Provided compelling evidence that the clinical benefit of teraplizumab in combination with CRT in terms of short-term response is maintained over long-term follow-up. The most common adverse reactions were hypothyroidism (31%), rash (29%) and hyperlipidemia (24%), with only one patient (2%) experiencing a grade 3 adverse reaction and no life-threatening adverse reactions. The combination of PD-1 inhibitor resistance and tumor immunosuppressive microenvironment resulted in accelerated failure of initial therapy in a small proportion of patients, necessitating intensive follow-up within the first 2 years.

In conclusion, immune-combination CCRT provides potent antitumor activity with acceptable toxicity and is expected to improve the prognosis of unresectable locally advanced ESCC. In addition, CCRT with radiation doses ≥60 Gy in several of the aforementioned studies resulted in significantly lower rates of local failure but significantly increased esophageal toxicity, leading to uncertainty about the optimal dose of immunotherapy in combination with RT. Notably, high or low PD-L1 expression in patients with ESCC did not result in additional survival benefits. Therefore, continued exploration of validated biomarkers in clinical practice could lead to improved screening of patients who benefit from immunotherapy.

4. Future prospects and conclusion

In recent years, advances in research have led to long-term survival and cure of some patients with unresectable locally advanced ESCC. However, the optimal treatment regimen and the corresponding beneficiary population cannot yet be matched, and RT methods and antitumor drugs will play a crucial role. Gao *et al* (51) suggested that 50 Gy combined with simultaneous chemotherapy may be sufficient to eliminate tumor cells in patients with RT-sensitive ESCC. However, for RT-resistant tumor cells, especially for esophageal cancer patients with ill-defined tumor regression during RT, without ulcer perforation or T4, the use of simultaneous dose-IMRT (SIB-IMRT) in the tumor region is an important research direction, which is expected to control the local recurrence rate to ~35% (51,52). This idea was validated in the ARTDECO study, where applying the SIB-IMRT technique achieved a favorable survival benefit without adding additional toxicities. In terms of RT techniques, Eze *et al* (53) reported a retrospective study of proton beam therapy (PBT) in the multimodal treatment of esophageal cancer, which suggested that PBT was associated with favorable OS, PFS and LRPFS compared with IMRT. Another study also showed that ESCC-specific and all-cause mortality were lower in patients treated with PBT compared with those treated with IMRT, with adjusted HR of 0.62 (95% CI, 0.58-0.7) and 0.72 (95% CI, 0.66-0.8), respectively. Side effects include pneumonia, fatigue and adverse cardiovascular events (54).

Numerous scholars have proposed that RT is crucial in releasing tumor antigens and modulating immune pathways by enhancing tumor antigen presentation, activating tumor-specific cytotoxic T cells, and improving tumor response to immunotherapy. In the era of immunotherapy, the possibility of narrowing the RT target area, reducing the RT dose, and selecting an appropriate combination of immunotherapy and simultaneous RT remain directions for future exploration. According to the current study, the combination of immunotherapy and dCRT is more suitable for patients with unresectable locally advanced ESCC with high tumor load and a high regional lymph node metastasis rate. With the development of imaging, 18F fluorodeoxyglucose PET is more accurate for the staging of esophageal cancer patients, which not only improves the accuracy of RT target area delineation, avoids the omission of tiny foci and reduces the rate of local recurrence, but also avoids additional irradiation of normal tissues, significantly reduces the toxic side-effects of the combined treatment, and improves the quality of life of patients (55). In addition, Wang *et al* (56) suggested that among PET/CT metabolic parameters (SUVmax, SUVean, SUVpeak, MTV and TLG), high baseline SUVmax and TLG may predict poor treatment response and lower survival in patients with ESCC receiving immunotherapy combined with CRT. In addition, high PET/CT metabolic parameters, especially TLG, are associated with immunosuppressive TME and deserve further exploration.

In conclusion, in clinical practice, as the understanding of the biology and antitumor immune properties of ESCC continues to deepen, the optimal combination of RT, chemotherapy and immunotherapy needs to be repeatedly weighed against efficacy and safety. Currently, five large-scale Phase III clinical trials, KUNLUN, RATIONAL-311, ESCORT-CRT, KEYNOTE-975 and SKYSCRAPER-07, as well as two Phase II studies: the trial related to tislelizumab ClinicalTrials.gov: NCT06061146 and the TENERGY study related to atezolizumab are actively underway to better evaluate the efficacy of anti-PD-1/L1 antibodies in combination with CCRT in the treatment of patients with unresectable locally advanced ESCC. In addition, exploring powerful biomarkers that predict survival to screen for optimal beneficiary population strategies is another area of research focus. It is expected that the addition of immunotherapies in the future will provide more precise treatment for patients.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LW, ZX, MS, HH and ZL performed literature review, and wrote reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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