Current and future perspectives in unresectable locally advanced esophageal squamous cell cancer (Review)

WEIJIA ZHANG[1], MIN ZHU[2], YING XIANG[2], YUJIAO SUN[2], SHUANG LI[1], JUN CAI[1] and HAI ZENG[1]

[1]Department of Oncology, First Affiliated Hospital of Yangtze University; [2]Department of Clinical Medicine, Medical School of Yangtze University, Jingzhou, Hubei 434000, P.R. China

Received January 11, 2024; Accepted February 28, 2024

DOI: 10.3892/or.2024.8724

Abstract. Definitive concurrent chemoradiotherapy has been the main standard treatment method for unresectable locally advanced esophageal squamous cell cancer (ESCC) since 1999. However, several disadvantages continue to be associated with this type of treatment, including a high local failure rate (reaching ~50% within 3 years) and a median overall survival (OS) time of 16.9 months. In addition, the 5-year overall survival rate of patients remains relatively low, at only ~21% for patients with ESCC with TNM stage T1-3N0-1M0. Burgeoning clinical trials and continually updating treatment modalities are currently in the process of being developed for the treatment of unresectable locally advanced ESCC. Compared with definitive concurrent chemoradiotherapy alone, clinical trials that have examined the efficacy of induction therapy, consolidation therapy, immunotherapy and targeted therapy have observed a prolonged median progression-free survival and OS. Salvage surgery can also bring benefits to some patients. Therefore, the present review aimed to provide a comprehensive overview on the latest progress that is being made in the development of treatment strategies for unresectable locally advanced ESCC, taking into account the several new challenges that need to be overcome.

Contents

Correspondence to: Professor Hai Zeng, Department of Oncology, First Affiliated Hospital of Yangtze University, 40 Jinlong Road, Jingzhou, Hubei 434000, P.R. China
E-mail: zenghai2022@139.com

Key words: esophageal cancer, concurrent chemoradiotherapy, induction therapy, consolidation therapy, immunotherapy, target therapy

1. Introduction

In 2020, there were ~604,000 cases of patients diagnosed with esophageal cancer (EC), with >544,000 cases of mortality associated with this disease reported worldwide (1). In China, the incidence rate of EC ranked sixth and the mortality rate ranked fifth among all types of cancer, with 193,900 related deaths from EC registered in 2016 (2). In particular, esophageal squamous cell cancer (ESCC) is the dominant histological subtype of EC in Asia and Eastern Europe as of 2016 (3).

Due to the lack of specific symptoms and effective screening strategies during the early stages of ESCC, patients with ESCC are frequently diagnosed after the cancer has already reached locally advanced stages, typically at T3-4 and/or with unresectable regional lymph node metastasis (4,5). Although the pathological complete response rate of ESCC after receiving neoadjuvant chemoradiotherapy can reach as high as 49%, as shown in 2012 (6), >50% patients with locally advanced ESCC require definitive radiation therapy. In 2013, a randomized controlled trial (RCT) study found no significant difference in the 5-year survival rate between definitive concurrent chemoradiotherapy and surgical treatment for patients with middle and lower thoracic ESCC (7). By 2020, radiation therapy achieved a 5-year survival rate similar to that of surgical treatment, at ~50% for cervical ESCC, increasing the opportunity of preserving the esophagus (8). Based on the results of the Radiation Therapy Oncology Group (RTOG) 85-01 (9) trial, concurrent chemoradiotherapy has become the standard treatment modality for unresectable locally advanced ESCC since the year 1999. Over the course of the past two decades, novel therapeutic therapies and strategies have continuously and gradually been introduced. The present review therefore aimed to elaborate in detail on the progress that has been made with novel treatment methods for unresectable locally advanced ESCC.

2. Surgery

Esophagectomy is the main treatment strategy for ESCC. However, as described in a previous study by the authors (10), compared to surgery alone, neoadjuvant therapy combined with surgery improved the rate of complete (R0) resection and prolonged the median overall survival time of patients with locally advanced resectable ESCC. When ESCC invades the aorta, airway, or spine, it was traditionally considered to be unresectable (11); however, the question remained whether an esophagectomy could benefit such patients. A previous single center, retrospective study investigated the possibility of esophagectomy for patients with EC at clinical stage T4 that invaded the airways (12). Following 4-6 weeks of conversion therapy with chemoradiotherapy, subtotal esophagectomy and regional lymph node dissection was performed; a reasonable 2-year overall survival (OS) rate of 29% was reported (12). Another prospective phase II study demonstrated that 40% (19/48) of patients with EC at clinical stage T4 or supraclavicular lymph node metastasis achieved R0 resection following conversion therapy with chemoradiotherapy, and their 2-year survival rate reached a notable 80% (13). However, it should be noted that, in that study (13), none of the surgeries involved airway or aortic resection, which suggests that only patients with successful conversion therapy may benefit from surgical treatment (11). For patients undergoing salvage esophagectomy, which is defined as esophagectomy following the failure of definitive chemoradiotherapy, the mortality rate within 90 days after salvage esophagectomy can reach 17.1%, and for patients who do not relapse after definitive chemoradiotherapy, the mortality rate within 90 days after surgery can reach 9.8% (14). Therefore, although salvage surgery may alleviate certain symptoms caused by tumor recurrence, the relatively high post-operative complications and mortality rate require this surgery to be performed in a highly selective population (15).

3. Concurrent chemotherapeutic regimens

The combination of cisplatin and 5-fluorouracil (5-FU) is the most commonly applied radical concurrent chemotherapeutic regimen for ESCC (9,16). Different concurrent chemotherapeutic regimens can result in different outcomes due to different adverse events (17). Compared with cisplatin, oxaliplatin has the advantages of low nephrotoxicity with less necessity for hydration (18). According to the American Joint Commission on Cancer (AJCC) Cancer Staging Manual, 6th edition (19), in a previous study, 229 patients with stage I-IVA ESCC were randomly divided into either the oxaliplatin, folic acid and 5-FU (FOLFOX) group or the cisplatin and 5-FU (DF) group, with both groups receiving 50 Gy radiotherapy delivered in 25 fractions. The objective response rate (ORR) was found to be 66% for the FOLFOX group, compared with 65% for the DF group. The median progression-free survival (PFS) time in the FOLFOX and DF groups were 9.7 and 9.4 months, respectively (P=0.640). In addition, the median overall survival (OS) time for the FOLFOX and DF groups was 20.2 and 17.5 months, respectively (P=0.70). Among all categories of adverse events recorded, paresthesia (47 vs. 3%), sensory neuropathy (18 vs. 1%), elevated concentrations of aspartate aminotransferase (11 vs. 2%) and alanine aminotransferase (8 vs. 2%) were found to be more common in the FOLFOX group. By contrast, an increase in the serum creatinine concentration (3 vs. 12%), mucositis (27 vs. 32%), hair loss (2 vs. 9%) were observed more common in the DF group (18).

For patients with renal dysfunction and the elderly, carboplatin may be used instead as a replacement for cisplatin (20). As such, the efficacy of carboplatin in combination with paclitaxel and 5-FU has been previously investigated. In a previous study (21), patients with stage IIa-IVa ESCC according to the AJCC 6th edition (19), were randomly divided into the following treatment groups: i) Paclitaxel combined with 5-FU; ii) paclitaxel combined with cisplatin; and iii) paclitaxel combined with carboplatin. All three groups received the same radiotherapy regimen, intensity-modulated radiotherapy (IMRT) was used, with the radiation dose of the planned target volume (PTV) being 61.2 Gy/34 F. The 1-, 2- and 3-year OS rates in the paclitaxel combined with 5-FU group were found to be 79.4, 62.6 and 57.2%, respectively. By contrast, the 1-, 2- and 3-year OS rates for the paclitaxel combined with cisplatin group were 81.3, 66.7 and 60.1%, respectively, whilst and those for the paclitaxel combined with carboplatin group were 79.4, 60.5 and 56.5%, respectively. No advantages could be observed in terms of either local recurrence-free survival or distant metastasis-free survival rates after comparing the three groups. However, a higher incidence of different acute grade 3 or 4 hematological toxicities was noted in the cisplatin group, such as neutropenia (60.8% in the cisplatin group vs. 17.8% in the 5-FU group vs. 34.6% in the carboplatin group; P<0.001) and thrombocytopenia (13.1% in the cisplatin group vs. 3.7% in the 5-FU group vs. 4.7% in the carboplatin group; P=0.010) (21).

An exploration of the efficacy of concurrent chemotherapy at a higher treatment intensity with docetaxel, cisplatin and 5-FU (DCF) was also previously conducted (22). The initial radiation dose was set at 61.2 Gy/34 F; however, due to severe esophagitis observed during the treatment period, the radiation dose was later reduced to 50.4 Gy/28 F. The number of cycles of DCF administered was also decreased from four to three. The results revealed that the overall clinical complete response rate was 52.4%, specifically 33.3% in the 61.2 Gy group and 60.0% in the 50.4 Gy group. The median PFS of the entire group of patients was 11.1 months, with the median OS of 29.0 months, and the 1-year OS rate of 66.1%, whereas the 3-year OS rate was 43.9%. Furthermore, in this identical entire group of patients, adverse events of grades ≥3 included leukopenia (71.4%), neutropenia (57.2%), anemia (16.7%), febrile neutropenia (38.1%), anorexia (31.0%) and esophagitis (28.6%) with 26.2% of the patients also experiencing esophageal stenosis following radiotherapy and chemotherapy, However, all cases of stenosis were alleviated after dilation treatment (22). Compare with those yielded by dual medicine chemotherapy (21), the DCF concurrent chemotherapy resulted in similar 1- and 3-year survival rates, but with a higher probability of bone marrow suppression and esophagitis. Therefore, in patients with ESCC coupled with a poor nutritional status, caution needs to be exercised regarding the use of DCF as their concurrent chemotherapy method.

Since patient tolerance to intravenous chemotherapy typically decreases with age, it may be difficult for patients aged ≥70 years to receive concurrent dual-drug chemotherapy. S-1 is a form of oral chemotherapeutic strategy that is widely applied

in East Asia, where studies have previously shown that it can achieve good levels of efficacy and safety for the treatment of ESCC (17,23). Wang *et al* (24) conducted a RCT to compare the feasibility of radical radiotherapy with or without S1 in patients with ESCC that satisfied the following categories: i) an age ≥70 years; ii) patients with ESCC staging II-III or limited to clinical stage IV with metastatic lymph node metastasis in the supraclavicular or abdominal trunk area according to the AJCC 6th edition (19); and iii) patients with an Eastern Cooperative Tumor Group (ECOG) performance score of ≤1. Subjects at risk of malnutrition would receive nutritional intervention through a nasal feeding tube or gastrostomy. S-1 was orally administered during radiotherapy, with four cycles of consolidation after the end of the radiotherapy. The radiotherapy employed was either IMRT or volume-modulated arc therapy. The radiation dose of PTV was administered at 50.4 Gy, whilst the planning gross target volume (GTV) was defined as gross target volume + uniform 0.5 cm edge, and the radiotherapy was administered at a dose of 59.92 Gy [equivalent dose in 2 Gy fractions (EQD2)=60.62 Gy]. The 1-year (72.2 vs. 62.3%) and 3-year (46.2 vs. 33.9%) OS rates in the radiotherapy + S1 [definitive concurrent chemoradiotherapy (dCCRT)] group were found to be significantly higher compared with those in the radiotherapy-alone group. In addition, the dCCRT group did not confer any increases in the incidence of adverse events at levels ≥3 associated with those treatment (24). A different retrospective study compared the efficacy and adverse events rates between single-agent and dual-agent as concurrent chemotherapy regimen. Single-agent regimens included 5-FU, S1, capecitabine, cisplatin, carboplatin, oxaliplatin, paclitaxel or docetaxel. The results revealed that for patients with unresectable ESCC, dual-agent concurrent chemotherapy tended to improve the 5-year PFS and OS rates compared with those in the single-agent group. The incidence of grade 3-4 toxicity events in single-agent group was lower compared with that in the dual-agent regimen group. However, the efficacy differences among the different single agents alone were not investigated (25).

In conclusion, based on the currently available clinical trial results, the preferred concurrent chemotherapy regimen for ESCC is cisplatin combined with 5-FU (26). Results from prospective studies have suggested that there is no significant difference in either the ORR or the 3-year OS rate, comparing among the different dual-agent combination chemotherapy regimens, although differences in adverse events have been observed (18,21). Compared with dual-agent chemotherapy (21), the triple-agent regimen of DCF does not appear to improve the 1- and 3-year OS rates, although the incidence of grade ≥3 adverse events is significantly increased (22). For elderly patients with EC who are >70 years of age, the addition of S1 into concurrent chemotherapy appeared to achieve longer 3-year OS rates compared with radiotherapy alone, with no apparent association with any increases in treatment-associated grade ≥3 adverse events (24). The findings of selected clinical trials are summarized in Table I.

4. Radiation dose

The RTGO 94-05 trial (16) previously established dCCRT with a standard radiation dose of 50 Gy/25 F as the standard treatment method for inoperable locally advanced ESCC. However, the locoregional failure (LRF) rate was found to reach 47% when this radiation dose was used (26). The treatment experience of patients with cervical cancer has led to the proposal that delivering sufficient radiation doses to tumors can lead to significant reductions in the local recurrence rates (27). Therefore, multiple clinical studies on the efficacy of curative radiotherapy for ESCC have used radiation doses of ≥60 Gy (21,24). For the treatment of locally advanced ESCC, a retrospective study (28) compared the efficacy and safety of simultaneous integrated boost (SIB)-IMRT at an EQD2 of 60.36-67.66 Gy and standard dose (SD)-IMRT with a radiation dose of 60 Gy/30 F during concurrent radiotherapy. After performing propensity matching analysis, compared with SD-IMRT, SIB-IMRT was found to significantly prolong of the median PFS (18 vs. 13 months; P=0.003) and OS (22 vs. 16 months; P=0.021). The 5-year local recurrence rates of SIB-IMRT and SD-IMRT were found to be 36.2 and 50.7%, respectively. Radiation pneumonitis (≥3) occurred in 2.9% of the patients who received SIB-IMRT therapy, compared with 7.2% of the patients in the SD-IMRT group (28). In addition, a previous meta-analysis (29) containing 18 relevant studies also reported that patients receiving ≥60 Gy radiation had a significantly higher OS rates compared with those receiving <60 Gy, particularly in Asian countries. However, it should be noted that since retrospective studies typically have a large time span of initiation, there may be significant differences in the technical equipment used and in processing factors. Therefore, even if a propensity score matching (PSM) analysis has been performed, there factors can remain that can confound the observed results (28).

By contrast, prospective studies (16,30) did not support the conclusions that ≥60 Gy radiation dose can achieve a significantly higher OS rate compared with 50.4 Gy or 50 Gy. The RTOG 94-05 trial (16) compared differences in efficacy between the radiation dose of 50.4 Gy/28 F and a higher radiation dose of 64.8 Gy/36 F in ESCC. No significant differences were observed in the median OS (13 vs. 18 months), the 2-year OS rate (31 vs. 40%) or the LRF rate (56 vs. 52%) between the two groups. The incidence rates of acute adverse events of grade ≥3 in the 64.8 Gy/36 F and the 50.4 Gy/28 F groups were 76 and 71%, respectively (16). Supporting these findings, another pair of different phase III clinical trials (31,32) also demonstrated that increasing the radiation dosage to 61.6 Gy or 66 Gy did not result in any significant benefits with respect to local control or median OS compared to 50.4 Gy or 50 Gy.

With 2D radiation therapy, extreme caution must be taken, since this method also frequently damages normal tissues due to the wide irradiation range applied. At present, IMRT and volumetric modulation arc radiotherapy (VAMAT) are widely used. It has been previously reported that these two radiotherapy technologies are advantageous in terms of target coverage and normal tissue protection compared with traditional 2D radiotherapy technologies (33,34). A previous meta-analysis (35) included three phase III RCT studies in which modern radiotherapy techniques were used, such as 3-dimensional conformal radiotherapy, IMRT, image-guided radiation therapy and VAMAT. Specifically, the efficacy and adverse events as a result of high dose (HD: ≥59.4 Gy/1.8 Gy) and standard dose (SD: 50 Gy/2 Gy or 50.4 Gy/1.8 Gy)

Table I. Summary of clinical trials of concurrent chemotherapeutic regimens.

Authors, year of publication	Study design	No. of patients	Treatment	Results	(Refs.)
Cooper *et al*, 1999	RCT	196	i) dCCRT: dCRT + PF; ii) RT	Year OS: 26% in the dCCRT group, 0% in the RT alone group; tumor residue: 26% in the dCCRT group, 37% in the RT alone group; lung toxicity (≥grade 3): 0.9% in the dCCRT group, 0 in the RT alone group; hematologic toxicity (≥grade 3): 6.8% in the dCCRT group, 0 in the RT alone group; esophageal toxicity (≥grade 3): 21.4% in the dCCRT group, 18.5% in the RT alone group	(9)
Conroy *et al*, 2014	RCT	229	i) dCRT + FOLFOX; ii) dCRT + PF	Objective response rate: 66% in the FOLFOX group, 65% in the PF group; median PFS: 9.7 months in the FOLFOX group, 9.4 months in the PF group; median OS: 20.2 months in the FOLFOX group, 17.5 months in the PF group; paresthesia (grade 1-4): 47% in the FOLFOX group, 3% in the PF group; Alanine aminotransferase elevated (grade 1-4): 8% in the FOLFOX group, 2% in the PF group; renal insufficiency (grade 1-4): 3% in the FOLFOX group, 12% in the PF group; neutropenia (grade 3-4): 29% in the FOLFOX group, 29% in the PF group; esophagitis (grade 3-4): 7% in the FOLFOX group, 9% in the PF group	(18)
Ai *et al*, 2022	RCT	321	dCRT + (paclitaxel + 5-fluorouracil); ii) dCRT + (paclitaxel + cisplatin); iii) dCRT + (paclitaxel + carboplatin)	1-Year OS rate: 79.4% in the 5-fluorouracil group, 81.3% in the cisplatin group, 79.4% in the carboplatin group; 3-year OS rate: 57.2% in the 5-fluorouracil group, 60.1% in the cisplatin group, 56.5% in the carboplatin group; neutropenia (grade 3-4): 17.8% in the 5-fluorouracil group, 60.8% in the cisplatin group, 34.6% in the carboplatin group; esophagitis (grade 3-4): 10.3% in the 5-fluorouracil group, 0.9% in the cisplatin group, 4.7% in the carboplatin group	(21)
Higuchi *et al*, 2014	Single-arm	42	dCRT + DCF (docetaxel + cisplatin + 5-fluorouracil)	Clinical complete response rate: 52.4%; median PFS: 11.1 months; median OS: 29.0 months; neutropenia (≥grade 3): 57.2%; esophagitis (≥grade 3): 28.6%;	(22)
Wang *et al*, 2023	RCT	330	i) dCCRT: dCRT + S1; ii) dCRT alone	1-Year OS rate: 72.2% in the dCCRT group, 62.3% in the RT alone group; 3-year OS rate: 46.2% in the dCCRT group, 33.9% in the RT alone group; 1-year PFS rate: 60.8% in the dCCRT group, 49.3% in the RT alone group; 3-year PFS rate: 37.3% in the dCCRT group, 27.9% in the RT alone group; neutropenia (grade 3-4): 5.1% in the dCCRT group, 3.5% in the RT alone group; esophagitis (grade 3-4): 11.9% in the dCCRT group, 5.6% in the RT alone group	(24)

RCT, randomized controlled trial; RT, radiotherapy; dCRT, definitive concurrent radiotherapy; dCCRT, definitive concurrent chemoradiotherapy; PFS, progression-free survival; OS, overall survival; FOLFOX, oxaliplatin + folicacid + 5-fluorouracil; PF, cisplatin + 5-fluorouracil.

radiotherapy combined with concurrent chemotherapy for stage I-IVa ESCC (where stage IVa refers to the spread of supraclavicular lymph nodes) were compared. The results revealed that there were no significant differences in the 1-, 2- or 3-year OS rates between the HD and the SD groups, nor were there any significant differences in the local recurrence-free rates in 2 or 3 years. The incidence of grade ≥3 treatment-associated toxicity in the HD group was found to be significantly higher compared with that in the SD group [odds ratio (OR), 1.36; P=0.048]. However, no significant differences in treatment-associated mortality were observed between the two groups (OR, 1.38) (35).

In conclusion, the recommended dosage of radiotherapy for locally advanced non-surgical ESCC for patients undergoing radical concurrent chemoradiotherapy appears to be 50.4 Gy/28 F or 50 Gy/25 F, even with the use of modern radiotherapy techniques (35). At present, to the best of knowledge, no RCTs have suggested that higher radiation doses are associated with any additional survival or local control probability benefits (30). A possible reason for this is that, as a hollow organ, the esophagus is not protected by surrounding tissues, unlike other types of tumors. As the radiation dose increases, the organ is more prone to esophagitis and esophageal perforation, suggesting that the esophagus is one of the most critical organs for which the radiation dosage require strict regulation (31,36). The radiation-resistance of ESCC may provide another reason. For radiation-resistant individuals, even with a radiation dose of 60 Gy, the tumor cells cannot be killed (30). The combination of radiotherapy with other treatment methods may therefore provide the direction of future treatment efforts (37). Selected studies on this topic are summarized in Table II.

5. Radiation field

Due to the hollow structure of the esophagus and the thickening of the esophageal wall during contraction, it is difficult to accurately determine the boundary of GTV using one specific examination method. Each detection method has its own set of own advantages and disadvantages. Gao *et al* (38) previously compared the length of esophageal tumors detected by endoscopy, CT images and barium meal followed by X-ray film analysis with the corresponding length measured pathologically following surgery. The results revealed that, for middle and lower ESCC, an endoscopic examination and barium meal-X-ray were able to predict the pathological length of the lesion more accurately. The average lesion length according to the pathological analysis was found to be 3.82±1.87 cm, whereas the measurements according to endoscopic examination and barium meal-X-ray examination were 3.88±1.93 cm and 3.78±1.77 cm, respectively. However, the length of the lesion was significantly overestimated by the CT images (4.48±2.48 vs. 3.82±1.87 cm; P<0.05). However, it should be noted that for early-stage ESCC, when there are no significant changes in the shape of the esophageal mucosa, it is difficult to diagnose esophageal lesions using barium meal followed by X-ray. In locally advanced ESCC, severe esophageal stenosis renders it difficult for an endoscope to pass through the esophagus to accurately determine the length of the lesion (39). In addition, the observer consistency index of fluorodeoxyglucose (FDG)-PET-CT was previously found to be 72.7%, compared with 69.1% when using CT alone (40). Both inflamed and tumor tissues are associated with a high glucose uptake, making it difficult for FDG-PET-CT imaging to distinguish between the two (41). However, [18F]-fluoro-3'-deoxy-3'-L-fluorothymidine (18F-FLT) can be used as a marker of cell proliferation, which can facilitate the delineation between tumors and inflamed tissues (42). Compared with FDG-PET-CT, the implementation of an FLT-PET-CT-based radiotherapy plan may significantly reduce the radiation dose erroneously delivered to the heart and lungs, courtesy of the advantage afforded by the more precise identification of tumors (43). The position of the esophagus is influenced both by breathing and heartbeat, whilst the position of the middle and lower esophagus is also affected by gastric peristalsis (38). The use of four-dimensional CT technology has been demonstrated to reduce the incidence of errors caused by the aforementioned peristaltic movements (44). MRI is a non-invasive and non-radiative technique that can provide accurate soft tissue contrast and is also recommended for the diagnosis of ESCC (45). Li *et al* (46) previously reported that the length of the ESCC tumor determined using endoscopy was similar to that measured using FDG-PET and MRI scans. In particular, no significant differences were noted in terms of the longitudinal length between GTV delineated on FDG-PET with lesions of uptake value ≥2.5 and GTV delineated on MRI-diffusion weighted images.

The range of tumor dispersal as determined under a microscope is also important for delineating the clinical target volume (CTV). Gao *et al* (38) previously collected surgical specimens of ESCC and analyzed the extent of tumor infiltration along the esophagus under a microscope. In ~94% cases of ESCC, the infiltration range of tumors under the microscope was observed to be 3 cm along the general tumor of the esophagus towards the proximal segment and 3 cm towards the distal segment.

Lymphatic tissues may also be connected extensively and vertically along the esophageal wall. Even in relatively early stages T1a or T1b, the probability of mediastinal and cervical lymph node metastasis can reach >50%, regardless of which segment of the esophagus the primary tumor is located in (47). This led to the theoretical basis and proposal of elective nodal irradiation (ENI). However, the results of subsequent clinical trials do not support this proposal, since a large irradiation field may lead to more severe adverse events. A previous study on the efficacy of large irradiation field (16) reported that 25-60% of patients will experience acute toxicity events of level ≥3. Due to the high incidence of adverse reactions caused by ENI irradiation, a radiation dose of 36 Gy has been recommended in the ENI region instead of a higher dose (48). After narrowing the irradiation range, whilst only irradiating the primary tumor and metastatic regional lymph nodes, only 8% experienced regional lymph node recurrence (49). Wang *et al* (50) retrospectively analyzed 131 patients with locally advanced cervical ESCC who underwent radical concurrent chemoradiotherapy. In the involved-field irradiation (IFI) group, the nodal CTV (CTV_{nd}) included the regional lymph node GTV (GTV_{nd}) and an edge of 0.3-0.5 cm with or without the involved lymph node regions, in which appropriate adjustments were made based on the anatomical barrier. In the ENI group, CTV_{nd} covered the high-risk lymph node area and

Table II. Summary of clinical trials of radiation dose in dCCRT.

Authors, year of publication	Study design	No. of patients	Treatment	Results	(Refs.)
Lan *et al*, 2022	Retrospective	138	i) SIB-IMRT: RT equivalent dose in 2-Gy fractions=60.36 Gy-67.66 Gy, combined with PF or DP; ii) SD-IMRT: 60 Gy/30 F, combined with PF or DP	5-Year local recurrence rates: 36.2% in the SIB-IMRT and 50.7% in SD-IMRT group; median PFS: 18 months in the SIB-IMRT and 13 months in the SD-IMRT group; median OS: 22 months in the SIB-IMRT group and 16 months in the SD-IMRT group; Radiation pneumonitis (grade ≥3): 2.9% in the SIB-IMRT group and 7.2% in the SD-IMRT group; radiation esophagitis (grade ≥3): 5.8% in the SD-IMRT group and 1.4% in the SIB-IMRT group	(28)
Minsky *et al*, 2002	Randomized controlled trial	218	i) High-dose group: RT 64.8 Gy/36F + PF; ii) Standard-dose group: RT 50.4 Gy/28F + PF;	Median OS: 13 months in the high-dose group and 18 months in the standard-dose group; 2-year OS: 31% in the high-dose group and 40% in the standard-dose group; local failure rates: 56% in the high-dose group and 52% in the standard-dose group; acute adverse events (grade ≥3): 76% in the high-dose group and 71% in the standard-dose group; delayed adverse events (grade ≥3): 46% in the high-dose group and 37% in the standard-dose group	(16)
Wang *et al*, 2023	Meta-analysis	796	i) High-dose group: RT ≥59.4 Gy/1.8 Gy, combine with PF, DP or FOLFOX4; ii) Standard-dose group: RT 50 Gy/2Gy or 50.4 Gy/1.8 Gy, combine with PF, DP or FOLFOX4	1-Year local regional PFS rate: RR=0.8 and P=0.042; 1-year OS rate: RR=0.98 and P=0.824; 3-year OS rate: RR=1.04 and P=0.502; 2-year local recurrence free rates: RR=0.95 and P=0.478; treatment-related toxicity (grade ≥3): OR=1.36 and P=0.048; treatment related mortality: OR=1.38 and P=0.323	(35)

RT, radiotherapy; SIB-IMRT, simultaneous integrated boost intensity-modulated radiotherapy; SD-IMRT, standard-dose intensity-modulated radiotherapy; PFS, progression free survival; OS, overall survival; RR, relative risk; OR, odds ratio; FOLFOX, oxaliplatin + leucovorin + fluorouracil; PF, cisplatin + 5-fluorouracil; DP, cisplatin + paclitaxel.

the lymph node area where metastasis occurred, including the lower neck, bilateral supraclavicular fossa and upper mediastinum (from the cricoid cartilage to the lower border of the azygos vein). Following PSM analysis, the median OS time was found to be 32.0 months, whereas the 1-, 3-, 5- and 8-year incidence rates were found to be 83.7, 48.5, 38.5 and 31.1% in the ENI group, respectively. By contrast, whereas in the IFI group, the median OS time were 45.2 months, whilst the 1-, 3-, 5- and 8-year incidence rates were 89.8, 52.5, 37.5 and 26.1%, respectively. The LRF rates were also similar between the ENI and IFI groups (36.7 vs. 30.6%). The incidence of leukopenia (59.2 vs. 38.8%) and neutropenia (30.6 vs. 14.3%) in the ENI group was higher compared with that in the IFI group (50). Similar conclusions were also drawn from another study conducted by Chen *et al* (51), who utilized neoadjuvant therapy. Follow-up results revealed that the ENI group had a higher probability of developing grade ≥2 radiation pneumonitis (30.3 vs. 17.6%; P=0.004) and pericardial effusion (26.7 vs. 11.8%; P=0.021). The probability of postoperative fistula occurring in the ENI group was also significantly higher (10.3 vs. 2.9%; P=0.026) (51). A prospective RCT study (52) also confirmed that the survival rates resulting from the use of ENI or IFI were similar, although the incidence of treatment-associated acute esophagitis and acute pneumonitis was higher in patients with thoracic ESCC when ENI was applied.

Compared with IFI, ENI should theoretically be able to kill cancerous lesions more potently, thereby increasing the probability of local control. However, the results of clinical trials do not support this prediction. ENI can lead to increases in heart, lung and bone marrow toxicity (51). In addition, the inability of ENI to enhance the efficacy of small cancerous lesions killing may be associated with the possibility that ENI can decrease lymphocyte levels. Uninvolved lymph nodes are crucial in mediating antitumor immune responses (53). A recent study (54) found that the estimated dose of radiation to immune cells was >2.178 Gy, which may lead to a decrease in cancer-specific survival and PFS rates.

The failure of radiotherapy for ESCC is mainly due to the survival of local residual cancer cells and recurrence, with a local recurrence rate of >40%, with the majority of local radiotherapy failures occurring within the GTV (55,56). It is therefore of utmost importance to combine multiple examination methods, such as endoscopy, esophagography, CT, MRI and PET to accurately deduce the GTV. Using a microscope to measure the infiltration length of tumor cells along the esophageal wall in surgical specimens of ESCC, the CTV should be defined as extending 3 cm above and below the esophageal GTV (38). Despite the wide range and high probability of lymph node metastasis in ESCC, clinical studies have confirmed that IFI and ENI irradiation can achieve similar local control rates, although the probability of pericardial effusion, pneumonia, esophagitis and bone marrow suppression is lower when IFI was applied (49).

6. Induction chemotherapy followed by dCCRT

Induction chemotherapy is able to eliminate micrometastasis, reduce tumor volume, improve internal hypoxia and provide favorable conditions for radical concurrent radiotherapy and chemotherapy (57). This treatment modality has achieved promising results in head and neck tumors (58). Therefore, for locally advanced unresectable ESCC, induction chemotherapy combined with dCCRT is theoretically a feasible approach.

Previous retrospective studies (59,60) have demonstrated that the combination of induction chemotherapy and dCCRT can confer survival benefits compared with dCCRT alone, with tolerable adverse reactions rates. Wang *et al* (60) retrospectively analyzed 267 patients with locally advanced thoracic ESCC who received radical concurrent chemoradiotherapy with or without induction chemotherapy, with two cycles of docetaxel and cisplatin induction chemotherapy arranged. The median follow-up time was 18 months. The results obtained revealed that the ORRs of the induction chemotherapy + dCCRT group and dCCRT alone group were 74.1 and 58.8%, respectively (P=0.035). In addition, the 3-year OS rates were 44.2 and 29.7%, respectively (P=0.028). The 3-year PFS rates were 34.8 and 15.4%, respectively (P=0.015). Subgroup analysis revealed that the 3-year OS (P=0.002), PFS (P=0.001) and local recurrence-free survival (P=0.002) rates of the effective for induction chemotherapy group were higher compared with those of the unresponsive to induction chemotherapy group, although the distant metastasis-free survival rate between the two groups was similar (P=0.116). However, the induction chemotherapy + dCCRT group had a significantly higher rate of grade ≥3 leukopenia compared with the dCCRT alone group (38.8 vs. 24.7%; P=0.048) (60).

By contrast, prospective studies (61,62) have not been able to confirm these conclusions. Minsky *et al* (61) previously studied 45 cases of clinical stage T1-4N0-1M0 ESCC. The induction chemotherapy regimen involved the use of 5-FU and cisplatin, once a month, for a total of three cycles. Subsequently, concurrent chemoradiotherapy was initiated, with an equivalent biological radiation dose of 64.8 Gy. In total, 91% patients completed the entire treatment plan. During the treatment process, 6 patients succumbed, of whom 5 (11%) succumbed due to treatment-associated complications. The median OS was 20 months (61), similar to that reported in the RTOG 85-01 trial (9). Another recent phase II RCT also failed to prove that induction chemotherapy was able to confer any survival benefits, with the exception of patients who responded effectively to the induction chemotherapy group (62). This previous RCT study (62) randomly divided 110 patients with locally advanced inoperable ESCC into the induction chemotherapy + dCCRT and dCCRT alone groups. The induction chemotherapy regimen was docetaxel (75 mg/m^2 on day 1) combined with cisplatin (75 mg/m^2 on day 1), once every 3 weeks, for a total of two cycles. In total, >92.7% patients in both groups received IMRT with the same equivalent biological radiation dose of 60 Gy. In the induction chemotherapy + dCCRT group, the proportion of patients completing concurrent chemotherapy for 2, 3, 4 and 5 weeks during radiotherapy was 100.0, 90.9, 83.6 and 65.5%, respectively. The corresponding proportions for the dCCRT alone group were 100.0, 98.2, 87.3 and 80.0%, respectively. The ORR for induction chemotherapy was 45.5%. The ORRs of the induction chemotherapy + dCCRT and the dCCRT alone groups were 74.5 and 61.8%, respectively. With a median follow-up of 24.8 months, the recurrence or death rates were found to be 70.9% in the induction chemotherapy + dCCRT group and 69.1% in the dCCRT alone group. The 3-year OS

(41.8 vs. 38.1%) and 3-year PFS (30.6 vs. 29.8%) rates in the induction chemotherapy + dCCRT and dCCRT groups were found to be similar. However, compared with patients who did not respond to induction chemotherapy, patients who responded to induction chemotherapy had significantly higher survival rates, with corresponding 3-year OS rates of 80.0 vs. 10.0% (P<0.001) (62). The results from that study (62) suggest that induction chemotherapy is able to serve as a means of screening for beneficiaries of such treatment.

There have also been studies that have attempted to increase the intensity of chemotherapy (63) or screen for responders to induction chemotherapy (64) to improve the efficacy of induction chemotherapy + dCCRT treatment. However, compared with dCCRT alone, the combination of induction chemotherapy with a triplet regimen (docetaxel, cisplatin and 5-FU) was not found to prolong the median OS of patient with locally advanced ESCC (63). Another retrospective study (64) divided patients with locally advanced ESCC into low-, medium- and high-risk groups according to the FDG-PET uptake value of esophageal tumors before treatment, tumor length and patient age. The results revealed that compared with those in the dCCRT alone group, the PFS and local recurrence-free survival rates in the induction chemotherapy + dCCRT group were significantly improved in high-risk patients [FDG-PET-maximum standardized uptake value (SUV_{max}) <9.7 and tumor length >5 cm, or FDG-PET-SUV_{max} ≥9.7 and age <67 years]. However, the addition of induction chemotherapy did not improve the prognosis for low- or medium-risk patients (64). Another previous meta-analysis (65) found that induction chemotherapy only prolonged the 1-year survival rate of paitents with non-surgical locally advanced ESCC, with no significant differences noted in the 2- and 3-year survival rates compared with those in the concurrent chemoradiotherapy alone group. This suggests that induction chemotherapy can only delay the time of tumor progression.

In conclusion, based on the cumulative results from currently available clinical studies, to the best of our knowledge, no evidence has yet been provided to support the prolongation of 2- or 3-year OS rates or PFS rates by induction chemotherapy for unresectable locally advanced ESCC. However, in patients who effectively respond to receive induction chemotherapy, the median OS and PFS may be extended (62). Despite the lack of high-level evidence, in clinical practice, >30% patients with locally advanced ESEC have received induction chemotherapy prior to dCCRT treatment (66). The results from the selected studies are summarized in Table III.

7. Consolidation chemotherapy following dCCRT

The main purpose of concurrent chemotherapy is to increase sensitivity to radiation. To ensure safety, low-intensity chemotherapy regimens are frequently used, such as reducing the dosage of chemotherapeutics (62) or extending the chemotherapy interval to 4 weeks (61). Insufficient chemotherapy intensity may lead to the incomplete eradication of subclinical metastasis disease, though consolidation chemotherapy may compensate for this deficiency.

Xia *et al* (67) retrospectively analyzed the efficacy of consolidation chemotherapy in patients with locally advanced ESCC that could not be surgically removed. The patients were divided into the induction chemotherapy + dCCRT group (n=52), dCCRT alone group (n=64) and dCCRT + consolidation chemotherapy group (n=70). All patients received IMRT as the radiotherapy modality, where the median equivalent biological radiation dose was 60 Gy. The results revealed that the 1-, 2- and 3-year OS rates in the dCCRT + consolidation chemotherapy group were higher compared with those in the dCCRT alone and induction chemotherapy + dCCRT groups (P=0.002). The 1-, 2- and 3-year OS rates of the induction chemotherapy + dCCRT group were 50.9, 37.5 and 25%, respectively. For the dCCRT alone group the 1-, 2- and 3-year OS rates were 72.2, 52.5 and 29.5%, respectively. For the dCCRT + consolidation chemotherapy group, the 1-, 2- and 3-year OS rates were 89.8, 59.0 and 42.5%, respectively (67). Another retrospective analysis (68) previously found that 3-4 cycles of consolidation chemotherapy achieved longer median OS compared with the group receiving only 1-2 cycles (55 vs. 21 months). In addition, a previous meta-analysis including 11 retrospective studies encompassing 2,008 cases of ESCC (69) also confirmed the dCCRT + consolidation chemotherapy could increase in the median OS [hazard ratio (HR)=0.72; P<0.001] and median PFS (HR=0.61; P=0.003) compared with that in the dCCRT alone group.

However, the results reported in the study by Chen *et al* (70) do not support the conclusion that consolidation chemotherapy can prolong the median OS (34.6 months in the dCCRT + consolidation chemotherapy group vs. 35.0 months in the dCCRT alone group), or even increase the 2-year local control probability. A previous prospective study (18) reported on the clinical course of 229 patients with stages I-IVA ESCC according to the AJCC 6th edition (19) who received either three cycles of consolidation chemotherapy comprising FOLFOX or two cycles of consolidation chemotherapy comprising DF after dCCRT. The median OS for the FOLFOX and DF groups were found to be 20.2 and 17.5 months, respectively. The median OS reported in this previous study (18) were similar to the results reported by other studies that did not apply consolidation chemotherapy (70). Although a number of additional prospective studies have adopted the regimen of consolidation chemotherapy (21,22,24), they did not compare the efficacy and adverse events between patients who received consolidation chemotherapy and those who did not.

There may be several reasons for the inconsistent conclusions drawn from studies on consolidation chemotherapy for ESCC. There is an issue with heterogeneity in retrospective studies (69). In addition, only those patients who do not respond effectively to dCCRT can benefit from consolidation chemotherapy. Zhao *et al* (71) previously reported that in patients for whom the efficacy of dCCRT was deemed poor (disease progression or stable disease), compared with those in the dCCRT alone group, the dCCRT + consolidation chemotherapy group exhibited significantly improved median OS (28 vs. 18.5 months; P=0.015) and median PFS (18.2 vs. 11.3 months; P=0.041). However, in patients who did respond (complete or partial remission) to dCCRT, the dCCRT + consolidation chemotherapy group did not exhibit improvements in the median OS (48.6 vs. 44.5 months; P=0.753) or median PFS (24.3 vs. 23.5 months; P=0.434) compared with dCCRT alone.

In conclusion, based on the currently available clinical research results, the retrospective studies do tend to support

Table III. Summary of clinical trials of induction chemotherapy followed by dCCRT.

Authors, year of publication	Study design	No. of patients	Treatment	Results	(Refs.)
Qiu *et al*, 2023	Retrospective	450	i) IC (cisplatin + 5-fuorouracil, or docetaxel/paclitaxel + cisplatin/nedaplatin/carboplatin/lobaplatin) + dCCRT group; ii) dCCRT alone group	Median OS: 38.5 months in the IC + dCCRT group and 28.8 months in dCCRT alone group; median progression-free survival time: 41.0 months in the IC + dCCRT group and 22.0 months in the dCCRT alone group; radiation esophagitis (grade ≥3): 2.5% in the IC + dCCRT group and 4.2% in the dCCRT alone group; Hematologic toxicity (grade ≥3): 75.2% in the IC + dCCRT group and 88.2% in the dCCRT alone group	(60)
Wang *et al*, 2019	Retrospective	267	i) IC (docetaxel + cisplatin) + dCCRT group; ii) dCCRT alone group	ORR: 74.1% in the IC + dCCRT group and 58.8% in the dCCRT alone group; 3-year OS rate: 44.2% in the IC + dCCRT group and 29.7% in the dCCRT alone group; leukopenia (grade ≥3): 38.8% in IC + dCCRT group and 24.7% in the dCCRT alone group	(60)
Minsky *et al*, 1996	Single-arm	45	IC (cisplatin + 5-fluorouracil) + dCCRT	Median OS: 20 months; total AE (grade ≥3) in induction chemotherapy: 61%; total AE (grade ≥3) in dCCRT: 72%	(61)
Liu *et al*, 2021	Randomized controlled trial	110	i) IC (docetaxel + cisplatin) + dCCRT group; i) dCCRT alone group	ORR: 74.5% in the IC + dCCRT group and 61.8% in the dCCRT alone group; 3-year OS rates: 41.8% in the IC + dCCRT group and 38.1% in the dCCRT alone group; 3-year OS rates: 80.0% in responders to IC and 10.0% in non-responders to IC, 38.1% in the dCCRT alone group; total AE (grade ≥3): 38.2% in the IC+dCCRT group and 34.5% in dCCRT alone group; esophagitis (grade ≥3): 16.3% in the IC + dCCRT group and 23.6% in the dCCRT alone group; Neutropenia (grade 3-4): 18.2% in the IC + dCCRT group and 7.3% in the dCCRT alone group	(62)
Wang *et al*, 2021	Meta-analysis	836	i) IC (platinum + fluorouracil, platinum + taxane, capecitabine, docetaxel plus cisplatin, fluoropyrimidine + platinum + taxane) + dCCRT group; ii) dCCRT alone group	1-Year OS rate: HR=0.446 and P<0.001; 3-year OS rate: HR= 1.065 and P=0.680	(65)

dCCRT, definitive concurrent chemoradiotherapy; IC, induction chemotherapy; AE, adverse events; ORR, objective response rate; OS, overall survival; HR, hazard ratio.

the notion of the survival benefits conferred by consolidation chemotherapy, although there is a lack of prospectiveclinical data to support it. Although several prospective studies have adopted consolidation chemotherapy (21,22), no comparisons have been made of the benefits conferred by consolidation chemotherapy addition. The results from selected articles are summarized in Table IV.

8. Immune checkpoint inhibitors combined with dCCRT

Induction with immune checkpoint inhibitors (ICIs) followed by dCCRT. Compared with chemotherapy alone, chemotherapy combined with ICIs has been demonstrated to achieve a higher ORR (72) and a prolonged median OS rate (73) in patients with metastatic ESCC. Therefore, this treatment has been proposed for unresectable locally advanced ESCC. However, to the best of our knowledge, results from only one clinical study are available at present.

A previous single-arm, phase II clinical trial (74) evaluated the efficacy and safety of induction chemotherapy plus camrelizumab followed by dCCRT in patients with unresectable locally advanced ESCC. The treatment regimen consisted of two cycles of induction therapy with nab-paclitaxel, carboplatin and camrelizumab. Subsequently, patients received dCCRT consisting of two cycles chemotherapy with 5-FU and cisplatin, with a radiation dose of 50-66 Gy delivered in 25-30 fractions. The confirmed ORR was 97.6%, whereas the 1-year PFS and OS rates were 74.2 and 87.6%, respectively. The most common grade ≥3 adverse treatment-associated complications were thrombocytopenia (23.9% of the cases), anemia (21.7%), leukopenia (17.4%), esophagitis (13.0%), an elevated level of aspartate aminotransferase (13.0%), mesopenia (10.9%) and an elevated level of alanine aminotransferase (8.7%). A total of one treatment-associated case of mortality was observed (74).

ICIs combined with dCCRT. It has been previously observed that the combination of radical radiotherapy and camrelizumab confers beneficial safety and efficacy profiles in patients with locally advanced ESCC who do not tolerate concurrent chemoradiotherapy (75,76). A phase Ib clinical trial (78) was conducted to investigate the efficacy of ICIs and concurrent chemoradiotherapy in unresectable locally advanced ESCC. A median follow-up time of 23.7 months, before which 20 patients with locally advanced ESCC were administered the programmed death-ligand 1 (PD-L1) inhibitor, camrelizumab, and the angiogenesis blocker, apatinib, which were combined with concurrent chemoradiotherapy (docetaxel plus cisplatin). This treatment resulted in OS and PFS rates ranging from 8.2-28.5 months and 4.0-28.5 months, respectively. The incidence rates of OS at 12 and 24 months were 85.0 and 69.6%, respectively. Radiation esophagitis (20% of the cases) and esophageal fistula (10% of cases) were the most common grade 3 treatment-associated adverse events (77). In another single-arm, phase II trial (78), toripalimab combined with dCCRT in 42 untreated and unresectable cases of stage II-IVA ESCC resulted in an 1-year OS rate of 78.4% and an 1-year PFS rate of 54.5%. However, a high incidence of adverse events was reported. Lymphopenia of grade ≥3 affected 86% patients, where 1 (2%) patient succumbed due to treatment-associated pneumonia (78). Dual immunotherapy with PD-L1 inhibitors and cytotoxic T-lymphocyte associated protein 4 inhibitors has also yielded beneficial therapeutic effects in other types of cancer (79,80). A small-sample prospective clinical study (81) previously enrolled 40 patients with stage T2-T3N0M0 or T1-T3N1-N3M0 ESCC according to the AJCC, 7th edition (82). The therapy consisted of two cycles of 5-FU, cisplatin, durvalumab (1,500 mg on day 1, per 3 weeks) and tremelimumab (75 mg on day 1, per 3 weeks, q3w), along with radiation therapy (60.2 Gy/28 F or 64.5 Gy/30 F) (81). After completing dCCRT, the patients received two additional cycles of consolidated durvalumab and tremelimumab treatment, followed by durvalumab monotherapy every 4 weeks for 2 years. The median follow-up time was 27.5 months. The median PFS and median OS rates were not achieved. The incidence of PFS and OS at 24 months was observed to be 57.5 and 75%, respectively. In the historical control group of this specific center (5-FU + cisplatin combined with concurrent radiotherapy), the median follow-up time was 26.1 months. The median PFS and OS times were 13.8 and 28.3 months, respectively. Compared with patients with PD-L1 combined positive score (CPS) <1, patients with PD-L1 CPS ≥1 had significantly longer PFS and median OS times. Among the adverse effects associated with immunotherapy, 1 patient developed grade ≥3 immune colitis, and 2 patients developed grade ≥3 immune mediated pneumonia. In addition, 1 patient experienced a grade 4 adverse event, namely an increase in lipases. No treatment-associated mortality was observed (81).

According to the results of the aforementioned small-sample prospective studies, the combination of ICIs and concurrent chemoradiotherapy may achieve superior efficacy compared with traditional radical concurrent chemoradiotherapy alone, with acceptable adverse events profiles. Phase III randomized trials, such as ESCORT-CRT (NCT04426955), KEYNOTE 975 (NCT04210115), RATIONALE 311 (NCT03957590) and KUNLUN (NCT04550260), are currently ongoing to investigate the survival benefits of ICIs combined with definitive concurrent chemoradiotherapy. It is anticipated that these results from such trials will clarify the role of immunotherapy in locally advanced ESCC (37).

ICI consolidation following dCCRT. In the CheckMate-577 trial (83), 1 year of administering adjuvant nivolumab after neoadjuvant concurrent chemoradiotherapy led to an improvement in the median disease-free survival time in patients with residual disease on pathology compared with a placebo group (22.4 vs. 11.0 months). The efficacy of treatment using immunotherapy consolidation following dCCRT was also investigated (83). A previous clinical study (84) enrolled 11 patients with unresectable locally advanced ESCC who underwent dCCRT, followed by consolidation therapy with camrelizumab. At 14-42 days after the end of dCCRT, camrelizumab (200 mg, day 1, q2w) was administered as consolidation treatment for 12 months. The disease control rate was found to reach 90%. The median PFS and OS were not reached at that point. In terms of safety, the incidence of adverse reactions was relatively low, with

Table IV. Summary of clinical trials of chemotherapy consolidation following dCCRT.

Authors, year of publication	Study design	No. of patients	Treatment	Results	(Refs.)
Xia *et al*, 2022	Retrospective	186	i) IC + dCCRT group; ii) dCCRT alone group; iii) dCCRT + CCT group;	1-Year OS rates: 50.9% in the IC + dCCRT group, 72.2% in the dCCRT alone group, 89.8% in the dCCRT + CCT group; 3-year OS rates: 25% in the IC + dCCRT group, 29.5% in the dCCRT alone group, 42.5% in the dCCRT + CCT group	(67)
Zhang *et al*, 2020	Retrospective	299	i) dCCRT alone group; ii) dCCRT + CCT group;	Year OS rates: 82.3% in the dCCRT + CCT group and 64.2% in the dCCRT alone group; 3-year OS rates: 46.9% in the dCCRT + CCT group and 33% in the dCCRT alone group; median OS:33 months in dCCRT + CCT group and 18 months in the dCCRT alone group; median OS: 21 months in 1-2 cycles of CCT group and 55 months in the 3-4 cycles of CCT group	(68)
Chen *et al*, 2017	Retrospective	524	i) dCCRT + CCT group; ii) dCCRT alone group;	Median PFS: 25.4 months in the dCCRT + CCT group and 23 months in the dCCRT alone group; median OS: 35.0 months in the dCCRT + CCT group and 34.6 months in the dCCRT alone group; 2-local recurrence rates: 45.8% in the dCCRT + CCT group and 49.2% in the dCCRT alone group	(70)
Conroy *et al*, 2014	Randomized controlled trial	229	i) dCCRT + CCT of FOLFOX; ii) dCCRT + CCT of PF	Median OS: 20.2 months in the dCCRT + CCT of FOLFOX group and 17.5 months in the dCCRT + CCT of PF group; 3-year OS rates: 19.9% in the dCCRT + CCT of FOLFOX group and 26.9% in dCCRT + CCT of PF group	(18)
Zhao *et al*, 2020	Retrospective	288	i) dCCRT + CCT group; ii) dCCRT alone group;	Median OS: Of patients who responded poorly to dCCRT, 28 months in the dCCRT + CCT group and 18.5 months in the dCCRT alone group; median OS: Of patients who responded well to dCCRT, 48.6 months in the dCCRT + CCT group and 44.5 months in the dCCRT alone group	(71)

IC, induction chemotherapy; dCCRT, definitive concurrent chemoradiotherapy; FOLFOX, oxaliplatin + leucovorin + fluorouracil; PF, cisplatin + 5-fluorouracil; OS, overall survival; CCT, consolidating chemotherapy; PFS, progression-free survival.

Table V. Summary of clinical trials of immunotherapy and dCCRT.

Authors, year of publication	Study design	No. of patients	Treatment	Results	(Refs.)
Peng *et al*, 2023	Single-arm	49	Camrelizumab + nab-paclitaxel + carboplatin + dCCRT	Objective response rate: 97.6%; 1-year PFS rate: 74.2%; 1-year OS rate: 87.6%; Esophagitis (grade ≥3): 13.0%; leukopenia (grade ≥3): 17.4%	(74)
Zhang *et al*, 2021	Single-arm	20	Camrelizumab + apatinib + dCCRT	Year OS rate: 85.0%; 2-year OS rate: 69.6%; total AE (grade ≥3): 45%; esophagitis (grade ≥3): 20%	(77)
Zhu *et al*, 2023	Single-arm	42	Toripalimab + dCCRT	1-Year OS rate: 78.4% ; 1-year PFS rate: 54.5%; lymphopenia (grade ≥3): 86%; succumbed due to treatment-related pneumonia: 2%	(78)
Park *et al*, 2022	Single-arm	40	Durvalumab + tremelimumab + dCCRT + durvalumab and tremelimumab consolidation + durvalumab maintenance for 2 years	1-Year OS rate: 75%; 2-year OS rate: 85.7% in PD-L1 CPS-positive and 45.5% in PD-L1 CPS-negative; esophagitis (grade 3-4): 10%; neutropenia (grade 3-4): 42.5%	(81)
Wang *et al*, 2022	Single-arm	11	dCCRT + consolidation with camrelizumab	Disease control rate: 90%; median PFS and median OS: not reached; treatment-related pneumonia (grade ≥3): 9.1%	(84)
Bando *et al*, 2022	Single-arm	40	dCCRT + consolidation with atezolizumab	cCR rate: 40.0%; cCR rate: 44.4% in PD-L1 <1% and 41.2% in PD-L1 ≥1%; median PFS: 3.2 months; 1-year PFS rate: 29.6%; median OS: 31.0 months	(85)

dCCRT, definitive concurrent chemoradiotherapy; AE, adverse event; OS, overall survival; PFS, progression-free survival; cCR: clinical complete response; PD-L1, programmed death-ligand 1; CPS, combined positive score.

the main adverse reactions being reactive skin capillary hyperplasia and pneumonia, both ranging from grades 1-2. However, there was one case of grade 3 treatment-associated pneumonia (84).

Bando *et al* (85) investigated the efficacy and safety of atezolizumab consolidation therapy for 1 year following dCCRT (radiation dose of 60 Gy) in patients with unresectable locally advanced ESCC. A total of 50 patients were enrolled, of whom 40 had primary non-surgical locally advanced ESCC (group A) and the other 10 had locally recurrent ESCC after surgery (group B). The clinical complete response rates of groups A and B were found to be 40.0 and 50.0%, respectively. The median PFS and 12-month PFS incidence rates in group A were 3.2 months and 29.6%, whereas the median OS and 12-month OS incidence rates were 31.0 months and 65.8%, respectively. Among 35 patients in which PD-L1 expression could be evaluated, the clinical complete response rates for patients with tumor proportion score of PD-L1 <1% and ≥1% were 44.4 and 41.2%, respectively. In particular, patients with higher populations of tumor-infiltrating $CD8^+$T cells and $PD\text{-}1^+CD8^+$T cells had a higher clinical complete response rate. No mortality-related events associated with the treatment were found (85). A summary of clinical trials of immunotherapy and dCCRT is presented in Table V.

9. Target therapy and dCCRT

Targeted therapy has been demonstrated to play a crucial role in the treatment of patients with advanced-stage ESCC (86). The treatment targets for squamous cell carcinoma are typically directed against epidermal growth factor receptor (EGFR) and angiogenesis. Cetuximab is a monoclonal antibody against EGFR that specifically targets EGFR to inhibit its activation, thereby hindering ESCC progression. A previous preclinical study demonstrated that cetuximab was able to enhance the radiosensitivity of ESCC cell lines (87). In addition, combining cetuximab with neoadjuvant chemoradiotherapy has been shown to lead to an improvement in the pathological complete response rate (88). However, this combination scheme has failed to prolong the median OS of patients with locally advanced ESCC. The SCOPE1 trial (89) investigated the feasibility of adding cetuximab to concurrent chemoradiotherapy in locally advanced clinical stage I-III ESCC according to AJCC 6th edition (19). The follow-up of 188 patients with ESCC who had already been enrolled revealed that the median OS time was shorter in the dCCRT plus cetuximab group (22.1 vs. 25.4 months; adjusted HR=1.53, P=0.035) (89).

Apatinib is a small-molecule tyrosine kinase inhibitor that is able to specifically bind to vascular endothelial growth factor-2 and human EGFR type 2. According to the study by Zhang *et al* (77), the combination of apatinib and camrelizumab combined with concurrent chemoradiotherapy led to a 24-month OS rate of 69.6% in locally advanced ESCC, although the treatment-associated grade ≥3 adverse events remain to be addressed (77). At present, studies on targeted therapy for ESCC are mainly focused on the second- and third-line treatment of advanced ESCC (86). However, it is expected that targeted therapy will serve a key role in the development of novel adjuvant and radical treatments for ESCC in the future.

10. Conclusions and future perspectives

In the present review, the latest advances in the treatment of unresectable locally advanced ESCC, including the selection of concurrent chemotherapy regimens, recommendations for radiation dose and target area and the value of combining dCCRT and induction chemotherapy or consolidation chemotherapy were all summarized and discussed. The combination of immune checkpoint inhibitors and dCCRT is a direction that warrants further exploration, although the timing ICI treatment initiation remains controversial. Further clinical studies are required to address this issue.

Targeted therapy for ESCC remains another research field that is garnering attention. Although the combination of chemoradiation and targeted therapy leads to an improved efficacy and lower drug resistance compared with monotherapy, the incidence of adverse events caused by combination therapy remains unacceptable at present. There are almost certain to be numerous intersections among signaling pathways that are regulated by the targeted therapy, which can easily lead to unforeseen complications. Therefore, when developing novel therapies for targeted medicine, it is necessary to consider adverse events as a primary parameter.

Acknowledgements

Not applicable.

Funding

The present study was supported by grants from the Development Fund Project of Yangtze University (grant no. WJ2019-22), the Hubei Provincial Health and Family Planning Commission Joint Fund Project (grant no. WJ2018H203) and the Jingzhou First People's Hospital Doctoral Research Initiation Fund Project (grant no. 2022DIF01).

Availability of data and materials

Not applicable.

Authors' contributions

HZ and WZ conceived and designed the study and wrote and revised the manuscript. MZ, YX and YS performed the initial literature search and prepared the manuscript. SL and JC reviewed and revised the manuscript. All authors have read and approved the final 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.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Maomao C, He L, Dianqin S, Siyi H, Xinxin Y, Fan Y, Shaoli Z, Changfa X, Lin L, Ji P and Wanqing C: Current cancer burden in China: Epidemiology, etiology, and prevention. Cancer Biol Med 19: 1121-1138, 2022.
3. Njei B, McCarty TR and Birk JW: Trends in esophageal cancer survival in United States adults from 1973 to 2009: A SEER database analysis. J Gastroenterol Hepatol 31: 1141-1146, 2016.
4. Sasaki Y and Kato K: Chemoradiotherapy for esophageal squamous cell cancer. Jpn J Clin Oncol 46: 805-810, 2016.
5. Huang FL and Yu SJ: Esophageal cancer: Risk factors, genetic association, and treatment. Asian J Surg 41: 210-215, 2018.
6. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, *et al*: Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 366: 2074-2084, 2012.
7. Teoh AY, Chiu PW, Yeung WK, Liu SY, Wong SK and Ng EK: Long-term survival outcomes after definitive chemoradiation versus surgery in patients with resectable squamous carcinoma of the esophagus: Results from a randomized controlled trial. Ann Oncol 24: 165-171, 2013.
8. Chen P, Zhao X, Zhou F, Song X, Hu S, Jin Y, Wang X, Han X, Fan Z, Wang R, *et al*: Characterization of 500 Chinese patients with cervical esophageal cancer by clinicopathological and treatment outcomes. Cancer Biol Med 17: 219-226, 2020.
9. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, Byhardt R, Russell AH, Beitler JJ, Spencer S, *et al*: Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation therapy oncology group. JAMA 281: 1623-1627, 1999.
10. Zeng H, Zhang F, Sun Y, Li S and Zhang W: Treatment options for neoadjuvant strategies of esophageal squamous cell carcinoma (review). Mol Clin Oncol 20: 4, 2023.
11. Ferri L: Clinical T4b esophageal cancer: Can we make an 'unresectable' tumour resectable? Ann Surg Oncol 27: 329-330, 2020.
12. Yamaguchi S, Morita M, Yamamoto M, Egashira A, Kawano H, Kinjo N, Tsujita E, Minami K, Ikebe M, Ikeda Y, *et al*: Long-term outcome of definitive chemoradiotherapy and induction chemoradiotherapy followed by surgery for T4 esophageal cancer with tracheobronchial invasion. Ann Surg Oncol 25: 3280-3287, 2018.
13. Yokota T, Kato K, Hamamoto Y, Tsubosa Y, Ogawa H, Ito Y, Hara H, Ura T, Kojima T, Chin K, *et al*: A 3-year overall survival update from a phase 2 study of chemoselection with DCF and subsequent conversion surgery for locally advanced unresectable esophageal cancer. Ann Surg Oncol 27: 460-467, 2020.
14. Mitchell KG, Nelson DB, Corsini EM, Vaporciyan AA, Antonoff MB, Mehran RJ, Rice DC, Roth JA, Sepesi B, Walsh GL, *et al*: Morbidity following salvage esophagectomy for squamous cell carcinoma: The MD Anderson experience. Dis Esophagus 33: doz067, 2020.
15. Miyata H, Sugimura K, Kanemura T, Takeoka T, Sugase T, Tanaka K, Makino T, Yamashita K, Yamasaki M, Motoori M, *et al*: Salvage surgery for recurrent disease after definitive chemoradiotherapy for esophageal squamous cell carcinoma. Ann Surg Oncol 29: 5657-5665, 2022.
16. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, Okawara G, Rosenthal SA and Kelsen DP: INT 0123 (radiation therapy oncology group 94-05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose versus standard-dose radiation therapy. J Clin Oncol 20: 1167-1174, 2002.
17. Ji Y, Du X, Zhu W, Yang Y, Ma J, Zhang L, Li J, Tao H, Xia J, Yang H, *et al*: Efficacy of concurrent chemoradiotherapy with S-1 vs radiotherapy alone for older patients with esophageal cancer: A multicenter randomized phase 3 clinical trial. JAMA Oncol 7: 1459-1466, 2021.
18. Conroy T, Galais MP, Raoul JL, Bouché O, Gourgou-Bourgade S, Douillard JY, Etienne PL, Boige V, Martel-Lafay I, Michel P, *et al*: Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): Final results of a randomised, phase 2/3 trial. Lancet Oncol 15: 305-314, 2014.
19. Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG and Morrow M (eds): Esophagus. In: American Joint Committee on Cancer (AJCC) cancer staging manual. 6th edition. New York, NY: Springer, pp167-178, 2002.
20. Rades D, Zwaan I, Soror T, Idel C, Pries R, Bruchhage KL, Hakim SG and Yu NY: Chemoradiation with cisplatin vs carboplatin for squamous cell carcinoma of the head and neck (SCCHN). Cancers (Basel) 15: 3278, 2023.
21. Ai D, Ye J, Wei S, Li Y, Luo H, Cao J, Zhu Z, Zhao W, Lin Q, Yang H, *et al*: Comparison of 3 paclitaxel-based chemoradiotherapy regimens for patients with locally advanced esophageal squamous cell cancer: A randomized clinical trial. JAMA Netw Open 5: e220120, 2022.
22. Higuchi K, Komori S, Tanabe S, Katada C, Azuma M, Ishiyama H, Sasaki T, Ishido K, Katada N, Hayakawa K, *et al*: Definitive chemoradiation therapy with docetaxel, cisplatin, and 5-fluorouracil (DCF-R) in advanced esophageal cancer: A phase 2 trial (KDOG 0501-P2). Int J Radiat Oncol Biol Phys 89: 872-879, 2014.
23. Zhou XL, Yu CH, Wang WW, Ji FZ, Xiong YZ, Zhu WG and Tong YS: Concurrent chemoradiotherapy with S-1 compared with concurrent chemoradiotherapy with docetaxel and cisplatin for locally advanced esophageal squamous cell carcinoma. Radiat Oncol 16: 94, 2021.
24. Wang X, Han W, Zhang W, Wang X, Ge X, Lin Y, Zhou H, Hu M, Wang W, Liu K, *et al*: Effectiveness of S-1-based chemoradiotherapy in patients 70 years and older with esophageal squamous cell carcinoma: A randomized clinical trial. JAMA Netw Open 6: e2312625, 2023.
25. Li J, Gong Y, Diao P, Huang Q, Wen Y, Lin B, Cai H, Tian H, He B, Ji L, *et al*: Comparison of the clinical efficacy between single-agent and dual-agent concurrent chemoradiotherapy in the treatment of unresectable esophageal squamous cell carcinoma: A multicenter retrospective analysis. Radiat Oncol 13: 12, 2018.
26. Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, Cooper J, Byhardt R, Davis L and Emami B: Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 326: 1593-1598, 1992.
27. Itami J, Murakami N, Watanabe M, Sekii S, Kasamatsu T, Kato S, Hirowatari H, Ikushima H, Ando K, Ohno T, *et al*: Combined interstitial and intracavitary high-dose rate brachytherapy of cervical cancer. Front Oncol 11: 809825, 2022.
28. Lan W, Lihong L, Chun H, Shutang L, Qi W, Liang X, Xiaoning L and Likun L: Comparison of efficacy and safety between simultaneous integrated boost intensity-modulated radiotherapy and standard-dose intensity-modulated radiotherapy in locally advanced esophageal squamous cell carcinoma: A retrospective study. Strahlenther Onkol 198: 802-811, 2022.
29. Chen Y, Zhu HP, Wang T, Sun CJ, Ge XL, Min LF, Zhang XW, Jia QQ, Yu J, Yang JQ, *et al*: What is the optimal radiation dose for non-operable esophageal cancer? Dissecting the evidence in a meta-analysis. Oncotarget 8: 89095-89107, 2017.
30. Xu Y, Dong B, Zhu W, Li J, Huang R, Sun Z, Yang X, Liu L, He H, Liao Z, *et al*: A phase III multicenter randomized clinical trial of 60 Gy versus 50 Gy radiation dose in concurrent chemoradiotherapy for inoperable esophageal squamous cell carcinoma. Clin Cancer Res 28: 1792-1799, 2022.
31. Hulshof MCCM, Geijsen ED, Rozema T, Oppedijk V, Buijsen J, Neelis KJ, Nuyttens JJME, van der Sangen MJC, Jeene PM, Reinders JG, *et al*: Randomized study on dose escalation in definitive chemoradiation for patients with locally advanced esophageal cancer (ARTDECO study). J Clin Oncol 39: 2816-2824, 2021.
32. Crehange G, M'vondo C, Bertaut A, Pereira R, Rio E, Peiffert D, Gnep K, Benezery K, Ronchin P, Noel G, *et al*: Exclusive chemoradiotherapy with or without radiation dose escalation in esophageal cancer: Multicenter phase 2/3 randomized trial CONCORDE (PRODIGE-26). Int J Radiat Oncol Biol Phys 111 (Suppl): S5, 2021.
33. Chandra A, Guerrero TM, Liu HH, Tucker SL, Liao Z, Wang X, Murshed H, Bonnen MD, Garg AK, Stevens CW, *et al*: Feasibility of using intensity-modulated radiotherapy to improve lung sparing in treatment planning for distal esophageal cancer. Radiother Oncol 77: 247-253, 2005.

34. Nicolini G, Ghosh-Laskar S, Shrivastava SK, Banerjee S, Chaudhary S, Agarwal JP, Munshi A, Clivio A, Fogliata A, Mancosu P, *et al*: Volumetric modulation arc radiotherapy with flattening filter-free beams compared with static gantry IMRT and 3D conformal radiotherapy for advanced esophageal cancer: A feasibility study. Int J Radiation Oncol Biol Phys 84: 553-560, 2012.
35. Wang X, Bai H, Li R, Wang L, Zhang W, Liang J and Yuan Z: High versus standard radiation dose of definitive concurrent chemoradiotherapy for esophageal cancer: A systematic review and meta-analysis of randomized clinical trials. Radiother Oncol 180: 109463, 2023.
36. Welsh J, Palmer MB, Ajani JA, Liao Z, Swisher SG, Hofstetter WL, Allen PK, Settle SH, Gomez D, Likhacheva A, *et al*: Esophageal cancer dose escalation using a simultaneous integrated boost technique. Int J Radiat Oncol Biol Phys 82: 468-474, 2012.
37. Wang R, Liu S, Chen B and Xi M: Recent advances in combination of immunotherapy and chemoradiotherapy for locally advanced esophageal squamous cell carcinoma. Cancers (Basel) 14: 5168, 2022.
38. Gao XS, Qiao X, Wu F, Cao L, Meng X, Dong Z, Wang X, Gao G, Wu TT, Komaki R and Chang JY: Pathological analysis of clinical target volume margin for radiotherapy in patients with esophageal and gastroesophageal junction carcinoma. Int J Radiat Oncol Biol Phys 67: 389-396, 2007.
39. Yang H and Hu B: Recent advances in early esophageal cancer: Diagnosis and treatment based on endoscopy. Postgrad Med 133: 665-673, 2021.
40. Vesprini D, Ung Y, Dinniwell R, Breen S, Cheung F, Grabarz D, Kamra J, Mah K, Mansouri A, Pond G, *et al*: Improving observer variability in target delineation for gastro-oesophageal cancer-the role of (18F)fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography. Clin Oncol (R Coll Radiol) 20: 631-638, 2008.
41. Pijl JP, Nienhuis PH, Kwee TC, Glaudemans AWJM, Slart RHJA and Gormsen LC: Limitations and pitfalls of FDG-PET/CT in infection and inflammation. Semin Nucl Med 51: 633-645, 2021.
42. Fernandez P, Zanotti-Fregonara P, Eimer S, Gimbert E, Monteil P, Penchet G, Lamare F, Perez P, Vimont D, Ledure S, *et al*: Combining 3'-Deoxy-3'-[18F] fluorothymidine and MRI increases the sensitivity of glioma volume detection. Nucl Med Commun 40: 1066-1071, 2019.
43. Han D, Yu J, Yu Y, Zhang G, Zhong X, Lu J, Yin Y, Fu Z, Mu D, Zhang B, *et al*: Comparison of (18)F-fluorothymidine and (18) F-fluorodeoxyglucose PET/CT in delineating gross tumor volume by optimal threshold in patients with squamous cell carcinoma of thoracic esophagus. Int J Radiat Oncol Biol Phys 76: 1235-1241, 2010.
44. Guo Y, Li J, Zhang P and Zhang Y: A comparative study of target volumes based on ^{18}F-FDG PET-CT and ten phases of 4DCT for primary thoracic squamous esophageal cancer. Onco Targets Ther 10: 177-184, 2017.
45. Vollenbrock SE, Voncken FEM, van Dieren JM, Lambregts DMJ, Maas M, Meijer GJ, Goense L, Mook S, Hartemink KJ, Snaebjornsson P, *et al*: Diagnostic performance of MRI for assessment of response to neoadjuvant chemoradiotherapy in oesophageal cancer. Br J Surg 106: 596-605, 2019.
46. Li H, Li F, Li J, Zhu Y, Zhang Y, Guo Y, Xu M, Shao Q and Liu X: Comparison of gross target volumes based on four-dimensional CT, positron emission tomography-computed tomography, and magnetic resonance imaging in thoracic esophageal cancer. Cancer Med 9: 5353-5361, 2020.
47. Van De Voorde L, Larue RT, Pijls M, Buijsen J, Troost EG, Berbée M, Sosef M, van Elmpt W, Schraepen MC, Vanneste B, *et al*: A qualitative synthesis of the evidence behind elective lymph node irradiation in oesophageal cancer. Radiother Oncol 113: 166-174, 2014.
48. Tamamura H, Hasatani K, Matsumoto S, Asahi S, Tatebe H, Sato Y, Matsusita K, Tameshige Y, Maeda Y, Sasaki M, *et al*: Evaluation of exposure doses of elective nodal irradiation in chemoradiotherapy for advanced esophageal cancer. Cancers (Basel) 15: 860, 2023.
49. Zhao KL, Ma JB, Liu G, Wu KL, Shi XH and Jiang GL: Three-dimensional conformal radiation therapy for esophageal squamous cell carcinoma: Is elective nodal irradiation necessary? Int J Radiat Oncol Biol Phys 76: 446-451, 2010.
50. Wang J, Wu Y, Zhang W, Chen Y, Liu Q, Jing S, Zhang J, Wu F, Wang J and Qiao X: Elective nodal irradiation versus involved-field irradiation for stage II-IV cervical esophageal squamous cell carcinoma patients undergoing definitive concurrent chemoradiotherapy: a retrospective propensity study with 8-year survival outcomes. Radiat Oncol 18: 142, 2023.
51. Chen X, Zhang Y, Zhou X, Wang M, Na F, Zhou L, Xu Y, Zou B, Xue J, Liu Y and Gong Y: Involved-field irradiation or elective-nodal irradiation in neoadjuvant chemo-radiotherapy for locally-advanced esophageal cancer: Comprehensive analysis for dosimetry, treatment-related complications, impact on lymphocyte, patterns of failure and survival. Front Oncol 13: 1274924, 2023.
52. Lyu J, LI T, Zhang X, Tian Z, Wang X, Chen L, LU B, Chen H, Yang J, Wang Q, *et al*: Involved field irradiation (IFI) versus elective nodal irradiation (ENI) in combination with concurrent chemotherapy for esophageal thoracic squamous cell cancer: A prospective, randomized, multicenter, controlled study. Chin J Radiat Oncol 7: 245-249, 2018.
53. Rahim MK, Okholm TLH, Jones KB, McCarthy EE, Liu CC, Yee JL, Tamaki SJ, Marquez DM, Tenvooren I, Wai K, *et al*: Dynamic CD8+ T cell responses to cancer immunotherapy in human regional lymph nodes are disrupted in metastatic lymph nodes. Cell 186: 1127-1143, 2023.
54. Wang X, Bai H, Gao M, Guan Y, Yu L, Li J, Dong Y, Song Y, Tao Z, Meng M, *et al*: Impact of radiation dose to the immune system on disease progression and survival for early-stage non-small cell lung cancer treated with stereotactic body radiation therapy. Radiother Oncol 186: 109804, 2023.
55. Reid TD, Davies IL, Mason J, Roberts SA, Crosby TD and Lewis WG: Stage for stage comparison of recurrence patterns after definitive chemoradiotherapy or surgery for oesophageal carcinoma. Clin Oncol (R Coll Radiol) 24: 617-624, 2012.
56. Wang Z, Guo J, Qin J, Zhang H, Zhao Y, Lu Y, Yan X, Zhang F, Zhang Z, Zhang T, *et al*: Accuracy of 3-T MRI for preoperative T staging of esophageal cancer after neoadjuvant chemotherapy, with histopathologic correlation. Am J Roentgenol 212: 788-795, 2019.
57. Kim SW, Kim IK and Lee SH: Role of hyperoxic treatment in cancer. Exp Biol Med (Maywood) 245: 851-860, 2020.
58. Cavalieri S and Licitra L: Induction chemotherapy is the best timekeeper in nasopharyngeal carcinoma. Cancer 126: 3624-3626, 2020.
59. Qiu J, Lin H, Yu Y, Ke D, Li H, Zheng H, Zheng Q, Wang Z, Lin M, Yang J, *et al*: Clinical outcomes and toxicities of locally advanced esophageal squamous cell carcinoma patients treated with early thoracic radiation therapy after induction chemotherapy. Int J Clin Oncol 28: 550-564, 2023.
60. Wang XS, Xi M, Bu SS, Xu G and Ge H: Comparative analysis between induction chemotherapy combined with concurrent chemoradiotherapy and chemoradiotherapy alone for thoracic esophageal squamous cell carcinoma. Chin J Radiat Oncol 28: 90-95, 2019.
61. Minsky BD, Neuberg D, Kelsen DP, Pisansky TM, Ginsberg R and Benson A III: Neoadjuvant chemotherapy plus concurrent chemotherapy and high-dose radiation for squamous cell carcinoma of the esophagus: A preliminary analysis of the phase II intergroup trial 0122. J Clin Oncol 14: 149-155, 1996.
62. Liu S, Luo L, Zhao L, Zhu Y, Liu H, Li Q, Cai L, Hu Y, Qiu B, Zhang L, *et al*: Induction chemotherapy followed by definitive chemoradiotherapy versus chemoradiotherapy alone in esophageal squamous cell carcinoma: A randomized phase II trial. Nat Commun 12: 4014, 2021.
63. Chan WL, Choi CW, Wong IY, Tsang TH, Lam AT, Tse RP, Chan KK, Wong C, Law BT, Cheung EE, *et al*: Docetaxel, cisplatin, and 5-FU triplet therapy as conversion therapy for locoregionally advanced unresectable esophageal squamous cell carcinoma. Ann Surg Oncol 30: 861-870, 2023.
64. Xi M, Liao Z, Deng W, Komaki R, Ho L and Lin SH: Recursive partitioning analysis identifies pretreatment risk groups for the utility of induction chemotherapy before definitive chemoradiation therapy in esophageal cancer. Int J Radiat Oncol Biol Phys 99: 407-416, 2017.
65. Wang J, Xiao L, Wang S, Pang Q and Wang J: Addition of induction or consolidation chemotherapy in definitive concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone for patients with unresectable esophageal cancer: A systematic review and meta-analysis. Front Oncol 11: 665231, 2021.
66. Waters JK and Reznik SI: Update on management of squamous cell esophageal cancer. Curr Oncol Rep 24: 375-385, 2022.
67. Xia X, Wu M, Gao Q, Sun X and Ge X: Consolidation chemotherapy rather than induction chemotherapy can prolong the survival rate of inoperable esophageal cancer patients who received concurrent chemoradiotherapy. Curr Oncol 29: 6342-6349, 2022.

68. Zhang AD, Su XH, Shi GF, Han C, Wang L, Liu H, Zhang J and Zhang RH: Survival comparision of three-dimensional radiotherapy alone vs chemoradiotherapy for esophageal squamous cell carcinoma. Arch Med Res 51: 419-428, 2020.
69. Xia X, Liu Z, Qin Q, Di X, Zhang Z, Sun X and Ge X: Long-term survival in nonsurgical esophageal cancer patients who received consolidation chemotherapy compared with patients who received concurrent chemoradiotherapy alone: A systematic review and meta-analysis. Front Oncol 10: 604657, 2021.
70. Chen Y, Guo L, Cheng X, Wang J, Zhang Y, Wang Y, Ke S and Shi W: With or without consolidation chemotherapy using cisplatin/5-FU after concurrent chemoradiotherapy in stage II-III squamous cell carcinoma of the esophagus: A propensity score-matched analysis. Radiother Oncol 129: 154-160, 2018.
71. Zhao Z, Zhang Y, Wang X, Geng X, Zhu L and Li M: Clinical response to chemoradiotherapy in esophageal carcinoma is associated with survival and benefit of consolidation chemotherapy. Cancer Med 9: 5881-5888, 2020.
72. Wu Z, Zheng Q, Chen H, Xiang J, Hu H, Li H, Pan Y, Peng Y, Yao X, Liu P, *et al*: Efficacy and safety of neoadjuvant chemotherapy and immunotherapy in locally resectable advanced esophageal squamous cell carcinoma. J Thorac Dis 13: 3518-3528, 2021.
73. Sun JM, Shen L, Shah MA, Enzinger P, Adenis A, Doi T, Kojima T, Metges JP, Li Z, Kim SB, *et al*: Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): A randomised, placebo-controlled, phase 3 study. Lancet 398: 759-771, 2021.
74. Peng F, Bao Y, Cheng C, Niu S, Song W, Li Y, Yu H, Xing X, Feng S, Wang X, *et al*: Induction chemotherapy plus camrelizumab followed by concurrent chemoradiotherapy in patients with unresectable locally advanced esophageal squamous cell carcinoma (ImpactCRT): A single-arm, phase II trial. J Clin Oncol 41 (Suppl 16): e16067, 2023.
75. Jing Z, Du D, Zhang N, Dai H, Wang X, Hua Y and Wu S: Combination of radiation therapy and anti-PD-1 antibody SHR-1210 in treating patients with esophageal squamous cell cancer. Int J Radiat Oncol Biol Phys 102: E31, 2018.
76. Zhang W, Yan C, Gao X, Li X, Cao F, Zhao G, Zhao J, Er P, Zhang T, Chen X, *et al*: Safety and feasibility of radiotherapy plus camrelizumab for locally advanced esophageal squamous cell carcinoma. Oncologist 26: e1110-e1124, 2021.
77. Zhang W, Yan C, Zhang T, Chen X, Dong J, Zhao J, Han D, Wang J, Zhao G, Cao F, *et al*: Addition of camrelizumab to docetaxel, cisplatin, and radiation therapy in patients with locally advanced esophageal squamous cell carcinoma: A phase 1b study. OncoImmunology 10: 1971418, 2021.
78. Zhu Y, Wen J, Li Q, Chen B, Zhao L, Liu S, Yang Y, Wang S, Lv Y, Li J, *et al*: Toripalimab combined with definitive chemoradiotherapy in locally advanced oesophageal squamous cell carcinoma (EC-CRT-001): A single-arm, phase 2 trial. Lancet Oncol 24: 371-382, 2023.
79. Calabrò L, Morra A, Giannarelli D, Amato G, D'Incecco A, Covre A, Lewis A, Rebelatto MC, Danielli R, Altomonte M, *et al*: Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): An open-label, non-randomised, phase 2 study. Lancet Respir Med 6: 451-460, 2018.
80. Kelley RK, Sangro B, Harris W, Ikeda M, Okusaka T, Kang YK, Qin S, Tai DWM, Lim HY, Yau T, *et al*: Safety, efficacy, and pharmacodynamics of tremelimumab plus durvalumab for patients with unresectable hepatocellular carcinoma: Randomized expansion of a phase I/II study. J Clin Oncol 39: 2991-3001, 2021.
81. Park S, Oh D, Choi YL, Chi SA, Kim K, Ahn MJ and Sun JM: Durvalumab and tremelimumab with definitive chemoradiotherapy for locally advanced esophageal squamous cell carcinoma. Cancer 128: 2148-2158, 2022.
82. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A (eds): AJCC cancer staging manual. 7th edition. New York, NY, Springer, 2010.
83. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, Mendez G, Feliciano J, Motoyama S, Lièvre A, *et al*: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med 384: 1191-1203, 2021.
84. Wang J, Cheng Y, Wu Y, Cao F, Liu Q and Gao G: 978P A prospective study of camrelizumab monotherapy following definitive concurrent chemoradiotherapy in patients with unresectable locally advanced esophageal squamous cell cancer. Ann Oncol 32 (Suppl 5): S838, 2021.
85. Bando H, Kumagai S, Kotani D, Saori M, Habu T, Tsushima T, Hara H, Kadowaki S, Kato K, Chin K, *et al*: 1211P A multicenter phase II study of atezolizumab monotherapy following definitive chemoradiotherapy for unresectable locally advanced esophageal squamous cell carcinoma (EPOC1802). Ann Oncol 33 (Suppl 7): S1102-S1103, 2022.
86. Yang YM, Hong P, Xu WW, He QY and Li B: Advances in targeted therapy for esophageal cancer. Signal Transduct Target Ther 5: 229, 2020.
87. Zhao G, Feng L, Ye T, Liu Y, Fan L, Ye C and Chen J: Cetuximab enhances radiosensitivity of esophageal squamous cell carcinoma cells by G2/M cycle arrest and DNA repair delay through inhibiting p-EGFR and p-ERK. Thorac Cancer 14: 2127-2138, 2023.
88. Brenner B, Purim O, Gordon N, Goshen-Lago T, Idelevich E, Kashtan H, Menasherov N, Fenig E, Sulkes A and Kundel Y: The addition of cetuximab to preoperative chemoradiotherapy for locally advanced esophageal squamous cell carcinoma is associated with high rate of long term survival: Mature results from a prospective phase Ib/II trial. Radiother Oncol 134: 74-80, 2019.
89. Crosby T, Hurt CN, Falk S, Gollins S, Mukherjee S, Staffurth J, Ray R, Bashir N, Bridgewater JA, Geh JI, *et al*: Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): A multicentre, phase 2/3 randomised trial. Lancet Oncol 14: 627-637, 2013.