Treatment options for neoadjuvant strategies of esophageal squamous cell carcinoma (Review)

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Abstract. Compared with postoperative adjuvant therapy, neoadjuvant therapy has more potential advantages, such as decreasing tumor stage, killing micrometastatic cells. Because of these advantages, neoadjuvant therapy is recommended for numerous types of tumor, such as breast, lung and rectal cancer. To determine the role of neoadjuvant therapy on overall survival and adverse for patients with resectable esophageal carcinoma. we summarized clinical studies on 7 types of neoadjuvant therapies in this review. Currently, patients with esophageal cancer (EC) in China mainly receive postoperative treatment with <30% of patients receiving neoadjuvant therapy. One reason for the limited use of neoadjuvant therapy in China is inaccurate staging based on imaging and neoadjuvant treatment may increase difficulties in surgery. After neoadjuvant therapy, there may be tissue edema, blurry surgical field of view and unclear tissue gaps, resulting in greater difficulty in surgical procedures. However, oncologists are interested in neoadjuvant treatment, especially neoadjuvant immunotherapy to treat EC. Concurrent chemoradiotherapy for esophageal squamous cell carcinoma (ESCC) is the most common neoadjuvant treatment regimen and increases the pathological complete response (pCR) and 5- and 10-year survival rates. Preoperative induction chemotherapy and sequential concurrent chemoradiotherapy are currently the most widely treatments used in clinical practice in China. However, this treatment strategy does not yield long-term survival. The pCR rate of neoadjuvant immunotherapy is greater than that of concurrent chemoradiotherapy but, to the best of our knowledge, no evidence of long-term survival benefit has been found in phase I and II clinical trials. Neoadjuvant treatment should be considered for patients with locally advanced ESCC.

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Contents

1. Introduction

Esophageal cancer (EC) is the sixth largest cause of cancer-associated deaths in the world. In 2020, there were 544,076 deaths from esophageal cancer patients worldwide, accounting for 5.5% of all malignant tumor mortality (1). Esophageal squamous cell carcinoma (ESCC) is the most common subtype of EC in Eastern populations (2) and accounts for >90% of EC cases in China (3); by contrast, this proportion is only 30-40% in Western populations (4). ESCC and esophageal adenocarcinoma (EADC) differ in tumor location, lymph node involvement and biological tumor behavior (5). Previous meta-analyses of neoadjuvant therapy did not distinguish between EADC and ESCC and the results of these studies are not sufficient to guide neoadjuvant treatment of ESCC in China (6,7). Hence, the current proportion of patients with ESCC receiving neoadjuvant therapy is only 22% in China because of uncertain results (8).

China has a high incidence of EC and most patients are at the locally advanced stage when diagnosed, with low quality of life, few treatment options and poor prognosis. There are several reasons for the low rate of neoadjuvant treatment for EC in China. First, endoscopic ultrasound, magnetic resonance imaging and PET-CT scanning are rarely used for preoperative evaluation of EC, resulting in some patients with locally advanced disease being misdiagnosed as early disease and receiving surgery. Secondly, neoadjuvant radiotherapy (nRT) has been reported to increase postoperative mortality (9). The current treatment model for most Chinese patients with EC is surgery followed by postoperative adjuvant therapy; however,

postoperative adjuvant therapy for EC does not yield benefits. Neoadjuvant therapy can improve the R0 resection rate of EC and prolong median survival without significantly increasing surgery-associated risks (10). Therefore, multidisciplinary treatment (11) and providing neoadjuvant therapy for eligible patients may improve the prognosis of patients with EC in China.

Neoadjuvant chemotherapy (nCT) for locally advanced ESCC is recommended by Chinese Society of Clinical Oncology (CSCO) (12) and Japanese guidelines (13). Both the National Comprehensive Cancer Network (NCCN) (14) and the CSCO recommend neoadjuvant chemoradiotherapy (nCRT) as a standard neoadjuvant treatment strategy for locally advanced ESCC. Neoadjuvant immunotherapy can also achieve high pathological complete response (pCR) (15). To the best of our knowledge, however, the relative survival benefits and postoperative mortality of different types of neoadjuvant treatment for ESCC have not been established. The present review aimed to summarize article the use of neoadjuvant therapy for locally advanced ESCC and the value of neoadjuvant immunotherapy.

2. nCT

Initial studies concluded that nCT does not improve long-term survival for patients with ESCC (16,17). In a phase III trial of 46 patients with potentially resectable ESCC, patients were randomized to receive either immediate surgery or surgery + preoperative CT (three cycles of fluorouracil at 1 g/m^2/day for 5 days and cisplatin at 20 mg/m^2/day for 5 days). The objective response rate (ORR) of CT was 50%. The resectability rate for patients was 79% in the surgery and 70% in the surgery + CT group (nCT group). The incidence of postoperative septic complications (41 vs. 26%) and respiratory disorders (48 vs. 31%) in patients undergoing preoperative CT was higher than in patients undergoing surgery alone. Surgical mortality was increased in the nCT (19%) compared with the surgery-alone group (10%). Two deaths may have been related to pharmaceutical treatment. Compared with those did not respond to preoperative CT, the median overall survival (OS) time of those who responded was extended by 8 months (13 vs. 5 months), however median OS for both the nCT and the surgery-alone group was 10 months (18).

United States of America Intergroup 113 trial proved that nCT is ineffectual (11). A total of 443 cases of EC were enrolled, of which 207 were ESCC. Patients in the nCT group received three cycles of cisplatin + 5-Fluorouracil) before surgery and two cycles after surgery (19). There was no significant difference in the proportion of R0 resection (63% in nCT vs. 59% in surgery-alone). The pCR of the nCT group was 2.5%. The 5-year survival rate was not significantly different and the median OS was 14.9 month in nCT and 16.1 month in surgery-alone group (HR=1.07; 95%CI 0.87-1.32). Long-term survival rate increased in patients with decreased tumor volume after nCT. However, perioperative morbidity and mortality did not increase in the nCT group (20).

Although most trials have not demonstrated that nCT can improve long-term survival of patients with ESCC, subgroup analysis demonstrates that survival is significantly prolonged in patients with tumor regression following nCT (16,18,19).

OEO2 randomized controlled trial (RCT) of preoperative CT for patients eligible for radical surgery of EC recruited 802 patients with stage I-III [Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC 6th) (21) EC, of which 30% of cases were ESCC (22). Patients in the nCT group received two cycles of cisplatin + 5-FU CT followed by surgical treatment. After a follow-up period of up to 6 years, nCT significantly improved the survival rate of operable ESCC. The 5-year survival rate of the nCT group was 23%, while that of the surgery-alone group was 17.1% (HR=0.84). The median OS was 16.8 in nCT and 13.3 month in surgery-alone group (HR=0.79; 95%CI 0.67-0.93). Median progression-free survival (PFS) was also better in nCT group (HR=0.75; 95%CI 0.63-0.89). The nCT group had significantly increased R0 resection rate (85.7 vs. 73.6% for surgery-alone). The treatment effect was comparable in EADC and ESCC. Similar to the INT 113, the perioperative morbidity and mortality in nCT group showed no increase (22).

The inconsistency between the results of INT 113 and OEO2 trials has caused controversy and may be due to the different study design. A total of 68% of patients in INT 113 received three CT cycles before surgery, while OEO2 used two CT cycles. The median time from start of INT 113 to surgery was longer than in OEO2 (93 vs. 63 days). Delaying surgery may lead to a decline in survival, but the results of other studies do not support this (23,24). The proportion of patients receiving surgery-alone in the INT 113 study was lower (80 vs. 92% in OEO2). Patients in the INT 113 study received postoperative adjuvant CT, while 10% of patients in the OEO2 study received preoperative RT. Increased efficiency of nCT can prolong survival. Compared with non-responders, the survival rate of responders receiving nCT is improved; subgroup analysis of responders showed no significant difference in survival between partial and complete responders (25).

More effective triplet regimens have been attempted (26-28). Japan Clinical Oncology Group 1109 trial confirmed the advantages of docetaxel, cisplatin and 5-fluorouracil as preoperative treatment for ESCC (26). A total of 600 thoracic ESCC, clinical stage IB/II/III (excluding T4, UICC/AJCC 7th) (29), patients who did not receive prior therapy were recruited from 41 Japanese institutions between November 2012 and February 2018 and randomly divided into three groups, two of which were nCT groups (arms A and B). Patients in arm A received two courses of preoperative cisplatin 80 mg/m^2, d1, 22 and 5-FU 800 mg/m^2, d1-5, 22-26 (CF). Patients in arm B received three courses of preoperative docetaxel 70 mg/m^2, d1, 22, 43; cisplatin 70 mg/m^2, d1, 22, 43 and 5-FU 750 mg/m^2, d1-5, 22-26, 43-47 (DCF). Both groups underwent esophagectomy + D2 lymphadenectomy. The time of surgery was ≤56 days after the completion of neoadjuvant treatment. Preliminary results showed that in arms A and B, 83.9 and 84.7% completed the scheduled treatment plan respectively. The median OS of the two- and the three-drug groups was 5.6 years and not reached, respectively. The OS rates after 3 years were 62.6 and 72.1%, respectively (HR=0.68). Compared with CF regimen, DCF regimen significantly improved OS (26).

Neoadjuvant DCF CT has significant survival advantages in patients with resectable ESCC, especially in patients aged ≤75 years (27). To decrease adverse reactions, the DCF regimen was modified and the modified regimen showed good efficacy.

The modified DCF regimen comprised infusion of docetaxel at a dose of 35 mg/m^2 for 2 h on days 1 and 8, cisplatin at a concentration of 12 mg/m^2 for 4 h on days 1-5 and continuous infusion of 5-FU at 600 mg/m^2 on days 1-5. Patients with stage II/III (UICC 7th) (29) ESCC were received modified DCF or conventional CF for two cycles. The proportion of patients with grade 2-3 pathological reactions in the modified DCF group (40%) was significantly higher than that in the CF group (11%), while the incidence of grade 3-4 neutropenia in modified DCF group (56%) was significantly higher than that in the CF group (0%) (28).

Using oral S1 instead of 5-FU intravenous infusion allows decreased doses of docetaxel and cisplatin. In a single-arm clinical study of 40 patients with ESCC treated with docetaxel 40 mg/m^2 and cisplatin 60 mg/m^2 on day 1 and S1 80 mg/m^2 on days 1-14, repeated every 4 weeks, for a maximum of 3 cycles, clinical response rate (RR) was 76% and the pathological RR of grade 2-3 tumors was 33% (18). Grade 3-4 blood toxicity was leukopenia (50%), neutropenia (68%) and febrile neutropenia (18%) (30).

In summary, compared with surgery alone, the clinical benefit of nCT in ESCC increases the R0 resection rate by 4.0-12.1% and the clinical RR is ~50%. Except for the OEO2 study which showed nCT extended the median OS by 3.5 months, the aforementioned clinical studies have failed to show long-term survival benefits. pCR rate of nCT is ~2.5% (31). nCT combining with two drugs is a common treatment for ESCC with clinical stage IB/II/III (UICC/AJCC 7th) (32). The three-drug regimen provides higher clinical efficiency and pathological reaction rate but the hematological toxicity is higher than the two-drug regimen. Patients with better tumor regression following nCT achieve substantial long-term survival. Selected papers are summarized in Table I.

3. nRT

RT blocks the blood supply to the tissue, resulting in fibrous scarring and increases difficulty of surgical dissection, particularly in postoperative wound healing, which may be a factor in the poor prognosis of ESCC (33). nRT is a local treatment method that can delay tumor growth or decrease tumor size (34). Certain clinical trials (35,36) have proved that nRT decreases tumor stage, improve complete resection rate and decrease local recurrence rate, without increasing surgical complications and mortality, but has limited benefits for long-term survival.

A prospective RCT compared the curative effect and adverse events of nRT combined with surgery and surgery-alone in locally advanced ESCC of 206 patients with tumors <8 cm in length and under the age of 65 years (37). X-rays with energy of 8 MV were selected for preoperative RT and anterior-posterior portals was used to deliver 40 Gy radiation dose to the total mediastinal lymph node drainage area and left gastric lymph node drainage area. Surgery was performed 2-4 weeks after RT. The nRT group showed better efficacy and similar adverse reactions compared with the surgery-alone group: Actual completion rate was 93 vs. 85; operative mortality was 5 vs. 6; incidence of intrathoracic anastomotic fistula was 0 vs. 1; positive rate of esophageal stump was 0 vs. 2; lymph node metastasis rate was 27 vs. 35% and 5-year survival rate was 35 vs. 30% in the nRT and surgery-alone groups, respectively; 5-year actuarial survival rate of patients who showed grade III RT response was 50% (37). The results of the aforementioned study are supported by the results of a RCT by Nygaard *et al* (38). In a prospective multicenter study, 186 patients with ESCC were randomly allocated to receive nRT or surgery-alone. Compared with surgery-alone, the 3-year survival rate (21 vs. 9%) was significantly prolonged in nRT group but the median OS was similar (8 vs. 7 months) (38).

In 1976, a prospective clinical study evaluated the feasibility of preoperative RT in 124 patients with ESCC (9). A total of 67 patients was randomly allocated to undergo 4000 rads of cobalt radiation; surgery was performed 8 days after final RT treatment. A total of 57 patients underwent surgery without RT. In the irradiation group, 14 patients died during the operation, while 11 patients died in the non-irradiation group, with non-significant difference between the two groups. For patients with tumors located in the middle of the chest, mortality of the RT group was higher than that of the non-RT group (11/29 vs. 4/19), but the difference was not significant. Among irradiated patients, the 5-year actuarial survival rate was 9.5%, while that of non-irradiated patients was 11.5% (9).

A meta-analysis of 15 RCTs compared 5-year survival, radical resection and surgical mortality rate and postoperative complication incidence of patients undergoing surgery-alone and preoperative RT followed surgery. Compared with surgery-alone, there was no significant difference in 5-year survival (OR=0.78, 95% CI 0.22-2.84), radical resection (OR=2.62, 95% CI 0.72-9.57) or surgical mortality rate (OR=0.83, 95% CI 0.34-2.03) and postoperative complication incidence (OR=0.66, 95% CI 0.31-1.41) in the preoperative RT group (39).

Previous radiotherapy techniques were relatively rudimentary and could not protect the exposure of heart and lung is not minimized, which may increase the perioperative cardiac and pulmonary toxicity and lead to increased perioperative mortality. Modern radiotherapy techniques, such as intensity modulated radiation therapy, can effectively protect normal organs and tissues in the human body. Use of intensity-modulated RT technology (IMRT) to control the volume of the lungs exposed to 10 Gy radiation <41% and the V30 of the heart <21% significantly increases the median OS of patients with ESCC (40). The meaning of V10 here is that the volume of the lungs exposed to 10 Gy radiation accounts for less than 41% of the total lung volume. The meaning of V30 here is that the volume of the heart exposed to 30 Gy radiation accounts for less than 21% of the total heart volume.

To the best of our knowledge, clinical studies on preoperative RT have not been performed since August 2002. Based on existing trials, nRT with radiation dose of 35-40 Gy is safe and reduces the probability of mediastinal lymph node metastasis by 7% but the long-term survival benefit is minimal (9,37,38). Selected papers are summarized in Table II.

4. nCRT

nCT- and nRT-alone have not been proved to increase median survival time; therefore these treatments have been combined as nCRT.

Table I. Studies using nCT in patients with ESCC.

First author, year	Study design	Patients	Treatment	Outcome	(Refs.)
Schlag *et al*, 1992	RCT	46 ESCC	i) nCT (F 1 g/m^2/day for 5 days, C 20 mg/m^2/day for 5 days, q21d) for 3 cycles + S; ii) S-alone	ORR, 50% in nCT. R0, 79 in S-alone vs. 70% in nCT. S-related mortality, 19 in nCT vs. 10% in S. mOS, 10 months in S-alone and nCT; 13 in responders vs. 5 months in non-responders.	(18)
Kelsen *et al*, 2007	RCT	443 EC, including 207 ESCC	i) nCT (F 1 g/m^2/day for 5 days, C 100 mg/m^2 d1, q28d) for three cycles pre- and two cycles post-surgery; ii) S-alone	pCR, 2.5% in nCT. R0, 59 in S vs. 63% in nCT. mOS in R0 was significantly superior to R1, R2 and not resected (26.4, 12.0, 6.0 and 2.9 months, respectively). mOS, 16.1 in S vs. 14.9 months in nCT; 36 in responders vs. 13.2 months in non-responders.	(20)
Allum *et al*, 2009	RCT	802 EC, including and 533 247 ESCC EADC	i) nCT (F 1 g/m^2/day for 4 days, C 80 mg/m^2 d1, q28d) for two cycles + S; ii) S-alone	R0, 73.6 in S vs. 85.7% in nCT. mOS in R0, R1, R2 and not resected, 25.2, 13.2, 9.0 and 2.0 months, respectively. mOS, 13.3 in S vs. 16.8 months in nCT. 5-year OS, 17.1 in S vs. 23.0% in nCT. Treatment effect was comparable in EADC and ESCC.	(22)
Ojima *et al*, 2016	RCT	73 ESCC	i) DCF (F 600 mg/m^2/day for 5 days, D 35 mg/m^2 d1 and 8, C 12 mg/m^2/day for 5 days, q21d) for two cycles + S ii) CF (F 800 mg/m^2/day for 5 days, C 80 mg/m^2 d1, q21d) for two cycles + S	ORR, 26 in CF vs. 43% in DCF. R0, 89 in CF vs. 87% in DCF. pCR (grade 2 + 3), 11 in CF vs. 40% in DCF. 2-year RFS, 39.3 in CF vs. 48.9% in DCF. 2-year OS, 57.1 in CF vs. 60% in DCF. Grade 3-4 neutropenia, 0 in CF vs. 56% in DCF.	(28)
Hayata *et al*, 2018	Single-arm	40 ESCC	D 40 mg/m^2 d1, C 60 mg/m^2 d1, S1 80 mg/m^2 on day 1-14, q28d, up to three cycles + S	ORR, 76%. R0, 85%. pCR, 10%. Grade 3-4 neutropenia, 68%.	(30)

RCT, randomized controlled trial; nCT, neoadjuvant chemotherapy; S, surgery; ORR, objective response rate; mOS, median overall survival; pCR, pathological complete response; EADC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; RFS, relapse-free survival; EC, esophageal cancer; DCF, docetaxel, cisplatin and 5-fluorouracil.

Phase III RCT trial Fax at the Francophone de Cance´rologie Digestive) 9901 aimed to assess whether nCRT improves the prognosis of patients with untreated stage I or II [UICC/AJCC 5th (41); T1 or T2, N0 or N1 and T3N0, M0] thoracic EC (median age, 57.8 years) suitable for curative resection; 70.3% of cases were ESCC and 29.2% were EADC. A total of 195 patients was randomly assigned to receive surgery-alone (n=97) or nCRT + surgery (n=98). The nCRT regimen was 45 Gy divided into 25 fractions for 5 weeks; two courses of CT were administered simultaneously, including 800 fluorouracil and 75 mg/m^2 cisplatin. Three-dimensional conformal RT (3D-CRT) treatment was administered. The clinical target volume (CTV) was defined as mediastinal tissue <3 cm above and below the gross tumor volume (GTV). The planning target volume (PTV) was defined as CTV + 1 cm proximal, distal and lateral edges to include the uncertainties caused by repositioning and patient movement. During RT, linear accelerator photon beams with energy ≥6 MeV was used. The nCRT underwent surgery 4-8 weeks after CRT completion, while the surgery-alone group underwent surgery <4 weeks after randomization. Median follow-up was 93.6 months. Before treatment, 19.0% of patients were stage I, 53.3 were IIA and 27.7 were IIB. R0 resection rates were 93.8 and 92.1, the 3-year OS rate was 47.5 and 53.0 (HR=0.99, 95% CI 0.69-1.40) and the postoperative mortality rate was 11.1 and 3.4% for nCRT and surgery-alone, respectively (42). FFCD 9901 trial showed

Table II. Studies using nRT in patients with ESCC.

First author, year	Study design	Number of patients	Treatment	Outcome	(Refs.)
Wang *et al*, 1990	RCT	206 ESCC	i) nRT: RT 40 Gy + S; ii) S-alone	Resection rate, 93 in nRT vs. 85% in S. Operative mortality, 5 in nRT vs. 6% in S. 5-year OS, 35 in nRT vs. 30% in S.	(37)
Nygaard *et al*, 1992	RCT	186 ESCC	i) nRT: RT 35 Gy + S; ii) S-alone	3-year OS, 21 in nRT vs. 9% in S. Median OS, 8 months in nRT vs. 7 months in S-alone.	(38)
Launois *et al*, 1976	RCT	124 ESCC	i) nRT: RT 40Gy + S; ii) S-alone	Operative mortality, 20.9 in nRT vs. 19.3% in S. 5-year OS, 9.5 in nRT vs. 11.5% in S.	(9)
Huang *et al*, 2017	Meta	442 ESCC	i) nRT: RT 40Gy + S; ii) S-alone	Resection rate, OR=2.62, 95% CI 0.72-9.57. Operative mortality, OR=0.83, 95% CI 0.34-2.03. Postoperative complication, OR=0.66, 95% CI 0.31-1.41. 5-year OS, OR=0.78, 95% CI 0.22-2.84	(39)

RCT, randomized controlled trial; ESCC, esophageal squamous cell carcinoma; nRT, neoadjuvant radiotherapy; S, surgery; mOS, median overall survival; meta, meta-analysis.

that nCRT did not provide any survival benefits, but increased postoperative mortality compared with surgery-alone in early stage ESCC (42). However, for locally advanced ESCC, nCRT increased median survival time.

Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) trial concluded that nCRT improves median OS compared with surgery-alone in ESCC with clinical stage T1N1 or T2-3N0-1M0 (UICC/AJCC 6th) (10). A total of 366 patients with potentially resectable EC were randomly assigned to surgery-alone or weekly CT and concurrent RT after surgery. CT regimen involved intravenous infusion of carboplatin with an area under the curve (AUC) of 2 mg/ml/min and paclitaxel at 50 mg/m^2 on days 1, 8, 15, 22 and 29. Starting from the first day of the first CT cycle, a total radiation dose of 41.4 Gy was administered in 23 fractions of 1.8 Gy (5 fractions/week). All patients were treated with 3D-CRT external beam radiation. GTV was defined by the primary tumor and the regional lymph nodes considered for metastasis. PTV was defined as the proximal and distal edges extending 4 cm outward and, in cases where the tumor extended to the stomach, a 3 cm distal edge was selected. A radial edge of 1.5 cm was provided around the GTV to include subclinical areas. In both groups, the median age was 60 years and the median length of the tumor was 4 cm. Most tumors were located at the distal end of the esophagus. Of all patients, 75% of cases were EADC and 23% were ESCC. A total of 91% patients in nCRT group received complete treatment plan of 5 weeks CT and 92% received the whole dose of radiation; 92% of patients in the nCRT group achieved complete resection, with no tumor <1 mm from the resection edge (R0) compared with 69% in the surgery group alone. pCR was 29% in nCRT group, moreover, pCR rate of patients with ESCC was significantly higher than that of EADC (49 vs. 23%). Median OS was 49.4 months in the nCRT group vs. 24.0 months in the surgery-alone group (HR=0.657, 95% CI 0.495-0.871). The impact of nCRT on OS was time-independent and absolute benefit of 10 year-OS was 13% (38 vs. 25%). During the 10-year follow-up period, cumulative local recurrence rate of nCRT and surgery-alone group was 21 and 40%, respectively. For both squamous and adenocarcinoma pathological types, the OS was significantly improved by nCRT. The grade 3-4 hematological toxic effects in nCRT group were leukopenia (6%) and neutropenia (2%), with the most common non-hematological grade 3-4 toxicity being anorexia (5%) and fatigue (3%). The incidence of post-operative complications was similar in both groups, with a hospital mortality rate of 4%. Pulmonary (46 vs. 44%) and cardiac complication (21 vs. 17%) were higher in nCRT group but rate of anastomotic leakage was lower (22 vs. 30%). The CROSS study showed that compared with surgery-alone, nCRT does not have a significant adverse effect on quality of life, which supports the feasibility of implementing nCRT in locally advanced ESCC. However, this treatment mode does not effectively prolong the long-term survival of patients with locally advanced ESCC.

Neoadjuvant Chemoradiotherapy for Esophageal Cancer) 5010 trial aimed to identify possible differences in the efficacy of the same treatment plan between Eastern and Western populations. A total of 451 patients with potentially resectable thoracic ESCC with clinical stage T1-4N1M0/T4N0M0 (UICC/AJCC 6th) were assigned to nCRT + surgery or surgery-alone groups. In the nCRT group, patients were given 25 mg/m^2 vinorelbine intravenously on days 1 and 8, 75 mg/m^2 cisplatin intravenously on day 1, or 25 mg/m^2 intravenously on days 1-4, once/3 weeks for a total of 2 cycles. A total concurrent

radiation dose of 40.0 Gy in 20 fractions, 5 days/week, was applied. All patients were radiated by external beam radiation using the 3D-CRT and photons of 6-8 MV energy. The GTV was defined as the primary tumor and the regional lymph nodes considered for metastasis. CTV was defined as an extension of the proximal and distal edges of 3 cm around the gross tumor, as well as a radial edge of 0.5-1.0 cm, to include subclinical lesions. PTV was defined as 8 mm edge extension of the CTV. In the nCRT group, surgery was performed 4-6 weeks after the end of CRT. Surgery-alone was performed after random allocation. pCR rate of the nCRT group was 43.2%. nCRT group had a higher R0 resection rate compared with surgery-alone (98.4 vs. 91.2%), better median OS (100.1 vs. 66.5 months) and a prolonged disease-free survival (100.1 vs. 41.7 months). The most common grade 3-4 adverse events during CRT were leukopenia (48.9%) and neutropenia (45.7%). The incidence of postoperative complications in the nCRT and surgery-alone groups was similar, except for arrhythmia (13 vs. 4.0%). The perioperative mortality rate in the nCRT group was not significantly higher than that in the surgery-alone group (2.2 vs. 0.4%) (43). Long-term follow up showed that, compared with surgery-alone, patients who underwent nCRT had longer OS (HR=0.74) and 5-year survival rate (59.9 vs. 49.1%, respectively). Compared with the surgery-alone group, DFS was prolonged in the nCRT group (HR=0.60) (44).

The results of NEOCRTEC5010 trial are in concordance with CROSS trial; however, the median survival reported in NEOCRTEC5010 was significantly longer than that in the CROSS study. The reason for this result may be 70% patients in NEOCRTEC5010 trial were aged <60 years, which was different from the CROSS subjects, and may have better tolerance to preoperative CRT. In the NEOCRTEC5010 study, patients underwent systematic lymphadenectomy; median OS of patients who underwent systematic lymphadenectomy was significantly better than those who did not undergo lymphadenectomy (HR=0.358), but there was no increase in postoperative complications. Compared with those with number of resected lymph nodes ≥20, those with lymph node dissection <20 significantly increased the local recurrence rate (18.8 vs. 5.2%) (45).

Studies have compared the efficacy and safety of nCRT and nCT (46,47). Klevebro *et al* (46) enrolled 181 EC patients with a median age of 63 years and clinical stage of T1-3, any N (exception of T1N0), and patients were randomly divided into nCT and nCRT groups. in the nCT and nCRT groups, the proportion of ESCC was 27 and 28% respectively. Treatment began <2 weeks after randomization. All CT regimens were cisplatin at 100 mg/m^2 on day 1 and FU at 750 mg/m^2/24 h on days 1-5, repeated every 21 days for a total of three cycles. RT was performed for CT cycles 2 and 3 using photon irradiation and a 3D-CRT planning system. The total dose of RT was 40 Gy, divided into 20 fractions, 5 days/week. Surgery was performed 4-6 weeks after completion of neoadjuvant therapy. Compared with nCT alone, nCRT results in higher pCR (28 vs. 9%) and R0 resection rate (87 vs. 74%), and a lower frequency of lymph node metastases (35 vs. 62%), without significantly affecting survival; 3-year survival rate of ESCC was 52% in nCT and 56% in nCRT group (46). Application of new RT technology, such as IMRT or volumetric-modulated arc therapy technology, does not improve the long-term survival. A retrospective analysis compared the efficiency of nCRT and nCT of ESCC in patients with histological stage of T1-2NM0 or T3-4N0-3M0 aged 18-75 years (47). A total of 158 patients in the nCRT group received paclitaxel combined with platinum CT once/week, with a median radiation dose of 45 Gy (40.0-50.4 Gy; 1.8-2.14 Gy/time) for primary and metastatic lymph nodes using IMRT or volumetric-modulated arc therapy RT. CT was performed with 21 days/cycle and the median number of cycles was 3 (range, 1-4). pCR rate of nCRT and nCT group was 28.5 and 9.2, 1-year OS rate was 96.2 and 70.3, 5-year OS rate was 78.4 and 53.3% and the incidence of anastomotic leakage was 8.2 and 1.5% respectively (47).

The JCOG1109 study showed that the neoadjuvant DCF is superior to CF in terms of OS and PFS but there is no notable difference in OS and PFS between CF and nCRT (26). Median PFS was 5.3 in nCRT and 2.7 years in CF (HR=0.77, 95%CI 0.59-1.01); median OS was 7.0 and 5.6 years (HR=0.84, 95%CI 0.63-1.12), respectively. nCRT and DCF were not compared. Grade 3-4 leucocytopenia and neutropenia incidence was 6.7, 63.8, 53.9 and 23.4, 85.2 and 44.5% in CF, DCF and nCRT groups, respectively. Compared with nCT, the nCRT group had a larger number of deaths due to other diseases (26).

The impact of nCRT on postoperative complications and mortality remains controversial (48). Meta-analysis by Sathornviriyapong *et al* (49) showed that compared with surgery-alone, nCRT yields significantly higher postoperative mortality and cardiopulmonary complications but does not increase the risk of anastomosis and other complications. Subgroup analysis showed that female patients and those with T3 disease exhibited the greatest increase in median survival (49).

In previous trials, patients who underwent surgery after receiving new adjuvant treatment had higher postoperative mortality, which may be partly due to trauma caused by open esophagectomy (48,49). However, compared with open esophagectomy, minimally invasive esophagectomy (MIE) significantly decreases such trauma, morbidity and mortality (50). A prospective, multicenter, randomized controlled clinical study compared the safety and efficacy of nCRT and nCT combined with MIE in the treatment of patients with locally advanced ESCC (28). From 2017 to 2018, 264 patients with ESCC with clinical stage cT3 to T4a, N0 to N1, and M0 (UICC/AJCC 8th) (51) were randomly assigned to the nCRT or nCT group. Both groups received CT regimen based on paclitaxel and cisplatin, while the nCRT group received an additional 40 Gy concurrent RT. At ~6 weeks after neoadjuvant therapy, MIE via thoracoscopy and laparoscopy was performed for both groups. Mean age of the included patients was 61.4 years and the incidence of postoperative complications in the nCRT and nCT groups was 47.4 and 42.6%, respectively. The 90-day perioperative mortality rate in the nCRT and nCT groups was 3.5 and 2.8%; there was no significant difference in R0 resection rates (97.3 vs. 96.2%). However, the pCR rate (35.7 vs. 3.8%) and rate of negative lymph nodes (ypN0, 66.1 vs. 46.2%) were higher in the nCRT than in the nCT group. Using intention to treat analysis, the 1-year OS rates were similar in the nCRT and nCT groups (87.1 and 82.6%, respectively). In addition, the mortality caused by tumor progression or recurrence in the nCRT group was significantly lower than that in the nCT group (6.8 vs.

14.4%). However, rate of death due to other causes was similar (6.1 vs. 3.0%). The preliminary results of the study showed that for locally advanced ESCC who received MIE after nCRT and nCT had similar safety and better histopathology results; however, there was no significant difference in 1-year survival rate (52).

Studies have investigated the population who benefit more from nCRT treatment. in ESCC (53,54). Al-Kaabi *et al* (53) evaluated correlation between pathological tumor RR and OS in 4,946 patients with locally advanced ESCC following the nCRT protocol used in the CROSS study. A total of 24% of patients achieved pCR, with 19% in EADC and 42% in ESCC. Compared with incomplete responders, complete responders had better predicted 5-year OS (62 vs. 38%). Among patients with incomplete response, patients with ypT+N+ had the lowest 5-year OS rate at 22%, followed by ypT0N+ and ypT+N0 (47 and 49%, respectively). The correlation between pathological tumor response and long-term survival rate accurately assessed individual prognosis and may guide treatment decisions (53).

Greally *et al* (54) reviewed patients with locally advanced ESCC who received induction CT and CRT underwent PET examination before and after induction CT. Among 111 patients, 63% responded to induction CT with PET (defined as ≥35% decrease in maximum standard uptake). Responders were given the same CT regimen during RT. Among 41 non-responders, 16 continued to receive the same CT and 25 switched to RT. Compared with non-responders, the median PFS (70.1 vs. 7.1 months) and OS (84.8 vs. 17.2 months) of PET responders were significantly improved. Changing the CT regimen did not alter prognosis of PET non-responders; median PFS and OS were 6.4 and 8.3 and 14.1 and 17.2 months in the modified and unchanged regimen groups, respectively (54).

For locally advanced resectable ESCC, the optimal dose of RT in nCRT is controversial. A retrospective analysis explored the difference in survival benefits of low-40.0-41.4) and high-dose RT (50.0-50.4) Gy in 644 patients (55). Propensity score HR of death was 0.92 (95%CI 0.7-1.19). Prospective trials are warranted to validate these results (55).

Network meta-analysis of 31 RCTs with 5,496 has showed that nCRT is beneficial to survival, although it often increases postoperative incidence rate and mortality (32). Compared with all other treatment options, including surgery-alone (HR=0.75, 95%CI 0.67-0.85), nCT (HR=0.83, 95%CI 0.70-0.96) and nRT (HR=0.82, 95% CI 0.67-0.99), nCRT improved median OS regardless of pathological type. When comparing nCRT with nCT, patients with ESCC exhibit a significant OS benefit (HR=0.83, 95%CI 0.70-0.97). However, when nCRT is compared with surgery-alone (RR=1.46, 95%CI 1.00-2.14) or nCT (RR=1.58, 95%CI 1.00-2.49), postoperative mortality increases (32).

In summary, nCRT improves median OS and R0 resection rate compared with surgery-alone in ESCC with clinical stage T1N1 or T2-3N0-1M0 (UICC/AJCC 6th) (10,44). Compared with nCT, nCRT yields higher pCR rate, however the improvement of long-term survival is controversial despite use of IMRT and volumetric-modulated arc therapy. The pCR rate of nCRT is 29.0-43.2%. After nCRT treatment, patients with tumor volume decreased and metastatic lymph node regression can achieve better median survival. The recommended RT dose in nCRT is 40.0-50.4 Gy and involved field irradiation as the target delineation of RT is the most widely used in clinical trials (46,47,52). Three-drug concurrent CT can obtain better pCR than two-drug CT; however, compared with surgery-alone or nCT, the frequency of grade 3-4 blood toxicity and the post-operative mortality rate are increased (32). Selected papers are summarized in Table III.

5. Neoadjuvant treatment with sequential CT and concurrent CRT

Induction CT can shrink tumor volume, provide smaller irradiation field for RT and decrease RT-related adverse events), which may improve the efficacy of nCRT therapy for EC (56). Clinical studies have explored the efficacy and AEs of neoadjuvant treatment with sequential CT and concurrent CRT (56,57). In a phase II study, Ruhstaller *et al* (56) explored the feasibility of induction CT followed by concurrent CRT in patients with pathologically confirmed EC, aged 18-70 years, with a performance status of 0 or 1. The tumors were locally advanced but resectable (stage T3/N0, T1-3/N+ or T4/Nx). A total of 30 patients with ESCC and 36 with EADC received induction CT of cisplatin and docetaxel at 75 mg/m^2 on the 1st and 22nd days, followed by RT with a total dose of 45 Gy (1.8 Gy once daily in 25 fractions, 5 days/week) and concurrent CT with cisplatin at 25 mg/m^2 and docetaxel at 20 mg/m^2, once/week for 5 weeks, followed by surgery. At the end of the second induction CT cycle, concurrent CRT was started. 3D-CRT and 6-18 MV photons were used. GTV included all known disease areas, 5 cm outward in the direction of the upper and lower margins of the esophageal tumor and 2 cm outward around the tumor to form the CTV. A total of 82% of patients completed neoadjuvant therapy and 86% of patients underwent surgery. R0 rate was 91.23% (52/57). Among patients receiving neoadjuvant treatment, 15 patients achieved complete, 16 patients were evaluated as PR (partial response) and 26 patients had poor pathological response. Median OS was 36.5 months and median event-free survival was 22.8 months. Patients with ESCC and good pathological response had a longer survival time. During CRT, grade 3-4 dysphagia and mucositis were rare (<9%). A total of five patients (9%) died of surgical complications (56).

However, another phase II trial of 126 patients showed that induction CT combined with concurrent CRT does not increase the pCR rate or prolong the OS of patients with ESCC compared with concurrent CRT-alone (58). The clinicopathological characteristics were similar, with a median age of 60 years; proportion of ESCC was 3.2%, proportion of clinical stage II was 41.3% and the proportion of stage III was 58.7%. Patients received radiation dose of 50.4 Gy, which was divided into 28 fractions and planning system of IMRT was used. The concurrent CT regimen was fluorouracil (250 mg/m^2/day, 24 h infusion, 5 days/week, for 5 weeks) and oxaliplatin (40 mg/m^2, once/week, 5 times in total). Surgery was conducted 5-7 weeks after the CRT. The same drugs were selected for induction CT, once/4 weeks for two cycles. The median OS of induction and non-induction CT group was 43.68 and 45.62 months and pCR rate was 26 (14/54) and 13% (7/55), respectively. Safety was similar in both arms (58).

nCT with DCF has shown higher RR than CF for ESCC (26). Satake *et al* (57) conducted a multicenter, phase I/II study to

Table III. Studies using nCRT in patients with ESCC.

First author, year	Study design	Number of patients	Treatment	Outcome	(Refs.)
Mariette *et al*, 2014	RCT	195, including 137 ESCC	i) nCRT: 3D-CRT 45 Gy/25 F + 5-fluorouracil 800 mg/m^2/day for 4 days, cisplatin 75 mg/m^2 d1 or d2, q28d) for two cycles + S; ii) S-alone	R0, 93.8% in nCRT vs. 92.1% in S (P =0.749). 3-year OS, 47.5% in nCRT vs. 53.0% in S (P=0.940). Postoperative mortality, 11.1% in nCRT vs. 3.4% in S (P=0.049).	(42)
van Hagen *et al*, 2012	RCT	366, including 84 ESCC	i) nCRT: 3D-CRT 41.4 Gy/23 F + carboplatin (AUC, 2 mg/ml/min weekly for 5 weeks) + paclitaxel (50 mg/m^2 weekly for 5 weeks) + S; ii) S-alone	R0, 92% in nCRT vs. 69% in S (P<0.001). pCR, 49% in ESCC nCRT. mOS, 49.4 in nCRT vs. 24.0 months in S (P=0.003).3-year OS of ESCC, 50% in nCRT vs. 25.6% in S (P=0.011). Pulmonary complications, 46% in nCRT vs. 44% in S. Cardiac complications, 21% in nCRT vs. 17% in S.	(10)
Yang *et al*, 2021	RCT	451 ESCC	i) nCRT: 3D-CRT 40 Gy/20 F + vinorelbine (25 mg/m^2 d1,8 q21d) + cisplatin (75 mg/m^2 d1, q21d) for two cycles + S; ii) S alone	R0, 98.4% in nCRT vs. 91.2% in S (P=0.002). pCR, 43.2% in nCRT. mOS, 100.1 in nCRT vs. 66.5 months in S (P=0.025). Grade 3-4 neutropenia during nCRT, 45.7%. Perioperative mortality, 2.2% in nCRT vs. 0.4% in S (P=0.212).	(44)
Klevebro *et al*, 2016	RCT	181, including 50 ESCC	i) nCRT: 3D-CRT 40 Gy/20 F, CF for three cycles + S; ii) nCT: Three cycles of cisplatin 100 mg/m^2 d1, fluorouracil 750 mg/m^2/day, days 1-5, repeated every 21 days + S	R0, 87% in nCRT vs. 74% in nCT (P=0.040). pCR rate, 28% in nCRT vs. 9% in nCT (P=0.002).3-year OS, 56% in nCRT vs. 52% in nCT (P=0.780).	(46)
Li *et al*, 2022	Retrospective	419 ESCC	i) nCRT: IMRT or VMAT 40.0-50.4 Gy/1.8-2.14 Gy/F + paclitaxel q1w + platinum q1w + S; ii) nCT: paclitaxel + platinum, q21d for three cycles + S	pCR, 28.5% in nCRT vs. 9.2% in nCT (P<0.001). 1-year OS, 96.2% in nCRT vs. 70.3% in nCT. 5-year OS, 78.4% in nCRT vs. 53.3% in nCT (P=0.140). Anastomotic leakage, 8.2% in nCRT vs. 1.5% in nCT.	(47)
Wang *et al*, 2021	RCT	264 ESCC	i) nCRT: 40 Gy/20 F + paclitaxel (50 mg/m^2 q1w) + cisplatin (25 mg/m^2 q1w) + S; ii) nCT: Paclitaxel (135 mg/m^2, q21d) + cisplatin (75 mg/m^2, q21d) + S	R0, 97.3% in nCRT vs. 96.2% in nCT (P=0.920). Postoperative complications, 47.4% in nCRT vs. 42.6% in nCT (P=0.480). pCR, 35.7% in nCRT vs. 3.8% in nCT (P<0.001). 1-year OS, 87.1% in nCRT vs. 82.6% in nCT (P=0.300).	(52)

Table III. Continued.

First author, year	Study design	Number of patients	Treatment	Outcome	(Refs.)
Chan *et al*, 2018	Meta	5,496	i) nCRT; ii) nCT; iii) nRT; iv) S-alone	nCRT improved mOS (nCT, HR=0.83, 95%CI 0.70-0.96; nRT, HR=0.82, 95% CI 0.67-0.99; S-alone, HR=0.75, 95%CI 0.67-0.85). Compared with S-alone, nCRT (RR=1.46, 95%CI 1.00-2.14) and nCT (RR=1.58, 95%CI 1.00-2.49) increased postoperative mortality.	(32)

RCT, randomized controlled trial; ESCC, esophageal squamous cell carcinoma; nCRT, neoadjuvant chemoradiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; CT, chemotherapy; RT, radiotherapy; AUC, area under the curve; S, surgery; pCR: pathological complete response; IMRT, intensity-modulated radiotherapy technology; VMAT, volumetric-modulated arc therapy; mOS, median overall survival; F, fraction; meta, meta-analysis.

evaluate the curative effect and safety of induction CT with DCF followed by nCRT in patients with unresectable locally advanced ESCC. Treatment plan was 70 mg/m^2 docetaxel and cisplatin on the first day and 750 mg/m^2 FU on the first to fifth days, repeated every 3 weeks for three cycles, followed by 70 mg/m^2 cisplatin on the 64th and 92nd days, 700 mg/m^2 FU on the 64th to 67th and 92nd to 95th days, concurrent with RT (60 Gy in 30 fractions, 5 days/week). 3D-CRT planning system was used. GTV was decided by pretreatment with CT and gastrointestinal endoscopy. CTV included GTV and metastatic lymph nodes and extended 3 cm outward at the upper and lower margins of the esophageal tumor, 1 cm outward around the tumor and 0-1 cm outward at the margin of the lymph node metastasis, without preventive radiation to the lymph node area. Of 35 patients enrolled, 48% had clinical stage T4 M0 (UICC/AJCC 6th) (21) and 39% had non-T4 M1 lymph node metastasis. Among patients with clinical stage T4, 15 cases had invaded trachea, two had invaded thoracic aorta and one had invaded pericardium and stomach. A total of 88% of patients completed all treatment plans; 39.4% of patients achieved complete clinical remission after completing nCRT. The median follow-up time was 41 months; median PFS and OS was 12.2 and 26.0 months, respectively, and the 3-year survival rate was 40.4%. The main grade 3-4 adverse reactions were neutropenia, leukopenia, anorexia and dysphagia. No treatment-associated mortality was found (57).

In a retrospective analysis, 103 patients with locally advanced EC, of which 65% were ESCC and 30% were EADC, received nCRT and radical resection; 41.7% also received induction CT (59). For 90% of patients, induction CT drugs were paclitaxel and platinum with a median of two induction CT cycles. pCR rate in induction and non-induction groups was 41.9 and 46.7%, respectively. The results of multivariate analysis showed that pCR was an independent prognostic factor for treatment failure time (HR=0.35), but not for OS. Positive lymph nodes were significantly associated with OS (HR=5.9) (59).

For locally advanced ESCC with clinical stage T4, surgery yields better 3-year DFS and OS than radical CRT following nCRT. A retrospective analysis included 726 patients with ESCC with clinical stage T4 who were treated between 2002 and 2017 (60). After 4 weeks of RT (median radiation dose, 40.71 Gy), 308 (42.4%) patients achieved clinical complete or partial remission and were evaluated as suitable for surgical resection. Among these, 74 patients received surgery and 234 patients received radical RT and CT. The 3-year DFS of the surgery and the radical RT and CT group was 48.5 and 22.1%, respectively; 3-year OS was 54.8 and 30.0%, respectively. It was suggested that for patients with stage cT4 ESCC, who achieved CR and PR after nCRT and were evaluated for surgery had higher 3-year DFS and 3-year OS rates than those who continued to complete radical CRT (60).

To the best of our knowledge, the clinical studies on neoadjuvant treatment with sequential CT and concurrent CRT are all phase I and II or retrospective analyses (56,58,60). Compared with the subjects included in the clinical research using other neoadjuvant treatment strategies, the subjects included in the clinical research using this strategy are later in stage and include T4 cases, so the prognosis may be worse. Induction CT prior to preoperative CRT is feasible, but addition of induction CT to standard CRT and surgery does not increase the pCR and OS rate in locally advanced ESCC.

6. Neoadjuvant immunotherapy and CT

Preclinical studies have demonstrated that the combination of programmed cell death 1 (PD-1) inhibitor and CT can enhance the host immune response and inhibit cancer cell immune escape (61-63). In the first-line treatment of patients with advanced or metastatic EC, pembrolizumab or camrelizumab combined with 5-FU and cisplatin has shown a survival advantage over CT alone (64,65). To the best of our knowledge, however, there is not enough evidence to sustain the use of neoadjuvant immunotherapy in patients with ESCC.

Yang *et al* (66) conducted a single-arm clinical study to check the safety and feasibility of combination of neoadjuvant PD-1 blocker and CT in 23 patients with resectable ESCC who had not previously received anti-tumor therapy (stage II or III, UICC/AJCC 8th) (51). Each patient received two cycles of neoadjuvant therapy, including camrelizumab (200 mg on day 1), nab-paclitaxel (260 mg/m^2 on day 1) and carboplatin (area under the curve 5 on day 1), with a cycle of 21 days, before surgery. Neoadjuvant therapy had acceptable side effects and no operation delay was observed. Grade 3-4 treatment-associated AEs included neutropenia (39.1%) and leucopenia (8.7%). The objective RR (ORR) and disease control rate were 90.5 and 100.0% respectively. A total of 20 patients underwent surgery and all of them achieved R0 resection. pCR occurred in 5 (25%) patients and major pathological reaction occurred in 10 (50%) patients. Compared with the non-pCR group, the proportion of patients with high tumor mutation load and expression of programmed death ligand 1 (PD-L1) in primary tumors in those achieving pCR was significantly increased. After treatment, the number of infiltrating PD-L1$^+$/CD163$^+$ cells in pCR group was significantly lower than that in non-pCR group (P=0.017) (66).

Neoadjuvant chemoimmunotherapy-esophageal squamous cell carcinoma) 2019 was a multicenter, phase II study aimed at evaluating the efficacy of neoadjuvant combination CT with camrelizumab in patients with resectable and locally advanced ESCC (clinical stage II-IVA, UICC/AJCC 8th) (51). Patients received two cycles of neoadjuvant immunochemotherapy (nIC); each 21-day cycle included camrelizumab (200 mg on day 1), nab-paclitaxel (260 mg/m^2 on days 1 and 8) and cisplatin (75 mg/m^2 on days 1-3). At ~6 weeks after nIC completion, surgery was performed. A total of 56 patients was enrolled and 51 underwent esophagectomy. The pCR rate was 35.3% (95%CI 21.7-48.9%). The ORR of nIC was 66.7% (95%CI 40.0-70.4%), and the severity of treatment-related adverse events (TRAEs) was low (grade 1-2, 75.0%; grade 3, 10.7%; grade 4-5, 0.0%). No perioperative deaths were found. A total of three (5.9%) patients experienced tumor recurrence and one (2.0%) died. The median PFS and median OS were not reached. Camrelizumab combined with nCT showed good efficacy and acceptable toxicity in resectable ESCC, providing a feasible and effective choice. Long-term survival analysis is in progress (67).

A clinical study enrolled patients with locally advanced resectable thoracic ESCC s with clinical stages of T1b-4a, N2-3 and M0 or M1 (UICC/AJCC 8th). Stage M1 was defined as lymph node metastasis limited to supraclavicular lymph nodes. Patients received intravenous injection of carlizumab (200 mg, day 1), nab-paclitaxel (100 mg/m^2, days 1, 8 and 15), and carboplatin (AUC, 5 mg/ml/min, day 1) before surgery, for two 21-day cycles. Safety was evaluated in patients receiving at least one dose of caleczumab. Among 60 patients, 55 (91.7%) completed two cycles of treatment, 51 underwent surgery and 50 patients (98.0%) achieved R0 resection; 20 (39.2%) patients achieved pCR (ypT0N0) and five (9.8%) patients showed complete response to the primary tumor with only residual lymph nodes (ypT0N+); 58 patients (96.7%) developed TRAEs, with the most common being leukocytopenia (86.7%); 34 patients (56.7%) had a grade ≥3 AE, and one patient (1.7%) had a grade 5 AE. There was no death at 30 or 90 days after surgery. Camrelizumab and CT have strong anti-tumor activity and no unexpected AEs occurred (68).

A systematic evaluation included published phase II or phase III clinical trials, including patients with resectable stage I-IV EC who received immune checkpoint inhibitors (ICIs) as a single therapy or in combination with other treatment methods before surgery. A total of 815 patients were included in 27 clinical trials. The combined rate of pCR was 31.4% (95%CI 27.6-35.3%), and the major pathological response (MPR) was 48.9% (95%CI 42.0-55.9%). Incidence of serious TRAEs was 26.9% (95%CI 16.7-38.3%). Most patients attained R0 resection (98.6%, 95%CI 97.1-99.6%). Total pCR rate in ESCC was 32.4% (95%CI, 28.2-36.8%) and MPR rate was 49.4% (95%CI 42.1-56.7%) (69).

In summary, the aforementioned studies demonstrated that neoadjuvant immunotherapy combined with CT has good clinical efficacy and safety in patients with locally advanced ESCC. The pCR rate of neoadjuvant immunotherapy is 20-50% and R0 surgical resection rate is ~98.6%. To the best of our knowledge, long-term follow-up results have not been reported; most of the aforementioned studies single-arm trials with small sample sizes and the combined CT schemes were inconsistent. It is necessary to conduct RCTs with long-term follow-up to verify the benefits of ICIs. Selected papers are summarized in Table IV.

7. Neoadjuvant immunotherapy and CRT

RT may increase perioperative complications but it may also improve the effect of immunotherapy. Therefore, clinical studies are required to investigate the feasibility of preoperative immunotherapy combined with RT for EC.

Preoperative Anti-PD-1 Antibody combined with Chemoradiotherapy for Locally Advanced Squamous Cell Carcinoma of Esophageus-1) clinical study enrolled 20 patients with resectable locally advanced ESCC. Regardless of status of PDL-1, patients received preoperative pemebruzumab combined with concurrent CRT (PPCT). Preoperative therapy included carboplatin (AUC, 2 mg/ml/min, weekly for 5 weeks), paclitaxel (50 mg/m^2, weekly for 5 weeks), RT (total dose of 41.4 Gy divided into 23 fractions, 5 fractions/week) and pembrolizumab (2 mg/kg) on days 1 and 22. The patients were scheduled for surgical treatment within 4-6 weeks of neoadjuvant therapy completion. All patients successfully received PPCT. A total of 65% of patients had AEs ≥grade 3 and one patient experienced grade 5 AEs. The most common grade 3 AE was lymphopenia (92%). A total of 18 patients underwent surgical treatment within 4-9 weeks of PPCT completion, with a pCR rate of 55.6%. A phase II multicenter study is under way to confirm the pCR rate of neoadjuvant immunotherapy and CRT (15).

A meta-analysis evaluated the feasibility of neoadjuvant immune-CRT (nICRT) and nICT for EC (70). A total of 20 clinical studies was included, including single-arm studies, of which five involved nICRT and 15 involved nICT. The overall rates of pCR, MPR and R0 were 32, 55 and 96% respectively. The pCR rates of nICRT and nICT were 41 and 30%, respectively. Both the nICRT and nICT groups achieved high R0 resection rate (96 vs. 99%). The incidence of grade 3 TRAEs

Table IV. Studies using neoadjuvant immunotherapy and chemotherapy in patients with ESCC.

First author, year	Study design	Number of patients	Treatment	Selected outcomes	(Refs.)
Yang *et al*, 2022	Single-arm	23 ESCC	Camrelizumab (200 mg d1 q21d) + nab-paclitaxel (260 mg/m^2 d1 q21d) + carboplatin (AUC, 5 5 mg/ml/min d1 q21d) for two cycles + S	Grade 3-4 neutropenia, 39.1%. ORR, 90.5%. R0, 100%. pCR, 25%	(66)
Liu *et al*, 2022	Single-arm	56 ESCC	Camrelizumab (200 mg d1, q21d) + nab-paclitaxel (130 mg/m^2 on days 1 and 8 q21d) + cisplatin (75 mg/m^2 in total on days 1-3 q21d) for two cycles + S	ORR, 66.7%. pCR, 35.3%. TRAEs, grade 1-2, 75.0%; grade 3, 10.7%; grade 4-5, 0.0%.	(67)
Liu *et al*, 2022	Single-arm	60 ESCC	Carlizumab (200 mg d1 q21d) + nab-paclitaxel (100 mg/m^2 d1,8,15 q21d) + carboplatin (AUC, 5 mg/ml/min d1 q21d) for two cycles + S	R0, 98.0%. pCR, 39.2%. AE ≥grade 3, 56.7%.	(68)
Ge *et al*, 2022	Meta	815, including 689 ESCC	ICI ± other treatment methods + S	R0, 98.6%. pCR, 31.4%. MPR, 49.4%. Overall serious TRAEs, 26.9%.	(69)

ESCC, esophageal squamous cell carcinoma; AUC, area under the curve; ORR, objective response rate; pCR, pathological complete response; TRAE, treatment-related adverse event; MPR, major pathological response; meta, meta-analysis; ICI, immune checkpoint inhibitor; S: surgery.

was 52 and 20% for nICRT and nICT, respectively. This suggested that the efficacy of nICRT is not superior to that of nICT, but the potential toxicity is increased (70).

In summary, nICRT is effective. The pCR rate is 55.6%, but, to the best of our knowledge, previous studies were mostly single-center, single-arm studies with small sample sizes. (15,71,72). There is a lack of high-quality prospective randomized controlled studies.

8. Neoadjuvant targeted therapy

A phase IB/II study evaluated the safety and effectiveness of adding cetuximab to preoperative nCRT for patients with locally advanced EC (73). Patients with clinical stage of T2-3N0-1M0, T1-3N1M0 or T1-3N0-1M1A received one cycle of induction CT of cisplatin (100 mg/m^2, day 1) and 5-FU (1,000 mg/m^2/day, days 1-5). After 4 weeks, concurrent CRT was applied. RT dose was 50.4 Gy and the concurrent CT regimen was cisplatin (75 mg/m^2) for two cycles and increasing doses of 5-FU. The patients were infused with cetuximab 10 times/week, 250 mg/m^2, and the load dose was 400 mg/m^2. Surgery was planned for 6-8 weeks after nCRT. A total of 64 patients received treatment and 60 completed nCRT. The median age was 65 years and the ratio of EADC:ESCC was 61:39. A total of 72% of patients had ≥grade 3 toxicity and two (3%) died. The clinical complete remission rate was 33%. Of the 55 patients undergoing surgery, 93% achieved R0 resection, 33% achieved pCR resection and 14% died after operation. The 5-year survival rate of all patients was 38% and the median OS was 23.4 months. Patients with ESCC had higher pCR (55 vs. 20%), local control (96 vs. 74%) and 5-year survival rate (58 vs. 25%). Following treatment with cetuximab combined with preoperative nCRT for patients with locally advanced EC, 72% of the patients experienced grade 3 treatment related toxicity, and 3% of patients die due to treatment related toxicity (73).

A phase IB/II trial demonstrated that adding cetuximab to preoperative CRT does not increase postoperative mortality (74). A phase III SAKK75/08 clinical trial has been conducted (75). Patients (median age, 61 years; 37% ESCC; 85% cT3/4a, 90% cN+) were assigned to receive cetuximab (n=149) or control (n=151; two cycles of induction CT, followed by concurrent CRT and surgery). The cetuximab group was treated with the same nCRT regimen. Before surgery, the dose of cetuximab was 250 mg/m^2, once/week, and the initial loading dose was 400 mg/m^2. Postoperative dose of cetuximab was 500 mg/m^2 every two weeks for 3 months. Induction CT included intravenous injection of cisplatin and docetaxel at 75 mg/m^2 on day 1, every 3 weeks. Concurrent CRT started 3 weeks after the second cycle of induction CT. 6-18MV photons were used for 3D-CRT with a total dose of 45 Gy (1.8 Gy/day, 5 times/week). IMRT, volume-modulated arc therapy and tomography were used. The PTV included all known disease areas, extending 5 cm outward at the upper and lower margins of the esophageal tumor and 2 cm outward around the tumor. Concurrent CT included intravenous injection of cisplatin at 25 mg/m^2 and docetaxel 20 mg/m^2, weekly, for 5 weeks. Surgery was performed 3-8 weeks after the completion of neoadjuvant treatment. R0 resection rate of cetuximab was 95 compared with 97% in the control group. The median PFS of cetuximab group was

2.9 years (95%CI 2.0-not reached) and that of control group was 2.0 years (95%CI 1.5-2.8; HR=0.79, 95%CI 0.58-1.07). The time to loco-regional failure after cetuximab treatment and R0 resection was significantly prolonged (HR=0.53, 95%CI 0.31-0.90). There was no difference in time to distant failure between the two groups (HR=1.01, 95% CI 0.64-1.59). Postoperative treatment-related mortality was 6% in both groups. Cetuximab did not increase AEs in neoadjuvant or postoperative treatment (75).

In summary, clinical research on the neoadjuvant targeted treatment of ESCC has showed that the combination CT with cetuximab improves long-term survival, but larger clinical studies are needed (73,75).

9. Conclusion

Neoadjuvant therapy for locally advanced ESCC is a developing treatment mode. Clinical studies have shown encouraging findings, such as decreased tumor stage and increased pCR rate. Limitations include the high incidence of toxicity during concurrent CRT; commonly used nCT and sequential concurrent CT do not show survival benefits and the target area and dose of nRT are still controversial (10,22,44,49,58,73). New methods combining biomarkers and new therapies, such as neoadjuvant immunotherapy, have potential. The results of an ongoing phase III clinical trial (76,77) may provide support the use of neoadjuvant treatment.

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Authors' contributions

HZ and WZ conceived and designed the study and wrote and revised the manuscript. FZ and YS designed the study and revised the manuscript. SL 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.

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