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REVIEW ARTICLE

Current neoadjuvant therapy for operable locally advanced esophageal cancer

Wenwei Yang[1] · Yaru Niu[1] · Yongkun Sun[1,2]

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Abstract

Locally advanced esophageal cancer has a poor prognosis, while an increasing number of patients are diagnosed with that. Neoadjuvant therapy has become a hot topic in treating locally advanced esophageal cancer to improve its survival benefit. The efficacy of neoadjuvant therapy followed by surgery has been confirmed by many studies, and neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy are included in the guidelines. In recent years, targeted therapy and immunotherapy have emerged, and more studies are evaluating the efficacy of combining them with neoadjuvant therapy for operable esophageal cancer patients. Even though the preliminary data is disappointing, many trials are still under investigation without improving survival benefits. New indexes used as surrogate endpoints (e.g., major pathologic response and pathological complete response) are emerging to accelerate the development and approval of neoadjuvant drugs. This review summarized the research progress in neoadjuvant therapy for locally advanced esophageal cancer and discussed which primary endpoint should be used in neoadjuvant therapy trials.

Keywords Esophageal cancer · Neoadjuvant chemotherapy · Neoadjuvant chemoradiotherapy · Targeted therapy · Immunotherapy

Abbreviations

EC	Esophageal Cancer
ESCC	Esophageal Squamous Cell Carcinoma
EAC	Esophageal Adenocarcinoma
NRT	Neoadjuvant Radiotherapy
NCCN	National Comprehensive Cancer Network
NCT	Neoadjuvant Chemotherapy
RCT	Randomized Clinical Trial
5-FU	5-fluorouracil
CF	Cisplatin plus 5-FU
VS	Versus
HR	Hazard Ratio
GEJ	Gastroesophageal Junction
PFS	Progression Free Survival
OS	Overall Survival
DFS	Disease Free Survival
NCRT	Neoadjuvant Chemoradiotherapy
pCR	pathological Complete Response
mOS	median Overall Survival
ECX	Epirubicin, Cisplatin plus Capecitabine
ECF	Epirubicin, Cisplatin plus 5-FU
EGFR	Epidermal Growth Factor Receptor
VEGFR	Vascular Endothelial Growth Factor Receptor
HER2	Human Epidermal Growth Factor Receptor-2
ASCO	American Society of Clinical Oncology
FLOT	Docetaxel, Oxaliplatin, Calcium folinate plus 5-FU
CAPOX	Capecitabine plus Oxaliplatin
PD-1	Programmed Death 1
PD-L1	Programmed Death Ligand 1
DCF	Docetaxel, Cisplatin plus 5-FU
MPR	Major Pathologic Response

✉ Yongkun Sun
hsunyk@cicams.ac.cn

[1] National Clinical Research Center for Cancer/Cancer Hospital, National Cancer Center, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

[2] National Cancer Center, National Clinical Research Center for Cancer/Hebei Cancer Hospital, Chinese Academy of Medical Sciences, Langfang 065001, China

Introduction

Esophageal cancer (EC) is the seventh most common cancer worldwide with over 604,000 new cases in 2020, and the sixth leading cause of cancer-related deaths globally (544,000 deaths in 2020) [1]. The five-year survival rate is only 15–20% [2]. Based on histology, EC is mainly classified into esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Other rare subtypes of esophageal cancer include melanomas, leiomyosarcomas, carcinoids, other carcinomas, and lymphomas [3]. They vary greatly in their biological behaviors and epidemiology. ESCC is the most common type of EC worldwide and is predominant in China, Japan and southeast Africa, while EAC patients account for most cases in the United States, Australia, and Western European countries [4–6].

For early-stage esophageal tumors, radical esophagectomy remains the mainstay of treatment. However, the five-year overall survival rate of patients treated with surgery is still poor (10-33%) [7]. Moreover, most patients are diagnosed with a locally advanced EC, which is defined as a tumor that invades the local structure or involves regional lymph nodes without distant metastases and cannot be resected directly (AJCC TNM staging system ≥ cT2 and/or cN1-3, M0). Therefore, surgery combined with systematic treatment, such as neoadjuvant chemotherapy (NCT), neoadjuvant chemoradiotherapy (NCRT), and perioperative chemotherapy, is necessary to improve a patient's survival benefits. Furthermore, targeted therapy and immunotherapy are also promising in EC treatment, and they are often combined with chemotherapy or chemoradiotherapy to optimize the neoadjuvant treatment of EC.

Neoadjuvant therapy, also named preoperative therapy, has become one of the research highlights in treating locally advanced EC. Neoadjuvant therapy benefits EC patients in multiple ways. Firstly, it can decrease the size of tumors, reducing the difficulty of surgery, completely resecting the tumors, and improving the R0 resection rate. Compared to adjuvant therapy, most patients can tolerate neoadjuvant therapy. A clinical trial indicated that 87% of patients could tolerate preoperative chemotherapy, while only half with good nutritional conditions could receive postoperative chemotherapy [8]. Before the surgery, undamaged blood vessels with sufficient oxygen supplements make the body sensitive to chemotherapy and radiotherapy. Moreover, preoperative therapy can eliminate micro-metastases, decrease the risk of distant metastasis, and limit tumor recurrence after resection.

In recent years, many pieces of research suggested that several novel neoadjuvant therapy regimens could improve the survival of locally advanced esophageal cancer patients. Therefore, the optimal treatment remains to be determined. This review summarized the current knowledge and recently available data about neoadjuvant therapy for locally advanced esophageal cancer.

Neoadjuvant chemotherapy (NCT)

Due to the poor overall survival rate in patients treated with surgery and the difficulty of most cancer patients tolerating postoperative chemotherapy, much of the attention has been shifted to neoadjuvant chemotherapy (NCT). Feri first proposed the concept of NCT in 1982 [9], and then many clinical trials were conducted to assess the benefit of neoadjuvant chemotherapy followed by surgery (Table 1). However, these studies showed conflicting results. Most of the early trials did not show a survival benefit of neoadjuvant chemotherapy compared to surgery alone, which could be explained by the small sample size, unreliable staging, and difficulty in assessing the quality of surgery.

NCT for locally advanced EAC

EAC was predominant in western countries; thus, a large number of studies carried out by western countries focused on EAC or included more patients with EAC histologic type. In 1998, a large-scale randomized clinical trial (RCT), Radiation Therapy Oncology Group trial 8911 (USA Intergroup 113), was conducted to compare the tumor responses to preoperative chemotherapy plus surgery versus surgery alone in 440 patients with locoregional esophageal cancer (53% of them is EAC, 47% is ESCC). Two hundred thirteen patients received preoperative chemotherapy, including three cycles of cisplatin and 5-fluorouracil (5-FU) (CF regimen), and surgery was performed two to four weeks after the third cycle of chemotherapy was completed. This group of patients also received two additional cycles of chemotherapy postoperatively. Other 227 patients experienced immediate surgery. After a median study time of 55.4 months, the median survival of patients who received chemotherapy plus surgery was only 14.9 months, while for those who only underwent surgery, it was 16.1 months. ($P = 0.53$) Therefore, preoperative chemotherapy did not bring survival benefits for patients with operable esophageal cancer. Furthermore, no survival difference was found between patients with ESCC and EAC. The toxicity of chemotherapy was well-tolerated [10]. In 2007, the updated data showed that R0 resection could significantly prolong survival, while R1 resection had an ominous prognosis, with only 5% of these patients achieving five-year survival. The participation of chemotherapy did not increase the R0 resection rate (63% VS 59%; $P = 0$ 0.5137), which might account for the failure of preoperative chemotherapy

Table 1 Clinical trials for neoadjuvant chemotherapy in esophageal cancer

Author	Number of patients	SCC (%)	AC (%)	Study design	Long-term survival	Surgical outcomes	Response to neoadjuvant chemotherapy
Roth et al. [16]	39	100	0	Surgery alone VS Pre- and post-CT: cisplatin + bleomycin + vinblastine	mOS 9 m vs. 9 m	Resection rate: 21% vs. 35%	ORR 47% (CR 5.9%)
Schlag et al. [17]	46	100	0	Surgery alone VS Pre-CT CF	mOS 10 m vs. 10 m	Resection rate: 79% vs. 70%	NA
Nygaard et al. [18]	85	100	0	Surgery alone VS Pre-CT cisplatin + bleomycin	mOS 7 m vs. 7 m	NA	NA
Maipang et al. [19]	46	100	0	Surgery alone VS Pre-CT cisplatin + bleomycin + vinblastine	mOS 17 m vs. 17 m 3-y survival rate: 36% and 31%, p = 0.186	NA	ORR 33% (CR 8.3%)
Law et al. [20]	147	100	0	Surgery alone VS Pre-CT CF	mOS 13 m vs. 16.8 m, p = 0.17	Resection rate: 95% vs. 89%	ORR 58% (CR 6.7%)
Baba et al. [21]	42	100	0	Surgery alone VS Pre-CT cisplatin + 5-FU + leucovorin	mOS 40.1 m vs. 34.1 m	NA	ORR 60%
Ancona et al. [22]	94	100	0	Surgery alone VS Pre-CT CF	mOS 24 m vs. 25 m 5-y survival rate: 22% and 34%, p = 0.55	Resection rate: 74.4% vs. 78.7%, Postoperative mortality: 4.2% vs. 4.2%	ORR 40% (CR 12.8%)
Cunningham et al. (MAGIC) [13]	503	0	100	Surgery alone VS Pre-and post-CT ECF	5-y survival rate: 23% vs. 36% (p = 0.009)	R0 resection rate 70% vs. 79% (p = 0.03) Postoperative morbidity 45% vs. 45% Postoperative mortality 6% vs. 6%	NA
Kelsen et al. (RTOG8911) [11]	440	47	53	Surgery alone VS Pre-CT CF	mOS 16.1 m vs. 14.9 m (p = 0.53), 2-y survival rate: 26% vs. 23% (p = 0.65)	R0 resection rate 59% vs. 63%; Postoperative mortality 6% vs. 6%	ORR 19% (CR 7%)
Allum et al. (OEO2) [7]	802	30.8	66.5	Surgery alone VS Pre-CT CF	5-y survival rate: 17% vs. 23% (p = 0.004)	R0 resection rate 54% vs. 60% Postoperative morbidity 42% vs. 41% Postoperative mortality 10% vs. 10%	NA
Schuhmacher et al. (EORTC 40,954) [23]	144	0	100	Surgery alone VS Pre-CT: cisplatin + 5-FU + d-L-folinic acid	mOS 52.53 m vs. 64.62 m 2-y survival rate: 69.9% vs. 72.7%	R0 resection rate 66.7% vs. 81.9%(p = 0.04) Lymph node metastases: 52 patients (76.5%) vs. 43 patients (61.4%; p = 0.018)	ORR 36.2% (5.8%)
Ychou et al. (ACCORD07) [8]	224	0	100	Surgery alone VS Pre- and post-CT CF	5-y survival rate: 24% vs. 38% (p = 0.02)	R0 resection rate 74% vs. 84% (p = 0.04) Postoperative morbidity 19% vs. 26% (p = 0.24) Postoperative mortality 5% vs. 5% (p = 0.76)	NA
Boonstra et al. [24]	169	100	0	Surgery alone VS Pre-CT: cisplatin + etoposide + leucovorine	mOS 12 m vs. 16 m 5-y survival rate: 17% and 26%	R0 resection rate 57% vs. 71%	ORR 30.6% (CR 7%)
Ando et al. (JCOG9907) [14]	330	100	0	Post-CT CF VS Pre-CT CF	5-y survival rate: 42% vs. 55% (p = 0.04)	R0 resection rate 91% vs. 96% (p = 0.04) Postoperative mortality 0.6% vs. 0.6%	ORR 38% (CR 7%)
Tryakin et al. [25]	121	93.4	6.6	Surgery alone VS Pre-CT: cisplatin + etoposide + leucovorine + 5-FU	mOS 18.0 m vs. 26.5 m 2-y PFS 30.7% vs. 43.5%	R0 resection rate 81.0% vs. 82.5% (p = 1.0) Postoperative mortality 12.1% vs. 11.7%	ORR 49.1% (CR 1.9%)

Table 1 (continued)

Author	Number of patients	SCC (%)	AC (%)	Study design	Long-term survival	Surgical outcomes	Response to neoadjuvant chemotherapy
Alderson et al. (OEO5) [26]	897	0	100	Pre-CT:CF VS Pre-CT: ECX	mOS 23.4 m vs. 26.1 m (p = 0·19)	NA	NA
Al-Batran et al. (FLOT4) [27]	716	0	100	Pre-and post-CT: ECF/ ECX VS Pre-and post-CT: FLOT	mOS 35 m vs. 50 m	NA	NA

Note: SCC: squamous cell carcinoma; AC: adenocarcinoma; CT: chemotherapy; mOS: median overall survival; ORR: overall response rate; CR: complete response; CF: cisplatin plus 5-FU; ECX: epirubicin, cisplatin plus capecitabine; ECF: epirubicin, cisplatin plus 5-FU; FLOT: docetaxel, oxaliplatin, calcium folinate plus 5-FU; NA: not available

to prolong the survival of these patients. Even though the preoperative chemotherapy lowered R1 resections (4% VS 15%; p = 0.001), it did not improve the prognosis for these patients. However, researchers found that patients who responded to preoperative chemotherapy showed better survival outcomes than nonresponding patients, suggesting that neoadjuvant chemotherapy still possesses advantages in treating locally advanced esophageal cancer [11].

On the contrary, another large RCT in this field, OEO2, was conducted by the United Kingdom Medical Research Council (MRC), showing promising results. This RCT recruited 802 patients with esophageal cancer designed to assess whether neoadjuvant chemotherapy (two cycles of cisplatin and 5-FU) plus surgery (CS group, n = 400) could improve the survival compared to resection alone (S group, n = 402). 60% of patients in CS group achieved R0 resection, while only 54% of S group achieved that [12]. According to the long-term follow-up analysis published in 2019, the survival benefit was evaluated by a hazard ratio (HR) of 0.84 (95% CI: 0.72–0.98; P = 0.03), which indicated the survival benefit remains significant. The five-year survival rate for CS group is 23%, compared with 17.1% for S group. Moreover, among the 802 patients, 30.8% are ESCC and 66.5% are EAC, and the subgroup analysis suggested that the treatment effect was reflected in both pathological types. The safety profile is good without additional serious adverse events. This RCT proved that preoperative chemotherapy followed by surgery could become the standard treatment for locally advanced esophageal cancer [7].

Even though preoperative chemotherapy has been gradually accepted and attracted considerable attention, some studies showed that the patients who received preoperative chemotherapy followed by surgery still had a high distant metastasis rate. Therefore, perioperative chemotherapy came up and showed considerable benefits for survival in two large clinical trials.

Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial was conducted from 1994 to 2002, which aimed to compare the therapeutic efficacy of perioperative chemotherapy followed by surgery with surgery alone in patients with locoregional adenocarcinoma of the stomach, the gastroesophageal junction (GEJ) or lower esophagus. Five hundred-three patients with adenocarcinoma were randomized to the perioperative chemotherapy plus surgery group (250 patients) and surgery group (253 patients). The perioperative chemotherapy regimen includes three preoperative cycles of epirubicin, cisplatin and fluorouracil (ECF) and three postoperative cycles of the ECF regimen. Based on the published data, five-year survival was achieved in 36.3% of patients in the perioperative chemotherapy group and 23% in the surgery group. Compared with the surgery group, patients in the perioperative-chemotherapy group tended to achieve progression-free survival (PFS) with a hazard ratio (HR) for progression of 0.66 (95% CI: 0.53–0.81; P < 0.001). Furthermore, patients undergoing perioperative chemotherapy are likely to gain a more prolonged overall survival (OS) (HR for death: 0.75; 95% CI: 0.60–0.93; P = 0.009). There was no difference in postoperative complications between these two groups [13]. With the promising results from this trial, neoadjuvant chemotherapy might become an option for patients with lower esophageal and GEJ adenocarcinoma. However, among the 503 patients, only 26% had lower esophageal or GEJ adenocarcinoma; thus, this regimen's value in treating esophageal cancer needs further research. Moreover, we did not know whether preoperative or postoperative chemotherapy contributed significantly to the longer OS.

Another phase III RCT carried out by the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) and the Federation Francophone de Cance'rologie Digestive (FFCD) in 28 French centers was aimed to evaluate the survival benefit of perioperative chemotherapy in locally advanced gastroesophageal adenocarcinoma. Two hundred twenty-four eligible patients with resectable adenocarcinoma of the lower esophagus, the gastroesophageal junction (GEJ), or stomach were randomly divided into perioperative chemotherapy plus surgery group (CS group; n = 113) or surgery alone group (S group; n = 111). Preoperative chemotherapy included two or three cycles of cisplatin and fluorouracil; postoperative chemotherapy consisted of three or four cycles of this regimen. The published results showed, compared with the surgery-alone group, CS group achieved

a significantly higher OS (HR for death, 0.69; 95%CI: 0.50–0.95; P = 0.02), disease-free survival (DFS) (HR for recurrence or death, 0.65; 95%CI, 0.48–0.89; P = 0.003), five-year survival rate (38% VS 24%) and R0 resection rate (84% VS 74%; P = 0.04). Furthermore, a multivariable analysis indicated that preoperative chemotherapy (P = 0.01) and tumor localization (P<0.01) were both prognostic factors for more prolonged survival [8]. These results conformed to the results of the OEO2 trial mentioned before. Based on these promising results, NCCN regarded perioperative chemotherapy as standard therapy in treating locally advanced gastroesophageal adenocarcinoma.

NCT for locally advanced ESCC

Several clinical trials were conducted in Asian countries to evaluate the efficacy of neoadjuvant chemotherapy in ESCC. Based on a Japanese study (JCOG9204) showing ESCC patients with postoperative chemotherapy showed longer DFS than those who performed surgery only, another RCT named JCOG9907 was conducted to compare preoperative chemotherapy with postoperative chemotherapy in patients with resectable stage II or III ESCC. One hundred sixty-six patients were assigned to the postoperative chemotherapy group and 164 to the preoperative group. Updated data showed the 5-year overall survival was superior in preoperative chemotherapy group (55% VS 43%, P = 0.04) [14]. Therefore, preoperative chemotherapy with cisplatin plus 5-fluorouracil followed by esophagectomy was accepted as the standard therapeutic approach for patients with locally advanced ESCC in Japan. A remarkable clinical trial, the JCOG1109 NExT trial, recently compared the efficacy between the DCF regimen, the CF regimen, and CF combined with radiotherapy as neoadjuvant treatment for locally advanced ESCC [15]. In the 2022 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, the research team reported that the DCF regimen was superior to the CF regimen in both OS (4.6 years vs. not reach) and PFS (2.7 years vs. not reach) with a high pCR rate of 19.8%. The toxicity of the DCF regimen is also well-tolerated. As a result, the DCF regimen might become a novel standard neoadjuvant treatment for locally advanced ESCC.

Neoadjuvant chemoradiotherapy (NCRT)

Neoadjuvant chemoradiotherapy (NCRT) means performing preoperative chemotherapy with concurrent radiotherapy before surgery, improving the tumor response and pathological complete response (pCR), reducing recurrences, and prolonging survival. The benefit of NCRT followed by surgery compared to surgery alone has been demonstrated in clinical trials in patients with operable locally advanced esophageal cancer (Table 2).

NCRT for locally advanced EAC

A study led by the Cancer and Leukemia Group B (CALGB9781) evaluated NCRT (including 5-FU plus cisplatin and radiation therapy) followed by surgery versus surgery alone in patients with resectable esophageal adenocarcinoma (75%) and squamous cell cancer (25%). Fifty-six patients were recruited and randomly assigned to the NCRT group (30 patients) and the surgery alone group (26 patients). The published data indicated NCRT plus surgery was superior to surgery alone, with a median overall survival (mOS) of 4.48 years versus 1.79 years (p = 0.002). Median PFS was 3.47 years among patients treated with NCRT and only 1.01 years among patients who underwent surgery alone. This study planned to recruit 475 patients, but the poor accrual led to early closure, and the small sample size made the trial less convincing [28]. However, the substantial survival benefit of NCRT showed in this study set the stage for another large clinical trial, the CROSS trial. Compared to esophagectomy, the CROSS trial is the most influential RCT of NCRT plus esophagectomy. From 2004 to 2008, a total of 366 patients with potentially curable EAC (275 cases, 75%), ESCC (84 cases, 23%), or large cell undifferentiated carcinoma (7 cases, 2%) of the esophagus or esophagogastric junction were recruited in this RCT. Among the 366 patients, 178 were randomized to the NCRT group (carboplatin plus paclitaxel for five weeks and concurrent radiotherapy followed by surgery) and 188 to the surgery-alone group. According to the published results, the NCRT group achieved a better R0 resection rate (92% versus 69%, p < 0.001) and mOS (49.4 months VS 24.0 months; HR for death: 0.657, 95% CI: 0.495–0.871, p = 0.003). Furthermore, these two groups had no significant difference in postoperative complications or perioperative mortality. Notably, a pCR was achieved in 29% of patients who underwent esophagectomy after chemoradiotherapy. The long-term results of the CROSS trial confirmed the survival benefit of NCRT plus surgery regimen. NCRT group achieved a higher OS at one year (81% VS 70%), two years (67% VS 50%), three years (58% VS 44%), and five years (47% VS 33%), and had significantly less locoregional progression (22% VS 38%; P < 0.0001) and less distant progression (39% VS 48%; P = 0.004) [29]. Based on the CROSS trial, NCRT, followed by esophagectomy, was regarded as a standard of care for patients with locally advanced esophageal and esophagogastric junction cancer.

Table 2 Clinical trials for neoadjuvant chemoradiotherapy in esophageal cancer

Study	Number of patients	SCC (%)	AC (%)	Study design	Long-term survival	Surgical outcomes	Response to neoadjuvant chemotherapy
Nygaard et al [18]	88	100	0	Surgery alone VS Pre-CRT: cisplatin + bleomycin + 35 Gy	mOS 7 m vs. 8 m 3-y survival rate 9% vs. 17%	Postoperative mortality 13% vs. 24%	NA
Le Prise et al. [33]	86	100	0	Surgery alone VS Pre-CRT CF + 20 Gy	1-y survival rate 47% vs. 47%	NA	CR 26.8%
Apinop et al. [34]	69	100	0	Surgery alone VS Pre-CRT CF + 40 Gy	mOS 7 m vs. 10 m 5-y survival rate 10% vs. 24%	NA	CR 10%
Walsh et al. [35]	113	0	100	Surgery alone VS Pre-CRT CF + 40 Gy	mOS 11 m vs. 16 m, P = 0.01 3-y survival rate 6% vs. 32%, p = 0.01	NA	pCR 25%
Bosset et al. [36]	282	100	0	Surgery alone VS Pre-CRT cisplatin + 37 Gy	mOS 18.6 m vs. 18.6 m 5-y survival rate 9% vs. 7%	NA	pCR 26%
Urba et al. [37]	100	25	65	Surgery alone VS Pre-CRT cisplatin + 5-FU + vinblastine + 45 Gy	mOS 17.6 m vs. 16.9 m 3-y survival rate 16% vs. 30%	NA	NA
Heise et al [38]	203	100	0	Surgery alone VS Pre-CRT cisplatin + 5-FU + etoposide + leucovorine + radiation	mOS 14 m vs. 20 m 5-y survival rate 17% vs. 26%	NA	ORR 70%
Lee et al. [39]	101	100	0	Surgery alone VS Pre-CRT CF + 45.6 Gy	mOS 27.3 m vs. 28.2 m, p = 0.69	R0 resection rate 87.5% vs. 100%	pCR 43%
Burmeister et al. [40]	256	37.1	61.7	Surgery alone VS Pre-CRT CF + 35 Gy	mOS 19.3 m vs. 22.2 m	R0 resection rate 59% vs. 80%, p = 0.0002	pCR 16%
Natsugoe et al. [41]	45	100	0	Surgery alone VS Pre-CRT CF + 40 Gy	5-y survival rate 41% vs. 57%, p = 0.58	NA	NA
Tepper et al. (CALGB9781) [28]	56	25	75	Surgery alone VS Pre-CRT CF + 50.4 Gy	mOS 1.79 years vs. 4.48 years, p = 0.002 5-y survival rate 16% vs. 39%	NA	pCR 33%
Cao et al. [42]	236	100	0	Surgery alone VS Pre-CRT cisplatin + 5-FU + mitomycin + 40 Gy	3-y survival rate 53.4% vs. 73.3%	Radical resection rate 73.3% vs. 98.3%	pCR 22.3% cCR 33.89%
Lv et al [43]	160	100	0	Surgery alone VS Pre-CRT cisplatin + paclitaxel + 40 Gy	mOS 36 m vs. 53 m 5-y survival rate 33.8% vs. 43.5%	Radical resection rate 80% vs. 97.4%	NA
Van Hagen et al. (CROSS) [30]	368	23	75.1	Surgery alone VS Pre-CRT carboplatin + paclitaxel + 41.4 Gy	mOS 24.0 m vs. 48.6 m 5-y survival rate 34% vs. 47%, p = 0.003	R0 resection rate 69% vs. 92%, p < 0.001 Postoperative mortality 4% vs. 4%	pCR 29%
Mariette et al. (FFCD9901) [31]	195	70.3	29.2	Surgery alone VS Pre-CRT CF + 45 Gy	mOS 41.2 m vs. 31.8 m 3-y survival rate 53.0% vs. 47.5%, p = 0.94	R0 resection rate 92.1% vs. 93.8%, p = 0.749 Postoperative mortality 3.4% vs. 11.1%, p = 0.049	pCR 33%
Yang et al. (NEOCRTEC5010) [32]	451	100	0	Surgery alone VS Pre-CRT vinorelbine + cisplatin + 40.0 Gy	mOS 66.5 m vs. 100.1 m, p = 0.025 DFS 41.7 m vs. 100.1 m, p < 0.001	R0 resection rate 91.2% vs. 98.4%, p = 0.002	pCR 43.2%

Note: SCC: squamous cell carcinoma; AC: adenocarcinoma; CRT: chemoradiotherapy; mOS: median overall survival; ORR: overall response rate; CR: complete response; pCR: pathological complete response; cCR: clinical complete response; CF: Cisplatin plus 5-FU; DFS: disease free survival; NA: not available

NCRT for locally advanced ESCC

In the subgroup analysis of the CROSS trial, 49% of ESCC patients achieved pCR, while only 23%of EAC patients achieved it (p = 0.008), and preoperative chemoradiotherapy could significantly improve the OS in patients with ESCC [30]. In other words, the CROSS trial showed that the NCRT could significantly improve the OS and pCR rate in patients with ESCC compared to EAC. A French multicenter randomized phase III trial, named FFCD9901 (NCT00047112), was conducted to assess whether NCRT plus surgery could bring survival benefits for patients with stage I or II EC. This study recruited 195 patients randomly allocated to NCRT, followed by the surgery group, including 5-FU and cisplatin for two cycles with a radiation dose of 45 Gy followed by surgery (98 patients) or surgery alone group (97 patients). Most patients had ESCC (70.3%) and 29.2% had EAC. However, the NCRT group showed a worse mOS (31.8 months VS 41.2 months) and a lower R0 resection rate (93.8% VS 92.1%, p = 0.749) than the surgery alone group. The NCRT group had a higher postoperative mortality rate of 11.1% versus 3.4% in the surgery alone group (p = 0.049) [31]. Although this RCT gained negative results, it pointed out that NCRT was unsuitable for early-stage esophageal cancer.

Compared to EAC, the CROSS trial showed that the NCRT could significantly improve the OS and pCR rate in patients with ESCC. To confirm the therapeutic efficacy of NCRT followed by surgery for locally advanced ESCC, another large trial, the NEOCRTEC 5010 trial, has been carried out. Four hundred fifty-one patients with resectable ESCC were randomly allocated to NCRT plus surgery group (224 cases) and the surgery alone group (227 cases). In the NCRT group, patients were administrated vinorelbine and cisplatin for two cycles with a total concurrent radiation dose of 40.0 Gy, followed by esophagectomy. Compared with the surgery alone group, the NCRT group gained a higher R0 resection rate (98.4% VS 91.2%; P = 0.002), a prolonged mOS (100.1 months VS 66.5 months; HR for death: 0.71; 95% CI:0.53–0.96; P = 0.025) and a better DFS (100.1 months VS 41.7 months). The pCR rate was 43.2% in patients who received preoperative chemoradiotherapy plus surgery. There was no statistically significant difference in postoperative complication rates and peritreatment mortality between these two groups [32]. This NEOCRTEC5010 trial further confirmed the NCRT plus surgery regimen with a good safety profile and prolonged OS and DFS in patients with locally advanced ESCC compared with surgery alone. It contributed to the application of NCRT followed by a surgery regimen for ESCC treatment in China. However, the FFCD 9901 trial, where the most enrolled patients had ESCC, showed that the OS was not different between the NCRT and surgery alone. These results opposed other trials in ESCC, which the difference in patients recruited might explain. Patients with early-stage EC but not locally advanced ESCC were recruited for this study. Thus the FFCD9901 trial is not comparable with the other studies.

Comparison between NCRT and NCT

As previously stated, NCT and NCRT have been confirmed to provide a more significant survival benefit than surgery alone in patients with locally advanced resectable EC. Based on various studies, different countries considered different treatment modalities as their standard modality. NCT was the standard modality for locally advanced ECs in Japan. Based on the outcomes of the CROSS study, NCRT was the favored treatment modality in certain Western nations. According to the NEOCRTEC5010 trial, NCRT also has become the standard treatment for locally advanced ESCC in China. Research on the comparison between NCT and NCRT is limited, and whether NCRT or NCT brings better efficacy for patients with locally advanced ECs is still unknown.

Several published prospective studies compared the outcomes of NCRT and NCT in EAC. The POET trial showed that patients treated with NCRT had a significantly higher pCR rate (15.6% vs. 2%) and tumor-free lymph nodes (64.4% vs. 27.7%). Although the primary end-point OS of the study was not met, it showed a trend in favor of NCRT, and the long-term results demonstrated that local PFS after surgery was significantly improved by NCRT [44, 45]. Burmeister et al. also reported that the patients with EAC in the NCRT group experienced an increased pCR rate, but the higher OS and the long-term survival rate were statistically insignificant [46]. Consistent with the outcomes of the POET trial and Burmeister et al.'s study, a higher pCR rate also existed in the NCRT arm in the Neo-Res trial, which was a large multicenter randomized controlled trial and recruited over 70% of patients with EAC [47, 48]. However, the tumor response was not converted to survival benefits as well.

As for ESCC, the research on the efficacy of NCRT versus NCT is limited. The CMISG1701 trial compared NCRT and NCT followed by minimally invasive esophagectomy (MIE) to treat locally advanced resectable ESCC. According to the initial results, it showed that patients undergoing NCRT had better histopathologic outcomes, including higher pCR rate (35.7% vs. 3.8%, P<0.01) and less lymph node metastasis (66.1% vs. 46.2%, P = 0.03). However, 1-year OS was similar between the two groups [49].

There are also several clinical trials ongoing. The Neo-AEGIS trial randomized patients with ACs of esophagus or

EGJ between pre- and post-operative chemotherapy versus NCRT [50]. The NeXT trial enrolled patients with ESCC who were randomized to the NCT arm with CF or DCF regimens and the NCRT arm with CF plus radiation regimen [15]. Another ongoing clinical trial, including 264 patients from eight hospitals in China that compared NCRT with NCT, followed by MIE for locally advanced ESCC, is currently being carried out (NCT03001596). Another ongoing therapeutic research, with 264 patients from eight hospitals in China, compares NCRT with NCT, followed by MIE for locally advanced ESCC. We eagerly await the results of this study.

Several meta-analyses were performed due to a lack of direct comparison. In 2020, a meta-analysis (NewEC study) of eight RCTs involving 1030 patients with resectable EC was published to provide clinical evidence for comparing NCRT with NCT. The OS benefit of NCRT over NCT was seen in this meta-analysis. It is the first time that a study demonstrated the survival superiority of NCRT over NCT in resectable EC [51]. Another network meta-analysis, including 26 studies, compared the efficacy of different treatment modalities, including surgery alone, NCT, NCRT, neoadjuvant radiotherapy, surgery followed by adjuvant chemotherapy, adjuvant radiotherapy, or adjuvant chemoradiotherapy. It reported that, compared to surgery alone, NCRT brought the largest benefit regarding OS and PFS/DFS and was associated with decreased locoregional recurrence or distant metastasis risks [52].

Overall, the optimal treatment strategy for locally advanced ECs remains controversial. The reasons why the higher pCR rate following NCRT did not convert into a survival advantage are still unknown. The toxicities of treatments and surgical complications might be the factors. The POET trial and NeoRes trial both showed higher risks of postoperative complications and postoperative mortality in the NCRT group. Therefore, developing new drugs, optimizing treatment modalities, or improving surgery technology might decrease toxicities and solve the problem.

Targeted therapy combined with neoadjuvant therapy

Due to the limited improvements in survival benefits gained from conventional neoadjuvant therapy, alternative strategies such as NCRT or NCT combined with targeted agents (e.g. epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor receptor (VEGFR) inhibitors, and human epidermal growth factor receptor-2 (HER2) inhibitors) are under exploration (Table 3).

EGFR inhibitors

Combining EGFR-targeted therapy (such as panitumumab, cetuximab, nimotuzumab, or gefitinib) with NCRT or NCT in patients with locally advanced esophageal cancer is not recommended due to the proven treatment-related toxicity without clinical benefit.

The American College of Surgeons Oncology Group (ACOSOG) Z4051 trial (NCT00757172) enrolled 70 patients with locally advanced resectable EAC. These patients received docetaxel, cisplatin, and panitumumab with radiotherapy followed by resection. Even though the pCR plus near-pCR rate was 53.7% (95% CI: 42.5 − 64.9%), patients did not achieve a prolonged median OS (19.4 months) nor 3-year survival rate (38.6%; 95% CI: 24.5 -60.8%) compared to a previous study. What is worse, 48.5% of these patients experienced at least grade 4 toxicity [55]. The PATC study, a multicenter phase II study, showed that adding panitumumab to CRT with carboplatin and paclitaxel was not improving the pCR rate [56]. Recently, the AIO/CAO STO-0801 (NCT01234324), a phase II trial, evaluated the role of panitumumab with perioperative chemotherapy (epirubicin, cisplatin, plus capecitabine, ECX) in patients with locally advanced esophagogastric cancer. However, the results suggested that adding panitumumab to ECX perioperative chemotherapy could not downstage the tumors in patients with locally advanced esophagogastric cancer [57].

Cetuximab is another promising EGFR blockade. A phase II RCT (NCT00551759) was designed to assess the efficacy of NCRT (oxaliplatin and 5-FU plus radiotherapy) together with cetuximab followed by surgery in treating patients with esophageal cancer or gastroesophageal junction cancer. Disappointingly, this trial was closed early due to unacceptable toxicities. Another prospective phase II trial (NCT00827671) evaluated whether adding preoperative cetuximab and radiotherapy to perioperative chemotherapy (3 cycles of ECX regimen before and after surgery) could improve the therapeutic efficacy with tolerable toxicity. However, the preoperative ECX caused considerable toxicity, and the subsequent treatment could not be started [54]. The SAKK 75/08 trial led by Ruhstaller randomly assigned 300 patients with resectable esophageal carcinoma to NCRT with or without neoadjuvant and adjuvant cetuximab groups. The NCRT plus targeted therapy group achieved a better median PFS and mOS, but they were no statistically significant improvements [53].

Nimotuzumab, a recombinant humanized IgG monoclonal antibody, can inhibit the EGFR signaling pathway [67]. Several studies evaluated nimotuzumab in combination with NCRT and achieved encouraging results [68–70]. However, the sample size is still limited. For this reason, a

Table 3 Clinical trials for neoadjuvant targeted therapy in esophageal cancer

Receptor	Antibody	Study	Number of patients	SCC (%)	AC (%)	Study design	Long-term survival	Surgical outcomes	Response to neoadjuvant therapy
EGFR	cetuximab	Ruhstaller et al. (SAKK 75/08, NCT01107639) [53]	297	37	63	Neoadjuvant cetuximab + docetaxel + cisplatin + radiation and adjuvant cetuximab VS Neoadjuvant docetaxel + cisplatin + radiation	mOS: 5.1 m vs. 3.0 m (p = 0.055)	R0 resection rate: 95% vs. 97%; Postoperative mortality: 6% vs. 6%	NA
	cetuximab	Kleinberg LR et al. (NCT00551759)	22	0	100	Neoadjuvant cetuximab + oxaliplatin + 5-FU + radiotherapy Adjuvant docetaxel + cetuximab	NA	NA	NA
	cetuximab	Inge Ubink et al. (NCT00827671) [54]	12	0	100	Neoadjuvant ECX + cetuximab + radiotherapy Adjuvant ECX	NA	NA	pCR 0
	panitumumab	Lockhar et al. (ACOSOG Z4051 trial, NCT00757172) [55]	70	0	100	Neoadjuvant Docetaxel + cisplatin + panitumumab + radiotherapy	mOS: 19.4 m 3-year OS rate: 38.6%	NA	pCR 33.3% near-pCR 20.4%.
	panitumumab	Sil Kordes et al. (PACT study) [56]	90	20	80	Neoadjuvant panitumumab + carboplatin + paclitaxel + radiotherapy	NA	R0 resection rate: 95%	pCR 22%
	panitumumab	Michael Stahl et al. (AIO/CAO STO-0801, NCT01234324) [57]	160	0	100	Perioperative ECX + panitumumab VS Perioperative: ECX	No significant difference in PFS and OS	No significant difference in postoperative morbidity	NA
	nimotuzumab	Saichun Qi et al. (NCT02409186)	64	100	0	Neoadjuvant nimotuzumab + paclitaxel + carboplatin + radiation	mOS: 68.2 m	NA	pCR 51.6%
HER2	trastuzumab	Hofheinz R et al. [58]	NA	0	100	Perioperative HER-FLOT (5-FU + leucovorin + oxaliplatin + docetaxel + trastuzumab)	NA	NA	NA
	trastuzumab	Fernando Rivera et al. (NCT01130337) [59]	36	0	100	Perioperative capecitabine, oxaliplatin and trastuzumab (XELOX-T)	18-month DFS: 71%; mOS: 79.9 m; 60 m OS: 58%	R0 resection rate: 90%	pCR 9.6%
	trastuzumab with or without pertuzumab	Wagner, A. D. et al. (INNOVATION TRIAL, NCT02205047) [60]	220	0	100	Cisplatin + capecitabine/5-FU VS Cisplatin + capecitabine/5-FU + trastuzumab VS Cisplatin + capecitabine/5-FU + trastuzumab + pertuzumab	NA	NA	NA
	Lapatinib	Shepard, G. et al. (NCT01769508) [61]	12	0	100	Preoperative radiotherapy + 5-FU + oxaliplatin + lapatinib	NA	NA	pCR 8%
	Lapatinib	Cunningham, D.et al (ST03 trial, NCT00450203) [62]	1103	0	100	Perioperative ECX + Lapatinib VS Perioperative ECX	NA	NA	NA

Table 3 (continued)

Receptor	Antibody	Study	Number of patients	SCC (%)	AC (%)	Study design	Long-term survival	Surgical outcomes	Response to neo-adjuvant therapy
	trastuzumab	Safran, H.et al(RTOG 1010, NCT01196390) [63]	203	0	100	Preoperative radiotherapy + trastuzumab + paclitaxel + carboplatin + postoperative trastuzumab VS Preoperative radiotherapy + paclitaxel + carboplatin	NA	NA	NA
	trastuzumab and pertuzumab	Hofheinz, R.et al (NCT02581462) [64]	81	0	100	Perioperative FLOT VS Perioperative FLOT + trastuzumab + pertuzumab	NA	NA	pCR 12% VS 35% (p = 0.02)
	trastuzumab and pertuzumab	Schokker, S.et al (TRAP trial ,NCT02120911) [65]	40	0	100	Neoadjuvant carboplatin + paclitaxel + radiotherapy + trastuzumab + pertuzumab	NA	R0 resection rate: 100%	pCR 34%
VEGFR	bevacizumab	Efraim Idelevich et al [66]	28	21.40	78.60	Neoadjuvant cisplatin + 5-FU + bevacizumab	mOS: 17 m	R0 resection rate: 43%	ORR 39%
	bevacizumab	Cunningham, D. et al. (ST03 trial, NCT00450203) [62]	1103	0	100	Perioperative ECX + bevacizumab VS Perioperative ECX	3-year OS: 48·1% VS 50·3%	NA	NA

Note: SCC: squamous cell carcinoma; AC: adenocarcinoma; CRT: chemoradiotherapy; mOS: median overall survival; ORR: overall response rate; CR: complete response; pCR: pathological complete response; ECX: epirubicin, cisplatin plus capecitabine; FLOT: docetaxel, oxaliplatin, calcium folinate plus 5-FU; NA: not available

large, multicenter, phase III trial (NCT02409186) is ongoing to evaluate the efficacy of chemoradiotherapy plus nimotuzumab in locally advanced ESCC. Unfortunately, the drug resistance of nimotuzumab has gradually been discovered, which impeded the development of nimotuzumab in neoadjuvant therapy for EC [71].

Overall, the monoclonal antibody targeting EGFR was not an option to combine with NCRT or NCT to treat locally advanced esophageal cancer.

VEGFR inhibitors

Monoclonal antibodies against the VEGFR have also failed to improve survival benefits. Idelevich et al. conducted a phase II study investigating the efficacy and tolerability of cisplatin and 5-FU plus bevacizumab as neoadjuvant therapy followed by surgery for patients with locally advanced esophageal cancer. After analysis, there was no statistically significant difference between the two groups of patients; thus, adding bevacizumab did not improve the resection rate or OS [66]. The ST03 trial (NCT00450203) was recently conducted to assess the safety and efficacy of adding bevacizumab, a VEGFR inhibitor, to perioperative ECX for treatment of resectable gastric, esophagogastric junction, or lower esophageal adenocarcinoma. Totally 1063 patients were recruited and randomly assigned to the chemotherapy alone group (533 patients) or chemotherapy plus bevacizumab group (530 patients). Finally, the results showed that adding bevacizumab to perioperative ECX did not improve OS, pCR or R0 resection rate compared to ECX alone but led to a higher risk of impaired wound healing [62]. Therefore, for resectable esophageal cancer, bevacizumab is also not recommended.

HER2 inhibitors

Even though adding EGFR or VEGFR blockades to neoadjuvant chemoradiotherapy was ineffective, some ongoing trials still investigate HER2 combined with NCRT regimen in patients with locally advanced EC. A previous study (the ToGA trial) has confirmed that obvious survival benefits could be improved by adding trastuzumab to chemotherapy in patients with metastatic EAC with HER2 overexpression or amplification [72]. Thus, this regimen might also potentially prolong the survival in patients with resectable HER2-positive EAC.

An ongoing landmark phase III RCT, RTOG 1010 clinical trial (NCT01196390), evaluated the therapeutic efficacy and safety of adding trastuzumab, a HER2 blockade, to neoadjuvant chemoradiation (radiation therapy plus paclitaxel and carboplatin) followed by esophagectomy in patients with locally advanced EAC and GEJ adenocarcinomas

containing HER2 overexpression. In total, 203 patients were enrolled, and the preliminary data presented at the ASCO annual meeting 2020 indicated that the addition of trastuzumab to trimodality treatment did not improve DFS. The median DFS time is 19.6 months for the trimodality treatment plus the trastuzumab group versus 14.2 months for the trimodality treatment without the trastuzumab arm (HR: 0.97). Moreover, the NCRT with trastuzumab group had a slightly shorter mOS time (38.5 months VS 38.9 months). No statistically significant increase in treatment-related toxicities with the addition of trastuzumab was observed [63]. In addition, Schokker et al. demonstrated the feasibility of adding dual HER2 monoclonal antibodies, trastuzumab plus pertuzumab, to preoperative chemoradiation (CROSS regimen) in a phase IB trial, TRAP study (NCT02120911), with a pCR rate of 33% [65].

HER2 blockade plus perioperative chemotherapy regimen is also promising and under investigation. Two phase II trials evaluated the addition of trastuzumab to perioperative treatment including docetaxel, oxaliplatin, leucovorin plus 5-FU (FLOT) regimen and capecitabine plus oxaliplatin (CAPOX) regimen. Trastuzumab plus FLOT achieved an R0 resection rate of 93% and trastuzumab plus CAPOX achieved an R0 resection rate of 90% [58, 59]. At ASCO annual meeting 2020, the phase II PETRARCA study (NCT02581462) showed that the addition of trastuzumab and pertuzumab to perioperative FLOT improved the pCR rate. It increased the nodal negative resection specimen rate compared to perioperative FLOT alone for HER2 positive resectable esophagogastric adenocarcinoma and the preliminary overall survival and disease-free data are promising [64]. Recently, a phase II trial (INNOVATION Trial, NCT02205047) was designed to compare the therapeutic efficacy of integration of trastuzumab, with or without pertuzumab, into perioperative chemotherapy (cisplatin plus fluoropyrimidine regimen) in treating patients with resectable, HER2-positive GEJ or gastric adenocarcinoma. The results from this study are eagerly awaited [60].

Lapatinib is a dual tyrosine kinase inhibitor targeting both HER2 and EGFR. A phase II study (NCT01769508) evaluated the safety and efficacy of lapatinib plus 5-FU and oxaliplatin in combination with radiotherapy as neoadjuvant therapy for patients with locoregional HER2-positive esophagogastric adenocarcinomas. Unfortunately, this trial was closed due to low accrual [61]. The phase II/III ST03 RCT also evaluated the efficacy of lapatinib in combination with perioperative chemotherapy (epirubicin, cisplatin, and capecitabine) in patients with HER2-positive esophagogastric cancer, while the results are unknown.

Currently, most research about neoadjuvant targeted therapy is still in the primary stage, and we are looking forward to obtaining more data about the efficacy of targeted therapy combined with neoadjuvant therapy in patients with EC.

Immunotherapy combined with neoadjuvant therapy

Immunotherapy is a novel emerging way to kill tumors. The programmed death 1 (PD-1) receptor binding on T-cells to the programmed death ligand 1 (PD-L1) on cancer cells leads to immunosuppression. Several PD-1 inhibitors and PD-L1 inhibitors were developed to block this process. The emergence of immune checkpoint inhibitors opened a new era for treating EC. The previous study has proved that nivolumab, a PD-1 inhibitor, could significantly prolong survival compared to placebo in pretreated patients with advanced gastric or GEJ cancer [73]. Moreover, it was confirmed that chemotherapy or chemoradiotherapy causes the activation of the immune microenvironment and radiotherapy promotes T-cell infiltration and antigen presentation, which is optimal for immunotherapy [74, 75]. Furthermore, most tumors post chemoradiotherapy developed obvious adaptive resistance mechanisms, leading to compensatory induction of multiple checkpoints to prevent tumor cell death [76]. Taken together, combining immunotherapy with preoperative chemotherapy or chemoradiotherapy might be a promising strategy to increase the tumor response and prolong survival time. Several clinical trials combining PD-1/PD-L1 inhibitors with preoperative or perioperative treatment for operable esophageal cancer are under investigation.

The efficacy of the addition of PD-1/PD-L1 inhibitors to NCT has been confirmed in many clinical trials. As mentioned before, nivolumab is effective for metastatic ESCC. Thus, the FRONTiER trial (NCT03914443) was carried out to evaluate the safety and efficacy of nivolumab added to neoadjuvant chemotherapy (CF or 5-FU plus cisplatin plus docetaxel (DCF) regimen) for locally advanced ESCC. This year, the published data showed that the most frequent AEs ($\geq$ grade 3) were neutropenia in 6 pts during the preoperative period. No grade 4 AEs or treatment-related deaths were observed. R0 resection was achieved in 12 patients (92.3%). A pCR was 33.3% in cohort A [77, 78].

In 2020, promising preliminary results of 3 clinical trials were released. A trial (NICE study) investigated the efficacy of combining camrelizumab with neoadjuvant chemotherapy (albumin paclitaxel and carboplatin). The pCR rate was 45.5%, which is independent of PD-L1 score. The radiologic response rate was 90.9% and the R0 resection rate was 100% [79]. Another single-arm, phase Ib/II trial (NCT03946969) evaluated the effect of sintilimab in combination with neoadjuvant chemotherapy (lipo-paclitaxel, cisplatin, and S-1). Four out of 15 patients achieved pCR

(26.7%) and 53.3% achieved major pathological response (MPR). The R0 resection rate was 100% [80]. A prospective, single-arm trial was designed to evaluate the safety and efficacy of toripalimab combined with nab-paclitaxel and S-1 as neoadjuvant therapy for resectable ESCC. The preliminary data showed that 50% of the enrolled patients were MPR and 16.67% were pCR. This regimen was well tolerated for resectable ESCC patients [81].

In 2021, Shen et al. published a satisfactory result of a single-group study evaluating the efficacy and safety of neoadjuvant PD-1 inhibitors combined with chemotherapy in locally advanced ESCC [82]. They designed the neoadjuvant treatment protocol, including pembrolizumab, nivolumab, camrelizumab, and NCT (albumin paclitaxel plus carboplatin). Finally, among the 28 patients, a high pCR rate (33.3%) and a high R0 resection rate (96.3%) were achieved with a good safety profile. The long-term efficiency of this regimen should be verified by longer follow-up.

As mentioned, immunotherapy combined with NCRT might potentiate a synergistic effect on EC treatment. A phase II study, PERFECT trial, combined atezolizumab, a PD-L1 inhibitor, with the CROSS protocol for resectable EC is ongoing (NCT03087864). The data presented at the ASCO annual meeting 2019 showed that pCR was 39%. Another study evaluating the efficacy of anti-PD-L1 antibody durvalumab combined with neoadjuvant capecitabine, oxaliplatin, and radiotherapy, was given to patients with resectable EC (NCT02735239). A clinical trial conducted by the Mayo Clinic investigated the therapeutic efficacy of a combination of pembrolizumab, an anti-PD-1 antibody, with NCRT (CROSS regimen) in patients with locally advanced gastric or GEJ adenocarcinoma (NCT02730546). PALACE-1 study was conducted to investigate the safety and activity of pembrolizumab combined with NCRT (carboplatin, paclitaxel and radiotherapy) for resectable ESCC (NCT03792347) [83]. Grade 3 and higher adverse events (AEs) were observed in 13 patients (65%). Lymphopenia was the most common grade 3 AE (92%). The pCR rate was 55.6%. A phase II multicentre study is undergoing for further confirmation of efficacy (NCT04435197). Another phase II trial (NCT02844075) assessed the potential benefit and safety of combining pembrolizumab with NCRT in ESCC [84]. Of a total of 28 enrolled patients, 26 patients received esophagectomy. The ASCO annual meeting in 2019 disclosed that the pCR in the primary tumor was achieved in 46.1% of patients who underwent surgery. The one-year OS rate was 82.1%. The most common treatment-related AEs was neutropenia (50.0%) in the neoadjuvant period. This study demonstrated that adding pembrolizumab to NCRT in ESCC brought promising efficacy with acceptable toxicity.

These studies profoundly impacted future immunotherapy for EC, while a critical question remains to be considered. Many studies indicated that immunotherapy plus NCT or NCRT regimen could lead to immune-related AEs, especially immune-related pneumonia. Further studies are supposed to explore how to maximize the efficacy of immunotherapy. Nowadays, many clinical trials involving neoadjuvant immunotherapy are under evaluation, and we are eager to gain more results from these studies (Table 4). In the future, more multicenter studies are required to confirm further the safety and efficacy of neoadjuvant therapy combined with immunotherapy in locally advanced esophageal cancer.

Primary endpoints in neoadjuvant therapy clinical trials: MPR or pCR?

With the development of neoadjuvant therapy, an increasing number of clinical trials for neoadjuvant therapy were conducted. Most randomized clinical trials traditionally used OS or PFS as primary endpoints, while it needs ten years or even additional time to achieve the endpoints, limiting the development and approval of neoadjuvant drugs. In this trend, new indexes, MPR and pCR, could be used as surrogate endpoints that have been sought to reflect the prognosis of cancers [85].

Pathological complete response (pCR) is defined as the absence of active tumor cells, which can show clinical benefits in a shorter time and accelerate the progress of clinical trials. According to several neoadjuvant trials conducted in breast cancer patients, the prognostic correlation between pCR and long-term outcomes was strongest; therefore, pCR has been approved as a surrogate endpoint for breast cancer neoadjuvant treatment studies [86, 87]. However, a large number of neoadjuvant studies for lung cancer showed the pCR was very low, then another pathological-related factor, MPR, was found viable as an endpoint in neoadjuvant trials for lung cancer. MPR is defined as a $\leq 10\%$ portion of active tumor cells in different parts of the tumor found after neoadjuvant therapy, which also correlates to OS. MPR can be observed more frequently than pCR [88]. MPR was used as the research endpoint of many ongoing trials of neoadjuvant therapy for lung cancer, which helped explore the effectiveness of MPR as a surrogate for survival [89–91]. Several ongoing neoadjuvant immunotherapy clinical trials for lung cancer use MPR as the primary endpoint, such as CheckMate816, KEYNOTE-671, IMpower030 and AEGEAN [85].

For esophageal cancer, an increasing number of neoadjuvant therapy studies use MPR or pCR as the primary or secondary endpoint. A single-arm phase II study (NCT03917966) was carried out by Wang et al. to assess the efficacy and safety of camrelizumab plus preoperative

Table 4 Clinical trials for neoadjuvant immunotherapy in esophageal cancer

Drug	ClinicalTrials.gov identifier	Started year	Phase	Tumor location	Number of patients	Study design
Nivolumab	NCT03914443	2019	Phase I	ESCC	36	Nivolumab + CF VS Nivolumab + DCF
	NCT03044613	2017	Phase I	EC Gastric Cancer	32	Nivolumab + carboplatin + paclitaxel + radiation VS Nivolumab + relatlimab + carboplatin + paclitaxel + radiation
Durvalumab	NCT02735239	2016	Phase I Phase II	EC	75	Durvalumab + CAPOX + radiation
Pembrolizumab	NA	2020	NA	ESCC	28	Pembrolizumab + nivolumab + camrelizumab + albumin paclitaxel + carboplatin
	NCT04435197	2020	Phase II	ESCC	143	Pembrolizumab + carboplatin + paclitaxel + radiation
	NCT03792347	2019	Phase I	ESCC	20	Pembrolizumab + carboplatin + paclitaxel + radiation
	NCT03221426	2017	Phase III	Gastric Cancer GEJ Cancer	1000	Perioperative pembrolizumab + cisplatin + capecitabine/5-FU VS Perioperative placebo + cisplatin + capecitabine/5-FU
	NCT02844075	2016	Phase II	ESCC	28	Pembrolizumab + paclitaxel + carboplatin + radiation
	NCT02730546	2016	Phase I Phase II	Gastric Cardia Adenocarcinoma GEJ Adenocarcinoma	68	Pembrolizumab + carboplatin + paclitaxel + radiation
Atezolizumab	NCT03448835	2018	Phase II	Gastric Cancer GEJ Cancer	20	Atezolizumab + capecitabine + oxaliplatin + docetaxel
	NCT03421288	2018	Phase II	Gastric Cancer GEJ Adenocarcinoma	295	Perioperative atezolizumab + FLOT VS Perioperative FLOT
	NCT03087864	2017	Phase II	EC	40	Atezolizumab + carboplatin + paclitaxel + radiation
Avelumab	NCT03399071	2017	Phase II	Gastric Adenocarcinoma EAC	40	Perioperative avelumab + FLOT
	NCT03490292	2018	Phase I Phase II	EC Gastroesophageal Cancer	24	Avelumab + carboplatin + paclitaxel + radiation
Teripalimab	NCT03985670	2019	Phase II	ESCC	30	Paclitaxel + cisplatin + teripalimab in the same day VS paclitaxel + cisplatin followed by teripalimab
Camrelizumab	NCT04225364	2020	Phase II	ESCC	56	Camrelizumab + paclitaxel + cisplatin
	ChiCTR1900026240.	2019	NA	Thoracic ESCC	11	Camrelizumab + carboplatin + albumin paclitaxel
	NCT03200691	2017	Phase II	ESCC	21	SHR-1210/Camrelizumab + radiation
Sintilimab	NCT03946969	2019	Phase Ib/II trial	ESCC	17	Sintilimab + lipo-paclitaxel + cisplatin + S-1
	NCT03940001	2019	Early Phase I	ESCC	20	Sintilimab + carboplatin + paclitaxel + radiation
Toripalimab	NA	2019	NA	ESCC	24	Toripalimab + albumin paclitaxel + S-1
	NCT04006041	2019	Phase II	ESCC	44	Toripalimab + paclitaxel + cisplatin + radiation

Note: ESCC: esophageal squamous cell carcinoma; EAC: esophageal adenocarcinoma; GEJ: gastroesophageal junction; CF: cisplatin plus 5-FU; DCF: docetaxel, cisplatin plus 5-FU; CAPOX: capecitabine plus oxaliplatin; FLOT: docetaxel, oxaliplatin, calcium folinate plus 5-FU; NA: not available

chemotherapy regimen for locally advanced ESCC, using MPR as the primary endpoint. The published data indicated that this regimen for locally advanced ESCC showed promising MPR with good tolerance [92]. Another phase II study, the TD-NICE study, evaluated the efficacy and safety of the PD-1 inhibitor tislelizumab combined with chemotherapy as neoadjuvant therapy in patients with resectable ESCC. The primary endpoint was also MPR, and they found that tislelizumab plus chemotherapy regimen has a promising antitumor activity for resectable ESCC with high rates of MPR and acceptable tolerability [93]. The pCR was used as a primary endpoint in many studies. NeoRes trial is a multicenter trial that recruited patients with carcinoma of the esophagus or the gastroesophageal junction. However, the results indicated that adding radiotherapy to neoadjuvant chemotherapy leads to a higher pCR rate without significantly affecting survival [47]. Another international cohort study also showed that the prognosis of pCR following different neoadjuvant regimes is different [94]. Whether pCR could become an alternative endpoint for EC still needs to be validated.

However, MPR is only an index for primary tumors, not for assessing lymph node metastasis. The setting of the critical value of MPR also needs more data to be confirmed. Moreover, the determination of MPR is easily affected by subjective factors. Further prospective studies need to be conducted to compare the efficacy of variable pathological response endpoints of clinical trials for esophageal cancer. Furthermore, due to the heterogeneity of cancers and the different therapy regimens, MPR and pCR should be standardized, making them possible to be used in all neoadjuvant trials.

Postoperative complications and mortality

One of the most critical problems with neoadjuvant therapy is related toxicity, which might lead to postoperative complications and mortality, and the most common surgical complications include anastomotic leak, pulmonary issues, and cardiac arrhythmia [95]. Therefore, several studies explored the difference in surgical complications and mortality between esophageal cancer patients receiving neoadjuvant therapy and those receiving surgery alone.

Kumagai et al. performed a meta-analysis comparing surgical complications and perioperative mortality between patients receiving neoadjuvant chemotherapy or chemoradiotherapy and receiving surgery alone for resectable esophageal and gastroesophageal junctional cancers [96]. The results suggested that no evidence confirmed that neoadjuvant chemotherapy or chemoradiotherapy increased the risk of postoperative complications, including cardiac, respiratory, and anastomotic leakage, 30-day mortality, and total postoperative or treatment-related mortality. However, in subgroup analysis, neoadjuvant chemoradiotherapy for ESCC showed an increased risk of total postoperative mortality (RR: 1·95, 1·06 to 3·60; P = 0·032) and treatment-related mortality (RR: 1·97, 1·07 to 3·64; P = 0·030) compared with surgery alone [96]. In another meta-analysis, the perioperative mortality following NCT for esophageal cancer was calculated to be about 2.0%, substantially lower than 5.1% after chemoradiotherapy. The morbidities of most postoperative complications, such as pulmonary complications and anastomotic leakage, were not different between the two groups. However, cardiovascular complications were significantly higher in the NCRT group, and patients with the EAC were more likely to experience postoperative cardiovascular complications [97]. Anastomotic leakage is one of the most common postoperative morbidities for esophageal cancer. Several scientists explored the factors that affected the incidence of anastomotic leaks. Juloori et al. found that the placement of the esophagogastric anastomosis within the preoperative radiation field is a strong predictor for anastomotic leakage in esophageal cancer patients treated with neoadjuvant chemoradiation plus surgery regimen [98]. The CROSS study showed that the incidence of anastomotic leakage in the NCRT group was 22% and that in the surgery alone group was 30%. Furthermore, in this study, the tumors were mostly located in the distal esophagus (58%) or at the esophagogastric junction (24%). Therefore, the higher anastomotic leakage incidence in the CROSS study may be related to the tumor location [30]. Further studies must be conducted to critically evaluate the factors affecting anastomotic leakage incidence and make an optimal surgical plan for esophageal cancer patients.

Recently, a study was published evaluating the safety and feasibility of esophagectomy after neoadjuvant immunotherapy plus chemoradiotherapy. Compared to patients treated with NCRT alone, the results showed that neoadjuvant immunotherapy plus NCRT did not increase the risk of developing surgical complications. Moreover, 30-day mortality and readmission rates were comparable across the two groups [99].

Future prospects

Esophageal cancer remains one of the leading causes of cancer-related deaths worldwide. Although esophagectomy combined with lymphadenectomy is the most efficient treatment to treat EC patients, most EC patients are diagnosed at a late stage with metastasis, and surgery alone cannot bring satisfying survival benefits for these patients. That is the reason why neoadjuvant therapy emerged. According to

a large amount of research, neoadjuvant therapy is essential in improving survival benefits for patients with locally advanced operable EC. The remarkable effectiveness and variety of regimens have made neoadjuvant therapy a research focus in EC. It is still uncertain which treatment regimen is better because EC can be histologically divided into ESCC and EAC, which respond to different regimens. Patients with EAC are more likely to have distant metastasis, while ESCC patients are more prone to local recurrence. Moreover, ESCC is more sensitive to radiotherapy. Therefore, EAC patients respond better to perioperative chemotherapy, while NCRT is the optimal treatment option for patients with locally advanced ESCC. However, many additional factors, including physical conditions, the prediction of pCR and recurrence, tumor histological behavior, and surgical method, may influence the efficacy of neoadjuvant therapy and the prognosis of EC patients. For example, pCR is associated with a better prognosis in EC patients. However, there are few reliable methods to identify this group of patients. In the future, we should find more indexes to predict pCR. There are several unresolved issues in neoadjuvant therapy for locally advanced ECs, including the optimal regimen, surgical intervals, the dose of radiation, and the high risk of recurrence. Therefore, we also need to construct more predictive models to identify patients with an increased risk of recurrence, which can guide physicians in designing an individualized regimen for each patient.

The clinical benefits gained from conventional therapy are limited, promoting locally advanced EC treatment innovation. With the emergence of targeted therapy and immunotherapy, the combination of targeted agents (e.g.VEGF inhibitors, EGFR inhibitors and HER2 inhibitors) or immune checkpoint inhibitors (e.g. PD-1 inhibitors and PD-L1 inhibitors) with NCRT or NCT come up and evaluated in a large number of clinical trials. Currently, HER2, PD-1 and PD-L1 inhibitors are relatively promising targeted agents, which might be an optimal option when combined with NCT or NCRT, and there are still several ongoing clinical trials. Neoadjuvant immunotherapy and targeted therapy have shown satisfactory outcomes and promising prospects, which provide more options for EC patients. In the future, more studies are needed to explore the appropriate sequence of immunotherapy and NCRT or NCT and the means to identify the most beneficiary population.

The efficacy of targeted drugs is still questionable. Firstly, targeted therapy cannot help patients achieve complete recovery due to drug resistance. Moreover, although the combined targeted therapy and other treatment reaches better efficacy and lower drug resistance, adverse events have also increased. Furthermore, because there are many crossovers between the signal pathways regulated by targeted drugs, it can cause other complications. The research on targeted drugs for EC treatment is still a hotspot. We believe that with many clinical trials undergoing, more effective targeted therapies for esophageal cancer will be developed.

Many clinical studies are ongoing to identify the best combination therapy regimen. We hope the results of ongoing clinical trials could bring us a deeper understanding of neoadjuvant therapy and make substantial breakthroughs in the near future.

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Declarations

Disclosure The authors declare that they have no conflict of interests.

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