Review Article

Surgical intervention after neoadjuvant therapy in esophageal cancer: a narrative review

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Background and Objective: Esophageal cancer is one of the common malignant tumors in China. Previous studies have shown that surgery alone is less effective. Neoadjuvant therapy refers to preoperative chemoradiotherapy, which is the standard treatment for locally advanced and operable esophageal cancer. Selection of appropriate surgical methods and timing after neoadjuvant therapy is of great significance for improving the prognosis of patients and reducing postoperative complications.

Methods: An online electronic search of all eligible literature through PubMed, Google Scholar, and the Cochrane Library database was conducted using a combination of the following keywords: esophageal cancer, neoadjuvant therapy, neoadjuvant chemotherapy, chemoradiotherapy, immunotherapy, targeting, surgery, complications. With a focus on the use of surgery after neoadjuvant therapy, Eligible articles were identified by one or both authors.

Key Content and Findings: Neoadjuvant chemoradiotherapy combined with radical surgical resection remains the current standard of care for resectable esophageal cancer, significantly improving survival and pathologic complete response (PCR) compared with preoperative chemotherapy Recently, studies have also found that immunotherapy combined with chemotherapy has a more advantageous pathological response in patients with locally advanced disease. Although the emergence of targeted drugs has led to a change in treatment mode from traditional chemoradiotherapy to precision therapy, the postoperative progression-free survival (PFS) and overall survival (OS) need to be explored as well as how surgery-related risks caused by treatment can be reduced. Traditionally, surgery is performed 4–6 weeks after neoadjuvant therapy, and optimal timing for surgery after treatment is still being explored as research progresses, the surgical method also should be determined according to the specific situation of the patient. Postoperative complications should be dealt with in a timely manner, and of course, active preoperative intervention is equally important.

Conclusions: Neoadjuvant therapy combined with surgery is the gold standard for resectable esophageal cancer. However, optimal timing of surgery after preoperative treatment remains unclear. Minimally invasive thoracoscopic surgery (including robotic surgery) has gradually replaced traditional open surgery. Active prevention before operation, accurate and meticulous operation during operation, and timely treatment after operation can minimize the incidence of adverse events.

Keywords: Esophageal cancer; neoadjuvant therapy; duration of surgery; surgical methods; postoperative complications

Submitted Jan 28, 2023. Accepted for publication Apr 23, 2023. Published online Apr 27, 2023.
doi: 10.21037/jtd-23-420
View this article at: https://dx.doi.org/10.21037/jtd-23-420

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Introduction

Esophageal cancer (EC) is a malignant tumor originating from the esophageal epithelium, and most cases are classified as either esophageal squamous cell carcinoma (ESCC) or esophageal adenocarcinoma cancer (EAC). Esophageal cancer is the seventh most common cancer and the sixth leading cause of cancer death worldwide (1,2). According to the report "Global Cancer Statistics 2020", there are about 604,000 new cases and about 544,000 deaths from EC worldwide each year, and the five-year survival rate is less than 20% (3). China has a high incidence of EC, and more than half of EC cases worldwide are diagnosed in China. Epidemiological data show that the new cases and deaths of EC in China account for 53.70% and 55.35% of the global total, respectively (4,5). At present, EC is a major threat endangering national health. Active prevention and treatment of EC is very important for reducing the mortality rate and improving the quality of life of patients. Currently, commonly used clinical treatment options for EC include radiotherapy, chemotherapy, and surgery. Clinically, about 50% of patients with esophageal cancer are at an advanced stage when diagnosed, resulting in a missed opportunity for optimal early surgical intervention (6). At this time, even if surgical intervention is adopted, it is difficult to obtain a good prognosis, with the 5-year survival rate after surgery ranging from 20–35% (7). The 2022 Chinese guidelines for the diagnosis and treatment of EC recommend neoadjuvant therapy for patients with cTis-2N1-3M0 or cT3-4aN0-3M0. In recent years, clinical studies have shown that preoperative neoadjuvant therapy can significantly improve overall survival (OS) of patients with locally advanced resectable EC, mainly by reducing the risk of locoregional recurrence and distant metastasis (8-10). Compared with traditional chemoradiotherapy, neoadjuvant therapy can improve the survival rate of advanced stage patients and increase the possibility of surgery to a certain extent (11). The application prospect of surgical intervention for EC after neoadjuvant therapy is good and worthy of clinical attention (12,13). We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-420/rc).

Methods

To complete this narrative review, we searched PubMed, Google Scholar, and Cochrane Library to identify relevant articles. The following combination of search terms was used: esophageal cancer, neoadjuvant therapy, neoadjuvant chemotherapy, chemoradiotherapy, immunotherapy, targeting, surgery, complications. Two authors conducted a full-text review of relevant literature (*Table 1*). Because our study was designed as a narrative review, the meta-analysis cited in this study did not use standard methodological methods or statistical analysis.

Definition and progress of neoadjuvant therapy for esophageal cancer

Neoadjuvant therapy for EC refers to treatment options, such as chemoradiotherapy, before surgery is performed for EC. Neoadjuvant therapy before esophagectomy is the standard treatment for locally advanced and operable EC (7). At present, neoadjuvant therapy for EC mainly includes neoadjuvant chemoradiotherapy (nCRT), neoadjuvant chemotherapy (nCT), and emerging immunotherapy combined with chemotherapy radiation therapy (CRT) (14).

nCT

The study of nCT in EC first began in the 1980s. At that time, commonly used chemotherapy regimens were double- or triple-drug regimens based on cisplatin [cisplatin + 5-fluorouracil (5-FU)/methotrexate/vincristine/bleomycin, among others]. Clinical studies have shown that nCT plays a small role in the treatment of esophageal cancer, because nCT does not significantly improve the survival of patients (15,16). However, study also found that the survival of patients with better pathologic complete response (PCR) was significantly longer, and the survival rate was double compared with that of patients with surgery alone (16). The advantage of preoperative systemic chemotherapy over surgery was also demonstrated in a major trial (17) and as a result, the exploration of nCT continues. nCT regimens vary. In a previous study involving 162 patients with ESCC and up to 5 years of follow-up, Sugimura *et al.* (18) reported that compared with patients treated with cisplatin + fluorouracil + doxorubicin, recurrence free survival (RFS) and 5-year OS of the cisplatin + fluorouracil + docetaxel group were significantly longer, and locoregional and distant recurrence rates were significantly lower in the subgroup of patients with advanced clinical tumor (T) and lymph node (N) stages. In addition, in a three-arm study of stages II and III locally advanced esophageal squamous cell carcinoma, the JCOG1109 NExT study, we found that preoperative

Table 1 Search strategy summary

Items	Specifications
Date of search	1/11/2022–30/11/2022
Databases and other sources searched	PubMed, Google Scholar, Cochrane Library
Search terms	Esophageal cancer, neoadjuvant therapy, neoadjuvant chemotherapy, chemoradiotherapy, immunotherapy, targeting, surgery, complications
Timeframe	The articles were published between August 1994 and November 2022
Inclusion and exclusion criteria	Inclusion criteria: written published clinical trials, meta-analyses, randomized controlled trials, reviews, and systematic reviews
	Exclusion criteria: editorials, comments, letters, meeting minutes, case reports
Selection process	Junli Ke and Jin Liang independently screened and reviewed all the initial articles, with additional review by Yujie Xie. Final inclusion was determined by all the authors

DCF significantly prolonged overall survival compared with preoperative CF (19). As a result, cisplatin + fluorouracil + docetaxel regimen is a candidate for neoadjuvant treatment of resectable ESCC. In 2022, Chidambaram *et al.* (20) conducted a meta-analysis of 22 clinical studies on the use of nCT in patients with locally advanced EC, involving a total of 2,666 patients. The results showed that compared with the docetaxel + cisplatin + 5-FU treatment regimen, the fluorouracil + leucovorin + oxaliplatin + docetaxel treatment regimen could improve the PCR of patients to a certain extent, but there was no significant difference between the two regimens [P=0.148, 95% confidence interval (CI): 0.080–0.259]. Therefore, comparison between different treatment regimens of nCT requires further exploration. In terms of the duration of nCT, Shiraishi *et al.* (21) conducted a multicenter phase II clinical trial in 2021 involving 180 patients with EC. The results showed that 3 courses of nCT resulted in a better response than 2 courses, and there was no significant increase in adverse events.

nCRT

nCRT refers to the chemoradiotherapy performed before the implementation of local treatment, which is suitable for locally advanced EC (clinical stage above T3, positive circumferential resection margin, and lymph node metastasis). The decade-long CROSS trial (22), which randomized 366 patients to 5 weekly cycles of preoperative carboplatin and paclitaxel plus concurrent radiotherapy or surgery alone, confirmed better OS in patients who received preoperative nCRT, with a significant 13% improvement in 10-year OS (38% *vs.* 25%). Li *et al.* (23) found that nCRT had advantages in PCR, R0 resection rate, and OS, and had lower postoperative adverse reactions than nCT. A previous study has shown that with the continuous innovation and development in the field of modern cancer treatment. The 5-year survival rate for esophageal cancer has increased from 19% in 1970 to 47% today. A significant improvement in survival depends on the widespread use of nCRT in advanced esophageal cancer (14). However, in two previous randomized trials in the United States and Europe, we found no significant increase in survival with nCRT as compared with nCT (24,25). But, in a phase II trial, we considered preoperative chemoradiotherapy as an option in esophageal adenocarcinoma with regard to margin involvement, although there was no difference in survival (26). The meta-analysis by Han *et al.* (27) included a total of 4,529 patients (nCT: 2,035; nCRT: 2,494). The 3-year survival rate, R0 resection rate, and PCR rate of nCRT were significantly higher than those of nCT, and the rates of local recurrence and distant metastasis were significantly lower than those of nCT. Postoperative complications have always been an area of concern in EC. Jin *et al.* (28) found in a meta-analysis that nCRT and neoadjuvant radiotherapy (NRT) did not significantly increase the risk of postoperative anastomotic leak in EC patients. nCRT has attracted a great deal of attention. The results of a meta-analysis of 31 clinical studies (29) showed that taxane regimens were equally effective as cisplatin plus 5-FU regimens in ESCC patients, but the OS of taxane regimens (P=0.03) was superior to cisplatin plus 5-FU regimens. In addition, the vinorelbine plus cisplatin regimen (30) has also been well tolerated and effective in Chinese ESCC patients. In addition to the above dual therapies, triple

Table 2 Common neoadjuvant chemotherapy and chemoradiotherapy regimens

Author	Year of publication	Therapeutic schedule	Clinical effect
Apinop *et al.* (15)	1994	Cisplatin + 5-Fu + surgery	Survival at 1 and 5 years was slightly better with combination therapy than with surgery alone
Wang *et al.* (16)	2021	Paclitaxel + cisplatin (nCT)/paclitaxel + cisplatin + external beam radiotherapy (nCRT)	PCR was higher and death due to tumor progression or recurrence was significantly lower in the nCRT group than in the nCT group
Sugimura *et al.* (18)	2021	Cisplatin + 5-Fu + docetaxel/cisplatin + 5-Fu + adriamycin	PFS and OS of the docetaxel group were better than those of the doxorubicin group
Chidambaram *et al.* (20)	2023	Cisplatin + 5-Fu + docetaxel/5-Fu + leucovorin + oxaliplatin + docetaxel	PCR was improved to some extent in the oxaliplatin group
Shiraishi *et al.* (21)	2021	Two courses of docetaxel + cisplatin + 5-Fu/3 courses of docetaxel + cisplatin + 5-Fu	A longer course of treatment resulted in a better pathological response without increasing the incidence of adverse events or postoperative morbidity
Eyck *et al.* (22)	2021	Carboplatin + paclitaxel + radiotherapy + surgery	Patients who received neoadjuvant chemoradiotherapy before surgery had better overall survival, with a significant 13% improvement in 10-year overall survival
Li *et al.* (23)	2021	Oxaliplatin + capecitabine + external beam radiotherapy (nCRT)/oxaliplatin + capecitabine (nCT)	Neoadjuvant chemoradiotherapy was effective in the treatment of advanced gastric cancer and worthy of promotion
Wang *et al.* (29)	2019	Taxanes + cisplatin + fluorouracil/ fluorouracil + cisplatin	Compared with traditional neoadjuvant chemotherapy regimens, taxane-based regimens were superior in terms of OS
Yang *et al.* (30)	2018	Vinorelbine + cisplatin + surgery	nCRT plus surgery could improve the survival of patients with locally advanced ESCC, and the adverse events were acceptable and controllable
Ohnuma *et al.* (31)	2018	Docetaxel + nedaplatin + fluorouracil	This regimen combined with chemotherapy was a promising preoperative regimen for resectable ESCC, with acceptable feasibility. The completion rate of the regimen was 89.3%, and the antitumor efficacy was strong
Zhang *et al.* (32)	2021	Paclitaxel + cisplatin + capecitabine	It could improve the PCR rate of advanced patients and reduce the incidence of adverse reactions

nCT, neoadjuvant chemotherapy; nCRT, neoadjuvant chemoradiotherapy; PFS, progression-free survival; OS, overall survival; ESCC, esophageal squamous cell carcinoma; PCR, pathological complete response.

therapy has also attracted clinical attention in recent years. The results of a phase II clinical trial (31) showed that the overall response rate of docetaxel, nedaplatin, and 5-FU combination chemotherapy was 87.0%. Another triple regimen (paclitaxel, cisplatin, and capecitabine) has resulted in excellent PCR rates with a low incidence of adverse effects in patients with locally advanced ESCC (32). The application prospect of nCRT in the field of EC is highly anticipated. The use of nCT and nCRT and the results of different treatment regimens are summarized in *Table 2*.

Neoadjuvant immunotherapy

Immunotherapy has evolved as a promising new treatment modality across cancer types (33). An available study (34) indicates that immune check-point inhibitors (ICIs) such as pembrolizumab and nivolumab can be used as a first-line treatment for patients with locally advanced EC. In 2020, Kojima *et al.* (35) randomized 628 patients with advanced EC to pembrolizumab or chemotherapy. Patients were identified in a phase 3 trial, with a positive score ≥10 had significantly higher 12-month OS with pembrolizumab

Table 3 Results of clinical trials of neoadjuvant immunotherapy

Author	Year of publication	Therapeutic schedule	Clinical effect
Paydary *et al.* (34)	2021	Nivolumab (immune group)/paclitaxel or docetaxel (chemotherapy group)	Overall survival was significantly improved with nivolumab versus chemotherapy and had a favorable safety profile
Kojima *et al.* (35)	2020	Pembrolizumab/paclitaxel, docetaxel, or irinotecan	The 12-month OS rate was significantly higher with pembrolizumab versus chemotherapy, with low adverse event rates
Hong *et al.* (38)	2021	Sintilizumab + pembrolizumab + camrelizumab + cisplatin + albumin + paclitaxel + surgery	Surgery after neoadjuvant chemotherapy was safe and effective. The increased risk of surgery was acceptable, and the postoperative complications were controllable
Huang *et al.* (39)	2021	Docetaxel + nidaplatin + pembrolizumab	The PCR and objective response rates of the combined chemotherapy group were significantly higher than those of the chemotherapy alone group

OS, overall survival; PCR, pathological complete response.

versus chemotherapy (43% *vs.* 20%) and significantly lower rates of adverse events with treatment (18.2% *vs.* 40.9%). In 2019, a multicenter phase III trial (34) involving 419 patients randomized to nivolumab or chemotherapy showed a median follow-up for OS of 10.5 months in the nivolumab group and 8.0 months in the chemotherapy group. At a minimum follow-up of 17.6 months, OS was significantly improved with nivolumab versus chemotherapy (10.9 *vs.* 8.4 months, P=0.019). To evaluate atezolizumab's stability after definitive chemoradiotherapy in locally advanced ESCC patients, the TENERGY trial (36) involved 50 patients with advanced EC. Blood samples were obtained at 3 time points (before CRT, after CRT, and 4 weeks after initiation of atezolizumab) for exploratory biomarkers. The study results have not yet been published and were ultimately found to require further attention. A study (37) has also shown that the combination of immunotherapy and chemotherapy in neoadjuvant therapy may have more advantages in terms of pathological response in patients with locally advanced resectable EC. In order to verify the effect of neoadjuvant immunotherapy combined with chemotherapy followed by surgery, Hong *et al.* (38) enrolled 76 patients and divided them into a surgery alone group and immunotherapy combined with chemotherapy followed by surgery group. The results showed that the complications of the 2 groups were similar, and there were no significant differences in intraoperative blood loss, intensive care unit (ICU) stay time, postoperative stay time, and hospitalization cost. Rates of 30-day mortality, 30-day readmissions, and ICU readmissions were also similar between the concurrent immunotherapy and chemotherapy group and surgery group. The emergence of neoadjuvant immunotherapy may provide a new treatment option for locally advanced EC. In a previous study by Huang *et al.* (39), 54 patients with advanced EC were randomly divided into immunotherapy group and chemotherapy group, and all received radical surgery after treatment. Compared with the chemotherapy alone group, the PCR rate and objective response rate of the chemotherapeutic combination group were significantly higher (30.4% *vs.* 9.7%, P=0.048; 86.9% *vs.* 95.7%, P=0.017), as was the tumor regression grade ≥2 (80.7% *vs.* 50.0%, P=0.013). Compared with traditional therapy, immunotherapy has been shown to have obvious advantages in many malignant tumors and may become the mainstream drug treatment for unresectable and progressive or metastatic EC. Neoadjuvant immunotherapy has been shown to be safe and effective. A large number of prospective clinical studies and more data support are also needed. *Table 3* shows the results of studies with neoadjuvant immune checkpoint inhibitors in patients with EC.

Neoadjuvant targeted therapy

Targeted therapy is a new treatment technology, which plays an important role in the treatment of esophageal cancer. Drugs included cetuximab and bevacizumab, which act on epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF), respectively. Drugs targeting surface antigens and other signaling pathways are in development (40). The results of a phase III trial by Ruhstaller *et al.* (41) found that in patients with resectable ESCC, cetuximab combined with other therapies (radiotherapy, chemotherapy, and surgery)

significantly controlled the development of regional ESCC and improved progression-free survival (PFS) and overall survival (OS), without an increase in toxicity and adverse events. In order to verify the clinical effect of nimotuzumab combined with chemotherapy, Han *et al.* (42) conducted a five-year study involving 21 patients with EC, and the results showed that the objective response rate was 38.1% and the disease control rate was 81%. The mean PFS was 7 months, and the 18-month OS was 10%, and no drug-related toxicities were noted during long-term follow-up. Regarding the EGFR pathway, in addition to the above 2 drugs, gefitinib (43) and icotinib (44) are also expected to be effective, but their therapeutic effects still need to be supported by more clinical trial data. Trastuzumab, a commonly used drug targeting the human epidermal growth factor receptor 2 (HER2) pathway, has a good effect in the treatment of most tumors but has little effect in EC. A phase II study by Makiyama *et al.* (45), which included 91 patients randomly assigned to paclitaxel or trastuzumab, confirmed that the median PFS was 3.2 months and 3.7 months in the paclitaxel and trastuzumab groups, respectively, and the median OS was 10 months and 10.2 months in the 2 groups, respectively. Overall response rates were 32% and 33%, respectively, and no biomarkers were found to correlate with response in the trastuzumab group. In contrast, a phase III study by Hecht *et al.* (46) involving 545 patients assigned 1:1 to placebo or lapatinib showed a median OS of 12.2 months and 10.5 months, and a median PFS of 6.0 months and 5.4 months, respectively, in the lapatinib and placebo groups. The response rate was significantly higher with lapatinib (53% *vs.* 39%). For gastrointestinal cancers, VEGFR inhibitors appear to be more commonly used (47). However, there are still many problems in the safety of EC treatment. Cunningham *et al.* (48) conducted a multicenter phase II and III trial involving 1063 patients with EAC who were divided into bevacizumab plus chemotherapy (experimental group) and chemotherapy alone (control group). The results showed that the 3-year OS rate was 50.3% in the control group and 48.1% in the experimental group. The incidence of postoperative anastomotic leakage was higher in the experimental group (24% *vs.* 10%). In the RAINBOW-Asia trial, Xu *et al.* (49) randomly assigned 440 patients to a ramucirumab group and the paclitaxel group. The results showed that the median PFS was 4.14 months in the ramucirumab group and 3.15 months in the paclitaxel group (P=0.0184). The median OS was 8.71 months with ramucirumab and 7.92 months with paclitaxel. At present, ramucirumab is one of the most commonly used second-line treatment options for EC in China. Althougha previous study (50) has found that crizotinib has some antitumor activity in EAC patients, it still needs to be further verified by large-scale clinical studies. With the continuous discovery of new targets, more and more targeted therapeutic drugs will be developed in the future.

Summary

Neoadjuvant therapy includes nCT, nCRT, immunotherapy and targeted therapy, etc. There is no effective evidence on which treatment method is the most beneficial for patients. At present, radiotherapy and chemotherapy are still the preferred clinical treatment for the vast majority of patients with esophageal cancer. Immunotherapy and targeted therapy have benefited limited specific patient groups, but the overall clinical application is still limited, and more trials are needed to verify their safety and efficacy. Common neoadjuvant targeted therapies are summarized in *Table 4*.

Timing of surgery after neoadjuvant therapy for esophageal cancer

In clinical practice, the timing of surgery after neoadjuvant therapy has a great impact on the clinical prognosis of patients, although specific optimal surgical timing remains unclear. Traditionally, the best time for surgery is 4–6 weeks after completing nCRT (51), but some scholars have suggested otherwise. Qin *et al.* (52) included 15,086 patients in a meta-analysis showing that compared with patients with an interval of fewer than 7–8 weeks after nCRT, the PCR rate was significantly improved in the group with a gap of 7–8 weeks (P=0.001), although both 2-year OS (P=0.002) and 5-year OS (P=0.0009) were significantly reduced for the longer period. Xiao *et al.* (53) randomized a total of 224 patients into group A (≤10 weeks) and group B (>10 weeks) in a 4-year study based on the timing of surgical treatment after nCRT. The results showed that among patients who achieved PCR after surgery, there was no significant difference in survival benefit between the A and B groups (P=0.618). However, in patients who did not achieve PCR, increasing the operation time reduced the survival rate (P=0.035) and accelerated cancer progression (P=0.036). The study by Roh *et al.* (54) included 348 EC patients divided into 3 groups (no nCRT before surgery, surgery within 35 days of nCRT, and surgery more than 35 days after nCRT). The incidence of anastomotic fistula

Table 4 Current status of neoadjuvant targeted therapies

Author	Year of publication	Therapeutic schedule	Clinical effect
Ruhstaller *et al.* (41)	2018	Docetaxel + cisplatin + external beam radiotherapy + surgery + cetuximab	Cetuximab significantly restrained the development of regional ESCC and improved progression-free and overall survival in patients with resectable ESCC without increasing toxicity or postoperative morbidity
Han *et al.* (42)	2017	Nimotuzumab plus paclitaxel, fluorouracil, or gemcitabine	Nimotuzumab combined with chemotherapy could achieve promising clinical results in locally advanced or metastatic esophageal cancer with no accumulation of toxicity and was well tolerated
Makiyama *et al.* (45)	2020	Paclitaxel and trastuzumab	The addition of trastuzumab still failed to improve PFS in patients with HER2-positive advanced G/GEJ cancer, and no beneficial biomarkers were identified
Hecht *et al.* (46)	2016	Oxaliplatin plus lapatinib	The response rate was higher with lapatinib than with placebo
Cunningham *et al.* (48)	2017	Epirubicin + cisplatin + capecitabine + bevacizumab	The addition of bevacizumab reduced survival and increased the incidence of postoperative complications
Xu *et al.* (49)	2021	Ramucirumab plus paclitaxel	The trial results supported the use of ramucirumab plus paclitaxel as second-line therapy in the predominately Chinese population with advanced gastric or GEJ adenocarcinoma

HER2, human epidermal growth factor receptor 2; PFS, progression-free survival; G/GEJ, gastric or gastroesophageal junction; ESCC, esophageal squamous cell carcinoma.

of the no nCRT group, ≤35 days after nCRT group, and the >35 days after nCRT group was 14.7%, 7.3%, and 20.0%, respectively, and the difference between the groups was statistically significant (P=0.020). These results suggested radical esophagectomy within 35 days of NCRT could significantly reduce the incidence of anastomotic fistula. Current studies have shown that patients who achieve PCR after nCRT have significantly longer OS than those who achieve a pathologically partial response or no response (55,56). However, whether delays in surgery after nCRT lead to increased likelihood of PCR and improved survival remains debatable. The study by Singla *et al.* (57) included a total of 226 EC patients divided into an early group (≤50 days) and advanced group (>50 days). The results showed that age, sex, comorbidities, Eastern Cooperative Oncology Group (ECOG) status, location, grade, and tumor histology were similar, and the difference in PCR rate between the early and late groups was not statistically significant (26.9% *vs.* 19.0%, P=0.24). A total of 8,489 patients were included in the study by Levinsky *et al.* (58). The patients were divided into a timely esophagectomy group (<90 days) and delayed esophagectomy group, and the results showed that the delayed esophagectomy group had a higher PCR rate (22.2% *vs.* 18.6%, P=0.043) and 90-day mortality (10.4% *vs.* 7.8%, P<0.01). In multivariate analysis, delayed esophagectomy was not independently associated with OS reduction. The optimal time for surgery is uncertain and needs further study and discussion.

Summary: The optimal timing of surgery is of great significance for the survival and prognosis of EC patients and the reduction of postoperative complications. However, the optimal timing for surgery after neoadjuvant therapy is still unclear, and the current clinical practice is to perform surgery for patients after 4–8 weeks before the emergence of new evidence, and the survival rate of patients will decrease after 10 weeks. Under the premise of ensuring clinical efficacy, surgery should be performed as soon as possible. We found that the timing of surgery had different effects on the survival prognosis of patients (*Table 5*).

Selection of surgical methods for esophageal cancer after neoadjuvant therapy

Neoadjuvant therapy combined with surgery is an effective strategy for the treatment of patients with advanced EC (59), but the choice of surgical method varies for individual patients. Currently available surgical techniques include Ivor Lewis esophagectomy (abdominal and right thoracic incision), McKeown esophagectomy (abdominal, right thoracic, and neck incision), the Sweet procedure (left

Table 5 Clinical studies of different surgical timing

Author	Year of publication	Timing of surgery after neoadjuvant therapy	Effect of action
Nilsson *et al.* (51)	2020	4–6 weeks	The timing of surgery after completion of nCRT was not important for short-term postoperative outcomes
Qin *et al.* (52)	2018	7–8 weeks	Prolonged time interval could significantly improve the pathological complete response rate of esophageal cancer but may be unfavorable for long-term survival
Xiao *et al.* (53)	2023	10 weeks	For patients who did not achieve PCR after neoadjuvant therapy, prolonged operation time led to lower survival rate
Roh *et al.* (54)	2019	35 days	Radical esophagectomy within 35 days after nCRT could reduce the incidence of anastomotic leakage
Singla *et al.* (57)	2018	50 days	PCR was not associated with the timing of surgical resection, and other considerations of surgical timing, including nCRT recovery and patient performance, may be more relevant than PCR
Levinsky *et al.* (58)	2020	90 days	Delayed esophagectomy was not independently associated with reduced overall survival, and delayed and salvage esophagectomy could be performed in patients who did not undergo esophagectomy in a timely manner after CRT

nCRT, neoadjuvant chemoradiotherapy; CRT, chemotherapy radiation therapy; PCR, pathological complete response.

unilateral thoracotomy), abdominal left thoracotomy, and transesophageal resection, among others (60). In 2022, a retrospective study published by Ising *et al.* (61) involving 7,163 patients divided into a conventional thoracotomy group and minimally invasive esophagectomy group confirmed that patients in the minimally invasive group had significantly more harvested lymph nodes than those in the open thoracotomy group. The R0 resection rate was 96.1% *vs.* 94.3% (P=0.053), postoperative hospital stay was 9 *vs.* 10 days (P=0.001), and postoperative survival rate was significantly higher for the minimally invasive group (P<0.001). Transthoracic and transabdominal approaches are common techniques for radical resection of EC. In a 2020 meta-analysis involving 2,331 patients, Wu *et al.* (62) found that patients in the transthoracic approach (TH) group had reduced intraoperative blood loss, shorter hospital stay, and lower incidence of pulmonary complications. The TH method may be more suitable for Siewert type II adenocarcinoma of the esophagogastric junction (AEG), especially for esophageal invasion ≤4 cm. However, the operation mode for Siewert type II AEG is still controversial. The prospective study of Huang *et al.* (63) included 10 patients with Siewert type II AEG who underwent total laparoscopic radical resection through the left diaphragm and left thoracic auxiliary hole, and the results showed it was a good surgical option for patients with esophageal tumors that have invaded <3 cm. A retrospective data study by Hu *et al.* (64) included 41 patients with AEG. The 3-year survival rate, upper resection margin, postoperative complications, and estimated benefit index of lymph node dissection were analyzed. Finally, it was confirmed that total gastrectomy through the abdominal cavity access approach may be the best surgical technique for advanced Siewert type II AEG. However, a multicenter study broke this conclusion and concluded that total gastrectomy and para-aortic lymph node dissection were not necessary. When the lesion involves the esophagus exceeds at 4.0 cm, subtotal esophagectomy plus superior mediastinum 106recR (right recurrent laryngeal nerve) resection is recommended. When it exceeds 2.0 cm, 110 stations of the lower mediastinum (paraesophageal) should be dissected (65). At the same time, study has found that the transcervical approach can completely remove the lymphatic chain along the recurrent laryngeal nerve at the cervicothoracic junction, which is helpful to improve the cure rate of surgery in patients with Siewert type II tumors (66). In terms of different surgical positions, Chen *et al.* (67) used the prone position, and the results showed that the R0 resection rate was 93.4%, and the negative circumferential resection margin rate was 96.7%. The median total lymph node dissection rate was 21%, and the thoracic lymph node dissection rate was 13%. The positive rates of lower mediastinal lymph nodes in upper, middle, and lower tumors were 1.1%, 3.5%, and 2.4%,

respectively. As a more traditional position, the lateral position is still widely used in clinical practice. In a study of 200 patients, Miura *et al.* (68) showed that the mean thoracic surgery time in the lateral position group was shorter than that in the prone position group (228.9 *vs.* 299.1 minutes, P<0.001), but the mean chest blood loss was significantly higher in the lateral position group (186.9 *vs.* 76.5 mL, P<0.001), the mean number of harvested thoracic lymph nodes was lower in the lateral position group than in the prone position group (23.5 *vs.* 26.9, P<0.05), and the incidence of pulmonary complications was significantly higher (30.8% *vs.* 15.4%, P<0.05). There was no significant difference in the 5-year OS rate and PFS rate between the 2 positions. For middle thoracic EC, Shi *et al.* (69) showed that the operation time of the Ivor Lewis group was significantly shorter than that of the McKeown group, and the incidence of anastomotic leakage, anastomotic stenosis, and pulmonary infection was significantly lower than that of McKeown group. With application of Da Vinci robotic-assisted thoracic surgery, new treatment options have emerged. Robotic surgery is an extension and progress of traditional minimally invasive surgery. due to better survival outcomes and a significantly reduced incidence of pulmonary complications (70). A previous meta-analysis by Angeramo *et al.* (71), which included 6,249 patients, showed that compared with conventional surgery, robotic esophagectomy resulted in less intraoperative blood loss and postoperative pneumonia [odds ratio (OR): 0.46, P<0.001] and lower overall morbidity (OR: 0.67, P<0.001), while achieving a higher R0 resection rate (OR: 2.84, P<0.001). In the study by Motoyama *et al.* (72), a total of 121 EC patients were randomly divided into conventional video-assisted thoracoscopic surgery (VATS) group and robot-assisted VATS group. The overall local recurrence rate in the surgical field was significantly higher in the conventional VATS group than in the robot-assisted VATS group (9% *vs.* 0%, P=0.039). At present, there are various surgical treatment methods for EC after neoadjuvant therapy. The choice of surgical methods should be based on the characteristics of the disease.

Summary: With the continuous progress and innovation of modern medical technology, surgical methods for EC after neoadjuvant therapy are gradually diversifying. The main surgical options include traditional thoracotomy, minimally invasive surgery, and robot-assisted surgery, among others. There is increasing evidence that the application rate of minimally invasive surgery has reached a high level, and robotic surgery is an emerging method that may replace minimally invasive surgery in the future. In the table, we document in more detail the current surgical procedures that are commonly used (*Table 6*).

Postoperative complications and management of esophageal cancer after neoadjuvant therapy

Postoperative complications of EC directly determine the quality of life and survival time of patients, and the prevention and appropriate treatment of complications are key. Although great progress has been made in the multimodal treatment of EC, the occurrence of postoperative complications continues to impact the prognosis and long-term survival rate of patients (73). In 2015, the Esophagectomy Complications Consensus Group (ECCG) reported that the most common complications after esophagectomy included pneumonia (14.6%), arrhythmia (14.5%), anastomotic leakage (11.4%), chylothorax (4.7%), recurrent laryngeal nerve palsy (4.2%), and tube necrosis (1.3%) (74). Pneumonia after esophageal surgery has a high incidence and significantly increases mortality and length of hospital stay (75). Therefore, in order to reduce the incidence of pneumonia, minimally invasive surgery is often performed instead of open surgery. In a single-center randomized controlled trial involving 118 patients who underwent open transthoracic esophagectomy (OTE group) or robot-assisted minimally invasive thoracoscopic esophagectomy (RAMIE group), van der Sluis *et al.* (76) showed that compared with the OTE group, overall procedural-related postoperative complications were significantly lower in the RAMIE group (59% *vs.* 80%, P=0.02), and intraoperative blood loss was significantly reduced (400 *vs.* 568 mL, P<0.001). In addition, the incidence of pulmonary complications was significantly lower in the RAMIE group (P=0.005), and the RAMIE group had better functional recovery at 14 days after operation (P=0.038). Because the esophagus is close to the left atrium, the occurrence of postoperative atrial fibrillation (AF) is sometimes unavoidable. The incidence of postoperative adverse events in patients with EC complicated with AF is significantly higher than that in patients without AF (OR =5.50), including 30-day mortality (OR =2.49), anastomotic leakage (OR =2.65), and pneumonia (OR =3.42) (77). A randomized clinical trial by Ojima *et al.* (77) involved 100 patients randomly assigned 1:1 to receive landiolol or placebo and confirmed a significantly lower incidence of AF after EC surgery (10% *vs.* 30%, P=0.012) and a significantly lower overall

Table 6 Surgical methods for resectable esophageal cancer

Author	Year of publication	Surgical methods	Clinical effect
Ising *et al.* (61)	2022	Robotic esophagectomy/endoscopic esophagectomy/conventional esophagectomy	Minimally invasive surgery could improve the R0 resection rate, shorten the length of hospital stay, and was more beneficial to long-term survival
Wu *et al.* (62)	2020	Transthoracic or laparoscopic resection of esophageal cancer was performed	The transabdominal approach could reduce the blood loss, shorten the length of hospital stay, reduce the incidence of pulmonary complications, prolong the 3-year overall survival, and was more suitable for EGJ in Siewert type II adenocarcinoma with diameter ≤4 cm
Huang *et al.* (63)	2021	Total laparoscopic radical resection was performed via left diaphragm and left chest	This procedure is effective against invasion. Siewert type II adenocarcinoma with 3 cm EGJ is a better choice
Hu *et al.* (64)	2019	Transabdominal approach and total gastrectomy were performed	This approach may be the best surgical technique for advanced Siewert type II AEG
Chen *et al.* (67)	2022	Thoracoscopic total interesophageal resection was performed in the prone position	Prone position was more suitable for middle and lower mediastinothoracic lymph node dissection
Miura *et al.* (68)	2019	Thoracoscopic resection of esophageal cancer in lateral decubitus position	There was no significant difference in surgical outcomes between the 2 positions
Shi *et al.* (69)	2021	Thoracoscopic and laparoscopic Ivor Lewis and thoracoscopic and laparoscopic McKeown procedures were performed	For the middle thoracic esophageal cancer, Ivor Lewis surgery was more suitable
Angeramo *et al.* (71)	2021	Robot-assisted minimally invasive esophagectomy for esophageal cancer	Patients undergoing robotic esophagectomy had less intraoperative blood loss, lower incidence of postoperative pneumonia, lower overall morbidity, and higher R0 resection rates
Motoyama *et al.* (72)	2021	Robot-assisted minimally invasive esophagectomy for esophageal cancer	The postoperative recurrence rate of robot-assisted esophagectomy was significantly lower than that of traditional laparoscopic esophagectomy

EGJ, esophagogastric junction; AEG, adenocarcinoma of the esophagogastric junction.

incidence of postoperative complications (P=0.046) in patients receiving landiolol. As one of the most serious postoperative complications, anastomotic leakage has attracted the attention of clinicians, but the best treatment is still unknown. A previous 10-year retrospective study by Plum *et al.* (78), which included 70 patients who received self-expanding metal stents (SEMS) for the treatment of anastomotic leakage after esophagectomy, found that 71.4% of the patients underwent successful esophageal stenting and the mortality rate was less than 20%. Postoperative chylothorax in patients with EC is caused by damage to the thoracic duct or its branches. At present, surgery is still the preferred intervention for the treatment of chylothorax, and no research results provide support for preoperative prophylactic ligation of the thoracic duct to reduce the incidence of postoperative chylothorax (79). In a study by Lin *et al.* (80), a total of 296 patients with EC were divided into conventional group (group A) and selective group (group B). The results confirmed that the incidence of postoperative chylothorax and chylothorax-related reoperation in group A was significantly higher than that in group B (9.1% *vs.* 0%, P<0.01) and (3.6% *vs.* 0%, P<0.01). The detection rate of chylous fistula (chylothorax and chylous ascites) in group B was significantly higher than that in group A (9.5% *vs.* 0%, P<0.01). In addition, study has shown that surgery after nCRT causes more adverse events (81). The reduction of complications is key to the success of surgery. With the emergence of new technologies, the incidence of postoperative complications is believed to be lower, but whether other complications will derive from

Table 7 The occurrence and treatment of postoperative complications

Author	Year of publication	Postoperative complications	Treatment measures	Effect of action
van der Sluis *et al.* (76)	2019	Pneumonia	Robotic minimally invasive alternative to open surgery	The robotic group had significantly lower overall postoperative complications, less intraoperative blood loss, and better postoperative recovery
Ojima *et al.* (77)	2017	Atrial fibrillation	Preoperative prophylactic heart rate control (landiolol)	Landiolol was effective and safe in the prevention of postoperative atrial fibrillation after esophagectomy
Plum *et al.* (78)	2019	Anastomotic fistula	All patients were treated with self-expanding metallic stents (SEMS)	Stent implantation was successful in 70% of patients, with low mortality
Jínek *et al.* (79)	2018	Chylothorax	Esophagectomy was performed with the introduction of prophylactic thoracic duct ligation	Prophylactic ligation of the thoracic duct did not reduce the incidence of chylothorax
Lin *et al.* (80)	2017	Chylothorax	Selective collective ligation of the thoracic duct	Selective thoracic duct ligation could reduce the incidence of postoperative chylothorax and chylothorax related reoperation

the new technology is still unknown.

In summary, there are many postoperative complications of EC, among which the most common complication is pulmonary infection, followed by AF, chylothorax, and anastomotic leakage, among others. Preoperative prevention and active postoperative intervention are important measures to reduce the incidence of complications and poor prognosis. However, the emergence of new technology will generate new complications. In addition to improving our surgical techniques, the proper arrangement of the whole perioperative period should not be ignored. Through the clinical studies described above, we found that active management of complications is particularly important (*Table 7*).

Deficiencies and prospects of surgical intervention after neoadjuvant therapy for esophageal cancer

EC is one of the most common malignant tumors in China. Surgical intervention after neoadjuvant therapy is one of the most common treatment methods for clinical patients. However, the current research on surgery after neoadjuvant therapy at home and abroad has the following shortcomings. First, although there are many options, individual responses of patients to different surgical methods vary. Therefore, actively exploring an individualized surgical plan suitable for different populations is important. Secondly, the optimal timing of surgery after neoadjuvant therapy is still unclear and needs further investigation. Finally, the effective prevention of surgical complications after neoadjuvant therapy is the focus of the clinical perioperative period and further research based on a large number of clinical trials is needed. This review briefly summarized the research progress for EC after neoadjuvant therapy, but the effect of different surgical methods on the prognosis of patients and effective measures for reducing postoperative complications need further analysis and summary. Our goal was to verify the stability of surgical intervention after neoadjuvant therapy by reviewing the important clinical trials related to the subject of this article. However, we found that this is not imminent 1 and requires a larger sample size and multicenter collaboration to obtain accurate data.

Conclusions

Esophageal adenocarcinoma is more common in Western developed countries, and more than half of the cases worldwide are esophageal squamous cell carcinoma. EC is a malignant tumor with high morbidity and mortality in China. Surgical intervention after neoadjuvant therapy is the first choice for reducing mortality and improving the prognosis of patients. However, the surgical method, optimal time of treatment, and postoperative complications are still the areas of clinical concern. Therefore, to improve the prognosis of patients and reduce postoperative complications, individualized surgical treatment at the optimal time after neoadjuvant therapy based on the specific situation of individual patients is important and worthy of clinical attention and ongoing exploration. At present, the efficacy of neoadjuvant therapy still needs to

be proved by a large number of trials, and neoadjuvant multimodal combination therapy may become a new direction in the future. On the basis of minimally invasive surgery, esophageal surgery can choose the most favorable way according to individual differences after different surgical approaches, fundamentally reduce the incidence of complications and further improve the survival rate of patients.

Acknowledgments

Funding: This work was supported by the Science and Technology Special Fund of Maoming City (No. 2020S003) and the Science and Technology Innovation Strategy Special Fund of Guangdong Province ("Big Project + Task List") project (No. 2021S006).

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-420/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-420/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-420/coif). All authors report that this work was supported by the Science and Technology Special Fund of Maoming City (No. 2020S003) and the Science and Technology Innovation Strategy Special Fund of Guangdong Province ("Big Project + Task List") project (No. 2021S006). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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(English Language Editor: A. Muijlwijk)

Cite this article as: Ke J, Xie Y, Liang J, Wang M, Lin W. Surgical intervention after neoadjuvant therapy in esophageal cancer: a narrative review. J Thorac Dis 2023;15(4):2261-2276. doi: 10.21037/jtd-23-420