

Review Article

Neoadjuvant therapy for non-small cell lung cancer and esophageal cancer

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Abstract: As the major malignant tumors in the chest, non-small cell lung cancer (NSCLC) and esophageal cancer (EC) bring huge health burden to human beings worldwide. Currently, surgery is still the mainstay for comprehensive treatment for NSCLC and EC, but the prognosis is still poor as the results of cancer recurrence and distant metastasis. Neoadjuvant therapy refers to a single or combined treatment before surgery, aiming to improve the therapeutic effects of the traditional therapies. Unfortunately, the clinical outcomes and effects of neoadjuvant therapy are still controversial due to its apparent advantages and disadvantages, and different patients may respond differentially to the same scheme of neoadjuvant therapy, which makes it urgent and necessary to develop personalized scheme of neoadjuvant therapy for different individuals. Therefore, this review summarizes the novel schemes and strategies of neoadjuvant therapy, which may help to significantly improve of life quality of patients suffering from chest-related malignancies.

Keywords: Chest-related tumors, non-small cell lung cancer, esophageal cancer, neoadjuvant therapy

Introduction

Lung cancer and esophageal cancer are major malignant tumors that affect people's health and quality of life, with global mortality rates ranking first and sixth, respectively [1]. Therefore, they are considered major malignant tumors in the chest [1]. For early and some locally advanced non-small cell lung cancer (NSCLC) and esophageal cancer (EC), comprehensive treatment with surgery as the mainstay is the preferred treatment [2, 3]. However, the prognosis of surgery alone is poor, with high rates of local recurrence and distant metastasis [2, 3]. Therefore, adjuvant therapy during the preoperative period is crucial, which has received increasing attention in recent years [4, 5].

Neoadjuvant therapy refers to a single or combined treatment before surgery aimed at reducing tumor burden and pathological staging, eliminating potential micro-metastatic lesions, reducing surgical difficulty and risk, increasing surgical resection rates, reducing postopera-

tive metastasis and recurrence rates, and ultimately benefiting patients in terms of quality of life and survival [6-8]. Neoadjuvant therapy has unique advantages [6-8], such as: 1. Patients have relatively better preoperative conditions, thus with better tolerance to the side effects of adjuvant therapy compare to post-operation; 2. At preoperative stage, it can increase blood supply to tumor bead, which helps to significantly inhibit the progression of tumors; 3. It can reduce the probability of subclinical residual lesions after surgery and early clear potential micro-metastatic lesions. Of course, neoadjuvant therapy also has some disadvantages [6-8], such as: 1. Patients may experience a decline in their condition or internal complications after treatment, which may delay the optimal timing of surgery or result in losing the opportunity for surgery; 2. Disease progression may occur during neoadjuvant therapy; 3. It may increase surgical difficulty or complexity; 4. It may increase the incidence or severity of postoperative complications.

Traditional neoadjuvant therapy regimens for NSCLC and EC typically focus on platinum-con-

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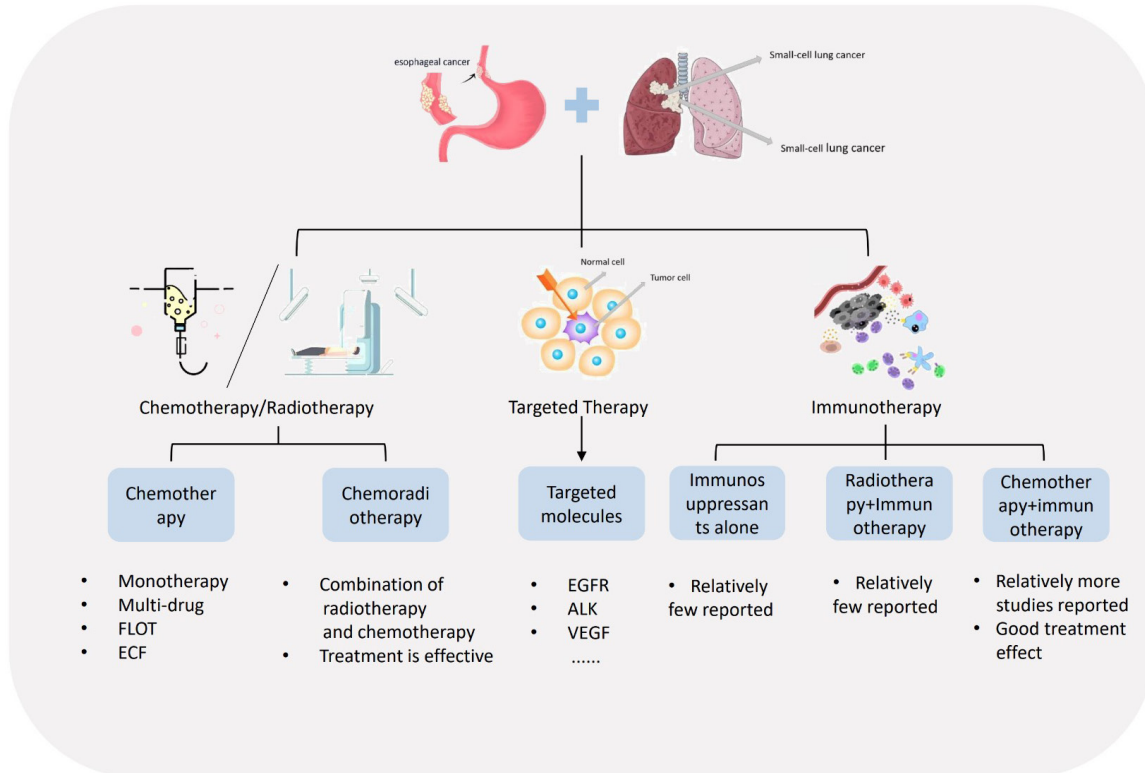


Figure 1. Overview and flow chart of all the neoadjuvant therapy strategies in this work.

taining chemotherapy, but the 5-year survival rate has only increased by 5% [9, 10]. Therefore, in recent years, neoadjuvant therapy models for NSCLC [3, 11] and EC [12, 13] have attracted much attention, and various treatment combinations have emerged [3, 11-13]. This paper summarizes the latest research advances in various types of neoadjuvant therapies, which are introduced and overviewed in **Figure 1**.

Neoadjuvant therapy for NSCLC

Research progress on neoadjuvant chemoradiotherapy in NSCLC

Neoadjuvant chemotherapy for NSCLC: Neoadjuvant chemotherapy involves administering chemotherapy to patients before surgery in order to reduce tumor burden, shrink tumor size, increase surgical resection rate, and improve treatment efficacy [6-8]. In the treatment of NSCLC, neoadjuvant chemotherapy has shown significant effects in improving patient survival rates and reducing tumor recurrence rates [3, 11]. By summarizing the current literatures, there are two main neoadjuvant

chemotherapy regimens for NSCLC, including monotherapy and combination therapy [3, 11]. Commonly used monotherapy regimens include paclitaxel (175 mg/mg, every 3 weeks) [14], docetaxel (75 mg/mg, every 3 weeks) [15], and cisplatin (90 mg/mg, every 3 weeks) [16], while combination therapy regimens include paclitaxel and cisplatin (TP) [17], docetaxel and cisplatin (DP) [18], and other targeted therapy regimens for specific gene mutations, such as EGFR-TKI (150 mg, every day) [19] and ALK inhibitors (450 mg, every day) [20]. The efficacy of neoadjuvant chemotherapy in NSCLC is mainly evaluated by tumor shrinkage, surgical resection rate, disease-free survival, and overall survival [6-8]. Study has found that after neoadjuvant chemotherapy, NSCLC patients have significantly increased surgical resection rates, significantly reduced tumor size, and significantly improved disease-free and overall survival rates [21].

Although the neoadjuvant chemotherapy for NSCLC has reached great success in recent days, their therapeutic efficiency is still limited as the results of gene mutation [22]. To resolve this, with the continuous development of

molecular biology technology, some gene detection techniques have also been applied in neoadjuvant chemotherapy for NSCLC [22]. For example, detecting gene mutations, such as EGFR [23], ALK [24], and ROS1 [25], can provide references for selecting more suitable treatment regimens for NSCLC patients. Studies have shown that under the guidance of gene detection technology, the treatment efficacy of neoadjuvant chemotherapy and patient prognosis have been significantly improved [22]. Personalization of chemotherapy regimens is an important direction in the research of neoadjuvant chemotherapy for NSCLC [26]. Developing personalized chemotherapy regimens based on different tumor characteristics, physical conditions, gene variations, and other factors can effectively improve treatment efficacy [26]. Research has shown that personalized chemotherapy regimens have better treatment efficacy and survival rates than standardized treatment regimens in neoadjuvant chemotherapy for NSCLC [27]. Overall, the clinical application and research progress of neoadjuvant chemotherapy in the treatment of NSCLC are increasingly prominent. With the continuous development of technology and theory, it is believed that neoadjuvant chemotherapy will play a more important role in the treatment of NSCLC.

Neoadjuvant chemo-radiotherapy for NSCLC: Neoadjuvant and chemo-radiotherapy refers to the combination of chemotherapy and radiotherapy before surgery to shrink the tumor volume and control tumor metastasis [28]. The main purpose of this treatment is to make the tumor surgically removable and improve the treatment effect after surgery [28]. In neoadjuvant chemo-radiotherapy, chemotherapy and radiotherapy can be carried out simultaneously or separately according to individual's characteristics, such as tumor type, tumor stage, and physical condition for individualized treatment [28]. Neoadjuvant chemo-radiotherapy can increase the surgical resection rate. Studies have shown that neoadjuvant chemo-radiotherapy can increase the surgical resection rate of NSCLC and thus improve the therapeutic effects [29, 30]. Besides, neoadjuvant chemo-radiotherapy can reduce the tumor volume. In NSCLC treatment, tumor volume is an important factor affecting the effectiveness of surgi-

cal treatment [31]. Neoadjuvant chemo-radiotherapy can reduce the tumor volume, making surgical treatment easier and reducing the range of surgical resection [31]. In addition, neoadjuvant chemo-radiotherapy can improve the therapeutic effects. For instance, in a study of 124 NSCLC patients, the 5-year survival rate was 45.3% after neoadjuvant chemo-radiotherapy, significantly higher than the survival rate of patients who only received surgical treatment [32]. As previously reported, postoperative recurrence is a serious problem faced by NSCLC patients [33]. Neoadjuvant chemo-radiotherapy can also reduce the postoperative recurrence rate and improve patient survival, and in a study of 91 NSCLC patients, the postoperative 3-year recurrence rate of the neoadjuvant chemo-radiotherapy group was 17.9%, significantly lower than the recurrence rate of the group that only received surgical treatment (40.9%) [33]. To summarize, neoadjuvant chemo-radiotherapy has made significant progress in the treatment of NSCLC. It can reduce the difficulty of surgery, increase the surgical resection rate, reduce the postoperative recurrence rate, and improve patient survival. With more attention and in-depth exploration, we believe that the application and research of neoadjuvant chemo-radiotherapy in NSCLC treatment will have a broader development prospect.

Discussion and comparison of the advantages and disadvantages of different neoadjuvant treatments: Neoadjuvant radiotherapy and chemotherapy are widely used in the treatment of NSCLC, and their efficacy is relatively certain, especially for stage IIIA (N2) NSCLC patients [1, 9, 10, 34]. Multiple studies have shown that compared with surgery alone, neoadjuvant radiotherapy and chemotherapy can significantly prolong overall survival (OS) of NSCLC patients [1, 9, 10, 34]. Pure neoadjuvant radiotherapy is less commonly used in NSCLC and is mostly combined with chemotherapy [35]. There has been ongoing debate about whether preoperative radiotherapy is necessary [35]. Fewer research results have shown that compared with preoperative radiotherapy alone or chemotherapy alone, preoperative neoadjuvant radio-chemotherapy can improve survival rates [35], while more trial results have shown that preoperative radio-chemotherapy did not benefit patients in terms of survival [36, 37]. The Na-

tional Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN) also recommend neoadjuvant chemotherapy for NSCLC patients with N2 lymph node positivity [35]. Therefore, there is still controversy regarding the comparison of the efficacy of the two treatments [35].

The neoadjuvant targeted therapy for NSCLC

Research progress and clinical application of neoadjuvant targeted therapy in NSCLC: Although traditional treatment methods such as surgical resection, chemotherapy, and radiotherapy have made some achievements in the treatment of NSCLC, their efficacy remains limited. In recent years, with the continuous progress of molecular biology and biotechnology, targeted therapy has become a new method for the treatment of NSCLC. Professor Wu Yilong and his team conducted CTONG1103 study [38], which included 72 patients with stage IIIA (N2) NSCLC with EGFR mutations. The study compared the efficacy of neoadjuvant targeted therapy with erlotinib and neoadjuvant platinum-containing chemotherapy, and the results showed that the erlotinib group was superior to the chemotherapy group in terms of PFS (progression-free survival), major pathological response (MPR), and toxicity reactions, but no benefit in overall survival (OS) was observed [38]. In addition, the ongoing NeoADAURA trial is a large-scale phase III clinical trial from multiple international centers [39]. This trial enrolled patients with EGFR-mutant stage II-III B NSCLC and compared osimertinib neoadjuvant targeted therapy combined with chemotherapy versus chemotherapy alone or simple chemotherapy. The primary endpoint was MPR, and the secondary endpoints included event-free survival (EFS), pCR, DFS, and OS. The results of this study are worth looking forward to [39]. Furthermore, more research evidence has shown that the efficacy of immune checkpoint inhibitors is not ideal for NSCLC patients with EGFR mutations (EGFRm) [39]. Therefore, neoadjuvant targeted therapy may be a good choice for those patients. The following section lists the representative targeted molecules currently applied to NSCLC patients and reviews their research progress and future challenges. Specifically, related targeted molecules action mechanism and clinical application status are summarized in **Table 1**.

Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) for the treatment of NSCLC: EGFR (epidermal growth factor receptor) is an important target molecule in NSCLC. Activation of EGFR can promote tumor cell proliferation and metastasis by activating signal transduction pathways [40, 41]. EGFR-TKI (epidermal growth factor receptor tyrosine kinase inhibitor) is a drug that inhibits EGFR tyrosine kinase activity and has been widely used in the treatment of NSCLC [19, 42]. The neoadjuvant treatment effect of EGFR-TKI has been confirmed in multiple clinical trials. A multicenter randomized controlled study from China tested patients with EGFR-negative advanced NSCLC and divided them into a standard chemotherapy group and an EGFR-TKI group, and the results showed that the OS of the EGFR-TKI group was significantly higher than that of the standard chemotherapy group, and the median PFS of the EGFR-TKI group was also significantly longer than that of the standard chemotherapy group [42, 43]. In addition, the EGFR-TKI group had fewer side effects and higher surgical resection rate [44]. Another clinical trial tested neoadjuvant EGFR-TKI treatment in NSCLC patients with sensitive EGFR mutations, and the results showed that this treatment regimen effectively controlled tumor growth, increased the possibility of surgical resection, and significantly improved patients' survival [45].

The inhibitors for anaplastic lymphoma kinase (ALK) in the treatment of NSCLC: ALK (anaplastic lymphoma kinase) is another important target molecule in NSCLC [24, 46]. ALK mutations can activate the signaling pathway, promoting tumor cell proliferation and metastasis. ALK inhibitors are drugs that can inhibit ALK activation and have been widely used in the treatment of NSCLC [24, 46]. A multicenter randomized controlled trial called J-ALEX was conducted on untreated advanced NSCLC patients with ALK mutations, dividing them into ALK inhibitor and chemotherapy groups [47]. The results showed that both OS and PFS were significantly higher in the ALK inhibitor group than in the chemotherapy group [47]. Another multicenter randomized controlled trial called ALEX was conducted on advanced NSCLC patients with ALK mutations, dividing them into ALK inhibitor and chemotherapy groups. The results also showed that both PFS and OS were significantly

higher in the ALK inhibitor group than in the chemotherapy group [48].

Prospects and challenges of targeted therapy in NSCLC: Neoadjuvant targeted therapy is an important field in NSCLC treatment and has made a lot of progress. EGFR inhibitors [40, 41] and ALK inhibitors [24, 46] are currently the most important targeted drugs in NSCLC treatment. These drugs can not only improve treatment efficacy but also reduce unnecessary toxic side effects. Future research should explore new target molecules and combination treatment regimens to improve the efficacy and survival rate of NSCLC treatment. In addition, more research is needed to explore new target molecules and treatment regimens for NSCLC patients who are negative for EGFR mutations and ALK rearrangements. However, there are still some problems with neoadjuvant targeted therapy. On the one hand, targeted drugs are expensive, which is a heavy economic burden for patients and limits their widespread use [24, 46]. On the other hand, there is still some resistance to current targeted therapy, which results in poor treatment efficacy [24, 46]. Therefore, future research needs to explore more effective and economical treatment regimens and strengthen research on drug resistance to targeted therapy.

Neoadjuvant therapy for EC

Research progress of neoadjuvant radiotherapy and chemotherapy in EC

Neoadjuvant chemotherapy for EC: Esophageal cancer is a highly malignant tumor, and for patients who are diagnosed early, surgical resection is the conventional treatment method [49]. However, for late-stage patients, the effect of surgical treatment is not ideal [49]. At this time, neoadjuvant chemotherapy is introduced into the treatment of EC [50, 51]. The role of neoadjuvant chemotherapy in the treatment of EC is mainly to reduce tumor volume and postoperative recurrence rate, and improve survival rate [50, 51]. Chemotherapy can reduce the volumes of lesion, lower the infiltration depth, and increase the possibility of surgical resection [52-54]. In addition, neoadjuvant chemotherapy can also clear micro-metastatic cancer cells in the body, reduce postoperative recurrence rate, and improve survival rate [52-54]. At present, common neoadjuvant chemo-

therapy regimens include FLOT (5-fluorouracil (15 mg/mg, every day), oxaliplatin (85 mg/kg, every two weeks), docetaxel (75 mg/kg, every three weeks), and uracil) and ECF (cisplatin (75 mg/kg, every three weeks), epirubicin (85 mg/kg, every three weeks), 5-fluorouracil (15 mg/mg, every day)). Clinical trial results have shown that the FLOT regimen has advantages in improving pCR (pathologic complete response) rate, reducing postoperative mortality rate, and improving overall survival rate [55, 56].

Neoadjuvant chemo-radiotherapy in EC: In recent years, neoadjuvant chemo-radiotherapy has become a hot research direction in the treatment of EC [57]. It can reduce surgical trauma, lower local recurrence rate and distant metastasis rate, and improve patient survival rate and quality of life [57]. Specifically, neoadjuvant chemo-radiotherapy uses radiotherapy and chemotherapy before surgery to reduce tumor volume, improve surgical resection rate, decrease postoperative recurrence rate, prolong survival and improve postoperative quality of life [57]. A multicenter, randomized, open-label clinical trial explored the therapeutic effect of neoadjuvant chemo-radiotherapy in EC and found that it significantly improved the prognosis of EC patients [57]. Some researchers investigated the application of neoadjuvant chemo-radiotherapy in the treatment of gastric cancer and esophageal cancer, and discussed the clinical results and predictive factors [58]. A randomized controlled trial investigated the efficacy of neoadjuvant chemo-radiotherapy combined with three-zone lymph node dissection in the treatment of EC and found that it significantly reduced patients' lymph node metastasis and recurrence rate [59]. Another study analyzed the survival rate of Chinese EC patients and found that neoadjuvant chemo-radiotherapy can significantly improve patients' survival rate and quality of life [60].

Discussion and comparison of different treatment effects for EC: Currently, the results of neoadjuvant therapy for esophageal cancer appear to be different from those for lung cancer [61]. The Dutch CROSS study [61] included predominantly adenocarcinomas (approximately 75% of the cases) and showed that compared with surgery alone, neoadjuvant chemo-radiotherapy combined with surgery significantly improved the R0 resection rate and median overall survival (mOS) from 24 months to 49.4

months. The Chinese NEOCRTEC5010 study [57], which included squamous cell carcinoma cases, also demonstrated that neoadjuvant chemo-radiotherapy combined with surgery was superior to surgery alone in terms of both R0 resection rate and mOS [57]. Both studies also indicated no significant differences in postoperative complications between neoadjuvant chemo-radiotherapy combined with surgery and surgery alone. Based on these two studies, the NCCN guidelines and Chinese Society of Clinical Oncology (CSCO) guidelines recommend neoadjuvant chemo-radiotherapy as the standard treatment for locally advanced resectable esophageal cancer [62].

However, there still exist important controversies in neoadjuvant therapy for esophageal cancer [63, 64]. Specifically, the Japanese JCOG9907 study suggested that neoadjuvant chemotherapy was the preferred treatment for locally advanced esophageal squamous cell carcinoma (ESCC) [63, 64]. In addition, the results of the JCOG1109 study showed that compared with neoadjuvant chemotherapy, neoadjuvant chemo-radiotherapy could increase the pathological complete response rate, but no significant survival benefit was observed [65]. Another meta-analysis of study on esophageal cancer also indicated that neoadjuvant chemo-radiotherapy failed to improve the 5-year survival rate compared with neoadjuvant chemotherapy [66]. In addition, for adenocarcinoma of the esophagus, most researchers believe that the evidence for neoadjuvant chemotherapy is more sufficient than that for neoadjuvant chemo-radiotherapy, especially for patients with high-risk systemic metastases, neoadjuvant chemotherapy may achieve better survival benefits [50]. This may also explain why some studies failed to obtain survival benefits. Furthermore, we should not ignore the possibility that neoadjuvant chemo-radiotherapy may increase the incidence of postoperative complications, such as anastomotic leakage [67]. The research progress of neoadjuvant radiotherapy and chemotherapy in this section is summarized and compared in **Table 2**.

Advancement of neoadjuvant therapy in EC

Research progress and clinical application of targeted therapy in EC: In the treatment of EC, targeted therapy is usually combined with other treatment modalities, with most studies focus-

ing on the combination of radiotherapy or chemotherapy with targeted therapy. EGFR is usually upregulated in ESCC [68], which is an important biomarker that can affect the proliferation and invasion of cancer cells [68]. Currently, the most studied targeted drugs for EGFR in ESCC are cetuximab and nimotuzumab [69, 70]. However, several studies on the combination of neoadjuvant radiotherapy/chemotherapy with cetuximab have shown disappointing results, with no significant improvement in pCR rate, increased toxicity, and no clear survival benefit compared to neoadjuvant radiotherapy alone [69, 70]. In contrast, the results of studies on the combination of neoadjuvant radio-chemotherapy with nimotuzumab seem more promising, and the use of nimotuzumab in combination with radio-chemotherapy improved R0 resection rate, pCR rate, and disease control rate (DCR), without significant increase in toxicity [71, 72]. In addition, some studies have shown that for some esophageal adenocarcinoma patients with positive HER-2 expression, the use of trastuzumab, a HER-2 targeted therapy drug, in combination with radio-chemotherapy improved the pCR rate and R0 resection rate [73, 74]. The main targets in targeted therapy for EC and the characteristics of combination of radio-chemotherapy with targeted therapy are summarized as follows.

Main targets for targeted therapy in EC: Currently, the main targets for targeted therapy in esophageal cancer include EGFR [75, 76], vascular endothelial growth factor (VEGF) [77, 78], phosphatidylinositol 3-kinase (PI3K) [79], ALK [80], BRAF [81], etc. Among them, the research on EGFR inhibitors [75, 76], VEGF inhibitors [77, 78], and PI3K inhibitors [79] are relatively intensive. Their targeted molecular mechanism of action and clinical application status are summarized in **Table 1**. EGFR inhibitors are currently one of the most studied targeted therapies [75, 76]. The expression of EGFR in EC is relatively high, and the application of EGFR inhibitors can inhibit tumor cell proliferation, promote cell apoptosis, and improve the sensitivity to radiotherapy and chemotherapy, thereby improving the treatment effect [75, 76]. In recent years, many EGFR inhibitors have been used in clinical treatment [82]. VEGF inhibitors are also widely studied [77, 78]. VEGF is also highly expressed in EC, and VEGF inhibitors can inhibit tumor angiogen-

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Table 1. Summary of relevant target molecules for neoadjuvant targeted therapy in non-small cell lung cancer/esophageal cancer

Target Molecule	Mechanism of Action	Clinical Application
EGFR	Inhibit the tyrosine kinase activity of EGFR, block its signaling pathway	Approved for the treatment of NSCLC and esophageal cancer.
ALK	Inhibit the activity of ALK fusion protein, block its signaling pathway	ALK inhibitors are approved for the treatment of NSCLC in patients with ALK-positive gene.
ROS1	Inhibit the activity of ROS1 fusion protein, block its signaling pathway	ROS1 inhibitors are approved for the treatment of NSCLC in patients with ROS1-positive gene.
BRAF	Inhibit the activity of BRAF protein, block its signaling pathway	BRAF inhibitors are used to treat NSCLC in patients with BRAF mutation.
PD-1/PD-L1	PD-1 inhibitors can block the binding of PD-1 and PD-L1, activate the immune system to attack tumor cells	Approved for the treatment of esophageal cancer and NSCLC.
VEGF	Inhibit the VEGF signaling pathway, inhibit tumor angiogenesis	Approved for the treatment of esophageal cancer and NSCLC.
HER2	Inhibit the tyrosine kinase activity of HER2, block its signaling pathway	Approved for the treatment of HER2-positive esophageal cancer and NSCLC.

Note: This table only lists some of the target molecules for new adjuvant targeted therapy for NSCLC and esophageal cancer, and there are other target molecules in clinical use as well. The treatment plan should be based on the patient's specific situation.

Table 2. Summary of clinical studies and progress of neoadjuvant radiotherapy and chemotherapy for non-small cell lung cancer/esophageal cancer

Disease type	Trail (or Name)	Phase	Stage (Or TNM)	Histologic Subtype	Neoadjuvant therapy	Number of Case	CT/RT	RO Resection Rate	mPR/pCR	Survival
NSCLC	Pass HI [16]	II	IIIA (N2)	AC: 15/Other: 12	CT (ACT) vs (ART)	0.54:2361	4EP/54-60 Gy	None	None	mOS: 28.7 m vs 15.6 m
	Rosell R [17]	III	IIIA (N2)	SCC: 42/AC: 14/Other: 4	CT (ART) vs (ART)	1.270833	MIC/40 Gy	None	None	mOS: 26 m vs 8 m
	Roth JA [18]	-	III	-	CT vs NIL	1.188889	CEP	None	None	DFS: 20 m vs 5 m
	Zhang CW [19]	-	IIIA/IIIB	SCC: 226/AC: 175/ASC: 6	cCRT vs RT vs CT	86:114:207	NP/40 Gy	91.6/84.1/81.2	None	3 year SR: 72.6% vs 63.2% vs 64.1%
	MIKOS P [20]	III	IIIA/N2	SCC: 78/AC: 100/Other: 53	CRT vs CT	117:115	DC/44 Gy	None	None	EFS: 12.8 m vs 11.6 m
EC	CROSS [31]	-	T1N1/T2-3N0-1	SCC: 84/AC: 275	CRT vs NIL	178:188	TC/41.4 Gy	92/69	None	mOS: 37.1 m vs 26.2 m OS: 49.4 m vs 24 m
	NEOCRTEC5010 [32]	III	T1-4N1M0/T4N0M0	SCC	cCRT vs NIL	224:227	NP/40 Gy	98.4/91.2	pCR: 43.2% vs NIL	mOS: 101 m vs 66.5 m DFS: 100.1 m vs 41.7 m
	JCOG9907 [34]	III	II/III (Excluding T4)	SCC	CT vs (ACT)	164:166	CF	None	None	5 year SR: 55% vs 43%
	JCOG1109 [36]	III	IB/II/III (Excluding T4)	SCC	CT vs CT vs CRT	199:202:200	CF vs DCF vs CF	90.3:94.5:98.9	pCR: 2.1 vs 19.8 vs 38.5	mOS: 5.6 y vs NR vs 7.0 y PFS: 2.7 y vs NR vs 5.3 y
	Cuunningham D [38]	III	-	AC	CT (ACT) vs NIL	250:253	ECF	None	None	5 year SR: 36% vs 23%
	Zhang G [39]	-	T1N+M0/T2-4aNO-3M0	SCC	CRT vs CT	194:133	CF or TC/32.4-50 Gy	99.5:99.2	pCR: 35.1 vs 6.0	mOS: 96 m vs 88 m 5 year SR: 59.5% vs 59.6%

Note: CT: Chemotherapy; RT: Radiotherapy; mPR: Major pathologic response; pCR: pathologic complete response; AC: Adenocarcinoma; SCC: Squamous cell carcinoma; ASC: Adenosquamous carcinoma; ACT: Adjuvant chemotherapy; ART: Adjuvant radiotherapy; CRT: Chemoradiotherapy; cCRT: Concurrent chemoradiotherapy; EP: Etoposide and cisplatin; MIC: Mitomycin and ifosfamide and cisplatin; CEP: Cyclophosphamide and etoposide and cisplatin; VC: Vinorelbine and cisplatin; DC: Docetaxel and cisplatin; TC: Paclitaxel and carboplatin; CF: Fluorouracil and platinum; DCF: Docetaxel and fluorouracil and platinum; ECF: Epirubicin and fluorouracil and cisplatin; mOS: Median overall survival; DFS: Disease-free survival; SR: Survival rate; EFS: Event-free survival; m: month; y: year; NR: Not reached; -: Not mentioned.

esis, reduce tumor blood supply, and thereby inhibit tumor growth and metastasis [77, 78]. Currently, VEGF inhibitors have also been used in clinical treatment [83]. The PI3K pathway plays an important role in esophageal cancer, and the application of PI3K inhibitors can inhibit tumor cell proliferation, promote cell apoptosis, and thereby inhibit tumor growth [79]. Currently, research on PI3K inhibitors is still in its early stages.

Combination of targeted therapy and chemoradiotherapy for EC: In addition, the efficacy of targeted therapy is also affected by factors such as tumor heterogeneity, molecular heterogeneity, and molecular changes before and after treatment [84, 85]. Therefore, personalized treatment is needed. At the same time, the combined use of targeted therapy also needs to be further explored to improve treatment outcomes. Recently, study has shown that the combination of targeted therapy and chemoradiotherapy significantly improved treatment outcomes, prolonged patients' OS and PFS survival, and reduced recurrence and metastasis rates [86]. Overall, the combination of targeted therapy and chemoradiotherapy has become an important treatment modality for EC and has achieved significant treatment outcomes [87]. With the advance of research, it is believed that the application of targeted therapy in the treatment of EC will become more widespread and in-depth.

Application of neoadjuvant immunotherapy for the treatment of chest-related malignancies

The application of neoadjuvant immunotherapy in the fields of NSCLC [34, 88] and EC [13, 89] has attracted a lot of attention. Immunotherapy has achieved significant success, especially in the field of programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) antibodies. A recent study has shown that neoadjuvant immunotherapy can shrink tumors, making lesions resectable, and is expected to improve the prognosis of NSCLC and EC [90]. A prospective study found that the use of neoadjuvant PD-1 antibody treatment can significantly improve the 5-year survival rate of NSCLC patients [90]. In addition, some studies have shown that neoadjuvant immunotherapy can increase the feasibility of surgery, thereby improving the treatment efficacy for EC [91].

However, neoadjuvant immunotherapy still faces some challenges and limitations. Firstly, not all patients respond well to immunotherapy, so screening suitable patients is necessary [92]. Secondly, immunotherapy may cause some adverse reactions, such as immune-related pneumonia, so it is necessary to closely monitor the patient's condition [92]. In addition, more large-scale clinical trials are needed to confirm the safety and effectiveness of neoadjuvant immunotherapy in clinical practice [93]. But with the deepening of research and the continuous development of technology, it is believed that this treatment method will be more widely used, bringing better treatment effects to lung cancer and esophageal cancer patients [93]. **Figure 2** provides an overview of the various neoadjuvant immunotherapies and lists typical clinical studies.

Neoadjuvant treatment using immunosuppressive agents alone

There is little research on neoadjuvant treatment using immunosuppressive agents alone [94]. In NSCLC, the CheckMate-159 study used Nivolumab alone for 2 cycles in the neoadjuvant treatment of stage I-III NSCLC, and the results showed good pathological response rates and good tolerability [94]. The NEOSTAR study compared neoadjuvant combination therapy with Nivolumab and lipilimumab to Nivolumab alone, and the results showed that neoadjuvant dual-immunotherapy had higher MPR and pCR rates [34]. In EC, no relevant studies on neoadjuvant treatment using immunosuppressive agents alone have been retrieved.

Neoadjuvant radiotherapy combined with immunotherapy

In the field of NSCLC, there are few studies on neoadjuvant radiotherapy alone, and its efficacy is controversial, which may be one of the reasons for the lack of related research on neoadjuvant radiotherapy combined with immunotherapy. Altorki et al. compared the treatment efficacy of combined stereotactic body radiotherapy (SBRT) with Durvalumab and Durvalumab alone, and the results showed that the number of MPR cases in the combination group was eight times that of immunotherapy alone [95]. The SQUAT study (WJOG 12119L) is a phase II clinical trial targeting stage IIIA/IIIB NSCLC for neoadjuvant concurrent chemo-

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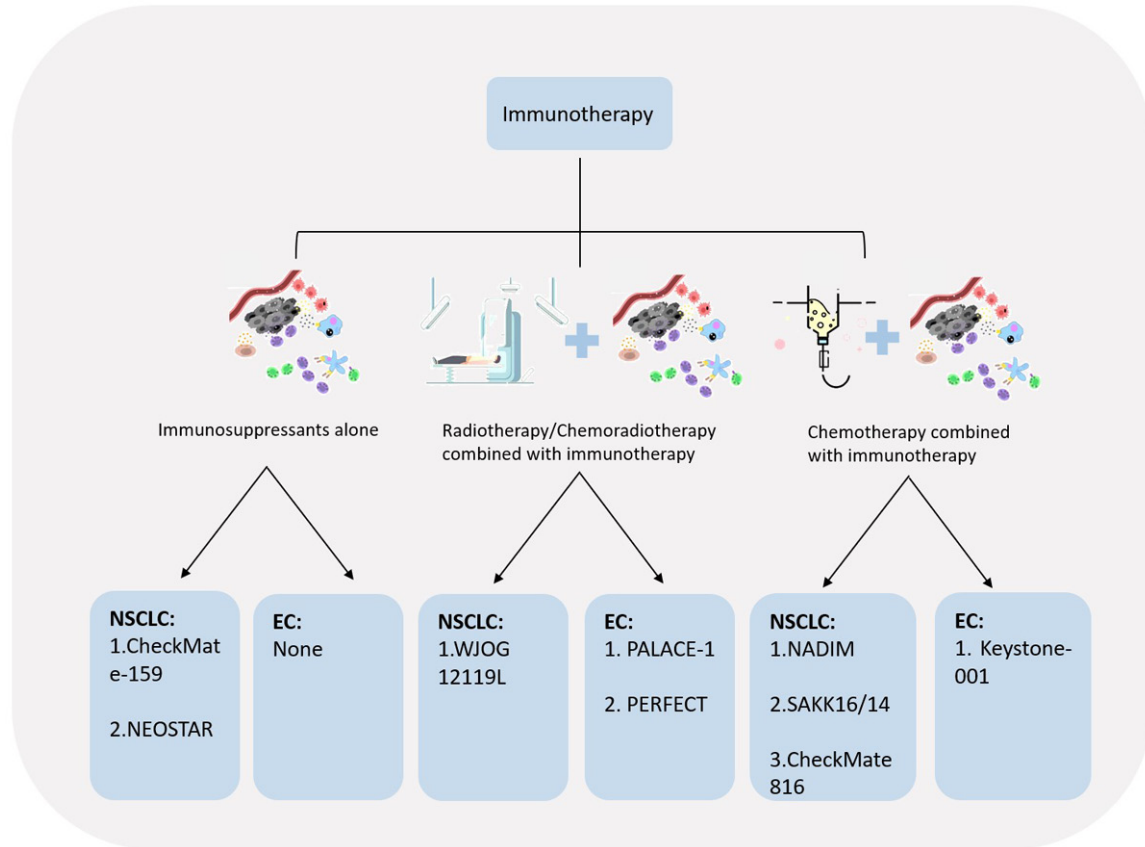


Figure 2. Various approaches of immunotherapy with corresponding studies reported.

immuno-radiation therapy research, and the results of this trial are still pending [96]. In the field of EC, there are no reports of neoadjuvant treatment with radiotherapy alone or in combination with immunotherapy. Currently, based on the CORSS study and the NEOCRTEC5010 study, neoadjuvant chemo-radiotherapy (nCRT) is combined with immunotherapy [57, 97]. The Chinese PALACE-1 study [98] combined nCRT with Pembrolizumab for locally advanced EC patients, and the results showed a pCR rate of nearly 56%, which was significantly better than the results of the CROSS and NEOCRTEC5010 studies [57, 97]; However, more than half of the patients experienced grade III adverse reactions. The Dutch PERFECT study [99] is a clinical trial on esophageal adenocarcinoma, which combines neoadjuvant CORSS regimen with Atezolizumab, and the results were similar to the CROSS study in terms of pCR rate and mOS, as well as treatment-related adverse events and postoperative complications. Therefore, based on the current research results, neoadjuvant chemo-radiotherapy combined with im-

muno-therapy does not seem to show significant benefits for EC, while the pCR rate seems to be significantly increased. This may be related to the increased incidence of complications in patients undergoing neoadjuvant chemo-radiotherapy combined with immunotherapy, as well as the increased toxicity and reduced compliance and tolerance to multimodal therapy [100]. It is still necessary to have more trial data to support whether it can ultimately translate into survival benefits.

Neoadjuvant chemotherapy combined with immunotherapy

In the field of NSCLC research, the NADIM study and SAKK16/14 study were the first to attempt neoadjuvant chemotherapy combined with immunotherapy and achieved good therapeutic results [101, 102]. Subsequently, the CheckMate816 study became the only phase III clinical trial with research results [34]. The study compared the efficacy of chemotherapy combined with Nivolumab and simple chemo-

therapy, and the results showed that the curative resection rate, MPR, and pCR of the chemotherapy combined with immunotherapy group were 83.2%, 36.9%, and 24.0%, respectively, which were nearly 5%, 28%, and 22% higher compared to the control group, respectively [34]. In addition, the median event-free survival (mEFS) also reached 31.6 months, which was nearly 11 months longer compared to the control group [34]. Nivolumab has also been approved by the Food and Drug Administration (FDA) for neoadjuvant treatment of NSCLC, and the scheme for its utilization is shown as follows: NSCLC patients are subjected to 3mg/kg Nivolumab for 60 min every three weeks, and the time for each drug administration lasts for at least 30 min, which has become the first neoadjuvant immune checkpoint inhibitor (ICI) approved for use in this field [34, 103]. Of course, there are more clinical trials waiting for results to be announced. In addition, for EC, many research results have shown that the pCR of simple preoperative chemotherapy is less than 10% [104, 105]. The classic CROSS study found that the pCR rate of nCRT was 29% [106]. The pCR rate of neoadjuvant chemotherapy combined with immunotherapy can reach 30-40% [107], showing its superiority in improving pCR. At the same time, this treatment plan can significantly increase the R0 resection rate, and its safety is good [108, 109], without a significant increase in postoperative complications. However, at present, most of the research on neoadjuvant chemotherapy combined with immunotherapy in the field of esophageal cancer is phase II trial, and further phase III clinical trials are needed for verification. In addition, more research is needed to answer how to select different cases for different neoadjuvant treatment plans.

Identification of novel biomarkers for neoadjuvant immunotherapy

Although neoadjuvant immunotherapy has broad application prospects in the fields of NSCLC and EC, the individual differences in therapeutic efficacy are large, so it is important to screen for effective biomarkers. Currently, research on biomarkers of neoadjuvant immunotherapy is still ongoing. In NSCLC, research on PD-L1 and tumor mutational burden (TMB) antibody is relatively mature [110, 111], but their predictive value still needs more data validation. In addition, research on the correlation

between biomarkers related to the tumor microenvironment [112], blood cells and ctDNA in peripheral blood [113], and the regulation of intestinal microbiota [114] and neoadjuvant immunotherapy is still ongoing. In esophageal cancer, there are currently no clear biomarkers for immunotherapy, although there is relatively more research on PD-L1 [115], but some studies have also shown that the benefit of neoadjuvant immunotherapy in esophageal cancer patients may be unrelated to the expression level of PD-L1 [116].

Summary and outlook

The role of neoadjuvant therapy in the fields of non-small cell lung cancer (NSCLC) [3, 11] and esophageal cancer (EC) [12, 13] is beyond doubt. With the diversification of treatment methods, we have a more diverse range of treatment options, from traditional neoadjuvant chemotherapy to combined radiotherapy and chemotherapy, to targeted therapy [40, 41], and more recently, immunotherapy [117, 118]. However, this also presents challenges and considerations in terms of treatment selection. Although neoadjuvant chemotherapy in NSCLC [3, 11] and neoadjuvant combined radiotherapy and chemotherapy in EC [12, 13] seem to have more abundant evidence support, the arrival of the era of targeted and immune therapies has brought about significant changes to the overall treatment landscape.

Recent studies have shown that immune therapy in combination with chemotherapy [119] or combined radiotherapy and chemotherapy [120, 121] may improve R0 resection rates and increase major pathological response (MPR) or pathological complete response (pCR). However, these treatments also face the risk of increasing treatment toxicity and postoperative complications [120, 121]. In addition, existing researches show that the efficacy of neoadjuvant immune therapy differs between squamous cell carcinoma and adenocarcinoma [122, 123]. Therefore, further exploration is needed to determine which immune checkpoint inhibitors have greater therapeutic advantages to address the current situation of the proliferation of immune checkpoint inhibitors. Moreover, there is a lack of evidence-based medicine to support the application of targeted and immune therapies in neoadjuvant treat-

ment [122, 123]. In the process of challenging traditional neoadjuvant treatment regimens, how to translate the improvement of pathological response rate into ultimate survival benefits requires more high-quality and persuasive research data to confirm [122, 123].

Furthermore, details such as timing, duration, and dosage of treatment also need to be considered. How should the timing of surgery be selected after the addition of immune therapy to neoadjuvant treatment? Which treatment duration (2 cycles, 3 cycles, or 4 cycles) is more advantageous in neoadjuvant treatment? How should the dosage of each treatment be determined in the combination of multiple treatments? These questions require further research to answer. Thirdly, during neoadjuvant treatment, there may be progression or pseudo-progression, leading to delayed surgery or missing the optimal surgical opportunity, even losing the chance for surgery [124]. When the optimal surgical opportunity is missed, how should rescue therapy be carried out? If the opportunity for surgery is lost, how should subsequent remedial treatment be selected? These are the severe problems we face. Fourthly, it is necessary to improve the accuracy of efficacy evaluation criteria. We need to further improve relevant diagnostic criteria such as imaging, pathology, and hematology to clearly judge the efficacy of neoadjuvant treatment and more accurately predict the prognosis. Fifthly, exploring reliable biomarkers related to neoadjuvant treatment is necessary. This will help us select appropriate treatment drugs and regimens for different patients and achieve true personalized neoadjuvant treatment. Finally, it is crucial to screen for the population that will benefit from different neoadjuvant treatment regimens. The presence of individual patient conditions and tumor heterogeneity means that different patients require different treatment methods [125, 126]. Therefore, we need to comprehensively incorporate patients' information to select the best neoadjuvant treatment regimen and achieve the best therapeutic effect.

Neoadjuvant therapy has been widely used in the field of NSCLC [3, 11] and EC [12, 13], and has achieved remarkable clinical efficacy. With the continuous advancement of technology, individualized neoadjuvant therapy will become a hot spot for future development [127, 128]. At

present, there are still many treatment methods and strategies that need to wait for the release of research results or need to be further explored and practiced, so the future work still has a long way to go. But we have reasons to believe that in the near future, neoadjuvant therapy will play a more important role in clinical practice, providing patients with better medical services.

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Disclosure of conflict of interest

None.

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