



# Neoadjuvant versus adjuvant chemoradiotherapy for esophageal carcinoma: a systematic review and meta-analysis

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**Background:** This study performed a systematic review of relevant literature compared neoadjuvant chemoradiotherapy followed by surgery (NCRT + S) with adjuvant chemoradiotherapy after upfront surgery (S + ACRT) and conducted a meta-analysis to evaluate the efficacy of these two treatment methods.

**Methods:** A PICOS/PRISMA selection protocol was used to identify eligible studies. Electronic databases, including PubMed, Scopus, EMBASE, Web of Science and the Cochrane Library were searched for relevant studies up to Mar 2019. We also conducted a manual search to identify any eligible studies. All outcomes of interest were evaluated by hazard ratio (HR) or odds ratio (OR) with their 95% CI. The meta-analysis was performed with STATA version 15.1 software.

**Results:** Eight studies reporting on 1,601 patients (763 in the NCRT + S group and 838 in the S + ACRT group) were included. The pooled analysis revealed that NCRT + S had a better overall survival (HR, 1.18, 95% CI, 1.03–1.35) compared to S + ACRT. The sensitivity analysis showed a robust conclusion and there was no evidence of significant publication bias ( $P=0.361$  for Egger's test). NCRT + S also had a better progression-free survival (HR, 1.24, 95% CI, 1.05–1.46), improved R0 resection rate (OR, 2.31, 95% CI, 1.61–3.32) and higher perioperative complications (OR, 1.67, 95% CI, 1.09–2.56) compared to S + ACRT.

**Conclusions:** NCRT + S may improve survival in patients with esophageal cancer compared to S + ACRT. More large-scale prospective randomized controlled trials are desperately needed to validate this result.

**Keywords:** Esophageal carcinoma (EC); chemoradiotherapy; esophagectomy; survival; meta-analysis

Received: 13 May 2020. Accepted: 11 November 2020; Published: 25 March 2021.

doi: 10.21037/aoe-20-46

**View this article at:** <http://dx.doi.org/10.21037/aoe-20-46>

## Introduction

Esophageal carcinoma (EC) is characterized by easy metastasis to lymph nodes and the haematological system even at an early stage. The 5-year survival is approximately 20% for resectable EC with surgery alone (1,2). To improve the outcomes, multidisciplinary treatments have been studied worldwide. However, chemotherapy or radiotherapy alone combined with surgery failed to show a significant benefit on survival (3). Chemoradiotherapy was

recommended for most cancers because chemotherapy can not only control systematic metastases but also exhibit a radio-sensitizing effect when concurrent chemoradiotherapy was used. Therefore, chemoradiotherapy combined with surgery should improve the chance of curative treatment. However, the optimal timing of chemoradiotherapy is still controversial for EC.

Neoadjuvant chemoradiotherapy (NCRT) followed by surgery (NCRT + S) has been studied for several decades

and most randomized controlled trials (RCTs) have shown that there was no significant survival benefit before the 21st century. However, these trials were criticized for low samples, inadequate trial design and poor treatments. The successful Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial reported that there was a significant survival benefit in the NCRT + S group, with a hazard ratio (HR) of 0.657 (95% CI, 0.495–0.871;  $P=0.003$ ) compared to surgery alone (4). The overall survival (OS) benefits were further confirmed after long-term follow-up for both squamous cell carcinoma (SCC) and adenocarcinoma (AC) subtypes (5). Most subsequent trials supported this result and NCRT + S is now recommended for locally advanced EC in many countries. In contrast, there were limited RCTs about adjuvant therapies (6). Many retrospective studies have shown that adjuvant chemoradiotherapy after upfront surgery (S + ACRT) can improve survival and decrease recurrences, especially for patients with pathological T3/4 or N1-3 stage, larger tumor size, poorly differentiated tumors, and R1/2 resections (7-9). A meta-analysis also demonstrated that S + ACRT yielded a significant survival benefit with tolerable toxicity for EC (10). Hence, S + ACRT remains another potential option for EC. The only published CRT comparing NCRT + S with S + ACRT also showed that there was no significant survival difference (11).

The debate about the optimal timing of chemoradiation combined with surgery will continue. This study reviewed all related studies comparing NCRT + S with S + ACRT and performed a meta-analysis to compare their efficacy and safety to identify more evidence for multimodal treatment of EC.

We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/aoe-20-46>).

## Methods

### *Identification of studies*

The inclusion criteria for the literature search were defined using the PICOS approach (Population: patients diagnosed with resectable EC; Intervention: NCRT + S; Control: S + ACRT; Outcome: OS, progression-free survival, R0 resection rate and perioperative complications; Study Design: RCTs and non-RCTs). Electronic databases, including PubMed, Scopus, EMBASE, Web of Science and the Cochrane Library were searched for relevant studies

until March 2019. The search terms were (“esophageal” OR “oesophageal” OR “esophagus” OR “oesophagus”) AND (“cancer” OR “carcinoma” OR “tumor” OR “neoplasm”) AND ((“neoadjuvant” OR “preoperative” OR “pre”) AND (“adjuvant” OR “postoperative” OR “post”)) OR (“perioperative” OR “peri”)) AND (“chemoradiotherapy”). All the retrieved studies were screened in Endnote X8.1 by two investigators. The reference lists of included studies, meta-analyses and systematic reviews were also manually searched to identify any eligible studies comparing the efficacy of EC between the NCRT + S group and the S + ACRT group directly.

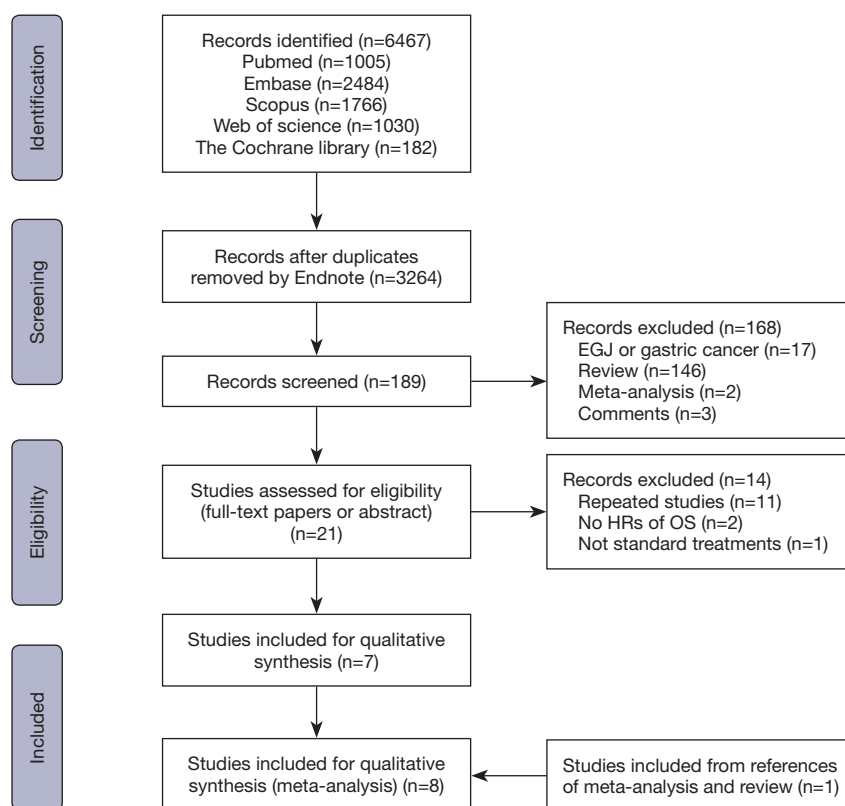
The following study selection criteria were applied: (I) esophageal SCC or adenocarcinoma; (II) data on OS must be reported; (III) only articles in English were eligible.

### *Data extraction*

The following information was extracted: first author; country; year of publication; data period; tumor stage; number of patients; treatment regimens; follow-up time; and outcomes including survival, R0 resection rate and complications. Data extraction was performed independently by two researchers (Mei Kang and Li Zhang). Yichun Wang resolved discrepancies.

### *Assessing the risk of bias and grading the quality of evidence*

Methodological quality/risk of bias was assessed using the Cochrane Risk of Bias tool (12) and Newcastle-Ottawa Scale (NOS) (available from: [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.htm](http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm)). The quality of the RCT was assessed using the Cochrane handbook for systematic reviews of interventions. A value of “high”, “low” or “unclear” to the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. A trial with a high risk of bias for anyone or more key domains was considered at “high risk”. A trial with a low risk of bias for all key domains was considered at “low risk”. Otherwise, it was considered “unclear”. The NOS was used to assess the quality of nonrandomized studies. There were eight items categorized into three dimensions: selection, comparability and outcome (cohort studies) or exposure (case-control studies). The results of the NOS range from zero to nine stars. The quality of individual studies was independently



**Figure 1** PRISMA flow diagram showing inclusion and exclusion of studies. EGJ, esophagogastric junction.

assessed by two reviewers (Mei Kang and Li Zhang) and discrepancies were resolved by Yichun Wang.

### Statistical analysis

Meta-analysis was performed with STATA version 15.1 software. The primary outcome was OS, and the secondary outcomes were progression-free survival (PFS), R0 resection rate and perioperative complications. The summary statistics were estimated by the HRs or odds ratios (ORs) with their 95% CIs. When HR was not available, they were estimated using the method described by Parmar *et al.* (13). The statistical heterogeneity of each study was assessed by the chi-square ( $\chi^2$ ) and I-square ( $I^2$ ) tests. Significant heterogeneity was confirmed if  $P \leq 0.1$  or  $I^2 > 50\%$ . If there was no significant heterogeneity between the included studies, a fixed-effects model was adopted. Otherwise, a random-effects model was employed. A funnel plot was used to detect publication bias among the primary outcomes.  $P < 0.05$  was considered statistically significant.

## Results

### Study selection

An overview of the literature selection shown in *Figure 1*. After the elimination of duplicates or irrelevant papers, twenty-one studies were eligible for final assessment. Among them, eleven studies were repeated data, two studies had no HRs of OS or survival curves, and one study did not meet the standard treatment regimens comparing NCRT + S with S + ACRT after reading the full-text paper (14). One study was found by searching the references of relevant reviews and meta-analyses (15). Finally, eight studies involving a total of 1601 patients (763 patients with NCRT + S and 838 patients with S + ACRT) were included in our meta-analysis (11,15-21). Two studies were not available to analyse the quality because they were published as abstracts (16,21). Five nonrandomized studies scored 6 stars or more according to the NOS (*Table 1*) (15,17-20) and the RCT had a low risk of bias (11). Hence, there was no study of low quality.

**Table 1** Summary of quality for retrospective control studies using NOS

NOS	Malaisrie, 2004 (15)	Hong, 2013 (17)	Chen, 2017 (18)	Hsu, 2017 (19)	Sadrizadeh, 2018 (20)
Total number of stars	7	7	6	7	7
Selection	★★★	★★★	★★★	★★★	★★★
1. Is the case definition adequate?	★		★		★
2. Representativeness of the cases	★	★	★	★	★
3. Selection of Controls		★		★	
4. Definition of Controls	★	★	★	★	★
Comparability	★★	★★	★	★★	★★
Comparability of cases and controls on the basis of the design or analysis					
Exposure	★★	★★	★★	★★	★★
1. Same method of ascertainment for cases and controls	★	★	★	★	★
2. Non-Response rate					

**Table 2** Characteristics of included comparative studies of NCRT + S and S + ACRT

Study	Country/region (state/province/city)	Data period	Type of studies	Stage	Number of cases		Median Follow up	OS difference
					NCRT + S	S + ACRT		
Malaisrie, 2004 (15)	US (Maywood)	1990.1–2001.12	RCS	II–III	27 (S: 6)	25 (S: 3)	33 M	P=0.76
Lv, 2010 (11)	China (Nanjing)	1997.1–2004.6	RCT	II–III	80 (S: 80)	78 (S: 78)	45 M	P=0.498
Davis, 2011 (16)	US (California)	1990.1–2001.12	RCS	LAEC	31 (S: minority)	27 (S: minority)	>60 M	P=0.755 (5-year)
Hong, 2013 (17)	US (Stanford)	1995–2002	RCS	II–III	126 (S: 39)	40 (S: 11)	46.5 M	P=0.06
Chen, 2017 (18)	China (Henan)	2006.6–2013.6	RCS	II–III	49 (S: 49)	73 (S: 73)	36.5 M	P=0.091
Hsu, 2017 (19)	Taiwan (Taipei)	2008–2013	RCS	II–III	286 (S: 286)	286 (S: 286)	31.7 M	P=0.315
Sadrizadeh, 2018 (20)	Iran (Masshad)	2006–2016	RCS	I–IV	90 (S: 75)	234 (S: 193)	24 M	P=0.69
Xu, 2018 (21)	China (Zhejiang)	2011.4–2015.11	RCT	II–III	74 (S: 74)	75 (S: 75)	42 M	P=0.044

These studies were not in the same institution. LAEC, locally advanced esophageal cancer; M, months; N, not available; RCS, retrospective controlled study; RCT, randomized controlled trial; S, squamous cell carcinoma.

### Characteristics of eligible studies

The included studies consisted of two prospective RCTs (11,21) and six retrospective control studies (15–20). Their characteristics are presented in *Table 2*. Most studies were conducted in Asian countries and region(s) (11,18–21), including three in China (11,18,21), one in Taiwan (19) and one in Iran (20). Four studies enrolled 1,001 patients with SCC only (11,18,19,21). For other studies, one enrolled 324 patients with SCC accounted for the majority (20) and three

enrolled 276 patients with AC accounted for the majority (15–17).

The chemoradiotherapy regimens of the eight studies are shown in *Table 3*. Cisplatin (DDP) plus fluorouracil (5-FU) was the most commonly used chemotherapy regimen. Other chemotherapy regimens included DDP plus paclitaxel (PTX), carboplatin (CBP) plus PTX or DDP plus 5-FU plus PTX. For radiotherapy in patients with NCRT, the clinical target volume encompassed the gross tumor with craniocaudal margins of 3–5 cm and transversal margins of 1–2 cm,

**Table 3** Treatment regimens of NCRT + S and S + ACRT for included studies

Author (year)	Surgery	Chemoradiotherapy	
		NCRT + S	S + ACRT
Malaisrie, 2004 (15)	Ivor-Lewis esophagectomy with 2 FL	R: 45 Gy/25 fractions to CTV and 5.4 Gy boost to GTV with a 2 cm cephalocaudad margin; CTV: GTV with 5 cm cephalocaudad margin and 2-cm radial margin; ENI  C: 5-FU day1–42, CBP day1, 22 and PTX day1, 22; or DDP day1/Week and 5-FU day1–4/Week1, 5, 8, 11	N
Lv, 2010 (11)	Esophagectomy through a left or right thoracotomy with 2 FL	R: 40 Gy/20 fractions. CTV: GTV with 4–5 cm proximal and distal margin and a 1–2 cm radial margin; IFI  C: PTX day 1, 22 and DDP day 1–3, 22–24 (2 cycles)	R: 50 Gy/25 fractions. CTV same to NCRT (30 cases); CTV was from 6th cervical vertebrae to 1st lumbar vertebrae, including tumor bed and lymph drainage from the supraclavicular regions to left gastric lymph nodes (48 cases)  C: Same to NCRT
Davis, 2011 (16)	Ivor-Lewis esophagectomy	N	N
Hong, 2013 (17)	Lesion excision or partial or total esophagectomy	R: N  C: mainly DDP based multi-agent	R: N  C: mainly 5-FU alone
Hsu, 2017 (19)	Three incision esophagectomy	R: 40 Gy/20 fractions. CTV: GTV with 3 cm proximal and distal margin and 1 cm radial margin; IFI  C: DDP day1–3 and 5-FU day1–5 (1 cycles)	R: 46–50 Gy, 2 Gy/day. CTV: tumor bed, supraclavicular, mediastinal and subcarinal area for upper and middle TEC. tumor bed, mediastinal and subcarinal area, and thoracic paraesophageal area for lower TEC  C: DDP day1–3 and 5-FU day1–5 (2 cycles)
Hsu, 2017 (19)	N	N	N
Sadrizadeh, 2018 (20)	N	R: 40–50 Gy/20 fractions. CTV: GTV with 5 cm proximal and distal margin and 2 cm radial margin; ENI  C: DDP day1–4 and 5-FU day1–4 (1st and 4th week)	R: N  C: Concurrent 5-FU and 4–6 cycles of 5-FU postoperatively

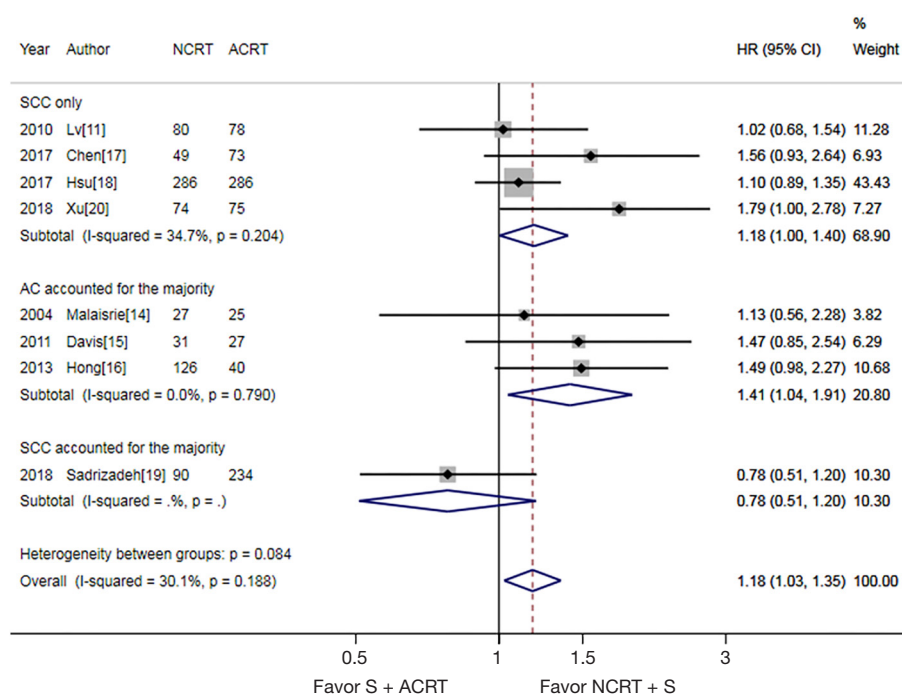
NCRT + S, neoadjuvant chemoradiotherapy followed by surgery; S + ACRT, adjuvant chemoradiotherapy after upfront surgery; C, chemotherapy; CBP, carboplatin; CTV, clinical target volume; DDP cisplatin; ENI, elective nodal irradiation; FL, lymphadenectomy; GTV, gross tumor volume; IFI, involved field irradiation; N, not mentioned or not available; PTX, paclitaxel; R, radiotherapy; 2FL, two-field lymphadenectomy; 5-FU, fluorouracil.

and elective nodal irradiation or involved field irradiation of regional lymph nodes. A total dose of 40–50.4 Gy for 4–5 weeks was commonly used. For radiotherapy in patients with adjuvant chemoradiotherapy, there was no uniform clinical target volume. Elective irradiation of the supraclavicular region, mediastinal region, left gastric region and tumor bed with a total dose of approximately 50 Gy

for 5 weeks was performed in these studies. Ivor-Lewis esophagectomy was the major surgical procedure. However, many details of the surgical procedure could not be found.

### Overall survival

As shown in *Figure 2*, the meta-analysis suggested that



**Figure 2** Forest plots of the HRs of OS in comparison of NCRT + S and S + ACRT. NCRT + S, neoadjuvant chemoradiotherapy followed by surgery; S + ACRT, adjuvant chemoradiotherapy after upfront surgery.

NCRT + S was associated with a significantly better OS, with a pooled HR of 1.18 (95% CI, 1.03–1.35). There was no significant heterogeneity detected among studies ( $I^2=30.1\%$  and  $P=0.188$ ). Survival benefits were also observed in both patients with SCC and SCC accounted for the majority, and patients with AC accounted for the majority. When we only focused on SCC, NCRT + S was also associated with a significantly better OS, with a pooled HR of 1.18 (95% CI, 1.00–1.40,  $I^2=34.7\%$  and  $P=0.204$ ).

### Progression-free survival

Three studies (879 patients) were available for PFS analysis (11,19,21). As shown in *Figure 3*, NCRT + S was associated with a significantly better PFS. The pooled HR was 1.24 (95% CI, 1.05–1.46). There was no significant heterogeneity detected among studies ( $I^2=41.2\%$  and  $P=0.183$ ).

### Complication and R0 resection rate

As shown in *Figure 4*, 3 studies (604 patients) (11,18,20) reported complications, and 4 studies (1,011 patients)

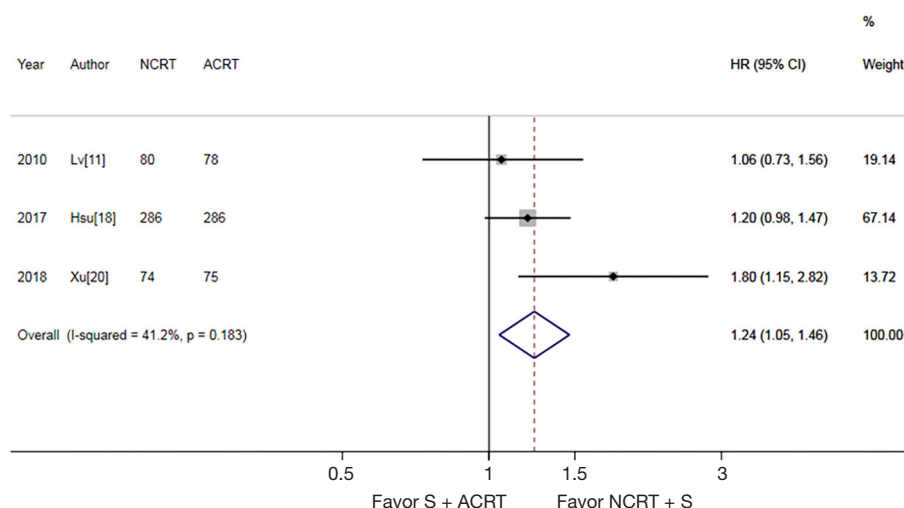
(11,18,19,21) reported the R0 resection rate. Though NCRT + S was associated with a higher R0 resection rate (OR, 2.31, 95% CI, 1.61–3.32), it was also associated with a higher incidence of complications (OR, 1.67, 95% CI, 1.09–2.56). There was no significant heterogeneity observed among studies ( $I^2=0.0\%$  and  $24.6\%$ ,  $P=0.616$  and  $0.266$  respectively).

### Publication bias and sensitivity analysis

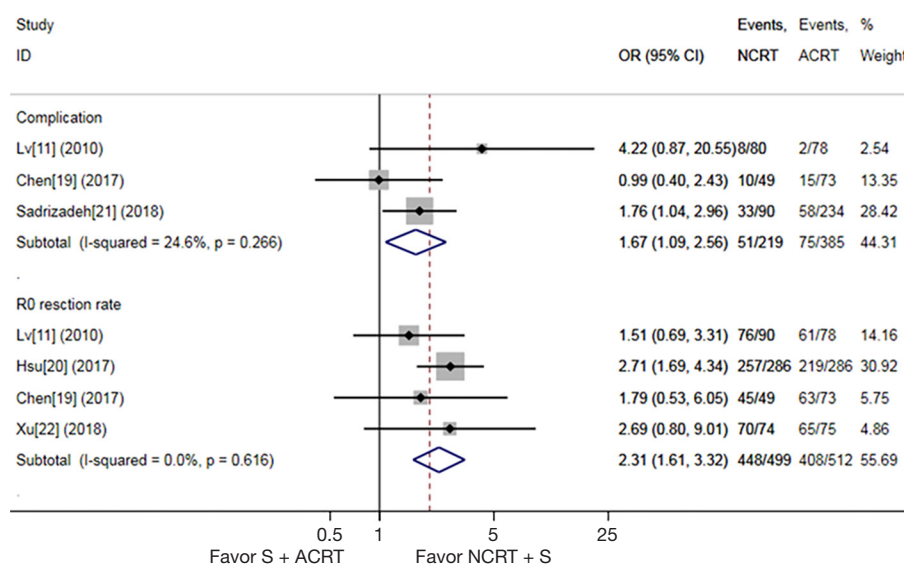
We used the leave-one-out approach to evaluate whether any single study had a remarkable impact on the pooled HRs for OS. The results of the sensitivity analysis demonstrated a robust conclusion (*Figure 5*). The funnel plots and the analysis with Egger's test ( $P=0.361$ ) implied no significant publication bias based on the pooled HRs of OS (*Figure 6*).

### Discussion

Surgery remains the cornerstone of curative treatment for resectable EC. To improve the poor survival of surgery alone for EC, the treatment has evolved into multidisciplinary



**Figure 3** Forest plots of the HRs of PFS in comparison of NCRT + S and S + ACRT. PFS, progression-free survival; NCRT + S, neoadjuvant chemoradiotherapy followed by surgery; S + ACRT, adjuvant chemoradiotherapy after upfront surgery.



**Figure 4** Forest plots of the ORs of incidence of complications and R0 resection rate in comparison of NCRT + S and S + ACRT. NCRT + S, neoadjuvant chemoradiotherapy followed by surgery; S + ACRT, adjuvant chemoradiotherapy after upfront surgery.

therapy. Due to the unsuccessful or even poor results of adjuvant radiotherapy after surgery (22-26), the focus of radiotherapy or chemoradiotherapy shifted to neoadjuvant therapies from the late 20th centuries. Neoadjuvant chemotherapy or chemoradiotherapy followed by surgery was associated with a survival benefit compared to surgery alone (27-29), and NCRT + S seemed to provide superior

OS compared to neoadjuvant chemotherapy (29). Therefore, NCRT + S is accepted in many countries. Though the role of adjuvant therapies is not recommended, they should be considered for patients with pathological upstaged clinical early EC who did not receive neoadjuvant therapies or patients with resectable locally advanced EC who received upfront surgery. A meta-analysis confirmed that S + ACRT

yielded a significant survival benefit compared to surgery alone (10). The published RCT also suggested that S + ACRT can provide a benefit in PFS and OS in patients with EC compared to surgery alone (11). Moreover, previous poor radiotherapy technologies, nonstandard irradiation fields and lack of safe and effective chemotherapy regimens should also be taken into consideration for the poor efficacy or serious complications of adjuvant therapies (22-26). Therefore, S + ACRT should be another potential combined modality therapy for selected EC.

Most retrospective studies (15-20) and the published RCT (11) suggested that there were no significant differences in OS between NCRT + S and S + ACRT. However, most studies showed a trend towards survival benefits in NCRT + S, except for one study (20). Only one study showed significant survival benefits in NCRT +

S (21). Our meta-analysis confirmed that NCRT + S can significantly improve OS (HR, 1.23, 95% CI, 1.09–1.40) and PFS (HR, 1.38, 95% CI, 1.19–1.60) compared to S + ACRT. Subgroup analysis also showed that NCRT + S may be better than S + ACRT for both SCC and AC. However, the number of patients with AC in these studies was low. The studies that enrolled patients with AC accounted for the majority were conducted in Western countries where lower thoracic EC and carcinoma of the esophagogastric junction was prominent. Hence, the treatment principle of esophageal AC may be similar to that of AC of esophagogastric junction (30). There was only one pooled study reporting the treatment of NCRT + S versus S + ACRT for clinical stage II and stage III EC separately, thus we could not perform subgroup analysis of stage (18).

The R0 resection rate can be improved for EC after NRCT due to an apparent downstage and a pathological complete response rate in almost one-third of patients. Additionally, NCRT may eliminate potential micrometastasis at an earlier time. These advantages may account for the survival benefit of NCRT + S. However, NCRT may also delay the time of surgery for patients who are not sensitive to NCRT. Another possible advantage for NCRT is the unchanged anatomy of the esophagus and adjacent tissues and organs, which can facilitate the delineation of the radiotherapy target volume. However, it is still difficult to design a suitable radiotherapy plan for EC because of the complex lymphatic drainage of the esophagus (31). Involved-field irradiation is commonly used for NCRT, which means that radiotherapy is mainly used to control visible lesions to facilitate surgery. To these

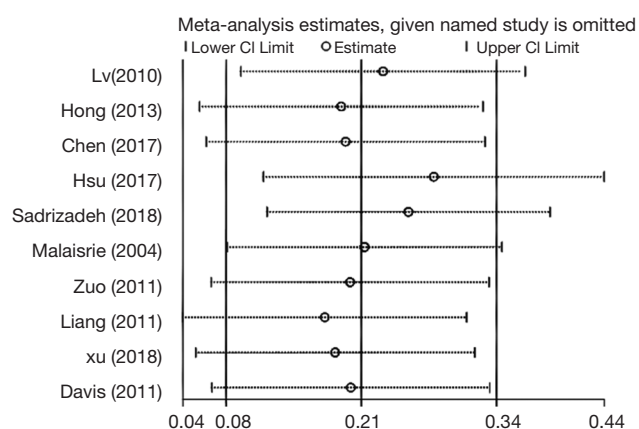


Figure 5 Sensitivity analysis of the summary HR of OS.

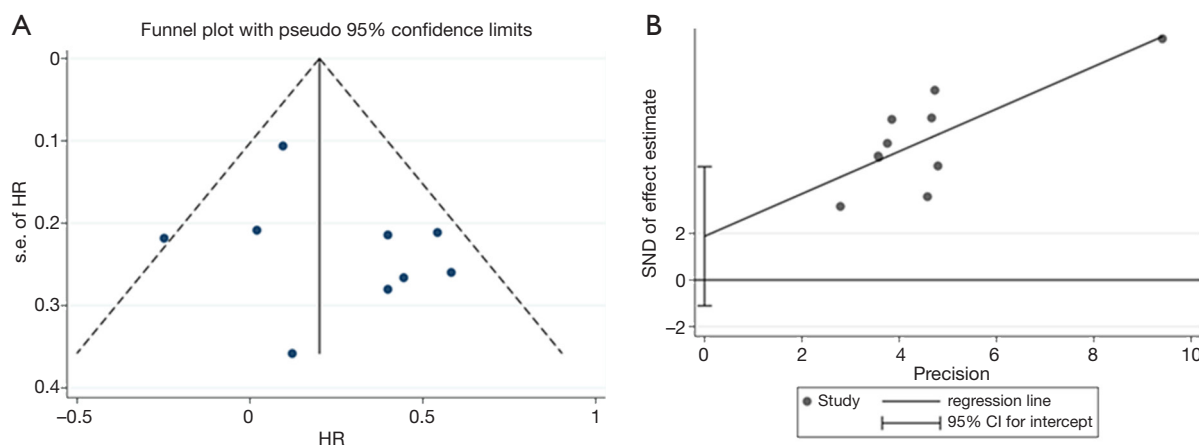


Figure 6 Risk of bias assessment for pooled HRs of OS. (A) Funnel plots; (B) Egger's funnel plots.

points, preoperative radiotherapy may have little benefit for some early stage EC (stage I and II). For clinical T2N0 EC, NCRT + S did not significantly improve outcomes compared with surgery alone (32). One RCT also demonstrated that NCRT + S cannot improve the R0 resection rate or survival in patients with stage I or II EC (33). Taken together, NCRT + S may be more suitable for clinical stage III EC. It was found that NCRT + S can improve the OS of patients with stage III EC but cannot improve the OS of patients with stage II EC compared to S + ACRT (18,34). Adjuvant therapies may be suitable for some clinical early stage EC with high risk or patients with upstaged EC after surgery, therefore avoiding overtreatment.

Treatment-related complications are also important factors in making our multidisciplinary treatment decisions. The impact of NCRT on postoperative mortality and morbidity is still a conflicting topic. A multicentre study found that NCRT + S was associated with more chylothorax and a trend towards more cardiovascular and thromboembolic events (35). A meta-analysis found that NCRT + S tended to have a significantly higher rate of postoperative mortality and cardiopulmonary complications (36). In our meta-analysis, the perioperative complications in NCRT + S were higher than those in S + ACRT (OR, 1.67, 95% CI, 1.09–2.56). However, many factors may affect the incidence of perioperative complications, including patient selection, preoperative treatment regimen, and surgical procedure. The difficulty of the operation may also increase as the location of the tumor shifts from the lower thoracic part to the upper thoracic part of the esophagus, thus increasing perioperative complications. S + ACRT may increase the risk of chemo-radiotherapy related toxicity due to the poor physical condition after surgery. Previous poor results and serious complications of postoperative radiotherapy lead to little use of ACRT (22–26). However, previous poor radiotherapy technologies and nonstandard irradiation fields of these studies should be taken into consideration to reevaluate the efficacy. Retrospective studies suggested that postoperative radiotherapy should be focused on some high recurrence regions after radical surgery, such as the lower neck, upper mediastinum, and paraaortic regions, where it is not cleared up or difficult for complete clearing up during surgery (37,38). Only one pooled study reported that there were no significant differences in severe haematologic toxicities, radiation-induced pneumonitis, anastomotic leakage and anastomotic stenosis between NCRT + S and S + ACRT (18). A meta-analysis demonstrated that S + ACRT did not increase the risk of pneumonitis, anastomotic

stenosis or severe hematologic toxicities (10). Additionally, new chemotherapy regimens should also be evaluated in neoadjuvant or adjuvant therapies.

This meta-analysis included eight studies concerning NCRT + S versus S + ACRT in the treatment of EC. Most of the studies were carried out in Asia and the histological type was SCC. Therefore, these results may be suitable for guiding the treatment of patients with esophageal SCC. Since the gene expression, pathogenetic mechanism and pathobiological behavior of esophageal AC and SCC are different (39), the treatment of esophageal AC may have some differences. There were many limitations to our meta-analysis. First, given the scarcity of RCTs, our meta-analysis included the results of all RCTs and non-RCTs and they were mainly non-RCTs. As a result, there may be some selection bias. In retrospective studies, NCRT + S may usually be chosen for patients with better condition, younger age and fewer complications. Second, the treatment regimens were not well controlled in different studies. The quality of surgical procedures and the target volumes and dosages of radiotherapy may affect the final results. Third, we could not identify and select the appropriate population most likely to benefit from NCRT + S. Except for the pathological type, many factors may affect the choice of treatment, such as stage, location of the tumor, tumor size, body condition, and age. Future studies will be needed to address the optimal subgroup populations for different treatment regimens. With the development of different treatment techniques, we need to reevaluate their merits and demerits using multidisciplinary therapy.

## Conclusions

Our meta-analysis showed that NCRT + S was associated with better OS and PFS, a higher R0 resection rate and more perioperative complications for EC compared to S + ACRT. Because most of the patients had esophageal SCC, these results might be more suitable for esophageal SCC. More prospective RCTs are desperately needed to confirm these results and address the optimal subgroup populations.

## Acknowledgments

*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the

PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/aoe-20-46>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aoe-20-46>). The authors have no 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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doi: 10.21037/aoe-20-46

**Cite this article as:** Zhang L, Wang Y, Xia W, Kang N, Kang M, Zhu L, Chen D, Niu L, Gao Y, Yang M, Wu L. Neoadjuvant versus adjuvant chemoradiotherapy for esophageal carcinoma: a systematic review and meta-analysis. *Ann Esophagus* 2021;4:5.