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REVIEW

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Neoadjuvant chemoradiotherapy or chemotherapy? A comprehensive systematic review and meta-analysis of the options for neoadjuvant therapy for treating oesophageal cancer

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Summary

Neoadjuvant therapy followed by surgery is a standard treatment for locally advanced oesophageal cancer. However, the roles of neoadjuvant chemoradiotherapy and chemotherapy in treating oesophageal cancer remain controversial. In this comprehensive meta-analysis, we examine the efficacy of adding radiotherapy to neoadjuvant chemotherapy for treating oesophageal cancer as reported in qualified randomized controlled trials (RCTs). We conducted a systematic literature search using PubMed, Embase, Cochrane Library databases, Google Scholar and the American Society of Clinical Oncology database to identify relevant studies up to 31 March 2016. Data including the pathological complete response rate, R0 resection rate and 3-year survival rate were extracted and analysed. Five qualified RCTs were included with a total of 709 patients. Meta-analysis showed that neoadjuvant chemoradiotherapy significantly increases the rates of pathological complete response and R0 resection in patients with oesophageal adenocarcinoma or squamous cell carcinoma (SCC). However, we found a significantly increased 3-year survival rate only in oesophageal SCC patients treated with neoadjuvant chemoradiotherapy compared with neoadjuvant chemotherapy (56.8 and 42.8%, respectively); relative risk (RR): 1.31 [95% confidence interval (CI) 1.10–1.58, $P = 0.003$]. In oesophageal adenocarcinoma patients, no significant survival benefit of neoadjuvant chemoradiotherapy was found compared with neoadjuvant chemotherapy alone (46.3 and 41.0%, respectively; RR: 1.13, 95% CI 0.88–1.45, $P = 0.34$). Our meta-analysis adds to the evidence showing that neoadjuvant chemoradiotherapy should be the standard preoperative treatment strategy for locally advanced oesophageal SCC. For oesophageal adenocarcinoma, neoadjuvant chemotherapy alone may be the best preoperative treatment strategy to avoid the risk of adverse effects of radiotherapy.

Keywords: Chemoradiotherapy • Chemotherapy • Oesophageal adenocarcinoma • Oesophageal squamous cell carcinoma • Meta-analysis

INTRODUCTION

Oesophageal cancer is the eighth most common malignant tumour worldwide and the sixth most common cause of death from cancer, and there are geographic differences in the occurrence rate [1]. Histologically, oesophageal cancer comprises mainly squamous cell carcinoma (SCC) and adenocarcinoma. In the highest-risk areas, such as China, 90% of cases of oesophageal cancer are oesophageal SCC [2], whereas in Western countries, oesophageal adenocarcinoma is the predominant pathological type [3]. Despite advances in treating oesophageal cancer, overall survival remains poor, with a 5-year survival rate of 15–34% [4].

To improve the prognosis of oesophageal cancer patients, recent studies have focused on neoadjuvant therapy. Both randomized controlled trials (RCTs) [5, 6] and meta-analyses [7] have reported that neoadjuvant therapy is more beneficial for patients with oesophageal cancer than surgery alone. In recent studies, neoadjuvant therapy for oesophageal cancer comprises mainly chemotherapy and chemoradiotherapy, but it is unclear whether one type of therapy is superior. A recent meta-analysis [8] reported similar postoperative morbidity and perioperative mortality rates for patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal cancer. However, only a few studies have compared the long-term efficacy of neoadjuvant chemoradiotherapy with that of neoadjuvant chemotherapy in patients with oesophageal cancer. Thus, it is unknown whether neoadjuvant chemoradiotherapy has long-term survival benefits over neoadjuvant chemotherapy for patients with resectable oesophageal cancer.

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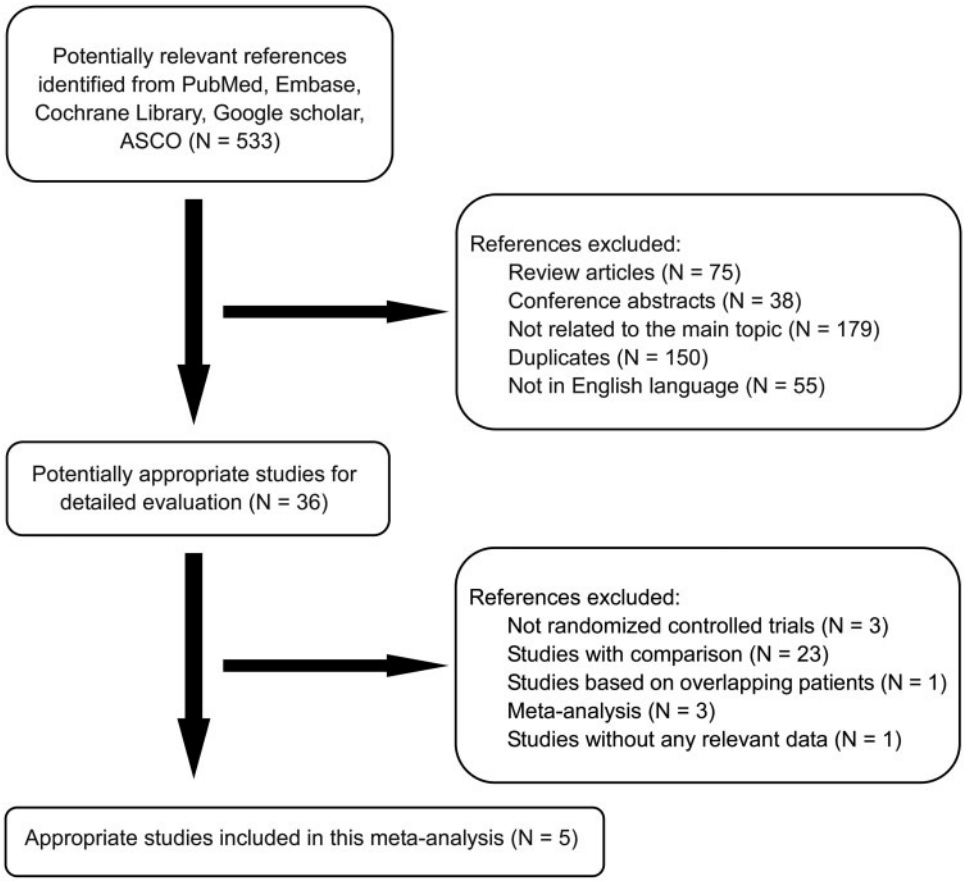

Figure 1: Flow chart showing the progress of trials throughout the review (ASCO: American Society of Clinical Oncology).

Two recent meta-analyses [4, 5] have explored the role of adding radiotherapy to neoadjuvant chemotherapy for treating resectable oesophageal cancer. Both of these studies included only two RCTs [9, 10], with a total of 194 patients, and the authors of the meta-analyses concluded that it remains unclear whether adding radiotherapy to neoadjuvant chemotherapy augments the efficacy of neoadjuvant therapy for treating oesophageal cancer. Therefore, it is not possible to conclude whether neoadjuvant chemoradiotherapy has a clear advantage in the treatment of oesophageal cancer compared with neoadjuvant chemotherapy with a limited sample size. A newly published meta-analysis [11] investigated whether induction chemoradiotherapy before surgery can improve survival compared with induction chemotherapy alone and found a long-term survival benefit of chemoradiotherapy compared with chemotherapy for oesophageal cancer patients. This meta-analysis included the same two RCTs [9, 10] as the previous meta-analyses [4, 5] and another three non-RCTs, which may have reduced the overall validity of these results when all those trials were pooled.

A recently published RCT [12] that compared neoadjuvant chemotherapy with neoadjuvant chemoradiotherapy for oesophageal cancer raised our interest in the effects of adding radiotherapy to neoadjuvant chemotherapy for treating this cancer. After carefully searching for relevant studies in databases, we found another two RCTs [13, 14] that fit the inclusion criteria of our current meta-analysis. Therefore we had the chance to conduct an up-to-date meta-analysis. The three meta-analyses mentioned above [4, 5, 11] did not examine the innate differences between oesophageal adenocarcinoma and SCC. Different pathological subtypes of oesophageal cancer have different sensitivities to chemotherapy or radiotherapy [15]. We believe that these pathological subtypes should be analysed separately when trying to identify the optimum neoadjuvant therapies for subtypes of oesophageal cancer. Therefore, in our current meta-analysis, we tried to identify the optimum neoadjuvant therapy for oesophageal adenocarcinoma and SCC separately by examining the most recent qualified RCTs. To our knowledge, our meta-analysis is the most comprehensive meta-analysis with the largest qualified sample size to compare the use of neoadjuvant chemoradiotherapy and chemotherapy for treating oesophageal cancers and the first to include subgroup analyses to identify the optimum neoadjuvant therapy for oesophageal adenocarcinoma and SCC.

MATERIALS AND METHODS

Search strategies

We performed systematic computerized searches of the PubMed, Embase, Cochrane Library databases, Google Scholar and the American Society of Clinical Oncology database for reports dated up to 31 March 2016. We used the following search terms: 'esophageal or oesophageal' AND 'cancer or carcinoma or neoplasm' AND 'neoadjuvant or preoperative' AND 'chemoradiotherapy or radiotherapy or radiation' AND 'chemotherapy' AND 'clinical trial'. All reference lists from the trials selected by electronic searching were scanned to identify other relevant trials.

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Table 1: Characteristics of the studies included in our meta-analysis

Author (ref)	Neoadjuvant therapy	Number of patients	Median age (years)	Pathological subtype	Stage	Neoadjuvant therapy strategy	Follow-up	Quality score
Nygaard et al. [13]	Chemotherapy	50	62.9	Oesophageal SCC	T1–2NxM0	Two cycles of cisplatin (100 mg/m^2/cycle) and bleomycin (50 mg/m^2/cycle)	>3 years	2 points
	Chemoradiotherapy	47	60.1	Oesophageal SCC	T1–2NxM0	Two cycles of cisplatin (100 mg/m^2/cycle) and bleomycin (50 mg/m^2/cycle), and 35 Gy in 20 fractions	>3 years	
Cao et al. [14]	Chemotherapy	119	NR	Oesophageal SCC	II/III/IV	Cisplatin (20 mg/m^2/day) + 5-fluorouracil (500 mg/m^2/day) + mitomycin (10 mg/m^2/day) regimen	>3 years	2 points
	Chemoradiotherapy	118	NR	Oesophageal SCC	II/III/IV	Cisplatin (20 mg/m^2/day) + 5-fluorouracil (500 mg/m^2/day) + mitomycin (10 mg/m^2/day) regimen, and daily fractions of 2 Gy (days 1–5, 8–12, 15–19, and 22–26) to a total dose of 40 Gy	>3 years	
Stahl et al. [9]	Chemotherapy	59	56.0	Oesophageal adenocarcinoma	T3–4NxM0	2.5 courses of cisplatin (50 mg/m^2), fluorouracil (2 g/m^2), and leucovorin (500 mg/m^2)	Median: 46 months	3 points
	Chemoradiotherapy	60	60.5	Oesophageal adenocarcinoma	T3–4NxM0	Two courses of cisplatin (50 mg/m^2), fluorouracil (2 g/m^2), and leucovorin (500 mg/m^2), and concurrent chemotherapy (cisplatin (50 mg/m^2), day 1 + 8 and etoposide (80 mg/m^2) days 3–5) to a total dose of 30 Gy given at 2.0 Gy/fraction, 5 fractions/week	Median: 46 months	
Burmeister et al. [10]	Chemotherapy	36	63.0	Oesophageal adenocarcinoma	cT2–3N0-1	Cisplatin (80 mg/m^2) and infusional 5-fluorouracil (1000 mg/m^2/day) on days 1 and 21	Median: 94 months	3 points
	Chemoradiotherapy	39	60.0	Oesophageal adenocarcinoma	cT2–3N0-1	The same drugs accompanied by concurrent radiation therapy commencing on day 21 of chemotherapy	Median: 94 months	

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Table 1: Continued

Author (ref)	Neoadjuvant therapy	Number of patients	Median age (years)	Pathological subtype	Stage	Neoadjuvant therapy strategy	Follow-up	Quality score
						and 5-fluorouracil reduced to 800 mg/m^2/day, and 35 Gy in 15 fractions over 3 weeks		
Klevebro et al. [12]	Chemotherapy	66	63.0	Oesophageal adenocarcinoma	cT1–3, any N	Three cycles of cisplatin, 100 mg/m^2 on day 1 and fluorouracil 750 mg/m^2/24 h on days 1–5. Each cycle lasted 21 days	>3 years	3 points
	Chemoradiotherapy	65	63.0	Oesophageal adenocarcinoma	cT1–3, any N	40 Gy was given (2 Gy once daily in 20 fractions, 5 days a week) concomitant with chemotherapy cycles 2 and 3	>3 years	
Klevebro et al. [12]	Chemotherapy	25	63.0	Oesophageal SCC	cT1–3, any N	Three cycles of cisplatin, 100 mg/m^2 on day 1 and fluorouracil 750 mg/m^2/24 h, on days 1–5. Each cycle lasted 21 days	>3 years	3 points
	Chemoradiotherapy	25	63.0	Oesophageal SCC	cT1–3, any N	40 Gy was given (2 Gy once daily in 20 fractions, 5 days a week) concomitant with chemotherapy cycles 2 and 3	>3 years	

SCC: squamous cell carcinoma; NR: not reported.

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Table 2: Main outcomes extracted from the studies included in our meta-analysis

Author (ref)	Pathological subtypes	Pathological complete response rate[a]		R0 resection rate[b]		3-year survival rate[c]	
		Chemoradiotherapy	Chemotherapy	Chemoradiotherapy	Chemotherapy	Chemoradiotherapy	Chemotherapy
Nygaard et al. [13]	Oesophageal SCC	NR	NR	26/21	22/28	8/39	2/48
Cao et al. [14]	Oesophageal SCC	27/91	2/117	116/2	103/16	86/32	68/51
Stahl et al. [9]	Oesophageal adenocarcinoma	7/38	1/48	43/2	41/8	28/32	16/43
Burmeister et al. [10]	Oesophageal adenocarcinoma	5/28	0/33	33/0	29/4	20/19	18/18
Klevebro et al. [12]	Oesophageal adenocarcinoma	12/44	4/55	48/6	42/17	28/37	32/34
Klevebro et al. [12]	Oesophageal SCC	10/14	3/16	20/4	16/3	14/11	13/12

SCC: squamous cell carcinoma; NR: not reported.
[a]Expressed as no. of patients with pathological complete response/no. of patients without.
[b]Expressed as no. of patients with R0 resection/no. of patients without.
[c]Expressed as no. alive/no. dead.

Study selection

The following criteria were used for study inclusion: (i) RCTs that compared neoadjuvant chemoradiotherapy with neoadjuvant chemotherapy for treating oesophageal cancer (either oesophageal adenocarcinoma or SCC); (ii) sufficient data could be obtained for analysis of the rate of R0 resection, pathological complete response and 3-year survival rate; (iii) for studies with overlapping patients, the most recent or completed study was chosen. The exclusion criteria were as follows: (i) studies that were not RCTs; (ii) papers without any relevant data that could be extracted for analysis; (iii) papers that were not published in English; and (iv) case reports, abstracts, conference reports, reviews and reports of experiments.

Data extraction and quality assessment

Two authors (Han-Yu Deng and Wen-Ping Wang) extracted the data independently from the reports and compared the results. To avoid bias, discrepancies were resolved by adjudication by a third author (Yu-Cang Wang). Data were carefully retrieved from full articles using a standardized data collection form. The following data were collected from each study: first author's name, year of publication, number and ages of patients, pathological subtypes, treatment strategies and follow-up. The outcome variables included the rate of R0 resection, pathological complete response and 3-year survival rate. The Jadad scale [16] was used to assess the quality of the RCTs, and was scored according to the randomization (0–2 points), blinding of the studies (0–2 points) and withdrawals (0 or 1 point). A high-quality study was defined as having a quality score ≥3 points. The risk of bias analysis was conducted using Review Manager® Version 5.1.7 for Windows (The Cochrane Collaboration, Software Update, Oxford, UK). The name of the first author and the year of publication of the article were used for identification.

Statistical analysis

We conducted one meta-analysis of the overall results for neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy in oesophageal cancers. We also conducted two separate subgroup meta-analyses: one meta-analysis for oesophageal adenocarcinoma and a second meta-analysis for oesophageal SCC. All analyses were performed according to the PRISMA guidelines [17] using the STATA 12.0 package (StataCorp, College Station, TX, USA). For dichotomous data such as the rates of R0 resection, pathological complete response, and 3-year survival, the relative risk (RR) and 95% confidence interval (CI) were calculated. For each study, between-study heterogeneity was assessed using the χ^2-based Q statistic and the I^2 test. Random-effects models were used for studies with high heterogeneity ($P < 0.1$ or $I^2 > 50\%$); otherwise, fixed-effects models were used. Subgroup analysis was conducted on the basis of the pathological subtypes of oesophageal cancers. Sensitivity analysis was performed by sequential removal of each study. A funnel plot was used to estimate potential publication bias. Asymmetry of the funnel plot was tested using Begg's and Egger's tests [18]. Statistical significance was set at $P < 0.05$.

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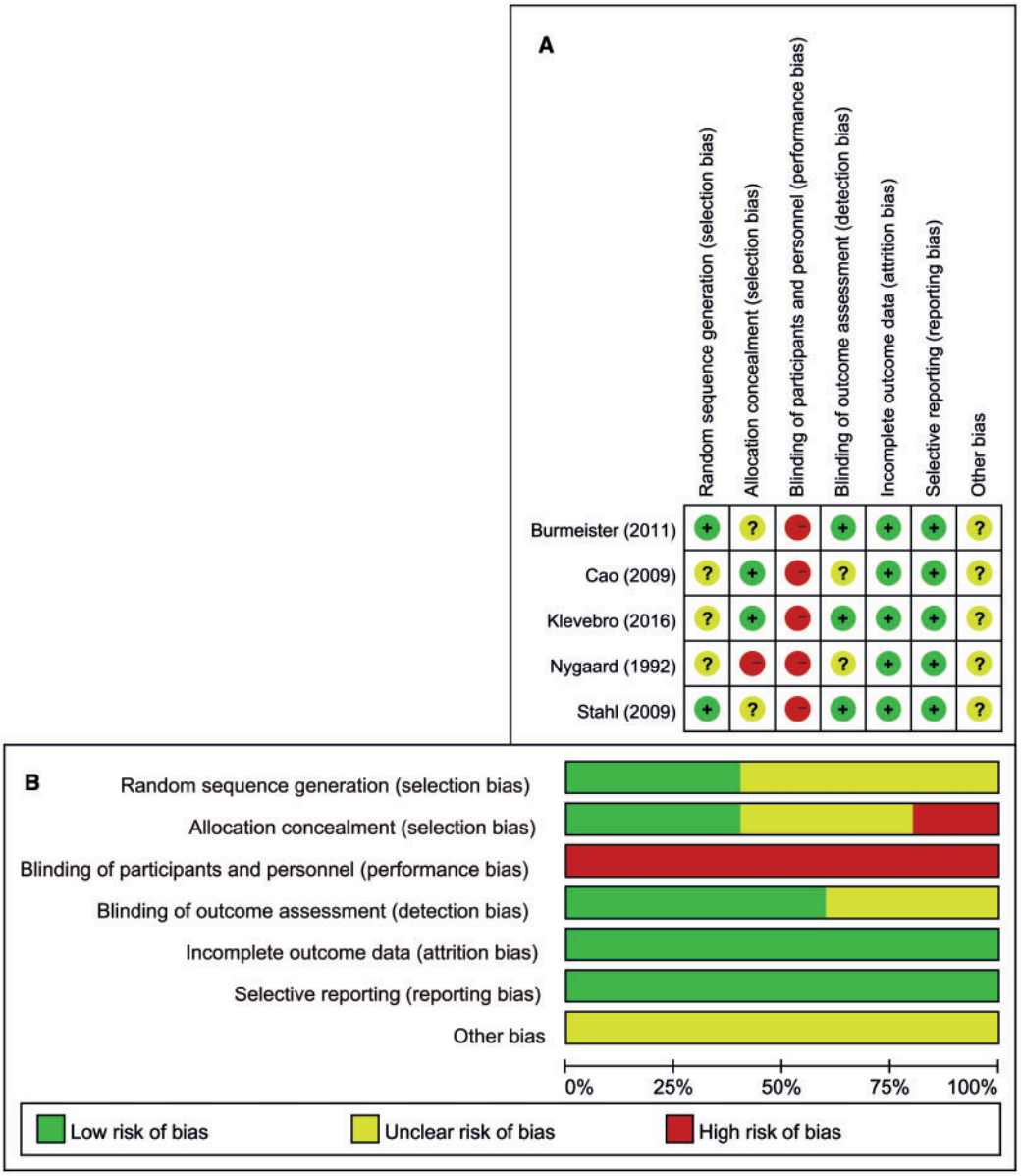

Figure 2: Risk of bias analysis for the RCTs. (**A**) Risk of bias summary: a review of authors' judgements about each risk of bias item for each included study; (**B**) risk of bias graph: a review of authors' judgements about each risk of bias item presented as percentages across all included studies.

RESULTS

Description of the included studies

A flow chart of our analyses is shown in Fig 1. Five RCTs [9, 10, 12–14] that satisfied the criteria, with a total of 709 patients, were included. The main data extracted from these included studies are listed in Table 1. The patients with resectable oesophageal cancer in these studies had a median age of about 60 years, and the demographic data were similar in the neoadjuvant chemoradiotherapy and chemotherapy groups. Only four studies compared neoadjuvant chemoradiotherapy with chemotherapy in patients with pathological subtype of either oesophageal adenocarcinoma or SCC. Only one study [12] explored the efficacy of neoadjuvant therapy in both oesophageal adenocarcinoma and SCC. In those studies, nearly all patients in the neoadjuvant chemotherapy group received the combination of cisplatin and fluorouracil, and patients in the chemoradiotherapy group received additional radiotherapy at a dose of 30–40 Gy. All of these studies had a relatively long follow-up. The data analysed in these studies were the rates of R0 resection, pathological complete response and 3-year survival rate. The rates of R0 resection and 3-year survival were reported by all of the included studies, and the rate of pathological complete response was reported by all studies except one [13] (Table 2).

Quality assessment and risk of bias

The results of the quality assessment of the included studies are shown in Table 1. All of the RCTs reported randomization and withdrawal of patients, but none mentioned study blinding.

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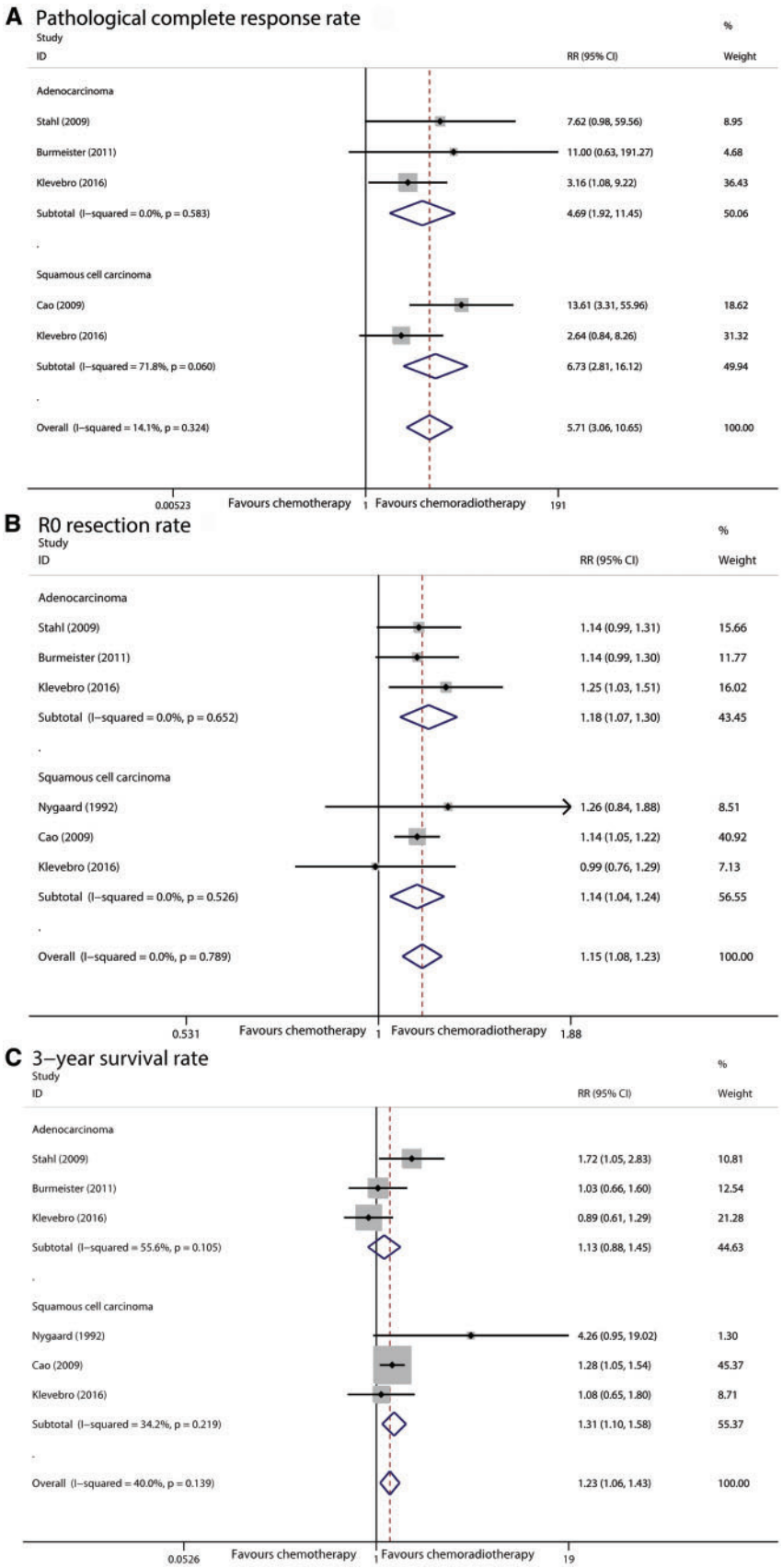

Figure 3: Forest plot of: (**A**) pathological complete response rate; (**B**) R0 resection rate; (**C**) 3-year survival rate.

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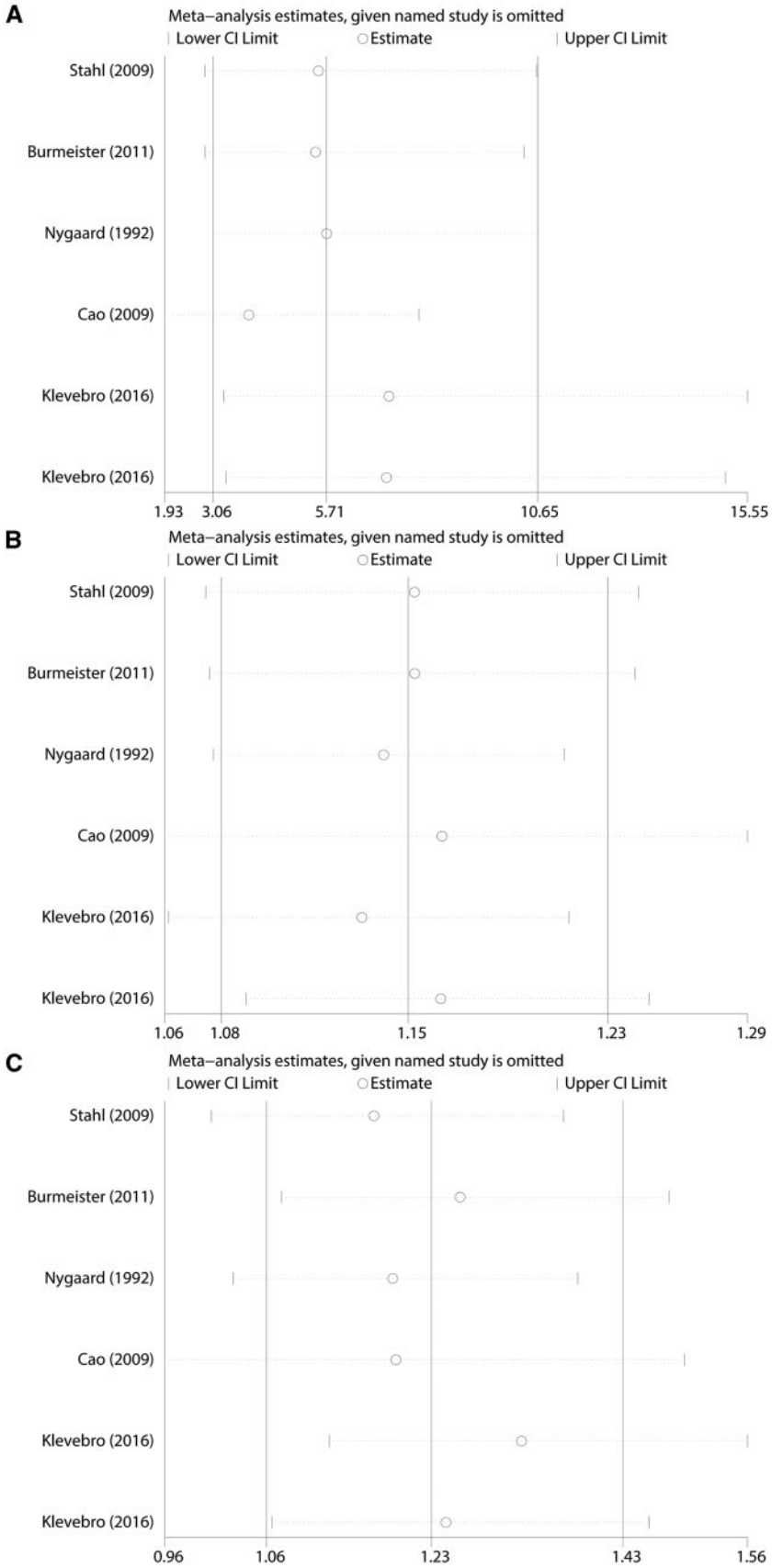

Figure 4: Sensitivity analysis for (**A**) pathological complete response rate; (**B**) R0 resection rate; (**C**) 3-year survival rate.

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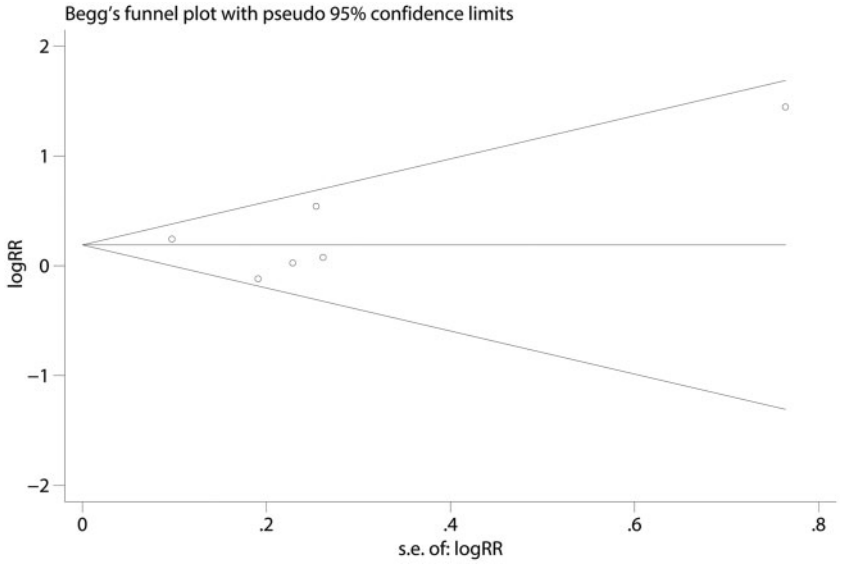

Figure 5: Funnel plot of the included studies for overall analysis of 3-year survival rate (Begg's test: $P = 0.26$; Egger's test: $P = 0.65$).

Three RCTs [9, 10, 12] with scores of 3 points used proper methods for randomization, but the other two RCTs [13, 14] with scores of 2 points did not provide details about randomization. Our analysis of the risk of bias in the RCTs shows concern about blinding bias, including performance and selection bias, in these studies (Fig. 2).

Meta-analysis of the overall results for oesophageal cancers

We included all RCTs in the overall analysis, giving a total of 709 patients. The pathological complete response rate was significantly higher in patients treated with neoadjuvant chemoradiotherapy (22.1%) than in those treated with neoadjuvant chemotherapy (3.7%) (RR: 5.71, 95% CI 3.06–10.65, $P < 0.001$, $I^2 = 14.1\%$) (Fig. 3A). The rate of R0 resection was significantly higher in oesophageal cancer patients treated with neoadjuvant chemoradiotherapy compared with neoadjuvant chemotherapy alone (89.1 and 76.9%, respectively) (RR: 1.15, 95% CI 1.08–1.23, $P < 0.001$, $I^2 = 0.0\%$) (Fig. 3B). The 3-year survival rate was significantly higher in patients treated with neoadjuvant chemoradiotherapy (52.0%) than in those treated with neoadjuvant chemotherapy alone (42.0%) (RR: 1.23, 95% CI 1.06–1.43, $P = 0.006$, $I^2 = 40.0\%$) (Fig. 3C).

Even though no obvious heterogeneities were observed in the overall analysis, oesophageal adenocarcinoma and SCC are different entities. We next performed separate subgroup analyses of oesophageal adenocarcinoma and SCC to explore the efficacy of adding radiotherapy to neoadjuvant chemotherapy in treating these subtypes of oesophageal cancers.

Meta-analysis of the results for oesophageal adenocarcinoma

Only three studies, with a total of 325 patients, reported the efficacy of adding radiotherapy to neoadjuvant chemotherapy for treating oesophageal adenocarcinoma. In oesophageal adenocarcinoma patients, neoadjuvant chemoradiotherapy yielded significantly higher rates of pathological complete response (RR: 4.69, 95% CI 1.92–11.45, $P = 0.001$, $I^2 = 0.0\%$) (Fig. 3A) and R0 resection (RR: 1.18, 95% CI 1.07–1.30, $P = 0.001$, $I^2 = 0.0\%$) (Fig. 3B). However, the 3-year survival rate did not differ significantly between oesophageal adenocarcinoma patients treated with neoadjuvant chemoradiotherapy and those treated with chemotherapy (46.3 and 41.0%, respectively) (RR: 1.13, 95% CI 0.88–1.45, $P = 0.34$, $I^2 = 55.6\%$) (Fig. 3C).

Meta-analysis of the results for oesophageal squamous cell carcinoma

Three studies, with a total of 384 patients, were included in the analysis of oesophageal SCC. In oesophageal SCC patients, neoadjuvant chemoradiotherapy yielded significantly higher rates of pathological complete response (RR: 6.73, 95% CI 2.81–16.12, $P < 0.001$, $I^2 = 71.8\%$) (Fig. 3A) and R0 resection (RR: 1.14, 95% CI 1.04–1.24, $P = 0.005$, $I^2 = 0.0\%$) (Fig. 3B). The 3-year survival rate was significantly higher in oesophageal SCC patients treated with neoadjuvant chemoradiotherapy than in those treated with chemotherapy (56.8 and 42.8%, respectively) (RR: 1.31, 95% CI 1.10–1.58, $P = 0.003$, $I^2 = 34.2\%$) (Fig. 3C).

Sensitivity analysis and publication bias

To evaluate the stability of our overall results, we performed sensitivity analysis by sequential removal of each study based on the overall analysis. The sequential removal of each study did not change the outcomes of the primary overall analysis (Fig. 4). Publication bias was tested using Begg's and Egger's tests, and suggested no publication bias. The funnel plot of the overall analysis of 3-year survival rate had a symmetrical appearance (Begg's test: $P = 0.26$; Egger's test: $P = 0.65$) (Fig. 5).

DISCUSSION

Oesophageal cancer is an aggressive disease with poor prognosis, and surgical resection is the standard treatment option for early

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stage oesophageal cancer. However, most patients with newly diagnosed oesophageal cancer present with locally advanced disease [19] and, for these patients, surgery alone is far from the optimum treatment strategy. Thus, recent studies have focused on multidisciplinary treatment strategies such as adjuvant therapy and neoadjuvant therapy. Accumulating evidence indicates that neoadjuvant therapy followed by surgery produces better overall survival than surgery alone for locally advanced oesophageal cancer [20]. However, controversy remains about whether neoadjuvant chemoradiotherapy is superior to neoadjuvant chemotherapy in the preoperative treatment of oesophageal cancers.

Only a few RCTs [9, 10, 12–14] have explored the value of adding radiotherapy to neoadjuvant chemotherapy in treating oesophageal cancer. However, their conclusions differed, and there is no agreement about whether neoadjuvant chemoradiotherapy is superior to neoadjuvant chemotherapy. Two previous meta-analyses [4, 5] compared neoadjuvant chemoradiotherapy with chemotherapy. Because of the limited number of RCTs (only two RCTs were included), both meta-analyses concluded that there is no significant survival benefit by adding radiotherapy to neoadjuvant chemotherapy for treating oesophageal cancers. A recent meta-analysis that included two RCTs and three non-randomized controlled studies [11] concluded that neoadjuvant chemoradiotherapy has a benefit for long-term survival in oesophageal cancer patients. However, the validity of this meta-analysis may be questioned because of the inclusion of three non-randomized studies.

The previously published meta-analyses did not address the fact that oesophageal adenocarcinoma and SCC are two distinct entities and, thus, treating them as a single entity may decrease the analytical power. The ability to draw a definitive conclusion about the efficacy of adding radiotherapy to neoadjuvant chemotherapy for treating oesophageal cancer requires the inclusion of all available RCTs (relatively high level of evidence) and separate analyses for oesophageal adenocarcinoma and SCC. After comprehensively searching the databases, we found five qualified RCTs [9, 10, 12–14] with a total of 709 patients. With this larger sample size, we were able to perform both an overall meta-analysis for oesophageal cancer and separate subgroup analyses for oesophageal adenocarcinoma and SCC.

In our meta-analysis, we found that neoadjuvant chemoradiotherapy significantly increased the rates of pathological complete response and R0 resection for patients with oesophageal cancer compared with neoadjuvant chemotherapy. Our subgroup analyses found the same results for both oesophageal adenocarcinoma and SCC, which supports the validity of our analyses. However, only oesophageal SCC patients obtained survival benefits from adding radiotherapy to neoadjuvant chemotherapy, and neoadjuvant chemoradiotherapy conferred no clear advantage over neoadjuvant chemotherapy in oesophageal adenocarcinoma patients.

Neoadjuvant therapy followed by surgery has become the standard treatment modality for locally advanced oesophageal cancer. Because neoadjuvant chemoradiotherapy seems to increase the rate of adverse effects compared with neoadjuvant chemotherapy alone in oesophageal cancer patients [21], it is important to determine whether adding radiotherapy to neoadjuvant chemotherapy confers survival benefit compared with neoadjuvant chemotherapy alone. Previous studies [4, 5, 9–14] have tried to compare these two neoadjuvant therapies, but there is no agreement on any definite role of adding radiotherapy to neoadjuvant chemotherapy for treating oesophageal cancer. Our current meta-analysis showed significantly higher rates of pathological complete response, R0 resection and 3-year survival for neoadjuvant chemoradiotherapy compared with neoadjuvant chemotherapy. Previous studies have shown that the combination of radiotherapy and chemotherapy can increase the efficacy of each modality for treating oesophageal cancers [22]. Therefore, our analysis adds to the evidence indicating that the combination of radiotherapy and chemotherapy is superior to chemotherapy alone as preoperative treatment for oesophageal cancer.

Even though the benefit of significantly increased rate of pathological complete response and R0 resection from neoadjuvant chemoradiotherapy was observed in both oesophageal adenocarcinoma and SCC groups, our analysis showed that adding radiotherapy to neoadjuvant chemotherapy significantly increased the 3-year survival rate only for patients with oesophageal SCC. This difference in the responses to chemoradiotherapy of these two subtypes of oesophageal cancer may be explained by intrinsic differences between the disease subtypes. Accumulating evidence suggests that oesophageal SCC responds better to chemoradiotherapy, whereas oesophageal adenocarcinoma seems to respond better to chemotherapy [20]. Previous studies have reported that patients with oesophageal SCC treated with neoadjuvant chemoradiotherapy had a higher pathological complete response rate and longer overall survival than patients with oesophageal adenocarcinoma [6, 19]. Therefore, both our overall results and subgroup results are consistent with the idea that neoadjuvant chemoradiotherapy should be the standard preoperative treatment strategy for locally advanced oesophageal SCC, whereas neoadjuvant chemotherapy alone may be the best preoperative strategy for adenocarcinoma for avoiding the adverse effects of radiotherapy. Further research is needed to confirm this conclusion.

Our current meta-analysis has several limitations. First, our sample size of 709 patients is still smaller than that in most meta-analyses. This may have affected our subgroup analyses, which limits our analytical power. Second, some of the included studies were not ranked as high quality, which could also decrease the validity of our meta-analysis. Third, we found possible heterogeneities in our subgroup analyses, which may relate to the small subgroup sample sizes or to differences in chemoradiotherapy dose or surgical procedures in the included studies. Fourth, there is a potential risk of bias in our analyses because performance and selection bias was found in the included RCTs.

Despite these limitations, our meta-analysis is the first to explore the role of radiotherapy added to neoadjuvant chemotherapy for treating oesophageal adenocarcinoma and SCC analysed separately. Our meta-analysis provides evidence that neoadjuvant chemoradiotherapy is beneficial in the preoperative treatment of oesophageal SCC whereas neoadjuvant chemotherapy alone may be best for treating oesophageal adenocarcinoma. There are two ongoing RCTs on this issue [23, 24], but we believe that more RCTs are needed to compare neoadjuvant chemoradiotherapy and chemotherapy in treating oesophageal SCC and adenocarcinoma as distinct entities.

CONCLUSIONS

Our current meta-analysis compared neoadjuvant chemoradiotherapy with neoadjuvant chemotherapy in the preoperative treatment of oesophageal cancer. We found that adding

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radiotherapy to neoadjuvant chemotherapy significantly increased the rates of pathological complete response and R0 resection for both oesophageal SCC and adenocarcinoma. However, a survival advantage of neoadjuvant chemoradiotherapy was observed only in patients with oesophageal SCC. We conclude that neoadjuvant chemoradiotherapy should be the standard preoperative treatment for oesophageal SCC, and neoadjuvant chemotherapy should be the preoperative treatment for oesophageal adenocarcinoma.

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Conflict of interest: none declared.

REFERENCES

[1] Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet 2013;381:400–12.
[2] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: Cancer J Clin 2015;65:87–108.
[3] Rustgi AK, El-Serag HB. Esophageal carcinoma. N Engl J Med 2014;371:2499–509.
[4] Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A *et al*. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011;12:681–92.
[5] Fu T, Bu ZD, Li ZY, Zhang LH, Wu XJ, Wu AW *et al*. Neoadjuvant chemoradiation therapy for resectable esophago-gastric adenocarcinoma: a meta-analysis of randomized clinical trials. BMC Cancer 2015;15:322.
[6] Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP *et al*. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015;16:1090–8.
[7] Wijnhoven BP, van Lanschot JJ, Tilanus HW, Steyerberg EW, van der Gaast A. Neoadjuvant chemoradiotherapy for esophageal cancer: a review of meta-analyses. World J Surg 2009;33:2606–14.
[8] Kumagai K, Rouvelas I, Tsai JA, Mariosa D, Klevebro F, Lindblad M *et al*. Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers. Br J Surg 2014;101:321–38.
[9] Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J *et al*. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 2009;27:851–6.
[10] Burmeister BH, Thomas JM, Burmeister EA, Walpole ET, Harvey JA, Thomson DB *et al*. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer (Oxf, Engl: 1990) 2011;47:354–60.
[11] Fan M, Lin Y, Pan J, Yan W, Dai L, Shen L *et al*. Survival after neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for resectable esophageal carcinoma: a meta-analysis. Thorac Cancer 2016;7:173–81.
[12] Klevebro F, Alexandersson von Dobeln G, Wang N, Johnsen G, Jacobsen AB, Friesland S *et al*. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol 2016;27:660–7.
[13] Nygaard K, Hagen S, Hansen HS, Hatlevoll R, Hultborn R, Jakobsen A *et al*. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. World J Surg 1992;16:1104–9.
[14] Cao XF, He XT, Ji L, Xiao J, Lv J. Effects of neoadjuvant radiochemotherapy on pathological staging and prognosis for locally advanced esophageal squamous cell carcinoma. Dis Esophagus 2009;22:477–81.
[15] Cohen DJ, Leichman L. Controversies in the treatment of local and locally advanced gastric and esophageal cancers. J Clin Oncol 2015;33:1754–9.
[16] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
[17] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[18] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[19] Ruhstaller T, Widmer L, Schuller JC, Roth A, Hess V, Mingrone W *et al*. Multicenter phase II trial of preoperative induction chemotherapy followed by chemoradiation with docetaxel and cisplatin for locally advanced esophageal carcinoma (SAKK 75/02). Ann Oncol 2009;20:1522–8.
[20] Zacherl J. The current evidence in support of multimodal treatment of locally advanced, potentially resectable esophageal cancer. Dig Dis 2014;32:171–5.
[21] Lund M, Alexandersson von Dobeln G, Nilsson M, Winter R, Lundell L, Tsai JA *et al*. Effects on heart function of neoadjuvant chemotherapy and chemoradiotherapy in patients with cancer in the esophagus or gastroesophageal junction—a prospective cohort pilot study within a randomized clinical trial. Radiat Oncol 2015;10:16.
[22] Mariette C, Piessen G, Triboulet JP. Therapeutic strategies in oesophageal carcinoma: role of surgery and other modalities. Lancet Oncol 2007;8:545–53.
[23] Nakamura K, Kato K, Igaki H, Ito Y, Mizusawa J, Ando N *et al*. Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT study). Jpn J Clin Oncol 2013;43:752–5.
[24] Keegan N, Keane F, Cuffe S, Cunningham M, Ravi N, Lee G *et al*. ICORG 10-14: Neo-AEGIS: A randomized clinical trial of neoadjuvant and adjuvant chemotherapy (modified MAGIC regimen) versus neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the esophagus and esophagogastric junction. In*: Conference ICORG 10-14: Neo-AEGIS: A randomized clinical trial of neoadjuvant and adjuvant chemotherapy (modified MAGIC regimen) versus neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the esophagus and esophagogastric junction*, 2014, p. TPS4145. http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/TPS4145.

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