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ORIGINAL ARTICLE

Meta-Analysis for the Therapeutic Effect of Neoadjuvant Therapy in Resectable Esophageal Cancer

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Abstract We aimed to review the therapeutic effects of neoadjuvant chemoradiotherapy (NCRT), chemotherapy (NCT), and radiotherapy (NRT) on patients with resectable Esophageal cancer (EsC) by comparison with surgery alone (SA). PubMed, EMBASE and Cochrane were searched for eligible studies published up to March 2015. Cochrane reviews were used for quality assessment. Eight primary outcomes were analyzed. Risk ratios (RRs)/ hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) were calculated using the random- or fixed- effects model. Heterogeneity was assessed using the Chi-square-based Q statistic and the I^2test. Publication bias was examined by the Begg's funnel plot. Totally 24 articles including 4718 EsC cases were eligible for this meta-analysis. The quality of the literatures was relatively high. Significant difference was found in five-year survival rate (RR = 1.45, 95% CI: 1.17–1.79, $P < 0.01$) between patients treated with NCT and SA, while the eight enrolled primary outcomes were all statistically different between NCRT and SA, and significant difference was identified in three-year survival between NCRT and NCT (RR = 1.35, 95% CI: 1.14–1.60, $P < 0.01$). No obvious publication bias was observed. NCRT and NCT provide an obvious benefit for EsC treatment over SA, and NCRT possesses a clear advantage compared with NCT.

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Introduction

Esophageal cancer (EsC) is the sixth deadliest cancer among all malignant tumors in mortality and affects more than 450 thousand people worldwide [1] . EsC is characterized with extremely aggressive nature and poor survival rate [2] and it is generally categorized as adenocarcinoma (AC) and squamous cell carcinoma (SCC). The American Cancer Society Cancer 2009 statistics reported that the 5-year survival rate for EsC patients is only 17%, with a better survival rate for local (33.7%) or regional (16.9%) compared with distant disease (2.9%) at presentation [3] Recent advances in the management of this neoplastic condition have led to small but significant improvements in survival [4].

Management of EsC has been refined since the last decades. Esophagectomy remains as the primary treatment and plays a pivotal role in dealing with this disease [5]. In case of persistent or recurrent EsC, salvage esophagectomy is really a possible option, this procedure, however, is considered to be associated with a high level of perioperative morbidity and mortality [6]. Chemotherapy and radiotherapy before surgery could improve the control of local or distant disease by increasing the surgical resect ability and down staging cancer, which is crucial to reduce the frequency of disease recurrence before operation [7]. Nonetheless, surgical resection, chemotherapy or radiation as a single modality treatment for EsC produces poor long-term survival, which prompts the evolution of neoadjuvant therapy in the form of chemotherapy and/ or radiation followed by surgery [8]. Comparing with surgery

alone (SA), neoadjuvant therapy has resulted in a better outcome in several randomized trials [8, 9]. Whereas, the roles of multimodal treatment with neoadjuvant chemoradiotherapy followed by surgery (NCRT), neoadjuvant chemotherapy followed by surgery (NCT), and neoadjuvant radiotherapy followed by surgery (NRT) in improving surgical results have been mixed and were disappointing for the reason that trials were generally small and lacked statistical power [10].

Previous meta-analyses [11, 12] provide strong evidence for the survival benefit of NCRT or NCT over SA in patients with ESC. However, researches on comparison of neoadjuvant treatments and SA performed in the past three years have not yet been assessed. Besides, differences of interventions on EsC were assessed according to just one or two indicators such as all-cause mortality and 2-year absolute survival. In the present study, we aimed to comprehensively compare the survival outcome of NCRT, NCT, NRT and SA in dealing with resectable EsC, and sought to provide a basis for the preferred therapies in clinical practice.

Materials and Methods

Data Sources and Search Strategy

A systematic search was performed through PubMed (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (http://www.embase.com) and Cochrane (http://www.cochrane.org/) up to March 2015 for all randomized controlled trials related to esophageal neoplasms management. Search strategy was applied as follows: [((chemoradiotherapy OR chemotherapy OR radiotherapy) AND neoadjuvant) AND (resectable AND (neoplasms OR carcinoma OR cancer) AND ((esophageal OR oesophageal) OR ((esophagogastric OR gastroesophageal) AND junction))].

Selection Criteria

Articles were selected by two investigators independently and the result was reviewed by a third investigator. Inclusion criteria of eligible studies were: i) a randomized controlled trial; ii) patients with diagnosis of resectable ESC; iii) primary outcome including perioperative mortality, disease recurrence, DFS, OS and/or one-, two- or five-year survival rate; iv) application of NCRT, NCT or NRT on resectable EsC; and v) no significant differences in age, gender, pathology or stage of tumor between the treatment group and control group. Studies were excluded if they were: i) reviews, reports, comments or letters; ii) not written in English.

Data Extraction and Quality Assessment

Two investigators independently extracted the following information from the eligible studies: the first author, year of publication, baseline characteristics of the participants such as gender and age, follow-up period, histological subtype (SCC and AC), treatment modalities and chemotherapeutics. Results were compared and reviewed by a third investigator until a consensus was reached.

The methodological quality of included articles was evaluated based on the Cochrane Handbook for Systematic Reviews of Interventions (updated in March 2011) by identifying, appraising and synthesizing research-based evidence and presenting it in an accessible format [13, 14].

Statistical Analysis

All statistical analyses were performed by RevMan 5.3. The heterogeneity among the included studies was assessed using the Chi-square-based Q statistic and the I^2 test (2, 3). $P < 0.05$ (Q statistic) or $I^2 \geq 50\%$ was considered as the presence of heterogeneity among studies, and then the random-effects model was chosen for meta-analysis; otherwise, the fixed effects model would be used.

According to the intervention, patients from the eligible researches were divided into four groups (NCRT, NCT, NRT and SA). Primary outcomes such as radical resection (R0), perioperative mortality, disease recurrence, DFS, OS and/or one-, two- or five-year survival rate were assessed in this analysis. Combined risk ratio (RRs)/ hazard ratio (HRs) corresponding to their 95% confidence intervals (CIs) were calculated to compare outcomes of NCRT vs. SA, NCT vs. SA and NCRT vs. NCT vs. NRT. $P \leq 0.05$ was considered as statistical difference. To determine the stability of these results, sensitivity analysis was performed by comparing the pooled results of the random-effects model with that of the fixed effects model. Publication bias was examined by the visual inspection of the Begg's funnel plot.

Results

Search Results and Study Characteristics

A total of 538 potentially relevant articles were obtained. Of these studies, 204 were excluded for duplicate publication. Then, 299were excluded (93 not related to resectable EsC, 73 without needed outcomes, 59 reviews or meeting reports, 41 non-TCTs and 34 non-English articles). After reviewing full-text of the remaining studies, we further excluded 11 articles (4 non-RCT studies, 3 without included primary outcomes, 2without the comparison of NRCT, NCT, NRT and/or SA, and 2with duplicated data). Finally, 24 articles

Table 1 Characteristics of the selected studies

Author, year	Age (NCRT/NCT/ NRT/SA, years)	Median follow-up (months)	Sample size (NCRT/ NCT/ NRT/SA)	Tumor type	Radiotherapy schedule	Chemotherapy schedule	Concurrent or sequential
NCRT vs. SA							
Bosset et al. [18]	56.7 ± 8.0/56.6 ± 7.6	55.2	282 (143/139)	SCC	five daily fractions of 3.7 Gy each	Cis 80 mg/m^2 on days 1, 2 before each course of radiotherapy	concurrent
Burmeister et al. [19]	61 (41–80)/62 (28–83)	65	256 (128/128)	SCC/AC	35 Gy in 15 fractions over 3 weeks	One cycle: cisplatin 80 mg/m^2 day 1; fluorouracil 800 mg/m^2 days 2–5	concurrent
Fujiwara et al. [22]	60.11/64.6	44.8/24.6	88 (52/36)	SCC	20 fractions of 2 Gy	5-FU 500 mg/m^2/day 120-h starting on day 1; Cis 15–20 mg/day by a 2-h on days 1–5 and repeated after 3 weeks	concurrent
Lee et al. [25]	63 (42–73)/ 63 (39–75)	25	101 (51/50)	SCC	45·6 Gy, 1·2 Gy per fraction over 28 days	Two cycles: cisplatin 60 mg/m^2 day 1; fluorouracil 1000 mg/m^2 days 3–5	concurrent
Lv et al. [26]	NA	45	160 (80/80)	SCC	40 Gy, 2 Gy per fraction over 4 weeks	Two cycles: cisplatin 20 mg/m^2 per day days 1–3 and 22–25; paclitaxel 135 mg/m^2 starting on day 1 and day 22 of radiotherapy	concurrent
Mariette et al. [28]	58.1 (40.1–76.4)/ 57.6 (36.9–74.3)	93.6	195 (98/97)	SCC/AC	45 Gy in 25 fractions over 5 weeks	FU 800 mg/m^2 per 24 h on days 1–4 and 29–32; Cis 75 mg/m^2 on day 1 or 2 and again on day 29/ 30.	concurrent
Natsugoe et al. [29]	NA	24	45 (22/23)	SCC	40 Gy, 2 Gy per fraction over 4 weeks	Cis 7 mg on days 1–5, 8–12, 15–19 and 22–26; FU 350 mg/day on days 1–28	concurrent
Tepper et al. [34]	60.9 (38–77)/ 61.9 (44–76)	72	56 (30/26)	SCC/AC	50.4 Gy, 1.8 Gy per fraction over 5.6 weeks	Two cycles: cisplatin 60 mg/m^2 day 1; fluorouracil 1000 mg/m^2 days 3–5	concurrent
Prise et al. [31]	NA	12	86 (41/45)	SCC	20 Gy in 10 fractions over 12 days	Two cycles: cisplatin 100 mg/m^2 day 1; fluorouracil 600 mg/m^2 days 2–5 and 22–25	sequential
Urba et al. [35]	62 (39–75)/ 64 (42–75)	98	100 (50/50)	SCC/AC	45 Gy, 1.5 Gy per fraction over 3 weeks	Two cycles: cisplatin 20 mg/m^2 days 1–5; fluorouracil 300 mg/m^2 days 1–21; vinblastine 1 mg/m^2 days 1–4	concurrent
Van Hagen et al. [36]	60 (36–79)/ 60(36–73)	45.4	386 (178/188)	SCC/AC	41.4Gy, 1.8Gy per fraction over 4-6 weeks	carboplatin 2 mg/ml/min, 5 weeks; paclitaxel 50 mg/m^2 on day 1 weekly	concurrent
Walsh et al. [37]	65 (37–75)/ 65 (47–75)	24	113 (55/58)	AC	40 Gy in 15 fractions over 3 weeks	Two cycles: cisplatin 75 mg/m^2 day 7; fluorouracil 15 mg/kg days 1–5	concurrent
NCT vs SA							
Allum et al. [15]	63 (36–84)/ 63(30–80)	72	802 (400/402)	SCC/AC		Two cycles: cisplatin 80 mg/m^2 day 1; fluorouracil 1000 mg/m^2 days 1–4	
Ancona et al. [16]	58 ± 9.7/58 ± 9.3	24	96 (48/48)	SCC		Two cycles: cisplatin 100 mg/m^2 day 1; fluorouracil 1000 mg/m^2 days 1–5	
Boonstra et al. [17]	60 (35–76)/ 60 (37–79)	14.5	169 (85/84)	SCC		Two cycles: cisplatin 80 mg/m^2 day 1; etoposide 200 mg/m^2 days 1–5	
Kelsen et al. [23]	62 ± 9.8/ 61 ± 9.4	46.5	467 (233/234)	SCC/AC		Cis 100 mg/m^2 on days 1, 29 and 58; FU 1000 mg/m^2 over 5 days on days 1–5, 29–33 and 58–62	
Law et al. [24]	64 ± 1.1/63 ± 1.1	17	147 (74/73)	SCC		Two cycles: cisplatin 100 mg/m^2 day 1; fluorouracil 1000 mg/m^2 days 1–5	

Table 1 (continued)

Author, year	Age (NCRT/NCT/ NRT/SA, years)	Median follow-up (months)	Sample size (NCRT/ NCT/ NRT/SA)	Tumor type	Radiotherapy schedule	Chemotherapy schedule	Concurrent or sequential
Maipang et al. [27]	64.2 (43–74)/ 64.8 44–74)	17	46 (24/22)	SCC		Two cycles: cisplatin 100 mg/m^2 day 1; bleomycin 10 mg/m^2 days 3–8; vinblastine 3 mg/m^2 days 1 and 8	
Schlag [32]	54.8/58.8	7.5	46 (22/24)	SCC		Three cycles: cisplatin 20 mg/m^2 days 1–5; fluorouracil 1000 mg/m^2 days 1–5	
Ychou et al. [38]	63 (36–75)/ 63 (38–75)	68.4	224 (113/111)	AC		three preoperative cycles: FU 800 mg/m^2/d days 1 to 5 and cis 100 mg/m^2 as a 1-h infusion, every 28 days, and 3 to 4 postoperative cycles	
NCRT vs. NCT							
Burmeister et al. [20]	60 (41–73)/ 63 (36–75)	70	75 (39/36)	AC	35 Gy in 15 fractions commencing day 22	1 cycle induction: cisplatin 80 mg/m^2 day 1 and fluorouracil 1000 mg/m^2 infusion over 96 h day 1. Followed by cisplatin 80 mg/m^2 day 1 and fluorouracil 800 mg/m^2 infusion over 96 h on day 1 Two cycles: cisplatin 80 mg/m^2 day 1, fluorouracil 1000 mg/m^2 infusion over 96 h day 1	Induction and concurrent
Stahl et al. [33]	60.6/56.0	46	119 (60/59)	AC	30 Gy, 2 Gy per fraction over 3 weeks, commencing 2 weeks after last day of induction chemotherapy	12 weeks (induction): fluorouracil 2000 mg/m^2 over 24 h day 1; folinic acid 500 mg/m^2 day 1; and cisplatin 80 mg/m^2 biweekly. Followed by cisplatin 50 mg/m^2 on day 1 and day 8 and etoposide 80 mg/m^2 on days 3–5, concurrent with radiotherapy 15 weeks: fluorouracil 2000 mg/m^2 over 24 h day 1, folinic acid 500 mg/m^2 day 1; cisplatin 80 mg/m^2 biweekly	Induction and concurrent
NCRT vs. NCT vs. NRT vs. SA							
Cao et al. [21]	NA	NA	473 (118/119/118/118)	SCC	2 Gy (days 1–5, 8–12, 15–19, and 22–26) to a total dose of 40 Gy	MMC 10 mg/m^2/day on day 1; Cis (20 mg/m^2/day) and 5-FU (500 mg/m^2/day) over 24 h on days 1–5	concurrent
Nygaard et al. [30]	66.1/ 62.9/ 60.1/ 61.4	18	186 (47/50/48/41)	SCC	35 Gy, 1·75 Gy per fraction over 4 weeks	Two cycles: cisplatin 20 mg/m^2 days 1–5; bleomycin 5 mg/m^2 days 1–5	sequential

Abbreviations: *NCRT* Neoadjuvant chemoradiotherapy, *NCT* Neoadjuvant chemotherapy, *NRT* Neoadjuvant radiotherapy, *SA* Surgery alone, *SCC* Squamous-cell carcinoma, *AC* Adenocarcinoma, *cis* Cisplatin, *5-FU* 5-fluorouracil, *MMC* Mitomycin, *NA* Not available

including 4718 EsC cases were retrieved for the present meta-analysis [15–38].

As shown in Table 1, 12 involved with comparison of NCRT vs. SA (n = 1868), eight with comparison of NCT vs. SA (n = 1997), two with comparison of NCRT vs. NCT (n = 194) and two with comparison of NCRT vs. NCT vs. NRT vs. SA (n = 659). Follow-up periods of all these quantified trials ranged from 12 to 98 months. Histological types of the involved cases included SCC and AC, and only disease recurrence were assessed by stratifying the cases with histological types.

Quality Assessment

Studies in this meta-analysis were all RCTs, therefore Cochrane reviews were used for quality assessment. All the quantified studies were with low risk of bias (selection bias and detection bias), and/or unclear bias for not mentioning the blinded method (Fig. 1). Two articles [33, 38] involved performance bias belongs to high risk of bias. These results signified a relatively high level of research selection.

Heterogeneity Test

Comparisons of NCT vs. SA, NCRT vs. SA and NCRT vs. NCT vs. NRT were conducted by RRs with 95% CIs of primary outcomes respectively. Significant heterogeneity was presented in disease recurrence (P = 0.003, I^2 = 72%; NCT vs. SA), radical resection (P < 0.01, I^2 = 87%) and disease recurrence (P = 0.04, I^2 = 50%) among studies involving NCRT vs. SA. When the meta-analysis was stratified by histological type, the heterogeneity across individual studies researching on disease recurrence between NCT and SA was eliminated. Nevertheless, no significant between-study heterogeneity was verified for other conditions.

Comparison of Primary Outcomes

Therapeutic effect of NCT vs. SA was compared based on six indexes from ten articles including 2331 cases (NCT/SA: 1168/1163, 15–17, 21, 23, 24, 27, 30, 32, 38]. Combined RR showed significant difference in five-year survival rate (RR = 1.45, 95% CI: 1.17–1.79, P < 0.01) between patients treated with NCT and SA, while no statistically difference was found in the other 5 outcome indicators. When the meta-analysis was stratified by histological type, disease recurrence of patients suffering from SCC and AC revealed significant difference between intervention with NCT and SA (RR = 1.22, 95% CI: 1.05–1.41, P = 0.01).

Therapeutic effect of NCRT and SA for EsC were contrasted by eight indexes from 14 studies including 2198 cases (NCRT/SA: 1093/1105) [18, 19, 21, 22, 25, 26, 28–31, 34–37]. The pooled results revealed significant differences in all of the eight indicators including R0 (RR = 1.15, 95% CI:

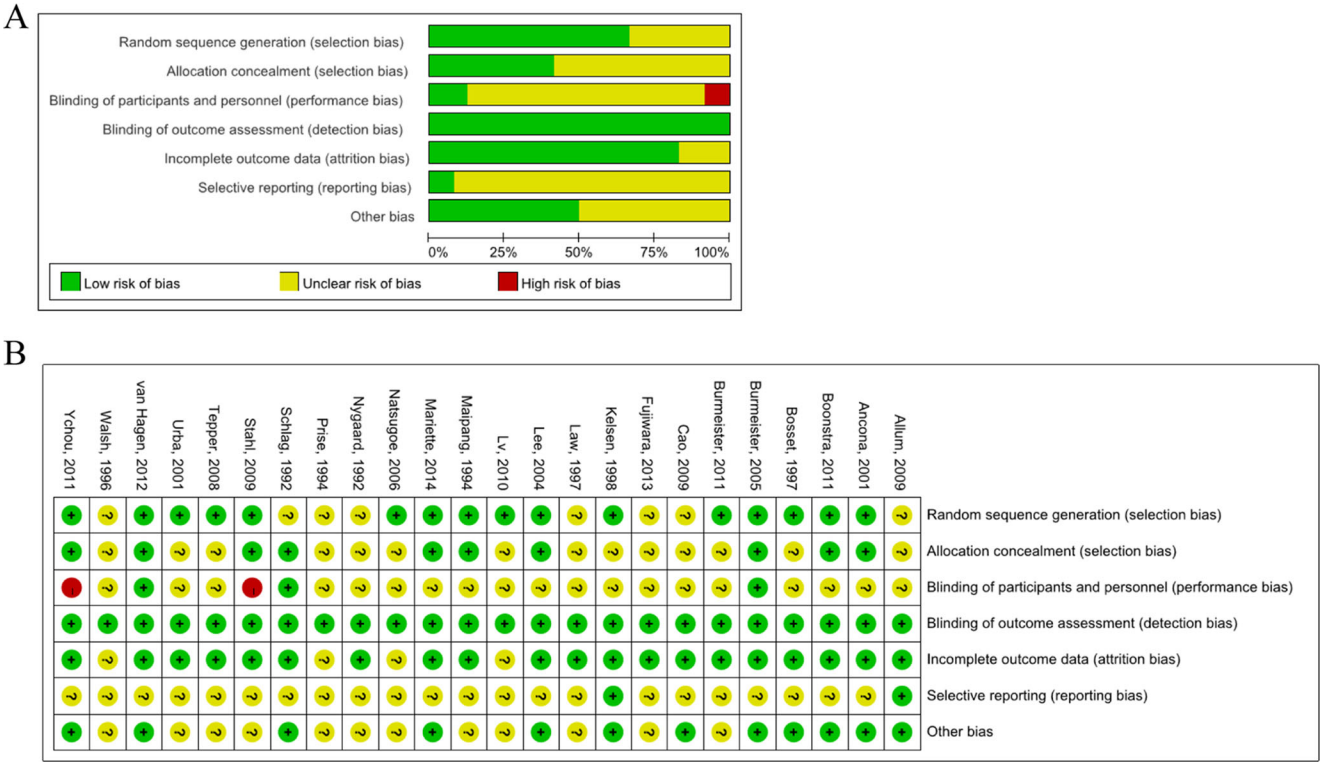

Fig. 1 Cochrane reviews for the eligible studies: **a** Risk of bias graph; **b** Risk of bias summary

1.02–1.30, $P = 0.02$), perioperative mortality (RR = 1.53, 95% CI: 1.04–2.25, $P = 0.03$), disease recurrence (RR = 0.73, 95% CI: 0.57–0.93, $P = 0.01$), DFS (HR = 0.63, 95% CI: 0.52–0.76, $P < 0.01$), OS (HR = 0.79, 95% CI: 0.68–0.92), $P < 0.01$), and one- (RR = 1.13, 95% CI: 1.03–1.23, $P < 0.01$), two- (RR = 1.30, 95% CI: 1.16–1.45, $P < 0.01$) and five-year survival rate (RR = 1.36, 95% CI: 1.15–1.61, $P < 0.01$).

Meanwhile, contrast of NCRT, NCT and NRT was performed by three-year survival rate and significant difference was identified between NCRT and NCT (RR = 1.35, 95% CI: 1.14–1.60, $P < 0.01$). There was no evidence of statistically difference between NCRT vs. NRT and NRT vs. NCT ($P > 0.05$).

Sensitivity Analysis and Publication Bias

Except for three-year survival rate of NRT vs. NCT, combined effects of all indexes showed no various differences between two models. The relatively symmetrical distribution of the funnel plot for NRCT vs. SA and NCT vs. SA reflected that there was no obvious publication bias among literatures.

Discussion

In our present study, totally 24 articles including 4718EsC patients and eight clinical outcomes were retrieved in this meta-analysis. Results demonstrated that patients statistically benefited from NCT in five-year survival rate when compared with SA. Significant differences were also verified in all of the eight analyzed indicators between NRCT and SA. Besides, three-year survival rates were statistically different in the NCRT group and NCT group.

In a previous meta-analysis, the meta-analysis of Gebski*et al.* [11] was renewed by Sjoquist*et al.* [12] via adding updated randomized trials, which provided strong evidence for a survival benefit of NCRT and NCT over surgery in patients with EsC, while a clear advantage of NCTR over NCT has not been established. Consistent with previously published meta-analysis, NRCT and NCT were found to be superior to SA in treating patients suffering from EsC according to our results. Previous researches draw this conclusion based on all-cause mortality and/or two-year absolute survival, while we enrolled six primary outcomes for consequences of NCT vs. SA, and two additional outcome indicators (DFS, OS) for NRCT vs. SA. Results reflected that EsC patients benefited from NCT with aspects of effective R0, improvement of five-year survival and reducing of SCC recurrence, while NRCT was superior to SA in all statistical indicators. In addition, pooled contrast of NCRT and NCT from four studies manifested significant difference in three-year survival rate, which is adverse with the peroration by Sjoquistet al. This disparity may be explained by the difference of enrolled monitoring indicators, studied population and/or eligible articles.

In our analysis, heterogeneity was discovered. When stratified by histological type, heterogeneity was eliminated in disease recurrence between NCT and SA, suggesting the possibility of histological type as one source of heterogeneity. On the other hand, patients in most of the eligible studies suffering from EsC clinically limited to stage one, two or three, while cases studied by Allum *et al.* were ranged through all stages. Moreover, chemotherapeutics used in these researched, such as fluorouracil, cisplatin, Cis-platinum, and 5-fluorouracil, were different from each other. Thus, both of different cancer stages of cases enrolled in different studies and difference in chemotherapeutics may contribute to the existence of heterogeneity.

The present meta-analysis has several limitations. Firstly, a relatively small number of studies were quantified in this meta-analysis, indicating that the results should be cautiously expounded. Secondly, results of our study might not reflect true therapeutic effect of NRT due to the deficiency of relevant researches. Thirdly, meta-analysis is a retrospective research tool which is subject to methodological deficiencies, such as poor representative of population and lack of appropriate control group.

Despite the above limitations, we concluded that NCRT and NCT provide an obvious benefit for EsC treatment over SA. Besides, NCRT possesses a clear advantage compared with NCT. However, rigorously designed studies including large number of studies and population are needed to confirm our results.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Pennathur A, Gibson MK, Jobe BA, Luketich JD (2013) Oesophageal carcinoma. Lancet 381:400–412
2. Vallbohmer D, Brabender J, Grimminger P, Schroder W, Holscher AH (2011) Predicting response to neoadjuvant therapy in esophageal cancer. Expert Rev Anticancer Ther 11:1449–1455
3. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ (2009) Cancer statistics, 2009. CA Cancer J Clin 59:225–249
4. Shahbaz Sarwar CM, Luketich JD, Landreneau RJ, Abbas G (2010) Esophageal cancer: an update. Int J Surg 8:417–422
5. Krasna MJ (2010) Multimodality therapy for esophageal cancer. Oncology (Williston Park) 24:1134–1138
6. D'journo XB, Thomas PA (2014) Current management of esophageal cancer. J Thorac Dis 6(Suppl 2):S253–S264
7. Baba Y, Watanabe M, Yoshida N, Baba H (2014) Neoadjuvant treatment for esophageal squamous cell carcinoma. World J Gastrointest Oncol 6:121–128

8. Shah RD, Cassano AD, Neifeld JP (2014) Neoadjuvant therapy for esophageal cancer. World J Gastrointest Oncol 6:403–406
9. Pandey D, Pandey R, Garg PK (2015) Neoadjuvant therapy and lymphadenectomy in esophageal cancer: both are essential to maximize survival benefit. Ann Surg. doi:10.1097/SLA.0000000000001160
10. Berry MF (2014) Esophageal cancer: staging system and guidelines for staging and treatment. J Thorac Dis 6(Suppl 3):S289–S297
11. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J (2007) Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol 8:226–234
12. Sjoquist KM, Burmeister BH, Smithers BM et al (2011) Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 12:681–692
13. Higgins JP, Green S (2008) Cochrane handbook for systematic reviews of interventions, vol 5. Wiley Online Library, Chichester
14. Higgins J, Green S (2011) Cochrane handbook for systematic reviews of interventions, vol 5.1.0. Wiley Online Library, Chichester
15. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE (2009) Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 27:5062–5067
16. Ancona E, Ruol A, Santi S et al (2001) Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma. Cancer 91:2165–2174
17. Boonstra JJ, Kok TC, Wijnhoven BP et al (2011) Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal squamous cell carcinoma: long-term results of a randomized controlled trial. BMC Cancer 11:181
18. Bosset J-F, Gignoux M, Triboulet J-P et al (1997) Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 337:161–167
19. Burmeister BH, Smithers BM, Gebski V et al (2005) Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 6:659–668
20. Burmeister BH, Thomas JM, Burmeister EA et al (2011) Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer 47:354–360
21. Cao XF, He XT, Ji L, Xiao J, Lv J (2009) Effects of neoadjuvant radiochemotherapy on pathological staging and prognosis for locally advanced esophageal squamous cell carcinoma. Dis Esophagus 22:477–481
22. Fujiwara Y, Yoshikawa R, Kamikonya N et al (2013) Neoadjuvant chemoradiotherapy followed by esophagectomy vs. surgery alone in the treatment of resectable esophageal squamous cell carcinoma. Mol Clin Oncol 1:773–779
23. Kelsen DP, Ginsberg R, Pajak TF et al (1998) Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 339:1979–1984
24. Law S, Fok M, Chow S, Chu K-M, Wong J (1997) Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. J Thorac Cardiovasc Surg 114:210–217
25. Lee J-L, Park S, Kim S-B et al (2004) A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma. Ann Oncol 15:947–954
26. Lv J, Cao X-F, Zhu B, Ji L, Tao L, Wang D-D (2010) Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma. World J Gastroenterol 16:1649
27. Maipang T, Vasinanukorn P, Petpichetchian C et al (1994) Induction chemotherapy in the treatment of patients with carcinoma of the esophagus. J Surg Oncol 56:191–197
28. Mariette C, Dahan L, Mornex F et al (2014) Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol 32:2416–2422
29. Natsugoe S, Okumura H, Matsumoto M et al (2006) Randomized controlled study on preoperative chemoradiotherapy followed by surgery versus surgery alone for esophageal squamous cell cancer in a single institution. Dis Esophagus 19:468–472
30. Nygaard K, Hagen S, Hansen HS et al (1992) 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 16:1104–1109
31. Prise EL, Etienne PL, Meunier B et al (1994) A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. Cancer 73: 1779–1784
32. Schlag PM (1992) Randomized trial of preoperative chemotherapy for squamous cell cancer of the esophagus. Arch Surg 127:1446–1450
33. Stahl M, Walz MK, Stuschke M et al (2009) Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 27:851–856
34. Tepper J, Krasna MJ, Niedzwiecki D et al (2008) Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 26:1086–1092
35. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M (2001) Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 19:305–313
36. Van Hagen P, Hulshof M, Van Lanschot J et al (2012) Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 366:2074–2084
37. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP (1996) A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 335:462–467
38. Ychou M, Boige V, Pignon J-P et al (2011) Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 29:1715–1721