



Addition of Induction or Consolidation Chemotherapy in Definitive Concurrent Chemoradiotherapy Versus Concurrent Chemoradiotherapy Alone for Patients With Unresectable Esophageal Cancer: A Systematic Review and Meta-Analysis

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Background: Concurrent chemoradiotherapy (CCRT) has become the standard of care in esophageal carcinoma patients who are not surgical candidates. The efficacy of induction chemotherapy (IC) or consolidation chemotherapy (CCT) for unresectable esophageal cancer (EC) treated with CCRT is unclear. We performed a systematic review and meta-analysis of published papers to evaluate the potential benefit of IC or CCT for patients with EC.

Methods: Eligible studies of IC followed by CCRT (IC-CCRT) vs. CCRT alone or CCRT followed by CCT (CCRT-CCT) vs. CCRT alone were retrieved through extensive searches of the PubMed, Science Direct, Embase, and Cochrane Library databases from the establishment of the database to July 31, 2021. Data such as 1-, 2-, 3-, and 5-year overall survival (OS), local recurrence rate (LRR), and distant metastasis rate (DMR) were collected for meta-analysis to evaluate the efficacy of IC/CCT.

Results: Four studies of IC-CCRT vs. CCRT including 836 EC patients and six studies of CCRT-CCT vs. CCRT including 1,339 patients with esophageal squamous cell carcinoma (ESCC) were finally identified in our analysis. Both IC-CCRT group [hazard ratio (HR) 0.446, 95% CI 0.286–0.693; $p < 0.001$] and CCRT-CCT group (HR 0.542, 95% CI 0.410–0.716; $p < 0.001$) exhibited statistically significant improvement in 1-year OS rate compared to that of CCRT, while the 2-year OS rate of IC-CCRT (HR 0.803, 95% CI 0.589–1.095; $p = 0.166$) or CCRT-CCT (HR 0.783, 95% CI 0.600–1.022; $p = 0.072$) was similar with that of CCRT. And the 3-year OS rate between IC-CCRT and CCRT was

similar (HR 1.065, 95% CI 0.789–1.439; $p = 0.680$). However, comparing with CCRT alone, the CCRT-CCT group had lower DMR [odds ratio (OR) 1.562, 95% CI 1.090–2.240; $p = 0.015$] and higher 3-year OS rate (HR 0.786, 95% CI 0.625–0.987; $p = 0.039$). Besides, no differences were observed between the CCRT-CCT and CCRT groups in 5-year OS rate (HR 0.923, 95% CI 0.706–1.205; $p = 0.555$) and LRR (OR 0.899, 95% CI 0.686–1.179; $p = 0.441$).

Conclusion: The study revealed the short-time survival benefit of additional IC or CCT compared to CCRT alone for patients with unresectable EC, and CCRT followed by CCT could significantly reduce the risk of distant metastases.

Keywords: concurrent chemoradiotherapy, induction chemotherapy, consolidation chemotherapy, meta-analysis, esophageal cancer

INTRODUCTION

Radiotherapy plays an important role in the comprehensive treatment of esophageal carcinoma. The RTOG 85-01 trial has demonstrated that concurrent chemoradiotherapy (CCRT) is superior to radiation alone, with a favorable long-term survival for nonoperative esophageal cancer (EC) patients (1). Although CCRT is the standard treatment for patients with locally advanced disease who are not surgical candidates or refuse surgery, the local recurrence rate (LRR) of CCRT remains up to 40%–60%, and the 5-year survival rate is extremely low once recurrence occurs (2, 3). Therefore, several intensified treatment modalities have been attempted to improve treatment outcomes, such as the addition of induction chemotherapy (IC) or consolidation chemotherapy (CCT).

Theoretically, the additional IC followed by CCRT (IC-CCRT) has potential benefit on response rate, early eradication of micrometastases, increased tumor radiosensitivity, and even prolonged overall survival (OS) because of tumor shrinkage (4). Byfield et al. (5) conducted the first clinical trial of IC followed by radiotherapy alone for EC patients in the 1980s, which achieved inspiring results. In contrast, Chen et al. (6) concluded that the additional IC failed to prolong OS, locoregional failure-free survival, or distant failure-free survival compared with CCRT alone.

CCT is defined as prolonged chemotherapy duration by administration of additional drugs at the end of a defined number of initial chemotherapy cycles after achieving a maximum tumor response in an individual patient. The rationale for CCT is based on a hypothesis stating that the early use of non-cross-resistant agents might increase the probability of killing more cancer cells (7). To date, several studies have been conducted to explore the efficacy of CCT for non-small-cell lung cancer patients, which all demonstrated that these management strategies were ineffective (8–10). Actually, patients received CCT following CCRT in RTOG 85-01 trials (1); the reason why RTOG

investigators added CCT to CRT had not been clarified. Up to now, the reports on CCRT followed by CCT (CCRT-CCT) were rare for EC patients, and the results were conflicting.

Due to a few publications, inconsistent conclusions, and lack of prospective randomized controlled studies, the value of the addition of IC or CCT for EC patients remains controversial. Thus, our study aimed to evaluate the outcomes of IC-CCRT or CCRT-CCT vs. CCRT alone in unresectable EC by means of a systematic review and meta-analysis, which could further provide better clinical guidance for the treatment of EC.

METHODS

Search Strategy

The PubMed, Science Direct, Embase, and Cochrane Library databases were searched from their inception to July 31, 2021. Search keywords included “esophageal or oesophageal” and “carcinoma or cancer or neoplasm” and “induction chemotherapy or neoadjuvant chemotherapy” and “consolidation or adjuvant chemoradiotherapy” and “concurrent or definitive chemoradiotherapy.” Additional papers were retrieved through hand-searching. The search was limited to human subjects and English-language published articles.

Inclusion Criteria and Exclusion Criteria

The inclusion criteria included the following: (1) studies that involved patients who had unresectable EC; (2) studies comparing the effects of IC-CCRT or CCRT-CCT vs. CCRT alone; (3) the hazard ratio (HR), odds ratio (OR), and 95% confidence intervals (CIs) in these studies were reported or could be calculated; (4) randomized controlled trials (RCTs) and cohort studies.

The exclusion criteria included the following: (1) studies that did not include survival data as endpoints; (2) studies whose patients underwent sequential treatments, neoadjuvant or adjuvant CRT combined with surgery, palliative CRT or radiotherapy alone; (3) studies only published as a letter or conference paper; (4) repeated reports on survival data of the same population; (5) studies that involved specific elderly population.

Abbreviations: CCRT, concurrent chemoradiotherapy; EC, esophageal cancer; ESCC, esophageal squamous cell cancer; EAC, esophageal adenocarcinoma; IC, induction chemotherapy; CCT, consolidation chemotherapy; OS, overall survival; LRR, local recurrence rate; DMR, distant metastasis rate.

Quality Evaluation

Case-control study evaluation guidelines were applied in order to evaluate the quality of each manuscript for the following criteria: 1) whether gender, age, and tumor location were clearly stated; 2) whether the comparability of the two groups was analyzed; 3) whether the statistical method was appropriate; 4) whether the test was designed as a prospective randomized control study; 5) whether biases were discussed in the study. A score was assigned for each of the five items, with a total score of ≥ 3 indicative of reliable quality. Two researchers independently reviewed the literature according to the unified quality standard, with results cross-checked. If there were some different opinions, a third researcher would be invited to solve the disagreement. The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11).

Outcome Measures

The outcome measures of this study were 1-, 2-, 3-, and 5-year OS rate, LRR, and distant metastasis rate (DMR) to examine the efficiency of various management strategies.

Statistical Analysis

Data were analyzed using Stata version 12.0. HR, OR, and 95% CI were used to measure the effect. Heterogeneity was assessed using the Q test. Statistical significance was set at $p < 0.05$. If there was a significant heterogeneity ($p \leq 0.05$), the random-effects model was adopted; otherwise, a fixed-effects model was used ($p > 0.05$). The combined effect size was tested by the z test. Funnel plots were created to evaluate the risk of publication bias.

RESULTS

Literature Search and Study Selection

After excluding 2,340 articles from a total of 2,350 citations, finally, 10 articles were subjected to our meta-analysis. A detailed study flow diagram is shown in **Figure 1**. Among the 10 articles, there were four studies including three retrospective studies and one prospective study that compared IC-CCRT with CCRT and six other retrospective studies that compared CCRT-CCT with CCRT (6, 12–20) (**Tables 1, 2**). The number of patients within these four studies on IC-CCRT vs. CCRT was 836, including 486 esophageal squamous cell carcinoma (ESCC) patients and 350 esophageal adenocarcinoma (EAC) patients. A total of 1,339 patients were included in the six other studies on CCRT-CCT vs. CCRT whose pathological types were all ESCC.

Outcome Data

Induction Chemotherapy Followed by Concurrent Chemoradiotherapy vs. Concurrent Chemoradiotherapy

Data regarding 1-year and 2-year OS rate were available in the three studies with 726 patients (6, 12, 13). The 1-year OS rate was significantly higher in patients who were treated with IC-CCRT (HR 0.445, 95% CI 0.286–0.693; $p < 0.001$; **Figure 2**). In addition,

three studies analyzed 3-year OS rate of the two groups (12–14). There was no significant difference in 2-year OS rate (HR 0.803, 95% CI 0.589–1.095; $p = 0.166$; **Figure 2**) and 3-year OS rate (HR 1.065, 95% CI 0.789–1.439; $p = 0.680$; **Figure 2**) between the two groups.

Concurrent Chemoradiotherapy Followed by Consolidation Chemotherapy vs. Concurrent Chemoradiotherapy

The six studies with 1,339 patients all reported 1- and 3-year OS rates of the CCRT-CCT group and CCRT group (15–20). Four articles reported 2-year OS rate of the two groups (15–17, 19). Four studies (16–18, 20) analyzed 5-year OS rate, and three studies (15–17) analyzed LRR and DMR of the two groups.

CCRT-CCT group had a significant advantage over the CCRT group in 1-year OS rate (HR 0.542, 95% CI 0.410–0.716; $p < 0.001$; **Figure 3**) and 3-year OS rate (HR 0.786, 95% CI 0.625–0.987; $p = 0.039$; **Figure 3**). The CCRT-CCT group had lower DMR (OR 1.562, 95% CI 1.090–2.240; $p = 0.015$; **Figure 4**). However, no differences were seen between the two groups in 2-year OS rate (HR 0.783, 95% CI 0.600–1.022; $p = 0.072$; **Figure 3**), 5-year OS rate (HR 0.923, 95% CI 0.706–1.205; $p = 0.555$; **Figure 3**), and LRR (OR 0.899, 95% CI 0.686–1.179; $p = 0.441$; **Figure 4**).

Sensitivity Analysis

Sensitivity analysis showed that the new combined HR/OR was similar with the original HR/OR (**Tables 3, 4**).

Publication Bias Analysis

Funnel plot was used to evaluate the publication bias. Egger's regression test was conducted to analyze the symmetry of the funnel plot. None of the articles demonstrated publication bias ($p > 0.05$) (**Figures 5, 6** and **Tables 5, 6**).

DISCUSSION

Our meta-analysis evaluated the value of additional IC or CCT in unresectable EC undergoing CCRT. The results showed that the additional IC or CCT may be an important factor affecting short-term survival but not long-term survival. To the best of our knowledge, this is the first meta-analysis to discuss the efficacy of IC in patients with unresectable EC treated with CCRT.

In theory, the addition of IC before CCRT has the potential advantage to degrade the stage and reduce the size of tumor. Chemotherapy response before radiotherapy is associated with reduced lung and heart irradiation and increased tolerance of the patients. Lu et al. (21) reported that additional IC for EC patients treated with neoadjuvant CCRT followed by esophagectomy was associated with a higher pathological complete response (pCR) rate (45.3% vs. 33.5%, $p = 0.005$) and better 5-year OS rate (90.5% vs. 48.1%, $p = 0.015$) compared to CCRT alone. Recently a multicenter randomized phase II trial showed that adding IC prior to trimodality therapy did not improve pCR but was associated with longer median OS (22). In our study, the IC-CCRT group had a higher 1-year OS rate

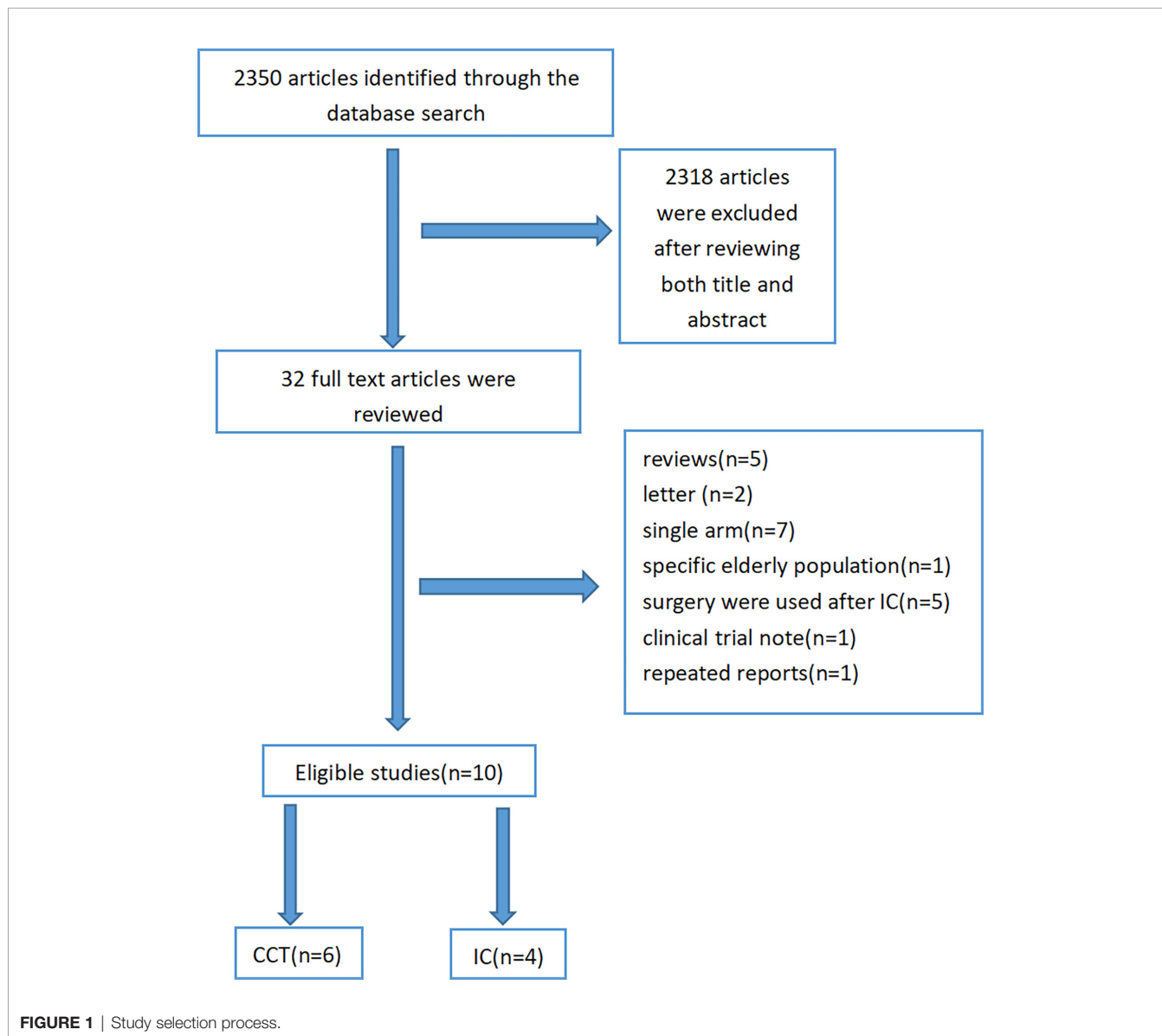


FIGURE 1 | Study selection process.

TABLE 1 | Basic characteristics of the included studies (IC-CCRT vs. CCRT alone group).

| Author | Year | Stage | ESCC /EAC | IC-CCRT/ CCRT alone | Radiation dose (Gy) | Current chemotherapy regimen | Induction chemotherapy | The cycles of IC | Quality evaluation |
|-----------------|------|---------|-----------|---------------------|---------------------|------------------------------|------------------------|------------------|--------------------|
| Chen et al. (6) | 2017 | II-IV | 60/0 | 41/19 | 50.4-66 | PF/TP/P/C/F | PF/TP/C | 1-3 | 4 |
| Luo et al. (12) | 2017 | III-IV | 170/0 | 85/85 | 60 (50-70) | DP | DP | 2 | 4 |
| Xi et al. (13) | 2017 | IB-III | 146/350 | 162/334 | 50.4 (41.4-66) | PTF/PF/TP/TF | PTF/PF/TP/TF | 2-4 | 4 |
| Liu et al. (14) | 2021 | IIA-IVA | 110/0 | 55/55 | 60 | DP | DP | 2 | 5 |

ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; DP, docetaxel plus cisplatin; TF, platinum plus taxane; PF, platinum plus fluorouracil; C, capecitabine; PTF, fluoropyrimidine, platinum plus taxane; PF, platinum plus fluoropyrimidine; TP, platinum plus taxane; TF, fluoropyrimidine plus taxane; IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy.

TABLE 2 | Basic characteristics of the included studies (CCRT-CCT vs. CCRT alone group).

| Author | Year | Stage | ESCC/ EAC | CCRT-CCT/CCRT alone | Radiation dose (Gy) | Current chemotherapy regimen | CCT regimen | The cycles of CCT | Quality evaluation |
|-------------------|------|--------|--------------|------------------------|------------------------|---------------------------------|----------------|----------------------|-----------------------|
| Wu et al. (15) | 2017 | I-III | 209/0 | 67/142 | ≥50.4 | PF | PF/ND/DP | 2 | 4 |
| Chen et al. (16) | 2018 | II-III | 524/0 | 262/262 | 50.4-66 | PF | PF | 2 | 4 |
| Chen et al. (17) | 2018 | II-IVB | 187/0 | 89/98 | 50-66 | PF/TP | PF/TP | 2 (1-4) | 4 |
| Chen et al. (18) | 2018 | I-IV | 124/0 | 65/59 | 50-74 | PF/PP | PF/P | 2-4 | 4 |
| Koh et al. (19) | 2020 | I-III | 73/0 | 56/17 | 50-70 | PF/P/F | PF/P/F | - | 4 |
| Zhang et al. (20) | 2020 | I-III | 222/0 | 113/109 | 50.4-66 | LFP/PF/TP | LFP/PF/TP | 1-4 | 4 |

ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; P, cisplatin; F, fluorouracil; PF, cisplatin plus fluorouracil; DP, docetaxel plus cisplatin; ND, nedaplatin plus cisplatin; PP, paclitaxel plus cisplatin; LFP, cisplatin plus 5-fluorouracil plus calcium folinate; TP, cisplatin plus paclitaxel; m, months; CCT, consolidation chemotherapy; CCRT, concurrent chemoradiotherapy.

over that of the CCRT group (HR 0.445, 95% CI 0.286-0.693; $p < 0.001$), but 2- and 3-year OS rate between the two groups was similar. Several possible reasons may explain this result. Firstly, our study focused on nonoperative EC patients; the treatment modality might influence the prognosis. Secondly, the additional IC might facilitate the elimination of occult micrometastasis for the patients with well response to chemoradiotherapy, whereas it might not carry out a

positive impact for poorly responding patients and seemed to have limited benefits in long-term survival. In the study by Luo et al. (12), the IC responders (51%) achieved significantly more favorable OS compared with the IC nonresponder group and the CCRT alone group ($p = 0.002$), and there was no significant difference in terms of OS between the IC-CCRT and CCRT groups. Liu et al. (14) also observed that patients who responded to IC had improved survival in

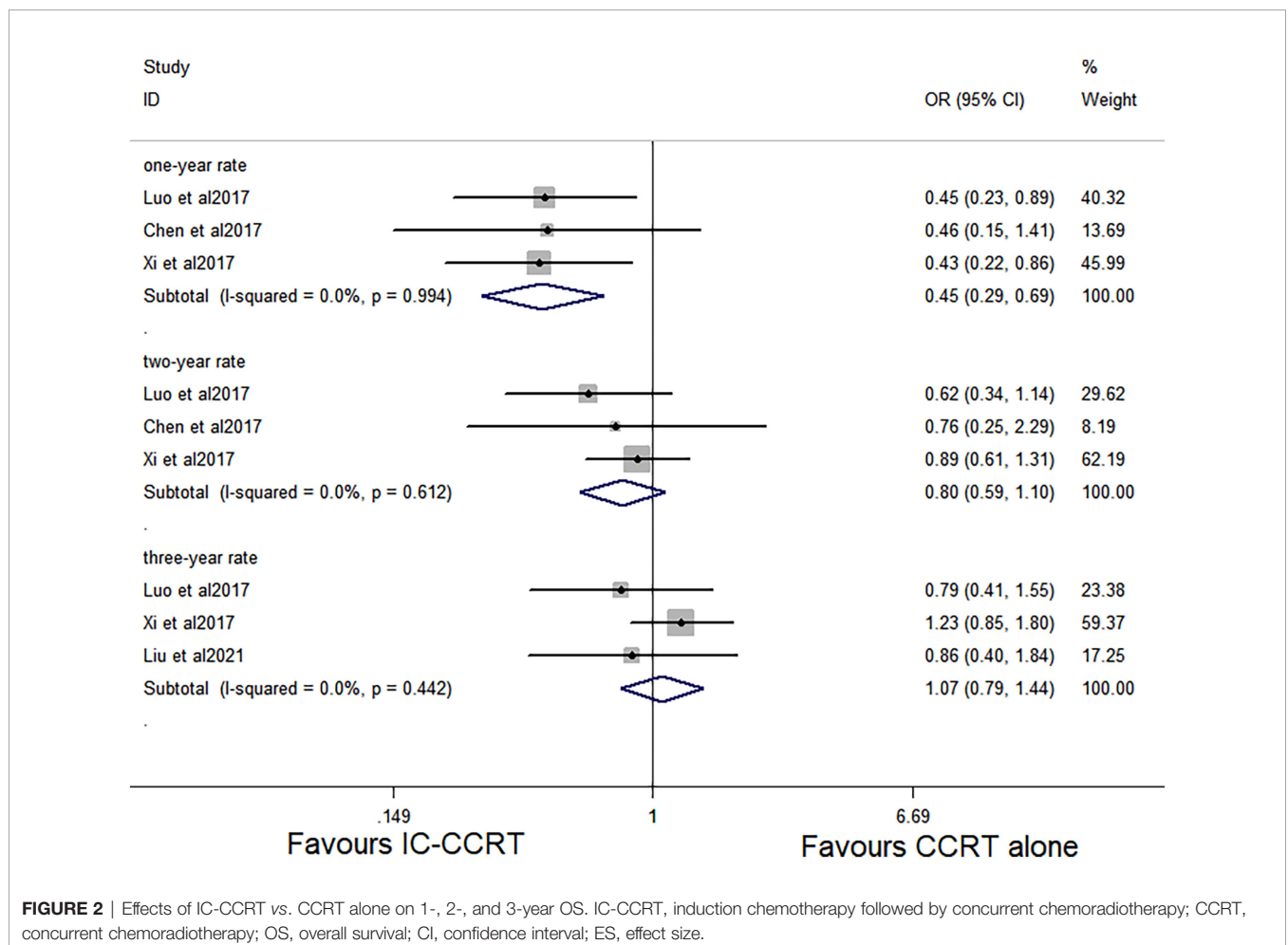


FIGURE 2 | Effects of IC-CCRT vs. CCRT alone on 1-, 2-, and 3-year OS. IC-CCRT, induction chemotherapy followed by concurrent chemoradiotherapy; CCRT, concurrent chemoradiotherapy; OS, overall survival; CI, confidence interval; ES, effect size.

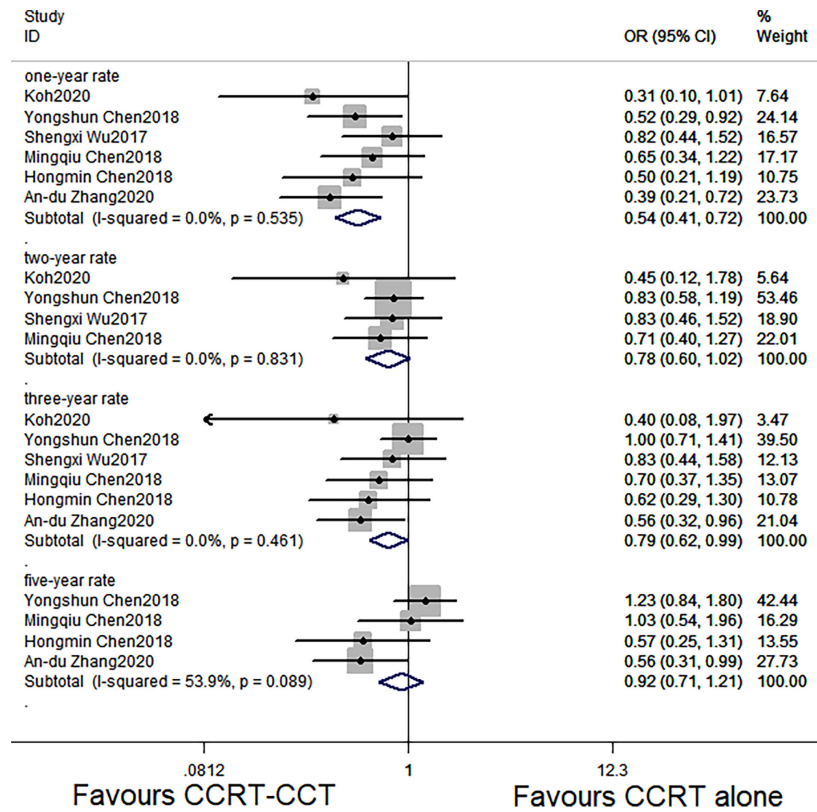


FIGURE 3 | Effects of CCRT-CCT vs. CCRT alone on 1-, 2-, 3-, and 5-year OS. CCRT-CCT, concurrent chemoradiotherapy followed by consolidation chemotherapy; CCRT, concurrent chemoradiotherapy; OS, overall survival; CI, confidence interval; ES, effect size.

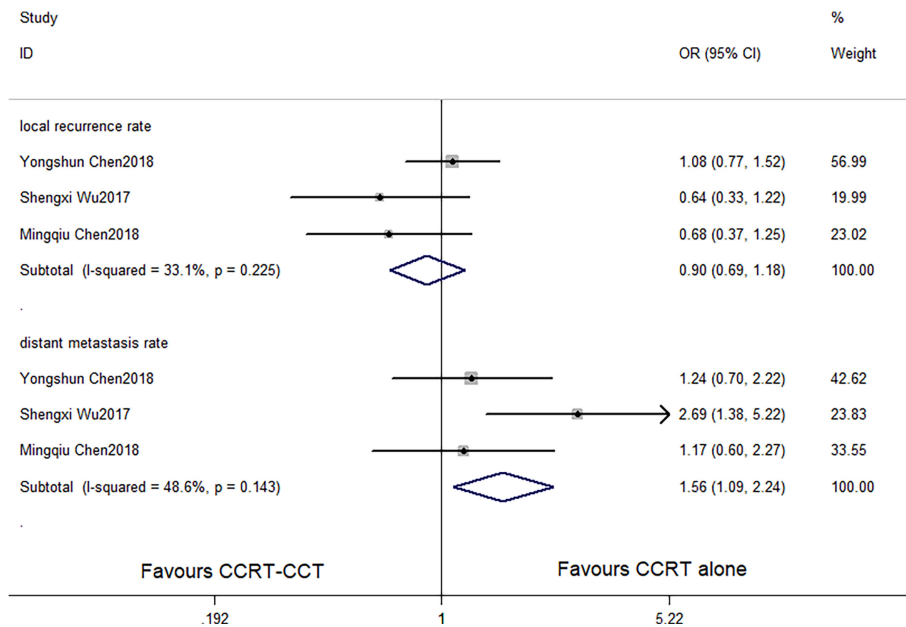


FIGURE 4 | Effects of CCRT-CCT vs. CCRT alone on local recurrence rate and distant metastasis rate. CCRT-CCT, concurrent chemoradiotherapy followed by consolidation chemotherapy; CCRT, concurrent chemoradiotherapy; CI, confidence interval; OR, odds ratio.

TABLE 3 | Sensitivity analysis for 1-, 2-, and 3-year OS rate (IC-CCRT vs. CCRT group).

| Items | Study omitted | Estimate | 95% CI | |
|--------------------|-----------------|----------|--------|-------|
| One-year OS rate | Chen et al. (6) | 0.525 | 0.357 | 0.774 |
| | Luo et al. (12) | 0.513 | 0.318 | 0.830 |
| | Xi et al. (13) | 0.587 | 0.397 | 0.869 |
| | Combined | 0.540 | 0.384 | 0.760 |
| Two-year OS rate | Chen et al. (6) | 0.886 | 0.737 | 1.064 |
| | Luo et al. (12) | 0.929 | 0.754 | 1.143 |
| | Xi et al. (13) | 0.811 | 0.625 | 1.053 |
| | Combined | 0.886 | 0.745 | 1.052 |
| Three-year OS rate | Luo et al. (12) | 1.067 | 0.914 | 1.245 |
| | Xi et al. (13) | 0.938 | 0.797 | 1.104 |
| | Liu et al. (14) | 1.043 | 0.913 | 1.192 |
| | Combined | 1.026 | 0.908 | 1.160 |

IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; OS, overall survival.

TABLE 4 | Sensitivity analysis for 1-, 2-, 3-, and 5-year OS rate, LRR, and DMR (CCRT vs. CCRT-CCT group).

| Items | Study omitted | Estimate | 95% CI | |
|--------------------|-------------------|----------|--------|-------|
| One-year OS rate | Wu et al. (15) | 0.588 | 0.467 | 0.741 |
| | Chen et al. (16) | 0.667 | 0.538 | 0.826 |
| | Chen et al. (17) | 0.625 | 0.501 | 0.780 |
| | Chen et al. (18) | 0.651 | 0.528 | 0.802 |
| | Koh et al. (19) | 0.649 | 0.522 | 0.805 |
| | Zhang et al. (20) | 0.687 | 0.551 | 0.857 |
| | Combined | 0.644 | 0.528 | 0.786 |
| Two-year OS rate | Wu et al. (15) | 0.872 | 0.745 | 1.020 |
| | Chen et al. (16) | 0.888 | 0.765 | 1.030 |
| | Chen et al. (17) | 0.896 | 0.770 | 1.042 |
| | Koh et al. (19) | 0.894 | 0.777 | 1.028 |
| | Combined | 0.888 | 0.779 | 1.011 |
| Three-year OS rate | Wu et al. (15) | 0.907 | 0.825 | 0.998 |
| | Chen et al. (16) | 0.873 | 0.793 | 0.961 |
| | Chen et al. (17) | 0.915 | 0.831 | 1.007 |
| | Chen et al. (18) | 0.923 | 0.843 | 1.009 |
| | Koh et al. (19) | 0.918 | 0.840 | 1.003 |
| | Zhang et al. (20) | 0.941 | 0.858 | 1.032 |
| | Combined | 0.914 | 0.840 | 0.995 |
| Five-year OS rate | Chen et al. (16) | 0.902 | 0.810 | 1.004 |
| | Chen et al. (17) | 0.971 | 0.893 | 1.056 |
| | Chen et al. (18) | 0.994 | 0.912 | 1.078 |
| | Zhang et al. (20) | 1.017 | 0.935 | 1.106 |
| | Combined | 0.977 | 0.906 | 1.054 |
| LRR | Wu et al. (15) | 0.965 | 0.717 | 1.299 |
| | Chen et al. (16) | 0.660 | 0.424 | 1.028 |
| | Chen et al. (17) | 0.965 | 0.712 | 1.306 |
| | Combined | 0.899 | 0.686 | 1.179 |
| DMR | Wu et al. (15) | 1.211 | 0.782 | 1.874 |
| | Chen et al. (16) | 1.799 | 1.134 | 2.855 |
| | Chen et al. (17) | 1.761 | 1.145 | 2.709 |
| | Combined | 1.562 | 1.090 | 2.240 |

CCT, consolidation chemotherapy; CCRT, concurrent chemoradiotherapy; DMR, distant metastasis rate; LRR, local recurrence rate; OS, overall survival.

the *post-hoc* analysis. Thirdly, histological types and tumor biological characteristics between ESCC and EAC are heterogeneous. Xi et al. (13) accounted for 41.9% of the total number of patients in the meta-analysis, and its negative results might impact the final analysis outcomes. However, in the sensitivity analysis after deleting this article by Xi et al. (13), the new results were consistent with the original results. How to predict the sensitivity to chemotherapy might be the decisive factor. Greally et al. (23) evaluated the predictive value

of PET following IC in ESCC patients and assessed the impact of changing chemotherapy during radiation in PET nonresponders. They found that PET after IC highly predicts outcomes in ESCC patients who receive chemoradiation. Early predictions of the efficacy of induction therapy are imminent and needed to further clinical research.

In this meta-analysis, the patients included in the studies of CCRT-CCT vs. CCRT were all with ESCC. It was noteworthy

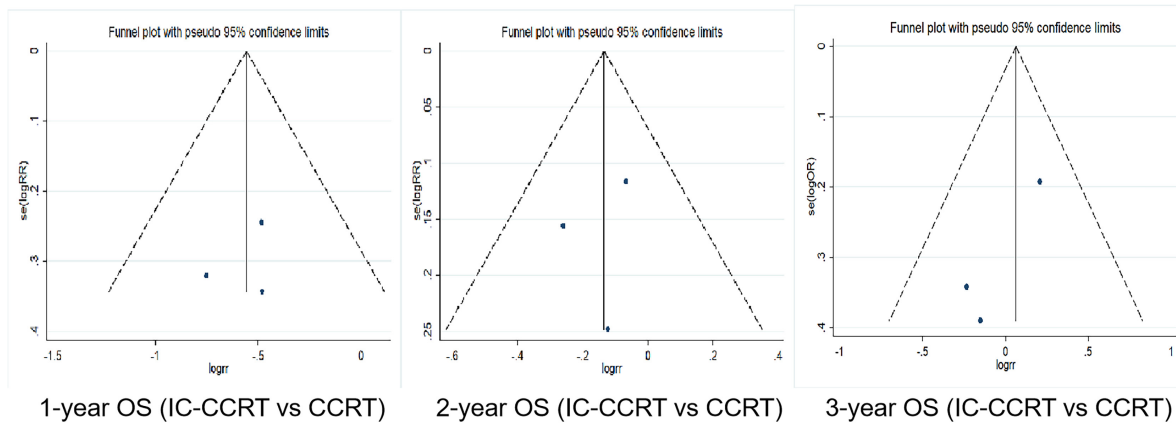


FIGURE 5 | Funnel plots for 1-, 2-, and 3-year OS rate between IC-CCRT group and CCRT alone group. OS, overall survival; IC-CCRT, induction chemotherapy followed by concurrent chemoradiotherapy; CCRT, concurrent chemoradiotherapy; CCRT, concurrent chemoradiotherapy.

that there were fewer patients developing distant metastases in the CCRT-CCT group than in the CCRT group [15 of 67 (22.4%) vs. 62 of 142 (43.7%), $p = 0.003$] in the study of Wu et al. (15), and the CCRT-CCT group had remarkably prolonged median OS of 26.4 months ($p = 0.04$), while the DMR and OS showed no differences in two other studies. In order to identify patients who may benefit from CCT, Chen et al. (17) conducted further analysis based on various prognostic factors, including clinical N-stage (N0, N1, and N2), clinical M-stage (M0 and M1), and so on, and no significant survival differences between CCRT-CCT and CCRT were observed in any subgroup. In our meta-analysis, the addition of CCT reduced the DMR ($p = 0.015$) and can improve 1- and 3-year OS rate. Koh et al. (19) validated the positive effect of intensified treatment on survival in ESCC patients with definitive CCRT by modern radiotherapy techniques, and 45.2% patients received radiotherapy with biologically effective dose (BED) ≥ 70 Gy. As the radiation doses in the involved studies were not uniform, whether the additional CCT is the main factor affecting prognosis needs to be further explored. Also, whether patients who responded poorly to CCRT could gain a survival benefit from CCT needs to be studied further. Kim et al. (24) divided patients who received CCT after CCRT into “good risk” and “poor risk” groups based on smoking >20 pack-years, dysphagia scores >2 , and so on. In the “good risk” group, patients with following CCT showed better OS than those without (30.4 vs. 12.0 m, $p = 0.002$), whereas patients failed to obtain benefits from CCT in the “poor risk group” (14.0 vs. 12.0 m, $p = 0.828$). In view of the 1- and 3-year OS survival improved by CCT, but not 2- and 5-year OS rate of our conclusion, the results were not robust enough and the value of CCT is still worthy of further exploration.

The emergence of immunotherapy has changed the traditional treatment modalities of advanced cancers including EC. A multicenter, phase II, proof-of-concept study is ongoing to assess the efficacy and safety of atezolizumab in locally advanced ESCC patients who previously were treated with CCRT (25). The

KEYNOTE-975 study (under recruitment) is a phase III randomized trial evaluating the efficacy of pembrolizumab in combination with definitive CCRT with fluorouracil and oxaliplatin or cisplatin in patients with locally advanced ESCC, EAC, and Siewert I adenocarcinoma of the gastroesophageal junction. Another ongoing phase III trial, BGB-A317-311, aims to assess the efficacy of tislelizumab vs. placebo in combination with CCRT and cisplatin and paclitaxel in localized ESCC. Relevant ongoing trials combining immunotherapy with CCRT in non-metastatic EC are represented in **Table 7**. These investigations provide new leads for the optimal treatment pattern for EC patients.

Our meta-analysis had some limitations. Firstly, as these studies were searched among published articles written in English, and statistical analysis was limited to the published data, language bias may exist. Secondly, nine of 10 included studies were retrospective studies, with the one prospective randomized study only including 110 cases. It was a pity that no randomized trial and prospective study with large cases has been published yet. Thirdly, we failed to perform subgroup analyses based on tumor stage, chemotherapy regimens, and radiation doses. As is well known, clinical stage is an independent prognostic factor. In our meta-analysis, approximately 10%–16% of the EC patients with stage I and stage IV were involved; although this factor of staging seems to be controlled and well balanced between the two groups in the original studies, this confounding factor still remains to be controlled in future studies. By far, there is still no consensus reached whether chemotherapy regimens influenced survival for EC patients with definitive concurrent chemoradiotherapy (dCRT) or not (26, 27); nevertheless, chemotherapy regimen and cycles of IC, CCT, and CCRT were inconsistent in our meta-analysis, which might have some potential impact on the result. Besides, we conducted sensitivity analysis in order to explore heterogeneity of dose delivery; after deleting each article in turn and reanalyzing the remaining research, the new results were

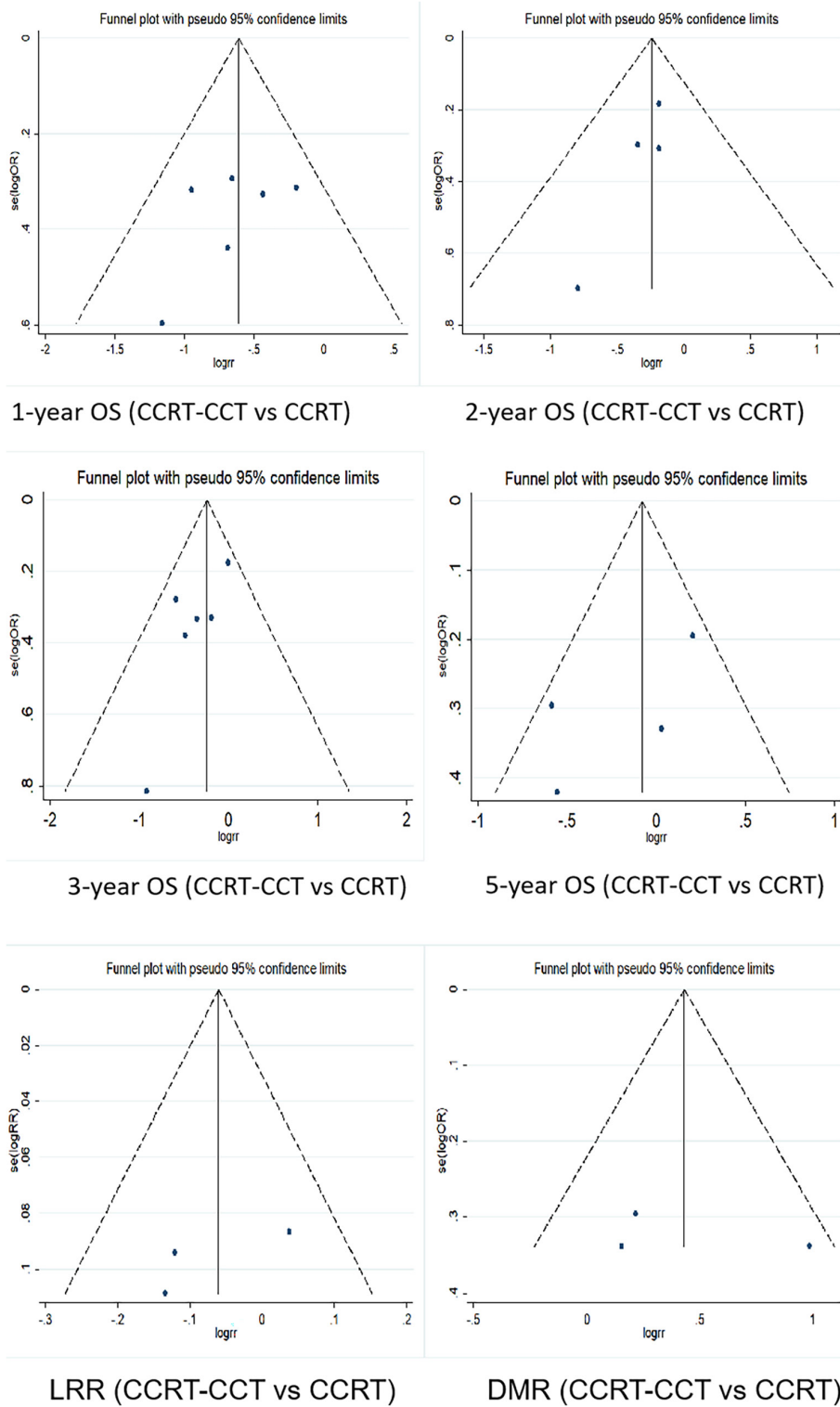


FIGURE 6 | Funnel plots for 1-, 2-, 3-, and 5-year OS rate, LRR, and DMR between CCRT-CCT group and CCRT alone group. OS, overall survival; LRR, local recurrence rate; DMR, distant metastasis rate; CCRT-CCT, concurrent chemoradiotherapy followed by consolidation chemotherapy; CCRT, concurrent chemoradiotherapy.

TABLE 5 | Publication bias results of selected articles (IC-CCRT vs. CCRT group).

| Items | t | 95% CI | p |
|--------------------|-------|---------|--------|
| One-year OS rate | -0.47 | -32.863 | 30.511 |
| Two-year OS rate | -0.40 | -24.901 | 23.382 |
| Three-year OS rate | -3.29 | -11.006 | 6.476 |

IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; OS, overall survival.

TABLE 6 | Publication bias results of selected articles (CCRT-CCT vs. CCRT group).

| Items | t | 95% CI | p |
|-------------------------|-------|----------|---------|
| One-year OS rate | -1.00 | -6.527 | 3.070 |
| Two-year OS rate | -2.66 | -2.785 | 0.657 |
| Three-year OS rate | -2.36 | -3.792 | 0.304 |
| Five-year OS rate | -1.56 | -12.670 | 5.927 |
| Local recurrence rate | -1.42 | -74.957 | 59.923 |
| Distant metastasis rate | 0.53 | -190.069 | 206.648 |

CCT, consolidation chemotherapy; CCRT, concurrent chemoradiotherapy; OS, overall survival.

TABLE 7 | Selected ongoing RCTs evaluating immunotherapy combined with CCRT and consolidation immunotherapy.

| NCT number | Country | Phase | Histology | Start date | Estimated completion date | Study treatment | Estimated enrollment |
|-------------|---------|-------|--------------|------------|---------------------------|---|----------------------|
| NCT04426955 | China | III | ESCC | 2020 | 2022 | CCRT ± concurrent and sequential SHR-1210 | 390 |
| NCT03957590 | China | III | ESCC | 2019 | 2023 | CCRT ± concurrent and sequential tislelizumab | 316 |
| NCT04210115 | Global | III | ESCC, EAC | 2020 | 2026 | CCRT ± concurrent and sequential pembrolizumab | 600 |
| NCT04550260 | US | III | ESCC | 2020 | 2025 | CCRT ± concurrent and sequential durvalumab | 600 |

CCRT, concurrent chemoradiotherapy; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; RCT, randomized controlled trial.

consistent with the original results. In addition, the recently published randomized studies (28, 29) showed that no differences in OS were observed between 50 and 60 Gy.

In conclusion, the study revealed that additional IC or CCT with CCRT could prolong short-term survival in unresectable EC patients. Besides, the addition of CCT could significantly reduce the risk of distant metastases. As all patients were diagnosed with ESCC in the CCT-relevant studies, whether the conclusion of CCT was also applicable to patients with EAC requires further verification.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

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AUTHOR CONTRIBUTIONS

All authors read and approved the final manuscript prior to submission. JuW and QP conceived and designed the study. SW and JiW contributed to data collection. JiW, SW, and LX performed the study and analyzed the data. JiW and LX wrote the paper. JuW and QP supervised the entire study and reviewed the final paper. All authors contributed to the article and approved the submitted version.

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