Efficacy and safety of chemoradiation therapy compared with chemotherapy for esophageal carcinoma
An updated meta-analysis of randomized controlled trials

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Abstract
Background: The role of the chemoradiation therapy (CRT) and chemotherapy (CT) in the treatment of esophageal carcinoma (EC) remains controversial. Therefore, we conducted this meta-analysis to compare the efficacy and safety of CRT with CT in the treatment of EC patients.

Methods: PubMed, Embase, Web of Science, and The Cochrane library were systematically reviewed for randomized controlled trials (RCTs) that compared CRT with CT. Outcomes included overall survival (OS), progression-free survival (PFS), pathological complete response (pCR), R0 resection, recurrence rate, mortality rate, and adverse events. Pooled estimates were expressed with hazard ratio (HR) with 95% confidence intervals (95% CIs) and risk ratio (RR) with 95% CIs.

Results: Eight RCTs involving 1274 patients were included in this meta-analysis. Compared with CT, CRT was not associated with significantly improved OS (HR = 0.91, 95% CI: 0.82, 1.01; P = 0.072) and PFS (RR = 3.62, 95% CI: 1.10, 11.95; P = 0.035). The pCR rate and R0 resection rate were significantly higher in the CRT group than that in the CT group (RR = 3.62, 95% CI: 1.10, 11.95, P = 0.035; RR = 1.18, 95% CI: 1.09, 1.27, P < 0.001; respectively). EC patients who received CRT had a higher mortality rate (RR = 2.50, 95% CI: 1.14, 5.48; P = 0.022) than those treated with CT, and the incidence of grade 3 or 4 adverse events was similar between the 2 groups (RR = 0.91, 95% CI: 0.62, 1.32; P = 0.612).

Conclusion: On the basis of the current evidence, our results suggested that CRT seemed to have benefit in the radical resection, but no effect in the survival benefits. Further large-scale, well-conducted RCTs are needed to verify our findings.

Abbreviations: AC = adenocarcinoma, ASC = adenosquamous carcinoma, CRT = chemoradiation therapy, CT = chemotherapy, EC = esophageal carcinoma, nCRT = neoadjuvant CRT, nCT = neoadjuvant CT, OS = overall survival, pCR = pathological complete response, PFS = progression free survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis, RCT = randomized controlled trial, RR = risk ratio, SCC = squamous cell carcinoma.

Keywords: chemoradiation therapy, chemotherapy, esophageal carcinoma, meta-analysis

1. Introduction

Esophageal carcinoma (EC) is one of the most malignant tumors with high mortality rate in the world, with >450,000 new cases diagnosed each year.[1] Although surgery is the primary modality that can cure patients, the majority of patients present with recurrences leading to death within 2 years after resection.[2] This is particularly true for high-risk patients with locally advanced tumor stage, wherein complete resection is impossible in a relevant number of patients and lymph node metastases were observed in almost all the patients.[2–4]

Recently, chemotherapy (CT) and chemoradiation therapy (CRT) have been used as neoadjuvant therapies before or after the esophageal resection to improve the long-term survival outcomes of patients with EC. Compared with surgery, preoperative CT demonstrated superior effects in esophageal cancer.[5,6] Moreover, preoperative CRT also proved to result in a longer survival time than surgery.[7,8] However, whether CRT could lead to a better treatment effect than CT remains controversial. Therefore, we conducted this meta-analysis of randomized controlled trials (RCTs) to compare the effects and safety of CRT with CT in the treatment of patients with EC.

2. Material and methods

2.1. Search strategy

The meta-analysis was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and
Meta-analysis (PRISMA). PubMed, Embase, Web of Science, and The Cochrane library were systematically searched from inception to February 10, 2017. The search terms used were as follows: (“oesophageal cancer” [All Fields] OR “esophageal neoplasms” [MeSH Terms] OR “esophageal” [All Fields] AND “neoplasms” [All Fields]) OR “esophageal neoplasms” [All Fields] OR (“esophageal” [All Fields] AND “cancer” [All Fields]) OR “esophageal cancer” [All Fields] AND (“chemoradiotherapy” [MeSH Terms] OR “chemoradiation” [All Fields] AND (“therapy” [Subheading] OR “therapy” [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutic agents” [All Fields]) AND (“drug therapy” [Subheading] OR (“drug” [All Fields] AND “therapy” [All Fields]) OR “drug therapy” [All Fields] OR “chemotherapy” [All Fields] OR “drug therapy” [MeSH Terms] OR (“drug” [All Fields] AND “therapy” [All Fields]) OR “chemotherapy” [All Fields]). There was no restriction on language and publication date. We also searched manually the references of the included studies and reviews until no further studies were found.

2.2. Study selection

The following inclusive criteria were applied: study design: RCT; population (adult patients who had histologically proven squamous cell carcinoma [SCC], adenocarcinoma [AC], or adenosquamous carcinoma [ASC] of the oesophagus); intervention (CRT); control (CT); outcome (overall survival [OS], progression-free survival [PFS], pathological complete response [pCR], R0 resection, recurrence rate, mortality rate, and adverse events).

2.3. Data extraction

A standardized data-extraction sheet was used to extract the following information: first author’s name, year of publication, country, number of patients in each group, patients’ characteristics, treatment regimens, and outcome data (OS, PFS, pCR, recurrence rate, R0 resection, mortality rate, and adverse events). Data extraction was conducted by 2 independent investigators (LY and XL), and discrepancies between them were resolved by discussion and consensus, and finally decided by a third investigator (LJH). For some studies that provided Kaplan-Meier curves rather than original values, we used the method recommended by Tierney et al to extract the hazard ratio (HR) as well as 95% confidence intervals (95% CIs). We also contacted corresponding author for data when it is necessary.

2.4. Risk of bias and grades of evidence

The assessment for risk of bias was conducted in adherence to guidelines outlined in the Cochrane handbook for systematic reviews of interventions (version 5.1.0). The quality of included studies was regarded as being at “low,” “unclear,” or “high” of bias according to the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; other bias. The quality of evidence for outcome measures was assessed using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. The GRADE profiler (GRADEpro, version 3.6) was used to construct a summary table.

2.5. Statistical analysis

We estimated the HR with 95% CI for time-to-event outcomes, and risk ratio (RR) with 95% CI for dichotomous outcomes. Before the data were synthesized, Cochrane Q χ² test and I² statistic were used to test the heterogeneity among the included studies. A P value <.1 or I² > 50% was considered to represent substantial heterogeneity. Poled estimates were calculated using a fixed-effects model (Mantel-Haenszel method) or a random-effects model (DerSimonian-Laird method), depending on the heterogeneity among the included studies. Whenever significant heterogeneity was identified, sensitivity analysis was conducted to explore the potential sources of heterogeneity. We also conducted subgroup analysis based on treatment procedure (definitive CRT, preoperative CRT, and postoperative CRT). The publication bias was not assessed because the number of included studies was <10. A 2-tailed P value <.05 was considered statistically significant except where a certain P value had been specified. All analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX).

2.6. Ethical review

Ethical approval was not necessary because this article is a meta-analysis and it does not involve the participants of ethics committee.

3. Results

3.1. Literature search

The search process of eligible studies is shown in Figure 1. The initial database search yielded 2137 records, of which 1542 records were excluded because of duplicate records. Then 584 were excluded based on title/abstract for various reasons (letters, case report, review, or conference abstracts), leaving 11 articles for full-text review. The remaining 11 articles were assessed for eligibility, and 3 of them were excluded because 1 was a single-arm trial, 1 used the chemoradiotherapy in both groups, and 1 compared low-dose with standard-dose chemoradiotherapy. Finally, 8 RCTs involving 1274 patients were included in this meta-analysis.

3.2. Study characteristics

The study characteristics are presented in Table 1. These studies were published between 1992 and 2016. The sample size ranged from 45 to 267. Of these included studies, 2 were conducted in Japan, 1 in France, 1 in Sweden, 1 in China, 1 in Finland, 1 in Australia, and 1 in Germany. Among the 1274 EC patients, 606 (47.6%) were histologically diagnosed with SCC, 617 (48.4%) were AC, and 51 (4.0%) were ASC. The tumor node metastasis staging system was used in the included studies, and most of patients were clinical stage II/III patients. In the CT group, cisplatin and 5-fluorouracil were used as the treatment regimens in most of the included studies, and dosage of radiotherapy in the CRT group ranged from 30 to 50 Gy. The patients’ characteristics, such as performance status (PS), histological subtype, tumor location, and clinical stage were well-balanced between the two groups.
3.3. Risk of bias and data quality

The details of risk of bias are presented in Fig. 2. Among these studies, 2 were regarded as being at low risk of bias,[20,22] 5 at unclear risk of bias,[21,23–26] and 1 at high risk of bias.[27] The main reason for the study with high risk of bias was that it was not a double-blind design; the main reason for 5 studies with unclear risk of bias was that the methods of blinding were not adequately described.

The GRADE evidence profiles for these outcomes were shown in Table 2. The quality of evidence was high for OS and adverse events, and moderate for PFS, pCR, R0 resection, recurrence rate, and mortality rate.

3.4. OS

All the included studies reported the data of OS.[20–27] Pooled estimates suggested that CRT did not significantly improve OS compared with CT (HR = 0.91, 95% CI: 0.82, 1.01; P = 0.072) (Fig. 3). There was no significant heterogeneity among the included studies (I² = 0.0%, P = 0.975).

Subgroup analysis based on the treatment procedure (definitive CRT, preoperative CRT, and postoperative CRT) suggested that CRT was not associated with an increased OS than CT no matter it was performed as definitive (HR = 0.94, 95% CI: 0.68, 1.29; P = 0.705), preoperation (HR = 0.90, 95% CI: 0.79, 1.03; P = 0.120), or postoperation (HR = 0.92, 95% CI: 0.75, 1.12; P = 0.390) (Fig. 3).

3.5. PFS

Four studies reported the data of PFS.[20,22,26,27] The aggregated results showed that CRT was not associated with an improvement in PFS (HR = 0.88, 95% CI: 0.75, 1.03; P = 0.111) (Fig. 4). There was no significant heterogeneity among the included studies (I² = 0.0%, P = 0.770).

Subgroup analysis based on the treatment procedure demonstrated that, patients treated with definitive CRT (HR = 0.93, 95% CI: 0.70, 1.24; P = 0.619), or preoperative CRT (HR = 0.86, 95% CI: 0.72, 1.04; P = 0.14) did not have prolonged PFS when compared with those treated with CT (Fig. 4).

3.6. pCR

Five studies presented the data of pCR.[20,22,23,26,27] Overall, the pCR rate in the CRT group and CT group was 36.9% and 23.2%, respectively. EC patients who were treated with CRT had

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**Table 1**

Baseline characteristics of patients in the trials included in the meta-analysis.

| Study          | Country   | Treatment regimen                                      | No. of patients | Male/female | Age (mean ± SD), y | Tumor type (SCC/AC/ASC) | Clinical stage (I/II/IB/III/IVA/VB) |
|----------------|-----------|--------------------------------------------------------|-----------------|-------------|--------------------|------------------------|-----------------------------------|
| Conroy T et al[22] | France    | FOLFOX + 50Gy radiotherapy                             | 134             | 110/24      | 61 (39–85)         | 114/19/1               | 0/31/10/67/8/19                 |
| JEOG[21]       | Japan     | Cisplatin + vindesine + 50Gy radiotherapy             | 127             | 110/17      | NR                 | 0/127/0                | 2/28/27/55/15/0                  |
| Klevebro et al[22] | Sweden   | Cisplatin + 5-fluorouracil + 40Gy radiotherapy        | 90              | 18/72       | 63 (38–74)         | 0/65/25                | 0/13/30/58/0/0                   |
| Cao et al[23]  | China     | Cisplatin + 5-fluorouracil + mitomycin + 40Gy         | 118             | 60/58       | NR                 | 118/0/0                | 0/9/10/3/6/0                    |
| Tachibana et al[24] | Japan    | Cisplatin + 5-fluorouracil + mitomycin                | 119             | 65/54       | NR                 | 119/0/0                | 0/8/10/8/3/0                    |
| Ngyard et al[25] | Finland   | Cisplatin + bleomycin + 5-fluorouracil + 50Gy radiotherapy | 22              | 20/2        | 61.2 ± 9           | 22/0/0                 | 1/5/4/8/0                       |
| Burmeister et al[26] | Australia | Cisplatin + 5-fluorouracil + 35Gy radiotherapy       | 47              | 33/14       | 60.1 (50–74)       | 47/0/0                 | 0/5/3/8/7                      |
| Stahl et al[27] | Germany   | Cisplatin + 5-fluorouracil + leucovorin + 30Gy radiotherapy | 48              | 28/20       | 66.1 (41–77)       | 48/0/0                 | 0/5/3/8/7                      |

AC = adenocarcinoma, ASC = adenosquamous carcinoma, FOLFOX = oxaliplatin, leucovorin, fluorouracil, infusional fluorouracil, JEOG = Japanese Esophageal Oncology Group, NR = not reported, SCC = squamous cell carcinoma, SD = standard deviation.
1.03, 95% CI: 0.86, 1.23; P < .001) (Fig. 6), with no significant heterogeneity among the studies (I² = 35.5%, P = .199).

3.8. Recurrence rate
Four studies reported the data of recurrence rate.\[21,24,26,27\] Overall, recurrence rate in the CRT group and CT group was 45.1% and 49.6%, respectively. Patients treated with CRT had a similar recurrence rate with those treated with CT (RR = 0.91, 95% CI: 0.76, 1.10; P = .346) (Fig. 7). No evidence of significant heterogeneity was observed among the studies (I² = 0.0%, P = .553).

Subgroup analysis based on the treatment procedure suggested that patients treated with preoperative CRT (RR = 1.00, 95% CI: 0.81, 1.23; P = .113) and postoperative CRT (RR = 0.73, 95% CI: 0.50, 1.08; P = .983) had a similar recurrence rate with those treated with CT (Fig. 7).

3.9. Mortality rate
Three studies reported the data of mortality rate.\[22,25,27\] Overall, the mortality rate in the CRT group and CT group was 13.8% and 5.5%, respectively. Patients who received the CRT had a higher mortality than those who received CT (RR = 2.50, 95% CI: 1.14, 5.48; P = .022) (Fig. 8). There was no significant heterogeneity among the studies (I² = 0.0%, P = .920).

3.10. Adverse events
All the studies reported the data of adverse events.\[20–27\] Overall, the incidence of grade 3 or 4 adverse events in the CRT group and CT group was 34.3% and 33.4%, respectively. Pooled estimates suggested that there was no significant difference in incidence of grade 3 or 4 adverse events between the 2 groups (RR = 0.91, 95% CI: 0.62, 1.32; P = .612).

4. Discussion
This is a further meta-analysis of 8 RCTs to compare the efficacy and safety of CRT with CT in the treatment of patients with EC. The present meta-analysis suggested that CRT significantly increased the rates of pCR and R0 resection in EC patients, but it did not prolong the PFS and OS. Moreover, patients who received CRT had a higher mortality rate than those who were treated with CT. The incidence of grade 3 or 4 adverse events was not significant difference between the 2 treatments. Our study confirmed that CRT had no survival advantages than CT in the treatment of EC.

There has been 1 published meta-analysis comparing the induction CRT with induction CT for EC.\[28\] Results from that study suggested that compared with induction CT, induction CRT significantly prolonged OS and disease-free survival (DFS), and it also increased the complication rate.\[28\] Our study expands on the previous meta-analysis to provide a better characterization of the evidence base for CRT and CT in the treatment of EC patients. First, there were more eligible RCTs and enlarged sample size in our analysis, which gives greater power to compare the effects of CRT with CT in EC patients.

In this meta-analysis, 8 RCTs with a total of 1274 patients were included. Second, all the studies included in this meta-analysis were prospectively, randomized.

a higher pCR rate than those treated with CT (RR = 3.62, 95% CI: 1.10, 11.95; P = .035) (Fig. 5). There was significant heterogeneity among the studies (I² = 89.1%, P < .001). Therefore, we conducted sensitivity analysis to explore the potential sources of heterogeneity. As shown in Fig. 5, the results from the study of Conroy et al\[20\] were completely out of range of the others, and this study might contribute to the heterogeneity. Thus, we excluded this study; however, the overall estimates of the remaining studies did not change substantially (RR = 5.08, 95% CI: 2.89, 8.95; P < .001). And no evidence of heterogeneity was identified among the studies (I² = 17.0%, P = .306).

Subgroup analysis based on the treatment procedure showed that, patients treated with preoperative CRT had a significantly higher pCR rate than those treated with CT (RR = 4.63, 95% CI: 2.39, 8.95; P < .005), whereas patients treated with definitive CRT had a similar pCR rate with those treated with CT (RR = 1.03, 95% CI: 0.86, 1.23; P = .764) (Fig. 5).

3.7. R0 resection
Four studies reported the data of R0 resection.\[22,23,26,27\] Overall, the rate of R0 resection in the CRT group and CT group was 87.5% and 74.1%, respectively. CRT was associated with an increased R0 resection rate (RR = 1.18, 95% CI: 1.09, 1.27; P < .001) (Fig. 6), with no significant heterogeneity among the studies (I² = 8.9%, P = .199).
Table 2

GRADE evidence profile.

| Quality assessment | Effect | No of patients | Relative (95% CI) | Absolute | Quality | Importance |
|--------------------|--------|----------------|-------------------|----------|---------|------------|
| Overall survival (better indicated by lower values) | | | | | | |
| 8 Randomized trials | Serious * | No serious inconsistency | No serious indirectness | No serious imprecision | Strong association | 639 | 635 | — | HR 0.91 higher (0.82 to 1.01 higher) | ⊗⊗⊗⊗ High | Critical |
| Progression free survival (better indicated by lower values) | | | | | | |
| 4 Randomized trials | Serious * | No serious inconsistency | No serious indirectness | No serious imprecision | None | 325 | 319 | — | HR 0.88 higher (0.75 to 1.03 higher) | ⊗⊗⊗⊗ Moderate | Critical |
| Pathological complete response | | | | | | |
| 5 Randomized trials | Serious † | No serious indirectness | No serious indirectness | No serious imprecision | Strong association | 153/415 (36.9%) | 96/414 (23.2%) | RR 3.62 (1.10–11.95) | 608 more per 1000 (from 23 more to 1000 more) | ⊗⊗⊗⊗ Moderate | Critical |
| R0 resection | | | | | | |
| 4 Randomized trials | Serious * | No serious indirectness | No serious indirectness | No serious imprecision | None | 246/281 (87.5%) | 209/282 (74.1%) | RR 1.18 (1.09–1.27) | 133 more per 1000 (from 67 more to 200 more) | ⊗⊗⊗⊗ Moderate | Important |
| Recurrence rate | | | | | | |
| 4 Randomized trials | Serious * | No serious indirectness | No serious indirectness | No serious imprecision | None | 105/233 (45.1%) | 116/234 (49.6%) | RR 0.91 (0.76–1.10) | 45 fewer per 1000 (from 119 fewer to 50 more) | ⊗⊗⊗⊗ Moderate | Important |
| Mortality rate | | | | | | |
| 3 Randomized trials | Serious * | No serious indirectness | No serious indirectness | No serious imprecision | None | 19/138 (13.8%) | 8/145 (5.5%) | RR 2.50 (1.14–5.48) | 83 more per 1000 (from 8 more to 247 more) | ⊗⊗⊗⊗ Moderate | Important |
| Adverse events | | | | | | |
| 5 Randomized trials | Serious * | No serious indirectness | No serious indirectness | No serious imprecision | Strong association | 190/552 (34.4%) | 186/557 (33.4%) | RR 0.91 (0.62–1.32) | 30 fewer per 1000 (from 127 fewer to 107 more) | ⊗⊗⊗⊗ High | Important |

CI = confidence interval, HR = hazard ratio, RR = risk ratio.

* One study was regarded as being at high risk of bias.
† A total of 1274 patients were enrolled.
‡ Substantial heterogeneity (I² = 89.1%) was found.
$x$ A total of 881 patients were enrolled.
controlled phase 2/3 trials. Whereas in the previous meta-
alysis, only 3 studies were RCTs, and the other 2 were
nonrandomized cross-comparison study and retrospective
study.[28] Observational studies were highly subject to selection
bias and confounding by indication. Furthermore, we were able
to evaluate the effects of CRT and CT in the R0 resection and
recurrence rate, which had not been discussed in the previous
meta-analysis.

Whether esophageal and esophagogastric-junction tumors
should be treated with preoperative CRT or with perioperative
CT remains unclear. In the Medical Research Council Adjuvant
Gastric Infusional Chemotherapy (MAGIC) trial[29] and the
Actions Concertees dans les Cancer Colorectaux et Digestifs
(ACCORD) 07 trial,[30] both results demonstrated that a
perioperative CT significantly improved the OS and PFS in
patients with operative gastric or lower esophageal ACs.
However, these trials included gastric tumors as well as
esophagogastric-junction tumors, and whether preoperative
CT had benefit effect in esophagogastric-junction tumors still
remained uncertain. In a phase 3 trial,[27] all the patients included
were esophagogastric-junction tumors, and they were randomly
assigned to preoperative CRT or CT. The results suggested that
preoperative CRT had a survival advantage than preoperative
CT, but this was not statistically significant. Similarly, Van
Hagen et al.[31] conducted a clinical trial comparing CRT
followed by surgery with surgery in patients with esophageal
or esophagogastric-junction tumors. In that study, there was a
substantial percentage of patients in CRT group had an
esophagogastric-junction tumor (22%), and patients in CRT
group had a prolonged survival. Thus, the authors supported the
treatment of preoperative CRT for patients with esophago-
gastric-junction tumors.

In this meta-analysis, we found that CRT could not
significantly improve OS and PFS in the treatment of EC patients
as compared with CT. Our results were in consistent with all of
the included studies. Klevebro et al.[22] conducted a randomized
clinical trial of neoadjuvant CRT (nCRT) versus neoadjuvant CT
(nCT) for cancer of the oesophagus or gastroesophageal junction.
In that study, patients in the nCT group were given 3 cycles of
cisplatin (100 mg/m²) and fluorouracil (750 mg/m²), whereas
those in nCRT group were given 40 Gy with a photon beam
linear accelerator concomitant with CT.[22] At the end of 3-year
follow-up, the OS in the nCRT and nCT groups was 47% and
49%, respectively ($P = .77$), and PFS in both groups was 44%.[22]
Despite CRT did not show survival benefits in EC patients, a trend toward prolonged survival of CRT was observed in patients with SCC,[26] and a trend toward poor survival was found in patients with AC.[23] In a prospectively randomized phase III trial, patients with locally advanced SCC were randomly allocated to receive CRT followed by surgery or CT followed by surgery.[26] At the date of evaluation, median survival in CRT and CT groups was 33.1 (95% CI: 24.0, open) and 21.2 (95% CI: 15.2, 27.2) months, respectively, which favored the CRT arm.[26] In another clinical trial, patients were treated with 3 cycles of platin/5-fluorouracil or platin/5-fluorouracil with concomitant radiotherapy.[121] The 3-year OS in the CT and CRT arms was 49% and 47%, respectively (P = .77).[122] Subgroup analysis based on tumor type also showed a longer OS of CT in the AC patients, although the difference was not statistically significant (HR = 1.06, 95% CI: 0.68, 1.66).[122] The authors suggested that the decreased OS time in CRT group could be explained by the lower radiotherapy dosage, which was 40 Gy.[121] However, because of the limited data, we were unable to conduct subgroup analysis based on tumor types to explore whether CRT had different survival effects in different types of EC.

With regard to the pCR, our results demonstrated that, EC patients who were treated with CRT had a significantly higher pCR rate than those treated with CT. pCR has been shown to be a good prognostic indicator in patients who have had CRT.[32,33] Previous studies have indicated that patients who have <10% viable tumor cells also have similar positive outcomes.[32–34] Although EC patients who have preoperative CRT achieve significantly prolonged pCR compared with those treated with CT, the survival outcomes between these patients were not significant different. One possible reason for this is that the addition of radiotherapy to CT may have no impact on the survival of a disease that has a high rate of systemic metastasis.[126]

There were several potential limitations in this meta-analysis that should be considered when interpreting our results. First, our study was conducted based on 8 RCTs, and 3 of them had a relatively small sample size (N < 100). Compared with large trials, studies with small sample size were more likely to overestimate the treatment effects. Second, these included studies lacked homogeneity in patients’ characteristics (age, tumor type, tumor location, ECOG performance status, and clinical stage), and treatment regimen (dosage of the chemotherapeutic regimens, and dosage of the radiation). These factors may increase the heterogeneity and have potential impact on the results. Third, because of the sparse data, we were unable to conduct subgroup analysis to assess the effects of CRT with CT in different pathological types of EC.

In summary, this meta-analysis indicates that CRT was associated with significantly increased pCR rate, R0 resection rate, and mortality rate in the treatment of EC, but it had no effects in survival outcomes. Moreover, in the subgroup analysis, no differences in OS and PFS were noted for patients receiving definitive, pre-operative, or postoperative CRT and those receiving CT. Preoperative CRT had a significantly higher pCR rate than CT. Despite no difference in survival, the improvement from CRT with respect to the pCR and R0 resection rate makes this treatment a reasonable option for EC. Considering the potential limitations in this study, further large-scale and well-conducted RCTs are needed to validate our findings, and investigate the effects of 2 treatments in different pathological types of EC.
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