Introduction

Esophageal carcinoma (EC) is one of the most common cancers and a leading cause of death, and is derived from various malignant cell types. The studies of Kumagai et al. and Duan et al. estimated that there were more than 400,000 deaths per year caused by EC worldwide. As the main types of EC, squamous cell carcinoma (SCC) and adenocarcinoma (AC) are one of the six common causes of mortality, with 77/100,000 deaths per year in China, 11/100,000 per year in Japan, and 4.99/100,000 per year in Western countries.

Although surgical resection for EC remains as the mainstream treatment over the past decades, surgery alone (SA) has been associated with a low long-term survival rate (SR). Most EC patients who underwent surgical resection alone suffered from 4–10% morbidity and 54–69% mortality and exhibited a 5-year survival of 15–24% after surgery. Chemoradiotherapy (CRT) could be administered before or after surgery; CRT before surgery as a neoadjuvant therapy is more often used in Europe and North America as compared to that in Asia. Neoadjuvant CRT followed by surgery (NCRTS) has shown poor outcomes for EC treatment whereas decreased recurrence and improved SR have been reported with various durations. Thus, a consensus on the role of NCRTS in patients with EC is absent at present.

In our previous meta-analysis, in comparison with SA, NCRTS can increase 1-, 3-, and 5-year SRs in patients with EC.

Key words: Esophageal Carcinoma; Meta-analysis; Neoadjuvant Chemoradiotherapy; Survival Outcomes
5-year SRs was revealed. However, the SRs were not related to increased postoperative morbidity and mortality in those who suffered from EC. Furthermore, concurrent CRT was superior to sequential CRT.[12] Moreover, the different survival effects after CRT in patients from various ethnicities or genetic backgrounds were not analyzed, thereby necessitating further investigation.[12]

To assess the association between NCRTS and survival outcomes and evaluate whether the newly published or updated clinical trials can influence the results of our previous study, a comprehensive search of randomized clinical trials (RCTs) comparing NCRTS versus SA was carried out, and an up-to-date meta-analysis was performed in this study.

**METHODS**

**Search strategy**

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines for the present report.[13] To identify all the published studies regarding neoadjuvant CRT and EC, we conducted an electronic search in the databases including PubMed, EMBASE, and the Cochrane Library. The following terminologies “esophageal neoplasm”, “carcinoma”, “adjuvant”, “chemotherapy”, “radiotherapy”, “combined modality therapy”, and “clinical trial” were searched by two independent investigators (up to August 2015). Manual searches of the reference lists of all the relevant studies and review articles were also conducted.

**Selection criteria**

The inclusion and exclusion criteria in the current updated meta-analysis were the same as the criteria in the previous meta-analysis.[12] The criteria for eligibility of the studies were as follows: (1) RCTs evaluating NCRTS versus SA; (2) articles that provided survival data between patients from the NCRTS and SA groups; (3) articles that described the cases and controls in the diagnosis and the sources; and (4) having risk ratio (RR) with 95% confidence interval (CI) or data that could be calculated. The articles were excluded from the study if they met the following criteria: (1) non-RCT; (2) controls including patients with malignant tumors; and (3) if the publications were duplicate studies, abstracts, reviews, or the reported data were from an abstract presented at a meeting.

**Data extraction and quality assessment**

The following data were extracted from newly included RCTs by two investigators independently: number of participants, publication time, country, tumor histology, NCRTS regimen and sequence (concurrent CRTS or sequential CRTS), patient outcomes including 1-, 3-, and 5-year SRs, and postoperative morbidity and mortality. The quality of the eligible studies was assessed using the Jadad et al.’s guidelines.[14] Randomization, blinded, withdrawals, generation of random numbers, and concealment of allocation, which are the essential aspects of RCT, were scored from 0 to 5. A threshold of ≥4 points was regarded as a high-quality study. Any discrepancy was resolved by group discussion to achieve a consensus.

**Statistical analysis**

This meta-analysis was carried out using the STATA software version 10.0 (StataCorp, College Station, TX, USA). The primary outcomes of this study were 1-, 3-, and 5-year SRs. The RR with 95% CIs as effective size was determined to assess the 1-, 3-, and 5-year SRs, postoperative morbidity, and postoperative mortality. The significance of the pooled RR was determined by the Z-test. Heterogeneity was determined using the Q-test.[15,16] A random effects model was applied when heterogeneity existed among studies whereas a fixed effects model was applied when there was no statistical heterogeneity.[17] Sensitivity analysis was conducted by excluding those studies with distinct outliers in the results.[18] Subgroup analyses were conducted for 1-, 3-, and 5-year SRs, as well as postoperative morbidity and mortality based on publication year, ethnicity, sequence, and histology. The publication bias was evaluated with a funnel plot, Begg’s test, and Egger’s test.[19,20] All the P values were two-sided, and P < 0.05 was considered statistically significant.

**RESULTS**

The process of the study selection is schematically illustrated in Figure 1. A total of 1120 articles from the initial search were identified and screened, and 53 studies were reviewed in detail. Finally, 16 studies were eligible, which included 11 RCTs[21-31] from the previous meta-analysis and 5 new RCTs [Table 1].[32-36] All these studies with a large, merged sample size were included in the updated analysis, randomly comparing EC patients with different therapies (NCRTS [n = 1305] vs. SA [n = 1244]), whereas the previous meta-analysis included a total of 1529 patients. The quality assessment by Jadad score [Table 1] encompassed

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**Figure 1: Flowchart of study selection and exclusion process.**
A total of 14 studies reported the effect of NCRTS versus SA and the 1-year SR. The summary RR showed that the NCRTS were associated with a higher 1-year SR [RR: 1.07, 95% CI: 1.02–1.13, \(P = 0.005\); Figure 2], and a nonsignificant heterogeneity was detected across the included studies (\(I^2: 21.5\%, P = 0.220\)). Similarly, pooled analysis suggested that patients who received NCRTS exhibited a significantly increased 3-year SR [RR: 1.26, 95% CI: 1.14–1.39, \(P < 0.001\); nonsignificant heterogeneity; Figure 3]. Finally, the summary analysis for the 5-year SR indicated that the comparison of NCRTS versus SA displayed a beneficial effect [RR: 1.36, 95% CI: 1.18–1.56, \(P < 0.001\); nonsignificant heterogeneity; Figure 4].

The data for the effect of NCRTS on postoperative morbidity were available from 13 studies. Overall, we noted that although the patients who received NCRTS reduced the risk of postoperative morbidity by 7.0%, the decrease was not statistically significant [RR: 0.93, 95% CI: 0.82–1.05, \(P = 0.254\); no evidence of heterogeneity; Figure 5]. Similarly, a significant effect between NCRTS and SA for postoperative mortality was not observed [RR, 1.17, 95% CI: 0.56–2.44, \(P = 0.684\); Figure 6].

### Table 1: Characteristics of 16 RCTs included in the final meta-analysis

| First author of study | Year of publication | Country     | Sample size, n | Sequence of chemoradiotherapy | Histology          | Jadad scores |
|------------------------|---------------------|-------------|----------------|------------------------------|--------------------|--------------|
|                        | NCRTS | SA | Total |                             |                    |              |
| Nygaard[21]            | 1992 | Norway | 47 | 41 | 88 | Sequential | SCC | 2 |
| Apino[22]              | 1994 | Thailand | 35 | 34 | 69 | Concurrent | SCC | 1 |
| Le Prise[23]           | 1994 | France | 41 | 45 | 86 | Sequential | SCC | 2 |
| Bosset[24]             | 1997 | France | 143 | 139 | 282 | Sequential | SCC | 3 |
| Urbal[25]              | 2001 | USA | 50 | 50 | 100 | Concurrent | SCC (25.0%); AC (75.0%) | 2 |
| An[26]                 | 2003 | China | 48 | 49 | 97 | Sequential | SCC | 3 |
| Lee[27]                | 2004 | Korea | 51 | 50 | 101 | Concurrent | SCC | 2 |
| Burmeister[28]         | 2005 | Australia | 128 | 128 | 256 | Concurrent | SCC (37.0%); AC (63.0%) | 3 |
| Natsugoe[29]           | 2006 | Japan | 22 | 23 | 45 | Concurrent | SCC | 2 |
| Tepper[30]             | 2008 | USA | 30 | 26 | 56 | Concurrent | SCC (25.0%); AC (75.0%) | 2 |
| Cao[31]                | 2009 | China | 118 | 118 | 236 | Concurrent | SCC | 2 |
| Lv[32]                 | 2010 | China | 158 | 80 | 238 | Concurrent | SCC | 4 |
| Yang[33]               | 2012 | China | 54 | 69 | 123 | Concurrent | SCC | 4 |
| van Hagen[34]          | 2012 | The Netherlands | 178 | 188 | 366 | Concurrent | SCC (75.0%); AC (23.0%); other (2.0%) | 2 |
| Mariette[35]           | 2014 | France | 98 | 97 | 195 | Concurrent | SCC (70.3%); AC (29.2%); undifferentiated carcinoma (0.5%) | 3 |

NCRTS: Neoadjuvant chemoradiotherapy followed by surgery; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; RCTs: Randomized clinical trials; SA: Surgery alone.
Although nonsignificant heterogeneity was observed for the outcomes, we conducted subgroup analyses for 1-, 3-, and 5-year SRs to evaluate the effect of NCRTS in specific subpopulations [Table 2]. First, we noted that NCRTS was associated with higher 1-year SR when the studies conducted in Western countries or patients receiving a concurrent sequence. Second, the patients who received NCRTS showed no significant effect on 3-year SR if the studies published before 2000, patients receiving sequential sequence, or patients suffering from AC. Third, NCRTS was not associated with 5-year SR when the studies published before 2000 or patients receiving a sequential sequence. Fourth, NCRTS significantly reduced the postoperative morbidity when the studies published in 2000 or after or patients suffering from AC. Finally, NCRTS was associated with a lower risk of postoperative mortality when the studies conducted in Eastern countries, patients receiving concurrent sequence, or patients suffering from SCC. Conversely, NCRTS significantly increased the postoperative mortality if the studies published before 2000, conducted in Western countries, patients receiving sequential sequence, or patients suffering from AC.

The results of Egger et al.\cite{20} and Begg and Mazumdar\cite{19} showed no evidence of publication bias for 1-, 3-, and 5-year SRs and postoperative morbidity. The funnel plot appeared to be symmetrical [Figure 7]. Although the results of Begg et al. showed no evidence of publication bias for postoperative mortality ($P = 0.428$), the results of Egger et al. showed potential evidence of publication bias for postoperative mortality ($P = 0.007$). However, the conclusions were not altered after adjustment for publication bias using the trim and fill method.\cite{37}

**Discussion**

This updated meta-analysis for survival benefits of NCRTS included the data from previously published studies and five new RCTs, with 80% more patients in comparison with the previous meta-analysis.\cite{10} The effect of NCRTS on survival outcomes for EC can be strengthened by the evidence from these additional studies. The results indicated that NCRTS could increase 1-, 3-, and 5-year SRs in patients with EC. The efficacy of NCRTS might be influenced by stratification analysis.

Our previously published meta-analysis explored the association between NCRT and the improvement of survival outcomes for EC; however, certain limitations were notable.\cite{10} First, some controversial results and conclusions were reported in the previous meta-analysis, which reported contradictory results with respect to the postoperative mortality and subgroup analysis of 3-year survival outcome, according to histology and ethnicity.\cite{10,38} Second, although some studies suggested concurrent CRT as a standard therapy for EC, a definite conclusion that the concurrent NCRTS was superior to sequential NCRTS due to its greater risk of adverse reactions was lacking because of insufficient evidence.\cite{1,39,40} Third, a significant increase in the survival outcomes for SCC or AC by NCRTS was indicated in the meta-analysis by Sjoquist et al.,\cite{8} whereas
Table 2: Subgroup analysis for survival outcomes

| Outcomes                  | Group                      | RR (95% CI) | P    | Heterogeneity (%) | P for heterogeneity |
|---------------------------|----------------------------|-------------|------|-------------------|---------------------|
| 1-year survival rate      | Publication year           |             |      |                   |                     |
|                           | 2000 or after              | 1.06 (0.99–1.14) | 0.085 | 43.8              | 0.067               |
|                           | Before 2000                | 1.04 (0.90–1.20) | 0.640 | 0                 | 0.866               |
|                           | Ethnicity                  |             |      |                   |                     |
|                           | Eastern countries          | 1.02 (0.96–1.08) | 0.558 | 20.7              | 0.272               |
|                           | Western countries          | 1.13 (1.04–1.22) | 0.003 | 0                 | 0.822               |
|                           | Sequence                   |             |      |                   |                     |
|                           | Sequential                 | 1.06 (0.93–1.12) | 0.380 | 0                 | 0.676               |
|                           | Concurrent                 | 1.08 (1.02–1.14) | 0.005 | 41.2              | 0.083               |
|                           | Histology                  |             |      |                   |                     |
|                           | SCC                        | 1.04 (0.97–1.10) | 0.244 | 17.7              | 0.280               |
|                           | AC                         | 1.08 (0.97–1.20) | 0.173 | 10.2              | 0.291               |
| 3-year survival rate      | Publication year           |             |      |                   |                     |
|                           | 2000 or after              | 1.30 (1.10–1.53) | 0.002 | 51.9              | 0.023               |
|                           | Before 2000                | 1.17 (0.85–1.61) | 0.347 | 0                 | 0.807               |
|                           | Ethnicity                  |             |      |                   |                     |
|                           | Eastern countries          | 1.28 (1.12–1.47) | <0.001 | 0       | 0.887               |
|                           | Western countries          | 1.30 (1.14–1.49) | <0.001 | 60.7    | 0.009               |
|                           | Sequence                   |             |      |                   |                     |
|                           | Sequential                 | 1.24 (0.94–1.64) | 0.130 | 0                 | 0.697               |
|                           | Concurrent                 | 1.30 (1.17–1.44) | <0.001 | 51.3    | 0.025               |
|                           | Histology                  |             |      |                   |                     |
|                           | SCC                        | 1.26 (1.13–1.42) | <0.001 | 3.3     | 0.411               |
|                           | AC                         | 1.22 (0.98–1.51) | 0.073 | 61.5              | 0.051               |
| 5-year survival rate      | Publication year           |             |      |                   |                     |
|                           | 2000 or after              | 1.41 (1.17–1.69) | <0.001 | 31.4    | 0.167               |
|                           | Before 2000                | 1.41 (0.41–4.90) | 0.587 | 66.2              | 0.085               |
|                           | Ethnicity                  |             |      |                   |                     |
|                           | Eastern countries          | 1.40 (1.14–1.71) | 0.001 | 0                 | 0.740               |
|                           | Western countries          | 1.42 (1.18–1.71) | <0.001 | 60.9    | 0.025               |
|                           | Sequence                   |             |      |                   |                     |
|                           | Sequential                 | 1.21 (0.75–1.95) | 0.440 | 45.6              | 0.175               |
|                           | Concurrent                 | 1.43 (1.24–1.65) | <0.001 | 38.1    | 0.115               |
|                           | Histology                  |             |      |                   |                     |
|                           | SCC                        | 1.37 (1.15–1.63) | <0.001 | 0                 | 0.807               |
|                           | AC                         | 1.79 (1.12–2.87) | 0.014 | 72.0              | 0.028               |
| Postoperative morbidity   | Publication year           |             |      |                   |                     |
|                           | 2000 or after              | 0.88 (0.77–0.99) | 0.041 | 0                 | 0.520               |
|                           | Before 2000                | 1.11 (0.85–1.45) | 0.427 | 0                 | 0.676               |
|                           | Ethnicity                  |             |      |                   |                     |
|                           | Eastern countries          | 0.98 (0.70–1.38) | 0.921 | 0                 | 0.567               |
|                           | Western countries          | 0.92 (0.80–1.05) | 0.216 | 13.9              | 0.321               |
|                           | Sequence                   |             |      |                   |                     |
|                           | Sequential                 | 1.08 (0.84–1.38) | 0.540 | 0                 | 0.774               |
|                           | Concurrent                 | 0.87 (0.75–1.01) | 0.060 | 0.9              | 0.426               |
|                           | Histology                  |             |      |                   |                     |
|                           | SCC                        | 1.02 (0.86–1.21) | 0.837 | 0                 | 0.805               |
|                           | AC                         | 0.44 (0.23–0.83) | 0.012 | –                 | –                   |
| Postoperative mortality   | Publication year           |             |      |                   |                     |
|                           | 2000 or after              | 1.06 (0.48–2.35) | 0.888 | 70.9              | <0.001              |
|                           | Before 2000                | 1.95 (1.01–3.77) | 0.048 | 4.6               | 0.351               |
|                           | Ethnicity                  |             |      |                   |                     |
|                           | Eastern countries          | 0.35 (0.26–0.48) | <0.001 | 23.0     | 0.273               |
|                           | Western countries          | 1.62 (1.09–2.40) | 0.017 | 6.9               | 0.378               |

Contd...
only improvements in the 3- and 5-year survival outcomes for SCC, but not AC, were evaluated in our previous meta-analysis. Moreover, the last searched article was an RCT published in 2009 in the previous meta-analysis, and the number of identified studies was limited. Therefore, it was deemed necessary to conduct an updated meta-analysis for exploring further information and demonstrating the efficacy of NCRTS.

The results of the previously published meta-analysis indicated that NCRTS increased the SR in patients with EC, which were similar to this updated meta-analysis. On the other hand, although 1-year SR reached a significant level in this updated meta-analysis, some other studies indicated that patients after NCRTS experienced increased survival benefits as assessed from 3- or 5-year survival outcomes but not from 1-year. The variability in the results between this meta-analysis and other studies might be attributable to the inadequate

| Outcomes | Group | RR (95% CI) | P    | Heterogeneity (%) | P for heterogeneity |
|----------|-------|-------------|------|-------------------|---------------------|
| Sequence | Sequential | 2.06 (1.10–3.87) | 0.024 | 4.6 | 0.351 |
| Histology | Concurrent | 0.59 (0.46–0.76) | <0.001 | 70.9 | <0.001 |
| SCC      | 0.67 (0.52–0.86) | 0.001 | 85.1 | <0.001 |
| AC       | 2.97 (0.98–9.00) | 0.054 | 0 | 0.712 |

SCC: Squamous cell carcinoma; AC: Adenocarcinoma; CI: Confidence interval; RR: Risk ratio; --: Not applicable.

Figure 7: Funnel plot for studies reported 1-, 3-, and 5-year SRs, postoperative morbidity and postoperative mortality between the NCRTS and surgery alone groups. SRs: Survival rates; NCRTS: Neoadjuvant chemoradiotherapy followed by surgery; SE: Standard error; RR: Risk ratio.
Estimates of alcohol-related oesophageal cancer

Meta-analysis of postoperative morbidity and perioperative complications induced by neoadjuvant concurrent chemotherapy and radiotherapy (NCRTS) before surgery is a suitable treatment option for patients with EC. However, the postoperative morbidity and mortality showed no significant association with NCRTS compared to SA. In a future study, an increased attention may be focused on the risk factors for the incidence of morbidity and mortality, including postoperative complications, histology, and NCRTS toxic effects.

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Conflicts of interest

There are no conflicts of interest.

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