



## Clinical evidence for association of neoadjuvant chemotherapy or chemoradiotherapy with efficacy and safety in patients with resectable esophageal carcinoma (NewEC study)

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### ABSTRACT

**Background:** The efficacy and safety of neoadjuvant treatment over surgery alone and that of neoadjuvant chemoradiotherapy (NCRT) over neoadjuvant chemotherapy (NCT) in resectable esophageal carcinoma remains inconclusive. This study (NewEC) used global data to comprehensively evaluate these comparisons and to provide a preferable strategy for patient subsets.

**Methods:** This study included a meta-analysis of randomized controlled trials (RCTs) identified from inception to May 2019 from PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and congresses and a registry-based cohort study with patients from Massachusetts General Hospital (Massachusetts, USA) and Guangdong Provincial People's Hospital (Guangzhou, China) recruited from November 2000 and June 2017, to cross-validate the comparisons among NCRT versus NCT versus surgery. The GRADE approach was used to assess quality of evidence in meta-analysis. Neural network machine learning propensity score-matched analysis was used to account for confounding by patient-level characteristics in the cohort study. The primary endpoint was overall survival (OS). The study was registered with PROSPERO CRD42017072242 and ClinicalTrials.gov NCT04027543.

**Findings:** Of 22,070 studies assessed, there were 38 ( $n = 6,993$  patients) eligible RCTs. Additionally, 423 out of 467 screened patients were included in the cohort study. The results from trials showed that NCT had a better OS than surgery alone (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.79–0.98; high quality) and was only favorable for adenocarcinoma (HR 0.83, 95% CI 0.72–0.96; moderate quality). High-quality evidence showed a significantly better OS for NCRT than surgery alone (HR 0.74, 95% CI 0.66–0.82) for both adenocarcinoma (HR 0.73, 95% CI 0.62–0.86) and squamous cell carcinoma (SCC) (HR 0.73, 95% CI 0.65–0.83). The OS benefit of NCRT over NCT was seen in the pairwise (HR 0.78, 95% CI 0.62–0.99; high quality) and network (HR 0.82, 95% CI 0.72–0.93; high quality) meta-analyses, with similar results before (HR 0.60, 95% CI 0.40–0.91) and after (HR 0.44, 95% CI 0.25–0.77) matching in the cohort study, leading to a significantly increased 5-year OS rate in both adenocarcinoma and SCC before and after matching. The increased benefits from NCT or NCRT were not associated with the risk of 30-day or in-hospital mortality.

**Interpretation:** NewEC Study provided high-quality evidence supporting the survival benefits of NCRT or NCT over surgery alone, with NCRT presenting the greatest benefit for resectable esophageal carcinoma.

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## Research in context

### *Evidence before this study*

We searched for “esophageal cancer”, “chemotherapy”, “surgery”, “chemoradiotherapy”, “neoadjuvant therapy”, and “randomized clinical trials” in public databases published from the inception to May 2019. Neoadjuvant chemotherapy (NCT) or chemoradiotherapy (NCRT) has been shown to be better than surgery alone in patients with resectable esophageal carcinoma, but higher quality evidence is needed as multiple new findings have emerged regarding this issue. Additionally, previous evidence-based findings and current guidelines have not established an advantage of NCRT over NCT and the feasibility to use short-term outcomes such as disease-free survival (DFS) as a surrogate for overall survival (OS).

### *Added value of this study*

This updated meta-analysis involved 6,993 patients with resectable esophageal carcinoma, representing an estimated sample size increase of 40.1% compared with the 4,188-patient sample size in a previous meta-analysis. Compared with surgery, either NCRT or NCT was associated with longer OS. Compared with NCT, NCRT resulted in a significantly improved OS; treatment effects were shown in both adenocarcinoma and squamous cell carcinoma (SCC), and in both patients with high-risk scores and low-risk scores. There was no significant difference among NCRT, NCT, and surgery alone in terms of the 30-day postoperative or in-hospital mortality. Additionally, the effect on DFS was strongly associated with that on OS in trials investigating NCRT or NCT versus surgery alone.

### *Implications of all the available evidence*

First, this study provided the most comprehensive high-quality evidence to date to strengthen the recommendation for both NCT and NCRT as better choices than surgery alone in patients with resectable oesophagus carcinoma. Second, we showed a substantial improvement of survival as well as a favorable safety profile with NCRT compared with NCT, for either adenocarcinoma or SCC, and for either patients with high or low risk of death. These findings further support the superiority and generalizability of the use of NCRT in resectable esophagus carcinoma. Third, this is the first study to clarify that DFS could serve as a potential surrogate endpoint for OS when investigating NCRT or NCT versus surgery alone in resectable esophageal carcinoma.

neoadjuvant chemotherapy (NCT) have greater clinical benefit than surgery alone among patients with resectable esophageal carcinoma [3,4]. However, as additional findings have emerged from recent studies investigating neoadjuvant interventions [5–7], for instance, the regimen comprising cisplatin and vinorelbine [5], an updated analysis is needed to confirm the beneficial role of NCRT or NCT.

Moreover, previous evidence-based findings and the current guidelines have established neither a clear survival advantage of NCRT over NCT nor an acceptable safety profile of the addition of radiotherapy to NCT [8–11]. As to esophageal adenocarcinoma, a meta-analysis revealed no significant survival difference between NCRT and NCT in direct comparison based on only two trials with no more than 100 patients in each group; [8] furthermore, a similar treatment effect was observed between NCRT and NCT in recent trials carried out by Klevebro et al [12] and Stahl et al. [13] Although squamous cell carcinoma (SCC) patients seem to be more sensitive to NCRT, the definitive superiority of NCRT in SCC is still unclear due to inconsistent results found in recent trials [3,7,12]. Therefore, high-quality studies are warranted to further clarify whether NCRT has superior clinical benefits over NCT in resectable esophageal carcinoma, specifically adenocarcinoma or SCC of the esophagus.

This NewEC Study aimed to perform an updated comprehensive meta-analysis of RCTs to evaluate the efficacy and safety of NCRT versus NCT versus surgery in resectable esophageal carcinoma. Next, we would further investigate the comparison between NCRT and NCT using cohort data.

## 2. Methods

### 2.1. Study design and patients

#### 2.1.1. Meta-analysis

This study included a meta-analysis of RCTs and an individual patient analysis of cohorts. The meta-analysis was conducted according to the Cochrane Collaboration recommendations and PRISMA statement. We searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for randomized clinical trials (RCTs) up to May 2019 using the following terms: “esophageal cancer”, “chemotherapy”, “surgery”, “chemoradiotherapy”, and “neoadjuvant therapy”. The proceedings of the American Society of Clinical Oncology, European Society for Medical Oncology and American Society for Therapeutic Radiology and Oncology as well as the references in the included RCTs and relevant meta-analyses were also reviewed manually.

For inclusion, RCTs had to evaluate the efficacy and safety of NCRT or NCT followed by surgery versus surgery alone or NCRT versus NCT as the primary schedule among patients with esophageal carcinoma or gastroesophageal junction carcinoma. Trials involving patients who had histologically proven adenocarcinoma or SCC of the stomach or lower third of the esophagus but did not separate the available data for esophageal cancer patients were excluded. We excluded studies whose abstracts or full texts were not in English and studies that did not have available data. Three investigators (S-PZ, A-LL, Y-YF) screened the titles and abstracts to choose relevant studies, and the eligibility of the studies that seemed to meet the inclusion criteria was confirmed by a full-text review. The data collected included the recruitment period, sample size, follow-up time, treatment group

## 1. Introduction

Esophageal carcinoma is the sixth leading cause of cancer-related mortality worldwide and is more prevalent in developing nations, such as China [1]. Even after surgery, survival remains poor in patients with resectable esophageal cancer, and the 5-year survival rate is only 25–35% [2]. Previous randomized clinical trials (RCTs) have reported that neoadjuvant chemoradiotherapy (NCRT) and

allocation, details regarding the chemotherapy and radiotherapy regimens, and patient and tumor characteristics. Full details methods are described in Supplemental Methods 1.

### 2.1.2. Cohort study

The retrospective cohort was reported according to the CONSORT guideline, STROBE statement and TRIPOD guideline. The cohort analyzed 423 individual patients at Massachusetts General Hospital (Massachusetts, USA) or Guangdong Provincial People's Hospital (Guangzhou, China) who underwent NCRT or NCT between November 2000 and June 2017 to estimate the benefit of NCRT versus NCT in patients with resectable esophageal carcinoma. Full description of cohort study is provided in Supplemental Methods 2.

## 2.2. End point definitions

The primary endpoint was overall survival (OS). The secondary end points included disease-free survival (DFS), R0 resection rate, pathologic complete response (pCR) and 30-day postoperative or in-hospital mortality. OS was calculated as the time from the date of the histologically documented diagnosis to the date of death or final follow-up. DFS was calculated from the date of R0 resection to the date of disease recurrence or death from any cause. R0 resection was defined as gross disease removed with negative margins (tumor-free resection margin). Incomplete resection (R1) was defined as residual gross disease or positive surgical margins (tumor removal  $\leq 1$  mm from any margin). pCR was defined as no evidence of residual tumor cells in the primary tumor site or resected lymph nodes. The clinical response rate after neoadjuvant treatment was evaluated by a CT of the chest and abdomen based on the modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines.

## 2.3. Statistical analysis

### 2.3.1. Meta-analysis

We initially conducted a pairwise meta-analysis of all direct treatment comparisons, and next we conducted a random-effects Bayesian network meta-analysis at a frequentist setting to further estimate the benefit of NCRT compared with that of NCT [14,15]. The network meta-analysis assumed that treatment effects were consistent across all included trials and the heterogeneity was common within networks, which meant the relative treatment effect of treatment A versus treatment B can be indirectly obtained from the comparisons of treatment A with treatment C and treatment B with treatment C [16]. We evaluated network consistency by comparing the direct and indirect estimates for each comparison [17]. The level of loop and design inconsistencies were addressed using a global inconsistency test in the design-by-treatment interaction model [18]. The treatment effect on the time-to-event outcome was estimated by the hazard ratio (HR) with 95% confidence interval (CI), and the dichotomous outcomes were evaluated by the risk ratio (RR) and risk difference (RD). Prespecified subgroup analyses were performed to examine the effects of NCT or NCRT according to tumor histology (SCC or adenocarcinoma), the timing of chemotherapy and radiotherapy (concurrent or sequential), and the chemotherapy regimen (platinum plus taxanes or platinum plus fluorouracil). The  $I^2$  statistic was used to assess the heterogeneity across the trials, and  $I^2 \geq 50\%$  indicated substantial heterogeneity. All analyses were performed on the basis of the intention-to-treat principle when possible. A trial sequential analysis (TSA) was used to decide whether a trial could be terminated early, and indicates whether a  $P$  value is sufficient to indicate a reliable effect for the benefit, harm, or futility before the required information size is reached. Pearson correlation coefficients ( $\rho$ ) and the coefficient of determination ( $R^2$ ) of a weighted linear regression model was used to estimate the strength of the potential correlation

between different clinical outcomes. Full methodologies are described in Supplemental Methods 3.

### 2.3.2. Cohort study

We first used Power Analysis and Sample Size software version 15 to conduct an a priori power analysis based on the 5-year survival rate to estimate the sample size, approximating a sample ratio of patients in the NCRT group to patients in the NCT group of 3:1, an  $\alpha$  significance level of 0.05, a power of 80%, a 5-year survival rate of 45% in the NCRT cohort, and a 15% difference between the NCRT and NCT groups (5-year survival, 45% versus 30%) pooled from three trials [7,13,19]. This estimation was based on the results of the meta-analysis of RCTs comparing NCRT with NCT in resectable esophageal carcinoma patients. Using these parameters, at least 409 patients (307 in the NCRT group and 102 in the NCT group) were required.

Propensity score matching based on neural network machine learning was performed using R package MatchIt, which was used to optimally reduce the treatment assignment bias caused by effects of potential confounders by making baseline characteristics more comparable between the NCRT and NCT groups [20,21]. Unlike conventional propensity score matching approach using logistic regression, neural network has no causal interpretation, presents a mixed function of the input data, and could achieve less bias or greater accuracy [21]. We built a propensity score model based on covariates including gender, post-neoadjuvant pathologic TNM stage, tumor location, and histology type, and calculated a propensity score for each patient. The NCRT and NCT individuals within each stratum of the data were matched using 2:1 matching protocol without replacement, using a nearest-neighbor algorithm with caliper width equal to 0.2. We constructed a model to predict the OS following post-neoadjuvant interventions, with the aim of evaluating NCRT versus NCT in patient subset with high-risk or that with death or low-risk of death. The prognostic accuracy was assessed by using operating characteristic curve analysis and by calculating the area under the curves. Decision curve analysis was performed to assess the clinical utility of the prediction model by quantifying the net benefits when different threshold probabilities were considered.

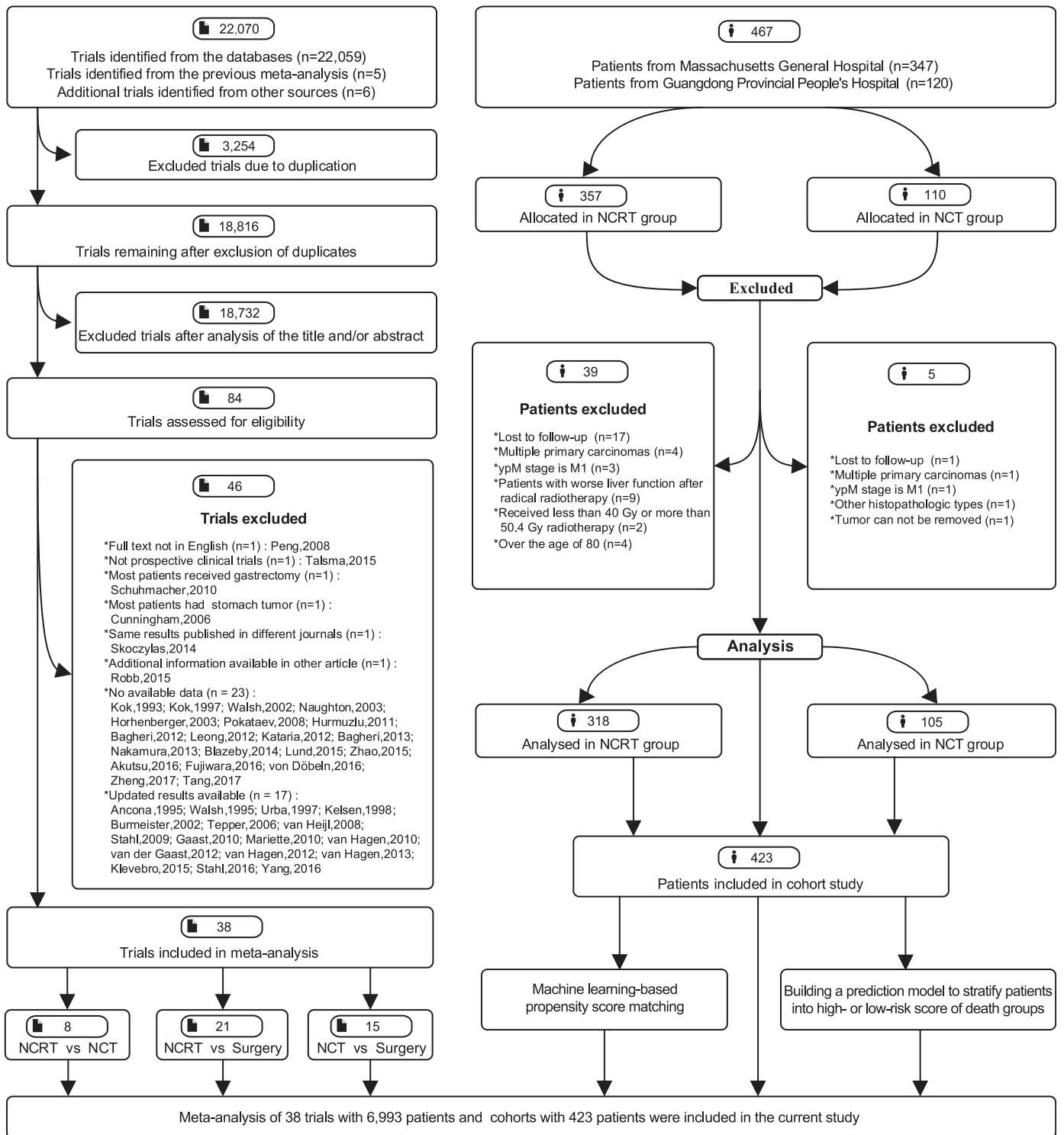
The  $\chi^2$  or Fisher's exact test was used to compare categorical variables. The Kaplan-Meier method was used to estimate median OS and generate survival curves, and survival was compared using the log-rank test and the restricted mean survival time ratio (RMSTR) of NCRT arm to NCT arm [22]. The HRs with their 95% CIs and the corresponding  $P$ -values from these analyses were estimated with a Cox regression analysis. Univariate and multivariate analyses were performed with the Cox proportional hazards model to investigate the effect of different factors on survival. All statistical tests were two-sided, and  $P$  values less than 0.05 were considered statistically significant. The statistical analyses were performed using R version 3.4.3. Full methodologies are described in Supplemental Methods 4.

The meta-analysis is registered with PROSPERO CRD42017072242 and the cohort study is registered with ClinicalTrials.gov. NCT04027543.

## 3. Results

### 3.1. Trials and patients' characteristics

Of 22,070 studies assessed, 38 RCTs [3–7,12,13,19,23–52] comprising 6,993 patients were eligible to be included in meta-analysis (Fig. 1); 18 RCTs compared NCRT with surgery alone, 12 RCTs compared NCT with surgery alone, 5 RCTs compared NCRT with NCT, and 3 RCTs (two 2  $\times$  2 factorial studies and one three-arm study) simultaneously compared the effects of NCRT, NCT and surgery. Twenty and seven RCTs included patients with SCC and adenocarcinoma, respectively, eleven enrolled patients with either SCC or adenocarcinoma, and one had no histological data. Most trials had a low risk of bias



**Fig. 1. Flowchart of study selection and design.** NCRT, neoadjuvant chemoradiotherapy; NCT, neoadjuvant chemotherapy.

(Supplemental Figures 1–2). The characteristics of each trial are summarized in Supplemental Table 1.

Of 467 patients screened, 423 patients were eligible to be recruited in cohort study (Fig. 1), including 318 (75.2%) patients who underwent NCRT and 105 (24.8%) patients who received NCT; the total number exceeded the estimated required sample size. We identified 192 patients, including 113 individuals from the NCRT group (48 [42.5%] adenocarcinoma and 65 [57.5%] SCC) and 79 individuals from the NCT group (25 [31.6%] adenocarcinoma and 54 [68.4%] SCC) via machine learning-based propensity score matching. The

demographic features are detailed in Supplemental Table 2; the baseline bias was largely reduced after matching.

### 3.2. NCT with higher efficacy than surgery alone in RCTs

Fifteen RCTs [3,4,7,23,40–47,50–52] involving 3,343 patients were included in the comparison of NCT with surgery. Compared with surgery, NCT significantly improved OS (HR 0.88, 95% CI 0.79–0.98,  $P=0.02$ ; high quality), DFS (HR 0.80, 95% CI 0.73–0.87,  $P<0.01$ ; high quality) and the R0 resection rate (RR 1.17, 95% CI

1.08–1.27,  $P < 0.01$ ; high quality) (Figs. 2A, 3 and Supplemental Figure 3). The 5-year OS rate was 27.9% with NCT and 19.7% with surgery (RR 1.42, 95% CI 1.18–1.71,  $P < 0.01$ ; high quality). TSA indicated that additional trials were unlikely to alter the outcomes of the R0 resection and 5-year OS rates (Supplemental Figure 4A and 5A). Adenocarcinoma patients who received NCT showed significantly better OS (HR 0.83; 95% CI 0.72–0.96,  $P = 0.012$ ) and 5-year OS rate (RR 1.56, 95% CI 1.04–2.34,  $P = 0.030$ ) than those who underwent surgery alone, but there was no clear difference between the two treatments in patients with SCC (Fig. 3 and Supplemental Table 3).

### 3.3. NCRT with higher efficacy than surgery alone in RCTs

Twenty-one RCTs [3,5–7,23–39] involving 3,138 patients were included in the comparison of NCRT with surgery. Compared with surgery alone, NCRT was associated with increased OS (HR 0.74, 95% CI 0.66–0.82,  $P < 0.01$ ; high quality), DFS (HR 0.72, 95% CI 0.62–0.82,  $P < 0.01$ ; high quality), 3-year OS (RR 1.28, 95% CI 1.09–1.49,  $P < 0.01$ ; moderate quality), 5-year OS (RR 1.51, 95% CI 1.28–1.78,  $P < 0.01$ ; high quality), and R0 resection rate (RR 1.16, 95% CI 1.07 to 1.25,  $P < 0.01$ ; moderate quality) (Fig. 2B, Fig. 3 and Supplemental Figure 6). The TSA analysis suggested conclusive evidence of the R0 resection and 5-year OS rates (Supplemental Figures 4B and 5B).

Among patients with adenocarcinoma, NCRT resulted in significant improvements in OS (HR 0.73, 95% CI 0.62–0.86,  $P = 0.000$ ), the 3-year OS rate (RR 6.01, 95% CI 1.88–19.17,  $P = 0.003$ ), and DFS (HR 0.69, 95% CI 0.52–0.92,  $P = 0.011$ ). The advantage of NCRT among SCC was seen with respect to OS (HR 0.73, 95% CI 0.65–0.83,  $P = 0.000$ ), the 3-year OS rate (RR 1.24, 95% CI 1.12–1.38,  $P = 0.000$ ), the 5-year OS rate (RR 1.67, 95% CI 1.31–2.13,  $P = 0.000$ ), and DFS (HR 0.65, 95% CI 0.55–0.77,  $P = 0.000$ ) (Fig. 3 and Supplemental Table 4).

Concurrent radiotherapy resulted in significant improvements in OS (HR 0.72, 95% CI 0.63–0.81,  $P = 0.000$ ) and the 5-year OS rate (RR 1.51, 95% CI 1.29–1.77,  $P = 0.000$ ) in NCRT versus surgery alone, but there was no significant benefit of NCRT with sequential radiotherapy. The OS benefits were observed in regimens containing platinum plus taxanes (HR 0.64, 95% CI 0.52–0.80,  $P = 0.000$ ), with an increased 5-year OS rate (RR 1.39, 95% CI 1.12–1.72,  $P = 0.003$ ), and in regimens containing platinum plus fluorouracil (HR 0.79, 95% CI 0.69–0.90,  $P = 0.000$ ), with an increased 5-year OS rate (RR 1.65, 95% CI 1.32–2.08,  $P = 0.000$ ) (Supplemental Table 4).

### 3.4. NCRT with higher efficacy than NCT in RCTs

Eight RCTs [3,7,12,13,19,23,48,49] involving 1,030 patients were included in the comparison of NCRT with NCT. Compared with NCT, NCRT was associated with increased OS (HR 0.78, 95% CI 0.62–0.99,  $P = 0.04$ ; high quality), 5-year OS rate (RR 1.48, 95% CI 1.06–2.07,  $P = 0.02$ ; moderate quality), R0 resection rate (RR 1.13, 95% CI 1.07–1.20,  $P < 0.01$ ; high quality), and pCR (RR 3.74, 95% CI 2.03–6.88,  $P < 0.01$ ; moderate quality) (Figs. 2C, 3 and Supplemental Figure 7). The benefit on the R0 resection rate was robust in the TSA (Supplemental Figure 4C). NCRT significantly improved OS in SCC (HR 0.65, 95% CI 0.50–0.86,  $P = 0.002$ ) and 5-year OS rate in adenocarcinoma (RR 1.49, 95% CI 1.01–2.20,  $P = 0.047$ ) (Fig. 3 and Supplemental Table 5).

Next, we conducted a network meta-analysis to compare 3,461 patients who received NCRT with 3,468 patients who received NCT. The pooled estimate yielded a significant enhancement in OS in favor of NCRT (HR 0.82, 95% CI 0.72–0.93,  $P = 0.002$ ; high quality; Fig. 3 and Supplemental Table 5).

### 3.5. NCRT with higher OS than NCT before and after matching in cohort study

In the cohort study, NCRT was associated with a significant improvement in OS (HR 0.60, 95% CI 0.40–0.91,  $P = 0.016$ ; RMSTR

1.41, 95% CI 1.16–1.72,  $P < 0.001$ ; Fig. 4A) compared with NCT before matching. Significant improvements were found in the 1-year (RR 1.08, 95% CI 1.01–1.06,  $P = 0.024$ ) and 5-year (RR 1.77, 95% CI 1.36–2.31,  $P < 0.001$ ) OS rates (Table 1). In the matched cohort, the OS advantage of NCRT over NCT reached a greater extent (HR 0.44, 95% CI 0.25–0.77,  $P = 0.004$ ; RMSTR 1.32, 95% CI 1.10–1.59,  $P = 0.003$ ; Fig. 4B). The differences in the 1-year and 5-year OS rates were also significant after matching (Table 1).

Adenocarcinoma patients treated with NCRT had significantly a higher 5-year OS rate than those who received NCT both before matching (RR 1.99, 95% CI 1.12–3.56,  $P = 0.019$ ) and after matching (RR 2.35, 95% CI 1.58–3.50,  $P < 0.001$ ) (Table 1). The OS advantage of NCRT was identified in SCC patients before matching (HR 0.54, 95% CI 0.30–0.96,  $P = 0.037$ ; RMSTR 1.41, 95% CI 1.11–1.80,  $P = 0.005$ ; Fig. 4C) and after matching (HR 0.46, 95% CI 0.24–0.88,  $P = 0.019$ ; RMSTR 1.30, 95% CI 1.04–1.63,  $P = 0.021$ ; Fig. 4D), leading to an increased 5-year OS rate both before matching (RR 1.84, 95% CI 1.32–2.56,  $P < 0.001$ ) and after matching (RR 2.47, 95% CI 1.37–4.46,  $P = 0.003$ ) (Table 1).

Before matching, NCRT was associated with higher OS rate than NCT in various subgroups, including patients aged over 60 years (HR 0.49, 95% CI 0.26–0.92), male patients (HR 0.59, 95% CI 0.38–0.93), patients who underwent R0 resection (HR 0.61, 95% CI 0.40–0.93), patients with an objective response to treatment (HR 0.38, 95% CI 0.22–0.67), and patients with an ECOG-PS higher than 2 (HR 0.15, 95% CI 0.04–0.55). These findings were consistent with the results after matching (Supplemental Figure 8).

### 3.6. NCRT with higher OS than NCT of high and low-risk score of death group in cohort study

We built a prediction model incorporating post-neoadjuvant pathologic tumor-node-metastasis (TNM) stage, age, best response to treatment, tumor location, and ECOG-PS prognostic factors to categorize patients into groups with high- or low- risk score of death, which could better predict OS after neoadjuvant intervention than the TNM staging system. The construction and validation of the prediction model are detailed in Section 2, Supplemental Figures 9–10 and Tables 6–7.

Patients with high-risk scores obtained significant OS benefits from NCRT over NCT (HR 0.51, 95% CI 0.27–0.96,  $P = 0.036$ ; RMSTR 1.29, 95% CI 1.01–1.64,  $P = 0.044$ ; Fig. 4E). The OS HR of NCRT versus NCT in the low-risk score group was not significant (0.82, 95% CI 0.47–1.45,  $P = 0.499$ ; Fig. 4F); however, after adopting RMSTR, which is a more robust quantitative method, a significant difference was detected (1.25, 95% CI 1.02–1.54,  $P = 0.036$ ). The NCRT group had a larger proportion of low-risk patients than did the NCT group (70.1% versus 56.2%; Supplemental Figure 11A). Compared with NCT, NCRT resulted in an increased 5-year OS rate in both the high-risk (HR 3.94, 95% CI 1.95–7.95,  $P < 0.001$ ) and low-risk (HR 1.35, 95% CI 1.02–1.78,  $P = 0.036$ ) groups, and difference in the 5-year OS rate was specifically seen among SCC patients with high-risk scores (RR 3.85, 95% CI 1.74–8.54,  $P < 0.001$ ) (Table 1). As expected, the high-risk group had a larger proportion of SCC patients than did the low-risk group (43.3% versus 33.3%; Supplemental Figure 11B).

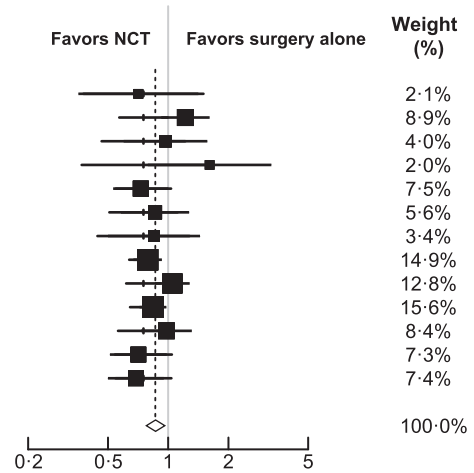
### 3.7. Benefit of NCRT or NCT was not offset by higher mortality

In the meta-analysis, we examined whether the benefit of NCRT or NCT was offset by a higher mortality rate. The 30-day postoperative or in-hospital mortality rate was 7.7% with NCT versus 8.0% with surgery alone, with an RD of -0.00 (95% CI -0.02–0.01,  $P = 0.73$ ); 7.3% with NCRT versus 3.9% with surgery alone, with an RD of 0.03 (95% CI -0.01–0.06,  $P = 0.11$ ); and 4.5% with NCRT versus 2.4% with NCT, with an RD of 0.01 (95% CI -0.02–0.03,  $P = 0.44$ ) (Fig. 3 and Supplemental Figure 12). There was no association between the OS benefits of the

**A** NCT vs Surgery

Trial	NCT (total)	Surgery alone (total)	Hazard ratio (95% CI)
Roth et al, <sup>40</sup> 1988	19	20	0.71 (0.36 to 1.42)
Nygaard et al, <sup>23</sup> 1992	56	50	1.22 (0.92 to 1.61)
Schlag et al, <sup>41</sup> 1992	22	24	0.97 (0.60 to 1.57)
Maipang et al, <sup>42</sup> 1994	24	22	1.61 (0.79 to 3.28)
Law et al, <sup>43</sup> 1997	74	73	0.73 (0.53 to 1.00)
Baba et al, <sup>47</sup> 2000	21	21	0.86 (0.58 to 1.27)
Ancona et al, <sup>44</sup> 2001	48	48	0.85 (0.50 to 1.44)
Banciewicz et al, <sup>50</sup> 2002	400	402	0.79 (0.67 to 0.93)
RTOG 8911, <sup>51</sup> 2007	216	227	1.05 (0.86 to 1.28)
OEO2, <sup>4</sup> 2009	400	402	0.84 (0.72 to 0.98)
Cao et al, <sup>3</sup> 2009	119	118	0.98 (0.73 to 1.31)
Boonsta et al, <sup>46</sup> 2011	85	84	0.71 (0.51 to 0.98)
Ychou et al, <sup>52</sup> 2011	113	111	0.69 (0.50 to 0.95)
<b>Total</b>	<b>1,597</b>	<b>1,602</b>	<b>0.88 (0.79 to 0.98)</b>

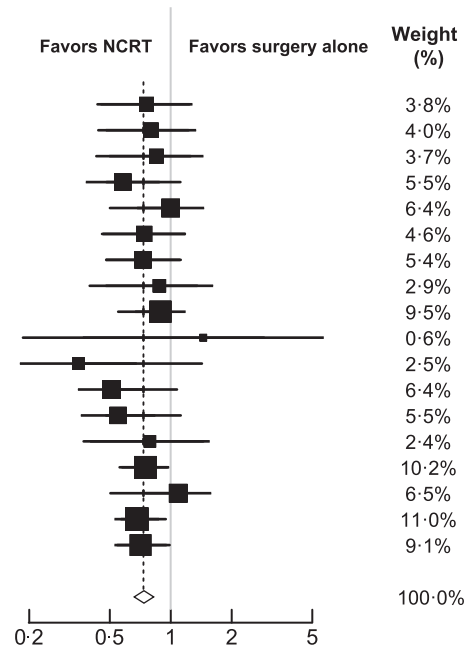
Heterogeneity:  $I^2=38\%$ ,  $\tau^2=0.0127$ ,  $p=0.08$   
 Test for overall effect:  $Z=-2.38$  ( $p=0.02$ )



**B** NCRT vs Surgery

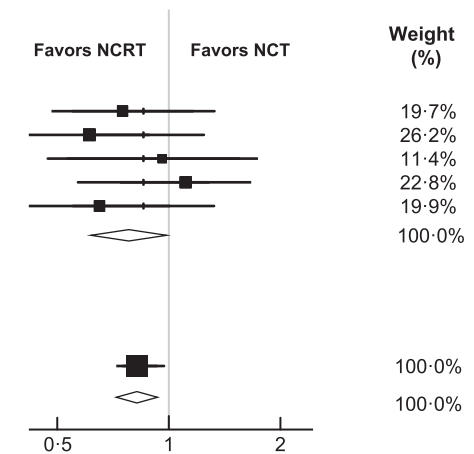
Trial	NCRT (total)	Surgery alone (total)	Hazard ratio (95% CI)
Nygaard et al, <sup>23</sup> 1992	53	50	0.76 (0.45 to 1.28)
Apinop et al, <sup>24</sup> 1994	35	34	0.80 (0.48 to 1.34)
Le Prise et al, <sup>25</sup> 1994	41	45	0.85 (0.50 to 1.45)
Walsh et al, <sup>26</sup> 1996	58	55	0.58 (0.38 to 0.88)
Bosset et al, <sup>28</sup> 1997	143	139	1.00 (0.68 to 1.46)
Walsh et al, <sup>29</sup> 2000	46	52	0.74 (0.46 to 1.19)
Urba et al, <sup>30</sup> 2001	50	50	0.73 (0.48 to 1.12)
Lee et al, <sup>31</sup> 2004	51	50	0.88 (0.48 to 1.62)
Burmeister et al, <sup>32</sup> 2005	128	128	0.89 (0.67 to 1.19)
Natsugoe et al, <sup>33</sup> 2006	22	23	1.45 (0.37 to 5.71)
CALGB 9781, <sup>34</sup> 2008	30	26	0.35 (0.18 to 0.68)
Cao et al, <sup>3</sup> 2009	118	118	0.51 (0.35 to 0.75)
Lv et al, <sup>36</sup> 2010	80	80	0.55 (0.36 to 0.84)
Teoh et al, <sup>37</sup> 2013	45	36	0.79 (0.40 to 1.56)
Bass et al, <sup>38</sup> 2014	104	107	0.75 (0.57 to 0.98)
FFCD 9901, <sup>27</sup> 2014	98	97	1.09 (0.75 to 1.59)
CROSS, <sup>6</sup> 2015	178	188	0.68 (0.53 to 0.88)
NEOCRTEC5010, <sup>5</sup> 2018	224	227	0.71 (0.53 to 0.96)
<b>Total</b>	<b>1,504</b>	<b>1,505</b>	<b>0.74 (0.66 to 0.82)</b>

Heterogeneity:  $I^2=22\%$ ,  $\tau^2=0.0123$ ,  $p=0.19$   
 Test for overall effect:  $Z=-5.36$  ( $p<0.01$ )



**C** NCRT vs NCT

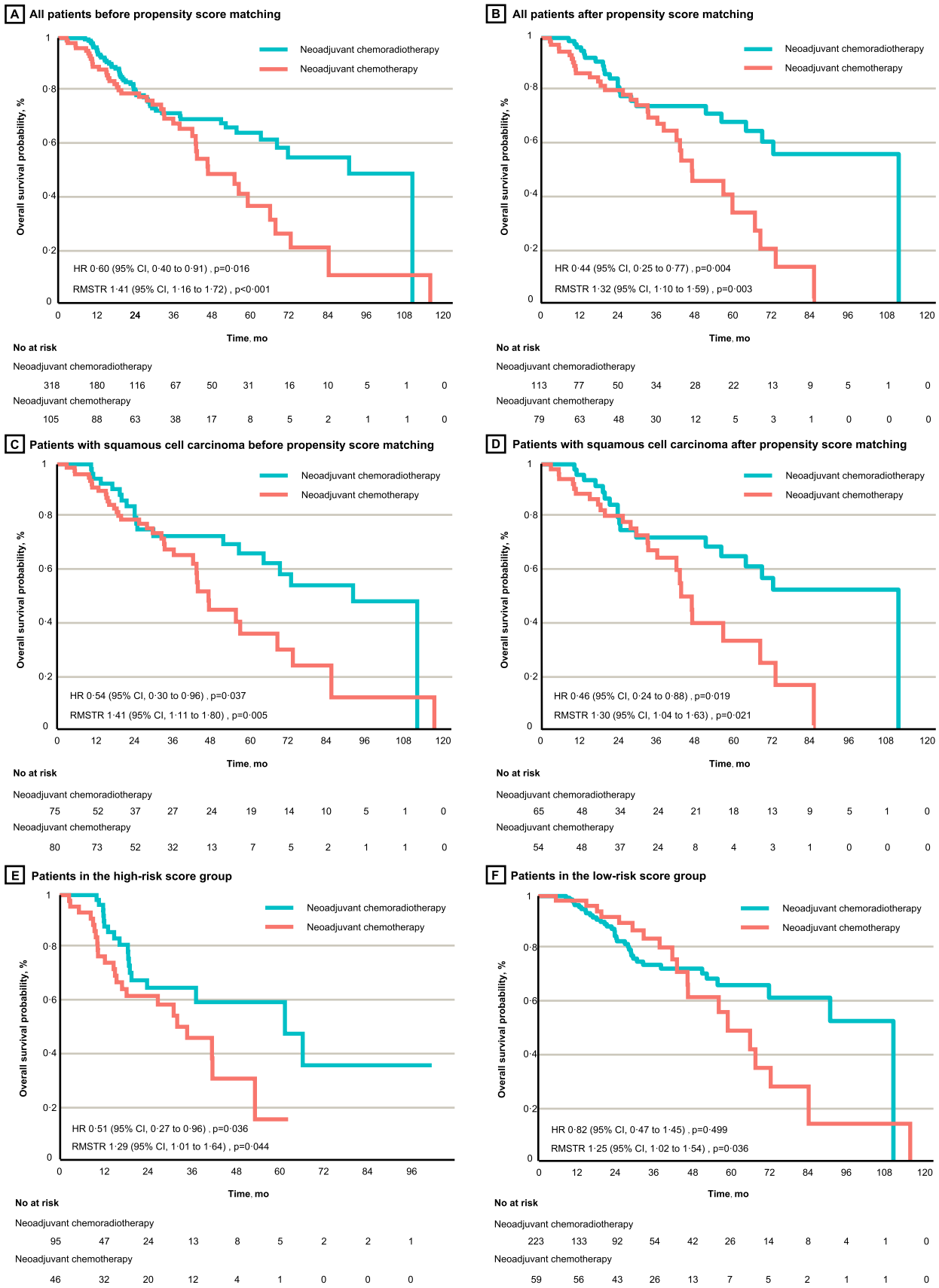
Trial	NCRT (total)	NCT (total)	Hazard ratio (95% CI)
<b>Individual trial</b>			
Nygaard et al, <sup>23</sup> 1992	53	56	0.75 (0.48 to 1.17)
Cao et al, <sup>3</sup> 2009	118	119	0.61 (0.42 to 0.89)
Burmeister et al, <sup>19</sup> 2011	39	36	0.96 (0.53 to 1.74)
Klembro et al, <sup>12</sup> 2016	90	91	1.11 (0.74 to 1.67)
POET, <sup>13</sup> 2017	60	59	0.65 (0.42 to 1.01)
<b>Total</b>	<b>360</b>	<b>361</b>	<b>0.78 (0.62 to 0.99)</b>
Heterogeneity: $I^2=30\%$ , $\tau^2=0.0213$ , $p=0.22$ Test for overall effect: $Z=-2.07$ ( $p=0.04$ )			
<b>Pooled trials</b>			
Network	3,461	3,468	0.82 (0.72 to 0.93)
<b>Total</b>	<b>3,461</b>	<b>3,468</b>	<b>0.82 (0.72 to 0.93)</b>
Heterogeneity: not applicable Test for overall effect: $Z=-3.04$ ( $p<0.01$ )			



**Fig. 2.** Meta-analysis results of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy versus surgery alone for overall survival. A, Neoadjuvant chemotherapy versus surgery alone. B, Neoadjuvant chemoradiotherapy versus surgery alone. C, Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy. The total number shown in the figure referred to number of patients with valid OS data. NCRT, neoadjuvant chemoradiotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval.



**Fig. 3. Summary of the pooled estimates and GRADE of efficacy and safety in the meta-analysis.** GRADE indicates Grading of Recommendations, Assessment, Development, and Evaluation Evidence. Mortality indicates 30-day postoperative or in-hospital mortality. CI, confidence interval. \*The results of Bayesian network meta-analysis.



**Fig. 4.** Overall survival of neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy in individual patient-level cohort study. A and B, All patients before and after propensity score matching, respectively. C and D, Patients with squamous cell carcinoma before and after propensity score matching, respectively. E and F, Patients with high-risk and low-risk scores for death, respectively. HR, hazard ratio; CI, confidence interval; RMSTR, restricted mean survival time ratio.



**Table 1**

Outcomes of neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy groups in the cohort study.

Variable	Before matching <sup>a</sup>		After matching <sup>b</sup>		High-risk score group <sup>c</sup>		Low-risk score group <sup>d</sup>	
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
<b>All patients</b>								
R0 resection:	1.00 (0.95 to 1.05)	1.000	0.99 (0.92 to 1.06)	0.788	1.04 (0.95 to 1.13)	0.396	0.98 (0.93 to 1.04)	0.450
ypN0	1.50 (1.15 to 1.95)	0.003	1.31 (0.94 to 1.82)	0.111	2.42 (1.17 to 5.03)	0.017	1.17 (0.91 to 1.51)	0.221
ypN+	0.68 (0.55 to 0.84)	<0.001	0.76 (0.57 to 1.02)	0.062	0.77 (0.61 to 0.96)	0.028	0.73 (0.51 to 1.04)	0.085
Survival rate:								
1-year	1.08 (1.01 to 1.16)	0.024	1.12 (1.02 to 1.23)	0.018	1.26 (1.06 to 1.49)	0.009	0.98 (0.94 to 1.02)	0.342
3-year	1.03 (0.89 to 1.19)	0.692	1.07 (0.89 to 1.28)	0.472	1.31 (0.94 to 1.80)	0.111	0.87 (0.76 to 1.00)	0.044
5-year	1.77 (1.36 to 2.31)	<0.001	1.99 (1.43 to 2.78)	<0.001	3.94 (1.95 to 7.95)	<0.001	1.35 (1.02 to 1.78)	0.036
<b>Patients with adenocarcinoma</b>								
R0 resection:	1.08 (0.93 to 1.25)	0.313	1.66 (1.16 to 2.39)	0.006	1.25 (0.88 to 1.78)	0.213	1.00 (0.88 to 1.15)	1.000
ypN0	1.78 (0.96 to 3.32)	0.067	1.22 (0.70 to 2.11)	0.483	7.04 (0.47 to 106.34)	0.158	1.40 (0.79 to 2.46)	0.249
ypN+	0.63 (0.46 to 0.88)	0.004	2.61 (1.21 to 5.64)	0.014	0.78 (0.52 to 1.16)	0.230	0.66 (0.39 to 1.13)	0.122
Survival rate:								
1-year	1.21 (1.00 to 1.48)	0.050	1.19 (1.04 to 1.36)	0.011	3.80 (1.31 to 11.01)	0.014	0.97 (0.94 to 0.99)	0.057
3-year	0.88 (0.72 to 1.09)	0.212	0.96 (0.80 to 1.15)	0.661	2.98 (0.87 to 10.23)	0.082	0.73 (0.66 to 0.80)	<0.001
5-year	1.99 (1.12 to 3.56)	0.019	2.35 (1.58 to 3.50)	<0.001	2.60 (0.75 to 8.96)	0.132	1.52 (0.86 to 2.67)	0.150
<b>Patients with squamous cell carcinoma</b>								
R0 resection:	0.98 (0.93 to 1.04)	0.450	0.97 (0.91 to 1.04)	0.350	0.99 (0.89 to 1.09)	0.853	0.98 (0.92 to 1.06)	0.531
ypN0	1.56 (1.13 to 2.14)	0.007	0.74 (0.51 to 1.10)	0.113	1.98 (0.85 to 4.61)	0.113	1.25 (0.92 to 1.69)	0.154
ypN+	0.61 (0.43 to 0.88)	0.006	1.25 (0.86 to 1.80)	0.242	0.74 (0.51 to 1.09)	0.113	0.60 (0.32 to 1.10)	0.111
<b>Variable</b>	<b>RR (95% CI)</b>	<b>P value</b>	<b>RR (95% CI)</b>	<b>P value</b>	<b>RR (95% CI)</b>	<b>P value</b>	<b>RR (95% CI)</b>	<b>P value</b>
Survival rate:								
1-year	1.04 (0.95 to 1.13)	0.396	1.22 (1.00 to 1.49)	0.050	1.04 (0.85 to 1.28)	0.703	1.00 (0.95 to 1.06)	1.000
3-year	1.09 (0.89 to 1.33)	0.405	0.99 (0.78 to 1.26)	0.934	1.16 (0.75 to 1.78)	0.505	0.97 (0.78 to 1.20)	0.784
5-year	1.84 (1.32 to 2.56)	<0.001	2.47 (1.37 to 4.46)	0.003	3.85 (1.74 to 8.54)	<0.001	1.41 (0.98 to 2.01)	0.064

The  $\chi^2$  exact test was used to obtain the *P* values. RR=risk ratio; CI=confidence interval; pCR=pathologic complete response; yp=postneoadjuvant pathologic; N0=no regional lymph node metastasis; N+=metastasis in regional lymph nodes; NR=not reached.

<sup>a</sup> Study patients before machine learning-based propensity score matching.

<sup>b</sup> Study patients after machine learning-based propensity score matching.

<sup>c</sup> Study patients with a high-risk score in our prediction model.

<sup>d</sup> Study patients with a low-risk score in our prediction model.

neoadjuvant treatments and the risk of 30-day postoperative or in-hospital mortality (Fig. 5A–B).

### 3.8. DFS was associated with OS in NCRT or NCT versus surgery alone

We further explored the potential surrogate endpoints for OS in the meta-analysis. The association between DFS and OS in NCT versus surgery alone gave rise to a high  $R^2$  value of 0.83 (95% CI 0.74–0.94; Fig. 5C), which yielded the regression equation as follow: OS=1.2890 × DFS-0.1596. DFS was also strongly associated with OS in NCRT (based on regimens comprising platinum plus fluorouracil or taxanes) versus surgery alone ( $R^2$ =0.72, 95% CI 0.56–0.93; Fig. 5D), which yielded the regression equation as follow: OS=0.98367 × DFS +0.01856. However, we did not observe any significant correlation between the R0 resection rate and the other outcomes (Supplemental Figure 13).

## 4. Discussion

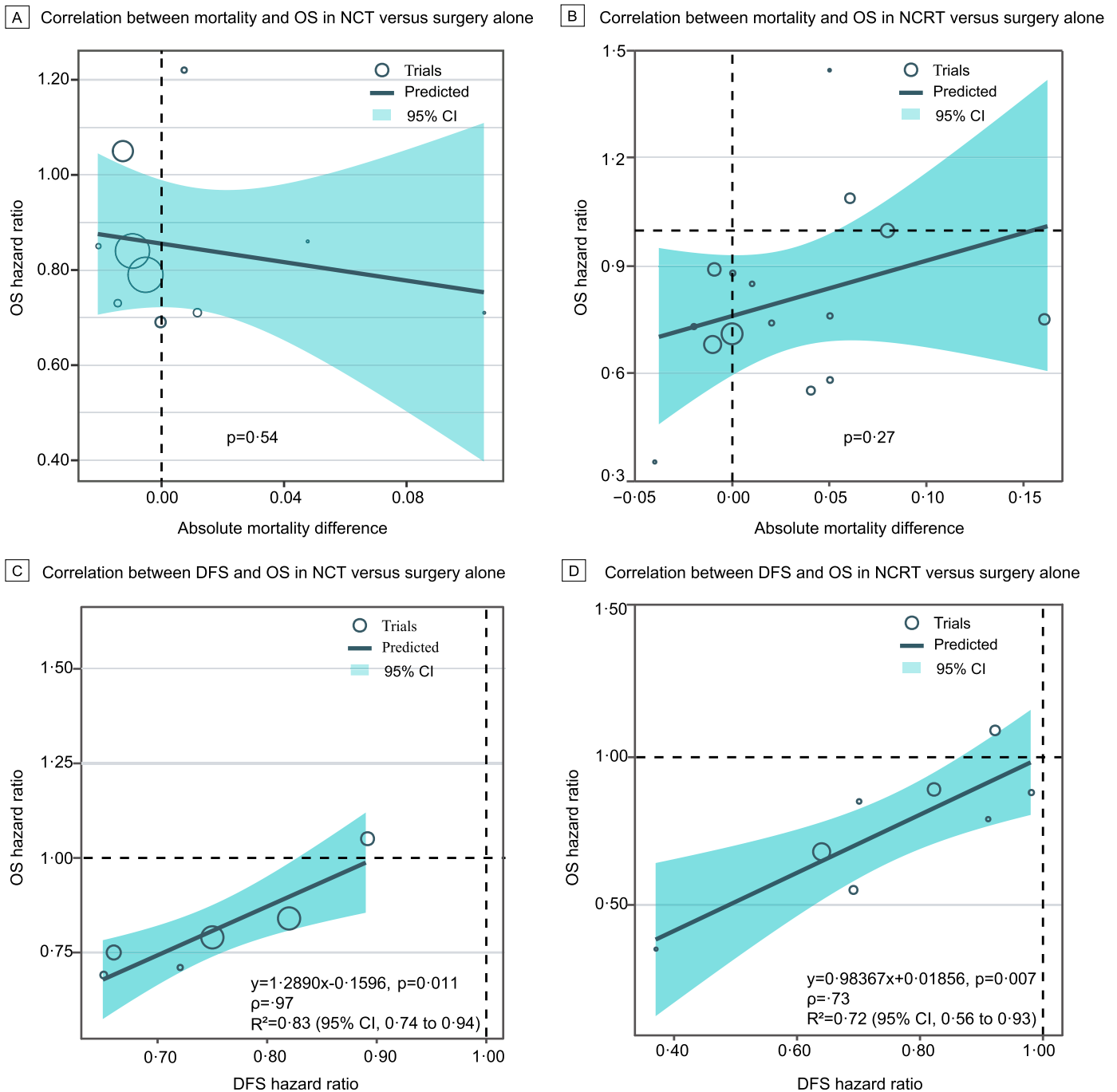
This study performed a meta-analysis of 38 RCTs involving 6,993 patients, which is based on the largest sample size to date, with an estimated sample size increase of 40.1% compared with the sample size in a previous meta-analysis (4,188 patients) [8]. The GRADE system indicated high-quality evidence in favor of both NCRT and NCT over surgery alone and indicated moderate to high evidence showing that compared with NCT, NCRT significantly prolonged survival, and increased the R0 and pCR rates among the patients with resectable esophageal carcinoma. The survival advantage of NCRT over NCT was further confirmed in cohort study at the individual patient level.

In patients with esophageal adenocarcinoma, our meta-analysis showed a trend towards longer OS following NCRT than following NCT, and the HR of NCRT versus surgery alone (HR 0.73, 95% CI 0.62–0.86; high quality) was better than that of NCT versus surgery alone (0.83, 0.72–0.96; moderate quality). Moreover, the

meta-analysis, coupled with cohort data demonstrated that compared to NCT, NCRT improves the 5-year OS rate in adenocarcinoma. Researchers designing new studies involving neoadjuvant treatments for resectable esophageal carcinoma should guarantee an increased recruitment of adenocarcinoma patients to further validate our findings.

Among the SCC patients, our meta-analysis provided high-quality evidence of a strikingly improved OS associated with NCRT compared with surgery alone, but this benefit was not observed among patients receiving NCT. The superiority of NCRT in SCC was further supported in the direct comparison of NCRT with NCT, which provided moderate quality evidence of the survival benefit in favor of NCRT. The cohort study suggested that in the SCC patients, NCRT significantly enhanced both OS and the 5-year OS rate compared with those of NCT, and this survival advantage was specifically identified in those who were concurrently graded as a high-risk score of death. Our study strengthens the evidence of the superior efficacy of NCRT in patients with SCC and highlights that clinicopathologic prediction model would aid in the selection of SCC patients.

We considered the possibility that any survival gains from adding neoadjuvant intervention to surgery or adding radiotherapy to preoperative chemotherapy might be offset by postoperative mortality. A previous meta-analysis revealed a negligible association between the risk of postoperative mortality and neoadjuvant interventions in resectable esophageal carcinoma [8]. Our updated meta-analysis further confirmed no significant difference among NCRT, NCT, and surgery alone in terms of the 30-day postoperative or in-hospital mortality, and the increased survival benefit conferred by NCRT or NCT was not associated with the risk of 30-day postoperative or in-hospital mortality in a linear regression model. Recent work has suggested rather than 30-day mortality, 90-day mortality might be more robust and firmer in the evaluation of the safety of trimodal therapy, particularly in the elderly; [53,54] therefore, future researches are needed to focus on different safety outcomes and more specific age-



**Fig. 5. Association of overall survival with mortality and disease-free survival.** A and B, Weighted linear correlation between overall survival and 30-day postoperative or in-hospital mortality for neoadjuvant chemotherapy versus surgery alone and neoadjuvant chemoradiotherapy versus surgery alone, respectively. C and D, Same as A and B but describing the correlation between overall survival and disease-free survival. OS, overall survival; DFS, disease-free survival; CI, confidence interval. Mortality indicates 30-day postoperative or in-hospital mortality.

based population. Moreover, ongoing randomized trials comparing NCRT and NCT (NCT04138212 and NCT03366883) and those comparing different radiation dose of NCRT (NCT03381651) in esophageal cancer would help to explore NCRT with an ideal safety profile over NCT.

Identification of appropriate chemotherapy strategy is essential to improve the treatment effect and to minimize the incidence of adverse events. The phase III FLOT4-AIO trial demonstrated that compared with fluorouracil or capecitabine plus cisplatin and epirubicin, a combination consisting of fluorouracil, leucovorin, oxaliplatin, and docetaxel improved OS, DFS and the R0 resection rate and had no significant difference in treatment-related adverse events among

resectable gastroesophageal junction or gastric adenocarcinoma [55]. By contrast, the OEO5 randomized trial investigating NCT in patients with esophageal or gastroesophageal junction adenocarcinoma demonstrated that compared with cisplatin plus fluorouracil, neoadjuvant capecitabine plus either epirubicin or cisplatin was associated with significantly higher toxicity with no meaningful difference in survival [56]. Moreover, the phase III ESO-Shanghai 1 trial evaluated NCRT for IIA-IVA esophageal SCC and showed a similar OS benefit but distinct aspects of side effects between paclitaxel plus fluorouracil and cisplatin plus fluorouracil [57], suggesting that personalized chemotherapy delivery should also provide insight into the difference in safety profile among chemotherapy regimens. In addition, immunotherapy

has achieved promising clinical benefits in second-line patients with inoperable esophageal carcinoma or non-small-cell lung cancer; [58,59] whether the combination of immunotherapy and chemotherapy could be an effective neoadjuvant strategy for resectable esophageal cancer is being investigated in ongoing trials (NCT03544736 and NCT04225364).

The strengths of our study come from its comprehensive assessment and validation of efficacy and safety outcomes. First, this study is the first to provide reliable evidence-based findings indicating the survival advantage of NCRT over NCT in resectable esophageal carcinoma, which has not previously been a consensus in current guidelines. Second, we provided a novel prediction model characterizing the risk of death, which was distinctively superior to TNM staging system and demonstrated both patients in the high-risk group and low-risk group could derive significant OS benefits from NCRT versus NCT. These findings further extended the superiority and generalizability of the use of NCRT. Third, in a previous meta-analysis [60], DFS was not confirmed as a good surrogate endpoint for OS in studies investigating neoadjuvant treatment for gastroesophageal cancers. However, that analysis described a highly heterogeneous group of patients treated with multiple neoadjuvant regimens. In our study, which included a larger sample size, we restricted the chemotherapy regimen of NCRT to platinum plus fluorouracil or taxanes and identified a strong correlation between DFS and OS when investigating NCRT versus surgery alone and NCT versus surgery alone. Therefore, we suggest that DFS could be an appropriate surrogate endpoint for OS in such circumstances. We additionally confirmed that the R0 resection was not a valid surrogate for both DFS and OS.

Several limitations affected our interpretation. First, this study had a retrospective nature and was limited by the heterogeneity of patient characteristics and treatments. Diverse patient region, surgical approaches, radiation dosages, and lack of standardization of imaging and staging modalities might obscure the impact of the neoadjuvant treatments, but we were unable to perform corresponding subgroup analyses owing to the limited data. Second, some potential confounders such as patient region were not considered in the construction of the propensity score model. The close similarity in results of the matched and unmatched analyses raised concern that the correlation due to matching may not have been optimally modeled. Third, our data were derived from limited centers; therefore, the generalizability of the findings required extensive validation in broader populations in future prospective trials. Additionally, our prediction model lacked tumor microenvironment-based variables. Hence, an integrated predictive biomarker based on more signatures, such as the methylation signature and tumor mutation burden should be considered to better guide appropriate neoadjuvant therapy.

In summary, our findings recommended that both NCRT and NCT had greater benefits on survival than does surgery alone and that, compared with NCT, NCRT significantly improved efficacy among patients with resectable esophageal carcinoma. We believe that the results of our study could guide future research and are important for policy and guideline revisions when choosing a treatment for patients with resectable esophageal carcinoma.

#### Declaration of Competing Interest

We declare no conflicts of interest.

#### Contributors

H-YZ, S-PZ, A-LL, Q-LG, Q-YO, ML, H-RY, and Y-FY conceived and designed the study. All authors analyzed and interpreted the data, and did the statistical analysis. H-YZ and S-PZ had full access to the data in the cohort study and take responsibility for the integrity and accuracy of the cohort data. A-LL, Q-LG, and Y-FY had full access to the data of meta-analysis and take responsibility for the integrity and

accuracy of the meta-analysis data. H-YZ, S-PZ, A-LL, Q-LG, Q-YO, D-GL, ML, H-RY, and Y-FY drafted the manuscript, and all authors revised the manuscript. H-YZ, S-PZ, ML, H-RY, and Y-FY provided administrative, technical, and material support. H-YZ, ML, H-RY, and Y-FY provided study supervision. All authors reviewed the manuscript and approved the final version

#### Consent for publication

Not applicable.

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#### Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100422.

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