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Definitive chemoradiotherapy versus neoadjuvant chemoradiotherapy followed by radical surgery for locally advanced oesophageal squamous cell carcinoma: meta-analysis

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Abstract

Background: The literature lacks robust evidence comparing definitive chemoradiotherapy (dCRT) with neoadjuvant chemoradiotherapy and surgery (nCRS) for oesophageal squamous cell carcinoma (ESCC). This study aimed to compare long-term survival of these approaches in patients with ESCC.

Methods: A systematic review performed according to PRISMA guidelines included studies identified from PubMed, Scopus, and Cochrane CENTRAL databases up to July 2021 comparing outcomes between dCRT and nCRS for ESCC. The main outcome measure was overall survival (OS), secondary outcome was disease-free survival (DFS). A meta-analysis was conducted using random-effects modelling to determine pooled adjusted multivariable hazard ratios (HRs).

Results: Ten studies including 14 092 patients were included, of which 30 per cent received nCRS. Three studies were randomized clinical trials (RCTs) and the remainder were retrospective cohort studies. dCRT and nCRS regimens were reported in six studies and surgical quality control was reported in two studies. Outcomes for OS and DFS were reported in eight and three studies respectively. Following meta-analysis, nCRS demonstrated significantly longer OS (HR 0.68, 95 per cent c.i. 0.54 to 0.87, $P < 0.001$) and DFS (HR 0.50, 95 per cent c.i. 0.36 to 0.70, $P < 0.001$) compared with dCRT.

Conclusion: Neoadjuvant chemoradiotherapy followed by oesophagectomy correlated with improved survival compared with definitive chemoradiation in the treatment of ESCC; however, there is a lack of literature on RCTs.

Introduction

Current national guidelines recommend that patients with locally advanced oesophageal squamous cell carcinoma (ESCC) be offered either definitive chemoradiotherapy (dCRT), or neoadjuvant chemoradiotherapy followed by radical surgery (nCRS)^{1,2}; however, the absence of clear guidance in favour of one treatment modality over another has led to significant variation in radical treatment strategies^{1,3,4}. This lack of clear evidence is reflected in at least one study highlighting the varied opinions regarding optimal treatment and a lack of either unified opinion or equipoise among surgeons and oncologists⁵.

While both dCRT and nCRS have been recognized as valid treatments for locally advanced ESCC^{1,6–11}, high-quality evidence supporting either treatment strategy over the other remains limited. Current national guidelines, including the National Comprehensive Cancer Network in the USA¹ and the National Institute for Health and Care Excellence in the UK², as

well as existing meta-analyses and a Cochrane review, draw exclusively upon the limited data from the only two randomized clinical trials (RCTs)^{12,13} comparing dCRT with nCRS. These failed to show any significant survival difference between the two treatment modalities, whereas more recent large-scale cohort studies have called this equipoise into question.

Despite ongoing interest in this topic, the quality of the majority of published data from cohort studies on this topic remains weak due to the high risk of bias from lack adjustment for relevant prognostic factors and the lack of stratified reporting of outcomes for patients with ESCC. Many studies group ESCC together with adenocarcinoma to represent oesophageal cancer as a whole, despite increasing recognition of the differences in tumour biology between the two histological subtypes, and differing responsiveness to treatments such as radiotherapy⁶.

Owing to the lack of clarity on comparative outcomes for the two predominant treatment strategies for ESCC, this study aims

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to perform a systematic review and meta-analysis of dCRT versus nCRS in patients with locally advanced ESCC.

Methods

Search strategy

A systematic review was performed according to the PRISMA Guidelines¹⁴. A systematic and comprehensive search was undertaken of MEDLINE, Embase, and Cochrane Library databases, searching for studies published until 23 July 2021. Searches of databases included the following terms: 'cancer of esophagus' or 'esophageal cancer' and 'chemoradiotherapy' and 'oesophagectomy' or 'esophagectomy'. The full search strategy with all the included search terms is presented in [Table S1](#). This systematic review and meta-analysis were prospectively registered on PROSPERO (CRD42021275438).

Inclusion and exclusion criteria

Inclusion criteria were: comparative studies that reported differences in patient survival after treatment for locally advanced (non-metastatic) ESCC with either dCRT or nCRS; studies communicated in the English language; studies

published between 2001 and 2020 inclusive; and high-quality studies as defined by criteria detailed below. Exclusion criteria were: studies that included patients with non-malignant indications for surgery or gastric malignancies; no stratification survival outcomes by patients with ESCC; non-comparative studies only reporting outcomes; studies not reporting overall survival (OS) or disease-free survival (DFS); case reports (fewer than five patients), review articles, conference abstracts; and studies including other operations and/or no surgical treatment.

After the primary literature search, three independent researchers screened the remaining titles and abstracts. Of the papers considered for inclusion, the full text was reviewed. When consensus on the inclusion of a study could not be reached, discrepancies were resolved by consulting the three senior researchers. Where multiple studies analysed the same data set or population, the most recent paper was selected unless different outcomes were reported.

Study outcomes

The primary outcome was OS, with secondary outcomes of DFS, as well as surgical outcomes in patients receiving nCRS. DFS

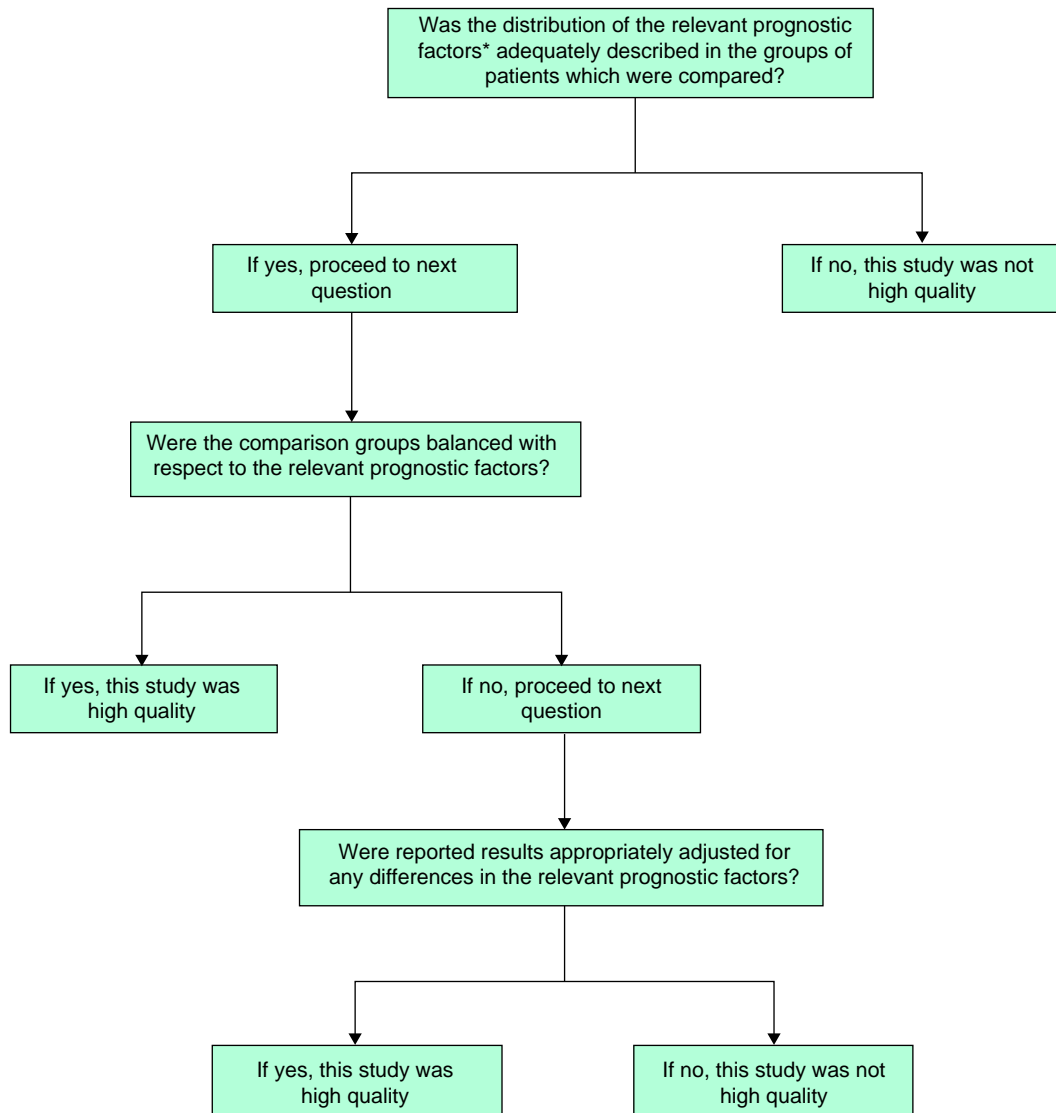


Fig. 1. Quality assessment flow chart

was defined as the time from surgery to first recurrence or last known follow-up.

Data extraction

Three researchers extracted the following data from the included studies: first author, year of publication, study interval, type of study design, number of patients, and geographical region. The reported patient characteristics were: age, BMI, sex, tumour site, anastomotic level and type, operation method (transthoracic, McKeown, minimally invasive, or transhiatal), and reported surgical outcomes in patients undergoing nCRS.

Assessment of study quality

Two researchers independently appraised the methodological quality and standard of outcome reporting of the included studies, with any discrepancies resolved through discussion among themselves or in consultation with the senior researchers. Studies were reviewed to assess evidence of control for major prognostic factors to assess risk of bias to determine the quality of studies, as shown in Fig. 1^{15,16}. Only studies meeting these criteria were included for subsequent meta-analysis. The quality of the included studies was assessed using the Risk of Bias In Non-randomized Studies of Exposures (ROBINS-E)¹⁷ and the Cochrane Risk of Bias for RCTs¹⁸.

Statistical analysis

This systematic review and meta-analysis was conducted in accordance with the recommendations of the Cochrane Library and PRISMA Guidelines^{14,19}. Data analysis was undertaken using R Foundation Statistical software (R 3.2.1; R Foundation for Statistical Computing, Vienna, Austria) as previously described, to produce a random-effects meta-analysis for each outcome, providing pooled odds ratios (ORs) with 95 per cent confidence intervals (c.i.). The I^2 test was used to evaluate statistical heterogeneity of the included studies, with levels of heterogeneity defined as not important (I^2 0–40 per cent), moderate (I^2 30–60 per cent), substantial (I^2 50–90 per cent), or considerable (I^2 75–100 per cent)²⁰. The chi-squared test was used for the same purpose, with a statistical significance level of $P < 0.050$ indicating the presence of statistical heterogeneity.

Results

Study characteristics

Of the 1068 studies identified from the literature search, 79 underwent full text review, of which 10^{12,13,21–28} were included in the systematic review and meta-analysis. Overall, 69 studies were excluded because of not having stratified outcomes by patients with ESCC (37 studies), not having high validity ($n = 18$), no inclusion of an nCRS cohort (six studies), no inclusion of a dCRT cohort (two studies), duplication with published studies

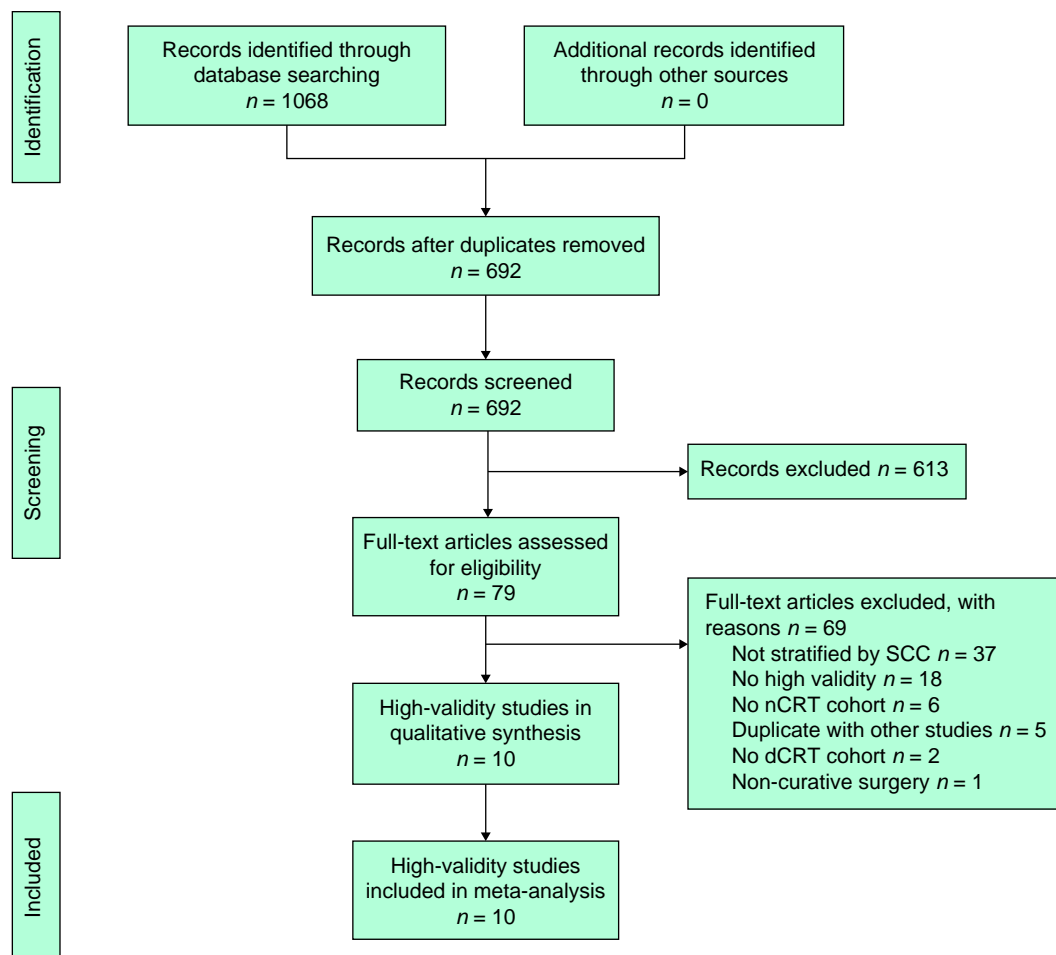


Fig. 2. dCRT, definitive chemoradiotherapy; nCRT, neoadjuvant chemoradiotherapy and surgery; SCC, squamous cell carcinoma

(five studies), and inclusion of non-curative surgery (one study). Reasons for exclusion are presented in [Table S2](#). Ten studies comprising 12 132 patients were included in the systematic review and meta-analysis as presented in [Fig. 2](#). Study, patient-, and tumour-level characteristics of included studies are presented in [Table 1](#). Studies identified were from Asia (four studies), Europe (three studies), North America (two studies), and South America (one study). All studies were either retrospective cohort studies (seven studies) or RCTs (three studies). The overall risk scores of the cohort studies according to ROBINS-E and RCTs according to the Cochrane Risk of Bias are reported in [Tables S3](#) and [S4](#) respectively.

Patient characteristics

The review included 14 092 patients, of which 64 per cent (8602 patients) received dCRT and 36 per cent ($n=4877$) received nCRS for ESCC. Tumour location was reported in six studies (12 132 patients) and rates of proximal, middle, and distal cancers were 22 per cent ($n=2619$), 37 per cent ($n=4497$), and 30 per cent ($n=3689$) respectively; however, tumour location between both groups was reported in six studies (dCRT, $n=7519$; and nCRS, $n=4525$). Rates of tumour location between dCRT and nCRS were similar for distal (15 per cent *versus* 15 per cent)

cancers, but higher with dCRT than nCRS for proximal (18 per cent *versus* 3 per cent), and middle (21 per cent *versus* 15 per cent) cancers. The majority of studies included patients with stage II–III ESCC (six studies), followed by stage I–III ($n=2$), stage I–IVA ($n=1$), and stage II–IV ($n=1$). The reported median follow-up across the included studies was 47.7 months (23.7–77.0 months).

Chemotherapy regimens

Oncological regimens were reported in six studies ([Table 2](#)). For chemotherapy regimens, in both dCRT and nCRS, cisplatin and 5-fluorouracil (5-FU) was used in three studies, followed by cisplatin and 5-FU/docetaxel in two studies, cisplatin and capecitabine in one study and 5-FU, folinic acid, epidoxorubicin, and cisplatin (FLEP) in one study. For radiotherapy regimens, the total dose delivered ranged from 40.0 to 66.0 Gy for dCRT and 40.0 to 50.4 Gy in nCRS.

Overall survival

OS was reported in eight studies, of which six reported a survival benefit with nCRS over dCRT; however, two studies did not demonstrate any survival benefit between the two treatment options. In a random-effects meta-analysis, patients who received

Table 1 Study and patient characteristics of included studies in the systematic review

Study name	Duration	Study country	Centres	Patients, (n)	Age, years (median [range])	Male, (%)	Clinical stage III, (%)
Randomized clinical trials							
Stahl 2005 ¹²	1994–2002	Germany	Multiple	172	57.0 (36.0–71.0)	80.2	16.9
Bedenne 2007 ¹³	1993–2000	France	Single	259	57.3 (9.2)*	93.4	NR
Park 2019 ²⁸	2012–2016	Korea	Single centre	37	60.0 (55.0–67.0)	96.3	54.1
Cohort studies							
Lee 2003 ²¹	1993–1996	Korea	Single centre	88	63.0 (42.0–81.0)	93.2	27.3
Liu 2017 ²²	2002–2012	Taiwan	Single centre	182	NR	78.0	75.8
Barbetta 2018 ²³	2000–2016	USA	Single	232	NR	54.3	66.0
Sheil 2018 ²⁴	2000–2014	Ireland	Single centre	222	NR	NR	NR
Wang 2019 ²⁵	2008–2014	Taiwan	Multiple registry	5832	NR	94.8	81.8
Duarte 2020 ²⁶	2000–2013	Brazil	Multiple registry	1347	NR	84.9	38.4
Kamarajah 2020 ²⁷	2004–2015	USA	Multiple NCDB	5621	NR	64.1	NR

Values are median unless otherwise indicated.

*mean (SD). NR, not reported; NCDB, National Cancer Database.

Table 2 Reporting of treatment regimens for definitive and neoadjuvant chemoradiotherapy of patients with oesophageal squamous cell carcinoma

Study name	Definitive chemoradiotherapy				Neoadjuvant chemoradiotherapy				Time to surgery (days)
	Chemotherapy regimen	Cycles, (n)	Radiotherapy dose, (Gy)	Radiotherapy fractions, (n)	Chemotherapy regimen	Cycles, (n)	Radiotherapy dose, (Gy)	Radiotherapy fractions, (n)	
Randomized clinical trials									
Stahl 2005 ¹²	FLEP	3	50–60	25–30	FLEP	3	40	20	NR
Bedenne 2007 ¹³	CF	5	45 or 66	NR	CF	2	45 or 66	NR	50–60
Park 2019 ²⁸	Cisplatin/capecitabine	2	50.4	28	Cisplatin/capecitabine	2	50.4	28	42–56
Cohort studies									
Lee 2003 ²¹	CF	4	60	40	CF	2	48	40	21–28
Liu 2017 ²²	Cisplatin + 5-FU/docetaxel	2	60	NR	Cisplatin + NVB/docetaxel	2	40	20	42
Barbetta 2018 ²³	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sheil 2018 ²⁴	NR	NR	NR	NR	CF	NR	40	15	NR
Wang 2019 ²⁵	NR	NR	NR	NR	NR	NR	NR	NR	NR
Duarte 2020 ²⁶	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kamarajah 2020 ²⁷	NR	NR	NR	NR	NR	NR	NR	NR	NR

FLEP, 5-fluorouracil, folinic acid, epidoxorubicin, and cisplatin; CF, cisplatin, 5-fluorouracil; 5-FU, 5-fluorouracil; NVB, navelbine.

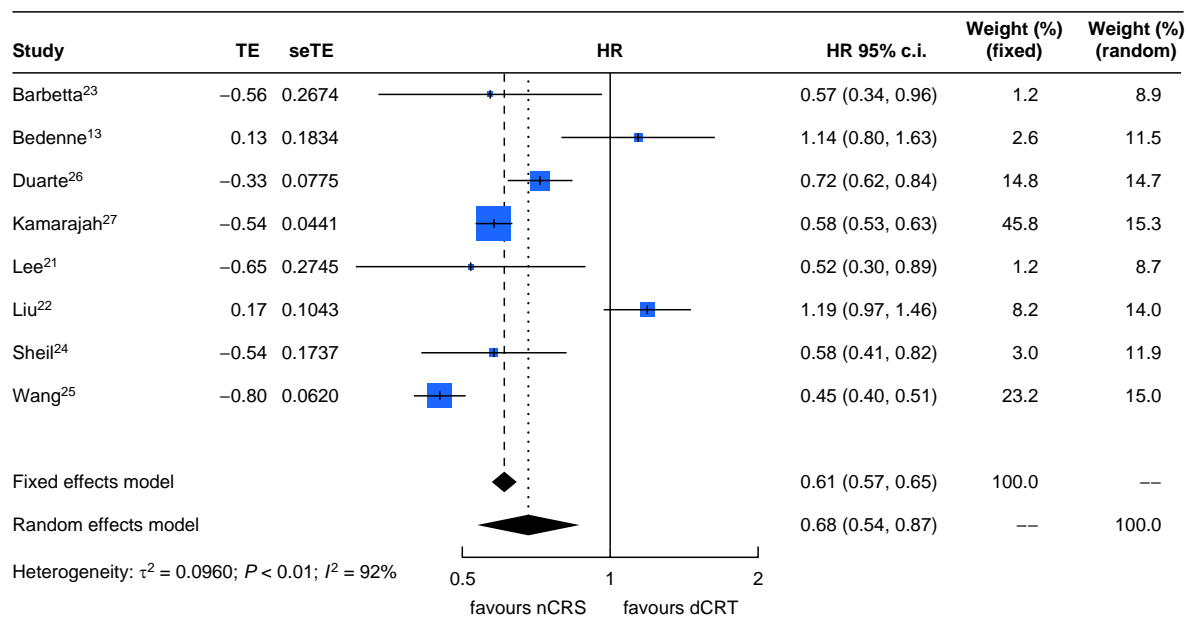


Fig. 3. Forest plot for effect of nCRS vs dCRT on overall survival. dCRT, definitive chemoradiotherapy; nCRS, neoadjuvant chemoradiotherapy and surgery; seTE, standard error of treatment estimate; TE, treatment effect

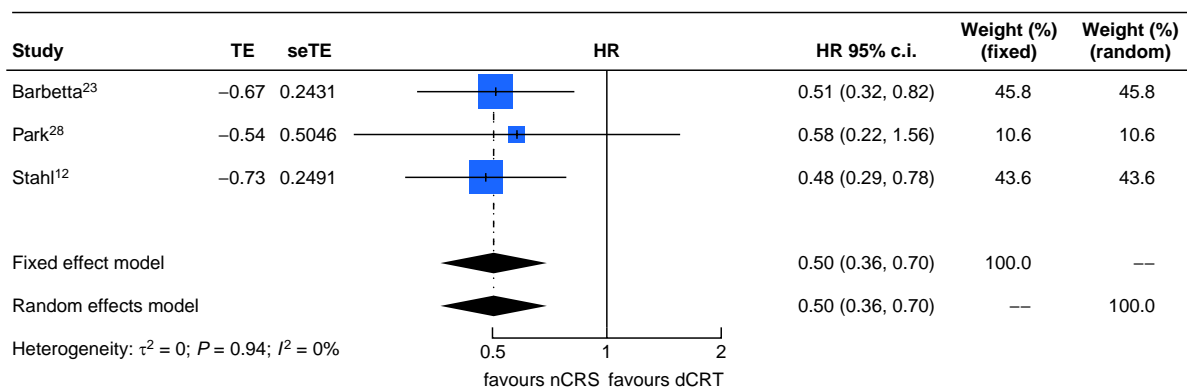


Fig. 4. Forest plot of effect of nCRS vs dCRT on disease-free survival. dCRT, definitive chemoradiotherapy; nCRS, neoadjuvant chemoradiotherapy and surgery; seTE, standard error of treatment estimate; TE, treatment effect

nCRS demonstrated significantly longer survival compared with those who received dCRT (HR 0.68, 95 per cent c.i. 0.54 to 0.87, $P < 0.001$; Fig. 3). There was significant heterogeneity ($I^2 = 92$ per cent, $P < 0.010$). Egger regression testing suggested that publication biases were minimal for reporting of OS ($P = 0.4$; Fig. S1).

Disease-free survival

DFS was reported in three studies, of which two reported a survival benefit for nCRS over dCRT, and one study reported no difference between groups. In a random-effects meta-analysis, patients who received nCRS demonstrated significantly longer survival than patients who received dCRT (HR 0.50, 95 per cent c.i. 0.36 to 0.70, $P < 0.001$; Fig. 4). Heterogeneity was low ($I^2 = 0$ per cent, $P = 0.94$). Egger regression testing suggested publication biases were minimal for reporting of OS ($P = 0.4$; Fig. S2). A sensitivity analysis was performed including only RCTs that demonstrated improvement DFS with nCRS over dCRT (HR 0.50, 95 per cent c.i. 0.32 to 0.77, $P = 0.002$; Fig. S3).

Histopathological outcomes

In patients receiving nCRS, histopathological margin status was reported in five studies. The overall rate of margin-negative resections was 75.1 per cent (263 of 350), ranging from 59.3 to 89.3 per cent. Pathological complete response (pCR) rates were reported in four studies. The overall rate of pCR was 29.1 per cent (90 of 309), ranging from 19.3 to 78.9 per cent. The outlier value of 78.9 per cent was reported by a study that randomized only patients that demonstrated clinical complete response to either dCRT or nCRS²⁸.

Discussion

This review synthesizes presently available high-quality evidence comparing dCRT versus nCRS treatment for ESCC. The resulting meta-analysis suggests that nCRS may offer advantages in OS and DFS compared with dCRT; however, it is important to note that there is a significant degree of heterogeneity, which may

reflect decision-making processes such as: persistence of tumour after completion of dCRT; recurrence more than 3 months after completion of dCRT (better prognosis); and local toxicity of dCRT (stenosis or perforation). Given the equipoise of current guidelines, and the preferential use of dCRT in some centres, data from this study have crucial implications in the decision-making process by those involved in the care of patients with ESCC globally²⁹. There is an urgent need to deliver high-quality research studies as previous trials were conducted more than a decade ago.

The conclusions of this meta-analysis stand in contrast to the two previous RCTs on the topic, which demonstrated no benefit in patients receiving surgery after chemoradiotherapy compared with dCRT alone^{12,13}. However, due to underlying quality issues within both these trials, their position of influence on modern treatment guidelines is increasingly being called into question³⁰. First, both these trials had small sample sizes and were underpowered for the main outcome. Furthermore, only 66 per cent of patients randomized to surgery in one RCT actually went on to receive surgery¹². These likely reflect difficulties in randomization and recruitment of patients to these trials⁵. Second, both RCTs lacked reporting surgical quality assurance, including the extent of lymphadenectomy performed. With a reported 90-day mortality of 13 per cent¹² and 9 per cent¹³, with a majority of deaths occurring in the perioperative interval, this is significantly higher than the perioperative mortality reported by high-volume centres^{31–36} and a recent population-based cohort study reporting a 90-day mortality rate of 8 per cent. Third, with reference to treatments, patients in the surgical arm of the trial by Stahl *et al.* received only 40 Gy of radiation in contrast with 50 Gy for patients in the non-surgical arm. This also highlights the variation internationally and within this study of what radiation dose is considered to be definitive³⁷. Further, consideration should be given to strict radiotherapy quality assurance and the finding that salvage oesophagectomy after radiotherapy doses of more than 55 Gy show prohibitive results in terms of morbidity and mortality³⁸.

To date, two other meta-analyses^{39,40} have partially compared nCRS with dCRT. One study was published some 10 years ago³⁹ and lacked sufficient detail to allow valid meta-analyses between the two treatment modalities, reporting only that nCRS was associated with improved long-term survival (HR 0.81, 95 per cent c.i. 0.70 to 0.95, $P=0.008$) and R0 rates (OR, HR 1.15, $P=0.043$) compared with upfront surgery (no comparison between dCRT and nCRS made). Second, another recent network meta-analysis⁴⁰ compared different treatments for oesophageal cancers and demonstrated that nCRS (HR 0.76, 95 per cent c.i. 0.67 to 0.85) and neoadjuvant chemotherapy and surgery (nCS) had significantly longer OS compared with surgery alone. Ranking analysis showed that nCRS with surgery was likely to be the best option in terms of efficacy; however, this review failed to perform stratified analyses for patients with ESCC and adenocarcinoma and to perform comparisons including dCRT.

The present review suggests a survival benefit for patients receiving nCRS, but also highlights the lack of prospective trial data involving modern treatment regimens. It suggests that a high-quality RCT incorporating current practices and treatments may be required to definitively address this question and alter the equipoise offered by current guidelines. The ongoing Swedish-led Neoadjuvant Chemoradiotherapy for Esophageal Squamous Cell Carcinoma *versus* Definitive Chemoradiotherapy with Salvage Surgery as Needed (NEEDS) trial, will aim to provide further evidence on the present topic and is currently in recruitment⁴¹.

The SANO trial⁴² on a related topic, seeks to compare intensive surveillance *versus* oesophagectomy in clinical complete responders with neoadjuvant therapy for oesophageal cancer.

Beyond survival outcomes, there are also few or no data comparing patient-related quality of life. With modern treatments resulting in increasing survival in ESCC overall, there is increasingly a focus on patient choice, acceptability of treatments, and the many factors that affect postoperative quality of life. Previous studies have suggested patients' willingness to trade a degree of survival benefit for convenience or perceived quality of life⁴³, and it is unclear to what degree intensive surveillance regimens after dCRT recommended by trials such as SANO might influence patient choice. Further, while standardization of oncological treatments must be aspired to, the rapid development in this area, such as recent data showing efficacy of nivolumab in oesophageal cancers, means that heterogeneity of treatments will continue to be a problem in considering the evidence for ESCC until an updated RCT is achieved⁴⁴. Finally, the role of surveillance for recurrence following dCRT⁴² and salvage oesophagectomy warrants closer evaluation, especially the high rates of morbidity and mortality in the latter.

There are several limitations to this study that must be considered. First, the selection criteria (adjusted or propensity-matched analysis) to address treatment selection bias and the potential for residual or unmeasured bias remains in retrospective cohort studies. These broadly include: decision-making of dCRT or nCRS by tumour location may not be captured as the former is preferred in patients with proximal cancers because surgery is associated with higher mortality; treatment protocols and preferences, which are varied across hospitals, including a wide range in radiation doses seen within the neoadjuvant group and the definitive chemoradiotherapy groups; and potential differences in approaches to clinical staging and adherence to current staging guidelines were not captured and may have led to heterogeneity and misclassification of clinical stage within the study cohort. Particularly OS data from the included studies demonstrated significant heterogeneity as reported in results, which limits generalizability of these findings; conversely, however, heterogeneity was low in the meta-analysis of DFS, with findings broadly in agreement with OS data.

Meta-regression was not performed owing to the small number of studies included. This study has sought to limit risk of bias by using a methodology to select only high-quality studies, and possibly the dearth of prospective trial data on this important topic means that a high-quality, up-to-date synthesis of available evidence as presented here is necessary and adds value to clinicians. Second, the specific regimens used for chemotherapy were not available in all included studies, especially in registry-based analyses. Therefore, any misclassification was likely to bias survival differences towards the null. As such, it was not possible to make any specific recommendations on the most effective chemoradiotherapy regimen based on any comparative data—although the most up-to-date trial data would seem to suggest the CROSS regimen⁶. Third, recurrence data are not widely reported across the included studies; thus, this present review was not able to analyse the pattern of recurrence following different therapeutic strategies. This would be especially important in the context of cohort studies outside RCTs where follow-up protocols may vary across studies and between nCRS and dCRT. Finally, there is variable reporting of surgical quality control, histopathological outcomes, and salvage oesophagectomies in patients undergoing dCRT, thus precluding a sensitivity analysis comparing patients receiving salvage

surgery after dCRT with nCRS. The potential issue of surgical quality control is also highlighted by the high rates of margin positivity reported in the present study, which are significantly higher than benchmarks recommended by the recent ECCG group^{45,46}. Though differences in histopathological assessment and patient populations may also play a role⁴⁷, this further draws attention to the need for additional prospective high-quality trial data on this topic.

There remains significant equipoise regarding the optimum radical treatment for ESCC. This meta-analysis suggests a possible benefit for nCRS, compared with dCRT, for both OS and DFS. High-quality prospective trial data are lacking and further research is urgently required to optimize patient care and outcomes

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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