Meta-analysis

Meta-analysis of neoadjuvant treatment modalities and definitive non-surgical therapy for oesophageal squamous cell cancer

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Background: **The standard treatment for resectable oesophageal squamous cell carcinoma (OSCC) is surgical resection with adequate lymphadenectomy. Most Western patients receive neoadjuvant chemotherapy or chemoradiotherapy (CRT). In recent years some patients have received CRT alone (definitive CRT, dCRT). This meta-analysis sought to clarify the benefits of neoadjuvant and definitive treatment for OSCC.**

Methods: **Eligible randomized controlled trials (RCTs) were identified using the Cochrane database, MEDLINE and Embase. Only RCTs with intention-to-treat analysis, and published hazard ratios (HRs) or estimates from survival data, were included.**

Results: **Nine RCTs involving neoadjuvant CRT *versus* surgery, eight involving neoadjuvant chemotherapy *versus* surgery, and three involving neoadjuvant treatment followed by surgery or surgery alone *versus* dCRT were identified. The HR for overall survival was 0·81 (95 per cent confidence interval 0·70 to 0·95; $P = 0·008$) after neoadjuvant CRT and 0·93 (0·81 to 1·08; $P = 0·368$) after neoadjuvant chemotherapy. The likelihood of R0 resection was significantly higher after neoadjuvant treatment (CRT: HR 1·15, $P = 0·043$; chemotherapy: HR 1·16, $P = 0·006$). Morbidity rates were not increased after neoadjuvant CRT (HR 0·94, $P = 0·363$) but 30-day mortality was non-significantly higher with combined treatment. Morbidity (HR 1·03, $P = 0·638$) and mortality (HR 1·04, $P = 0·810$) rates after neoadjuvant chemotherapy and surgery did not differ from those after surgery alone. None of the RCTs reporting outcome after dCRT demonstrated a significant survival benefit, but treatment-related mortality rates were lower (HR 7·60, $P = 0·007$) than with neoadjuvant treatment followed by surgery or surgery alone.**

Conclusion: **For patients with resectable OSCC, a significant survival benefit for neoadjuvant CRT was evident, with no increase in morbidity rate. dCRT did not demonstrate any survival benefit over other curative strategies.**

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Introduction

Treatment of resectable oesophageal cancer remains controversial as oesophageal squamous cell carcinoma and oesophageal adenocarcinoma are studied together in most clinical trials. There is general consensus that the two cancers should be considered as different diseases[1]. With the exception of a small number of patients with early cancers confined to the mucosa, attempted curative therapies for squamous cell carcinoma involve either neoadjuvant treatment (chemotherapy or chemoradiotherapy, CRT) followed by oncological resection[2], or CRT alone[3,4]. Two previous meta-analyses have shown significant advantages for neoadjuvant treatment regarding local tumour control and disease-free survival[5,6]. There is still debate, however, about the adverse effects of neoadjuvant therapies and whether they increase

perioperative morbidity and mortality rates[7]. A number of randomized controlled trials (RCTs) and long-term follow-up data from previous trials addressing multimodal therapy concepts have been published recently. The present meta-analysis was therefore undertaken to include these recent results and further evaluate multidisciplinary treatments for oesophageal squamous cell carcinoma.

Methods

The objective, inclusion and exclusion criteria, outcome parameters, and methods of analysis were predefined. A systematic literature search was conducted independently by two authors using validated methods according to recommendations of the Cochrane Collaboration[8]. The search strategy was based on combinations of medical subject heading terms without any restrictions on publication date, but confined to the English language. The last search was carried out on 31 March 2010. Search terms included the following medical subject headings: oesophageal squamous cell cancer, surgery, radiotherapy, chemotherapy, chemoradiation, neoadjuvant and definitive treatment. Searched databases include the Cochrane Library database CENTRAL, MEDLINE, Premedline, Journals Ovid, Embase, Biosis and the Science Citation Index Database. Reference lists of retrieved relevant articles were also searched and previous published meta-analyses identified for additional trials[2,9–11].

Study selection

All stages of study selection, data abstraction and quality assessment were done independently by two reviewers. Search findings were screened for potentially eligible studies and restricted to RCTs, reviews of the literature and meta-analyses. Only trials with analysis by intention to treat were included. Abstracts and full articles were obtained for detailed evaluation. Any disagreements during the selection, extraction and assessment process were resolved by discussion with a third author.

Eligibility criteria

Publications that met the following criteria were eligible for inclusion: pathological diagnosis of invasive oesophageal cancer; patient survival as an outcome measure; RCTs comparing neoadjuvant CRT[12–22] or chemotherapy[15,18,23–30] *versus* surgery alone, and RCTs comparing neoadjuvant treatment or surgery with defintive CRT (dCRT)[3,4,31]. RCTs that included patients with oesophageal adenocarcinoma but reported squamous cell cancer and adenocarcinoma survival data separately were also included. If a study generated multiple publications, the most comprehensive report was used.

The methodological quality of included studies was assessed using a standard form to extract prespecified parameters[32–35]. The critical appraisal of extracted data included analysis of the randomization procedure, allocation concealment, sample size calculation, consistency of the study population, length and quality of follow-up, rate of patients lost to follow-up, and statistical analysis of individual trials.

The meta-analysis examined the following outcomes: 1-, 2-, 3- and 5-year survival rates, frequency of complete (R0) resection, overall morbidity and mortality rates, and rates of cancer recurrence.

Estimates of survival probabilities were obtained from individual trials using the most reliable data available (hazard ratio, HR, with 95 per cent confidence interval, c.i.). Resection was defined as any resection (curative or palliative), not including surgical bypass operations or explorative procedures. Complete resection was defined as microscopically complete R0 resection. For morbidity and mortality, 30-day values were used. Overall recurrence was defined as any type of cancer recurrence (radiological, symptomatic, biopsy-proven; local, regional, distant; or any combination of these).

Statistical analysis

Statistical analyses were performed using Review Manager (RevMan) software, version 5.0 (Cochrane Collaboration, Oxford, UK). Heterogeneity of reported effects between considered trials was assessed by the inconsistency statistic (I^2) and connected χ^2 test. In consideration of the heterogeneous nature of any surgical procedure resulting from environment, centre and surgeon, random-effects models were employed to estimate population HRs with 95 per cent c.i. by the inverse variance method[36,37]. If a reference provided insufficient information regarding estimates of HRs and 95 per cent c.i., reported total numbers of deaths, median survival times and P values from the log rank test were used for estimation of effect sizes and confidence limits as suggested by Parmar and colleagues[38]. For frequency data, such as operative mortality, morbidity and R0 resection rates, the population risk and/or HRs were estimated by the Mantel–Haenszel method along with 95 per cent c.i. Two-sided $P < 0{\cdot}050$ was considered statistically significant.

As diverse treatment modalities were evaluated, the eligible studies were grouped into different treatment approaches for comparison: neoadjuvant CRT *versus* surgery, neoadjuvant chemotherapy *versus* surgery, and

dCRT *versus* neoadjuvant treatment followed by surgery or surgery alone.

Results

Fig. 1 gives an overview of data extraction for meta-analysis and review of the literature[39]. Twenty eligible studies were identified. There were eight RCTs[3,4,15,22,31,40–42] that had not been not included in the most recently published meta-analysis[2]. With the exception of five trials[14,19,20,23,25], all were restricted to squamous cell carcinomas.

Nine RCTs with 1099 patients (published 1992–2008) compared neoadjuvant CRT with surgery alone[12–14,16–21] (*Table 1*). Two trials were considered separately as they had incomplete survival data[15,22] but resection, morbidity and mortality rates were included where applicable[15]. Eight RCTs compared neoadjuvant chemotherapy with surgery alone[18,23–30]. These trials, published between 1988 and 2002, involved 1707 patients (*Table 2*). Two trials were again reported separately because they had incomplete survival data[15,41], but resection, morbidity and mortality rates were included where applicable[15]. Three RCTs (512 patients, published 2005–2006) compared outcome after dCRT with neoadjuvant treatment and surgery[3,4] or surgery alone[31] (*Table 3*).

All RCTs contained sufficient data to obtain estimates of effects of multimodal treatments. Although most trials did not provide sufficient details of randomization methods, allocation concealment was considered not to be compromised. Formal quality assessment could not be incorporated, as the reporting methods of the different studies varied considerably.

Neoadjuvant chemoradiotherapy followed by surgery *versus* surgery alone

In the nine RCTs comparing neoadjuvant CRT with surgery alone[12–14,16–21], 554 of 1099 patients received CRT before surgery. Six studies were restricted to squamous cell cancer and three[14,19,20] also enrolled patients with adenocarcinoma (*Table 1*). The mean(s.d.) age was 60·8(2·5) years and 87 per cent of the patients were men. The sample size ranged from 56 to 282 patients. Inclusion criteria were uniform in all RCTs with locally advanced but resectable oesophageal carcinoma. For preoperative tumour staging, all patients underwent endoscopy with biopsy. Computed tomography (CT) was performed routinely in six studies[12–14,17,19,20], but endoscopic ultrasonography (EUS) in only two[17,19]. No study used positron emission tomography (PET)–CT for staging. Preoperative tumour node metastasis (TNM)

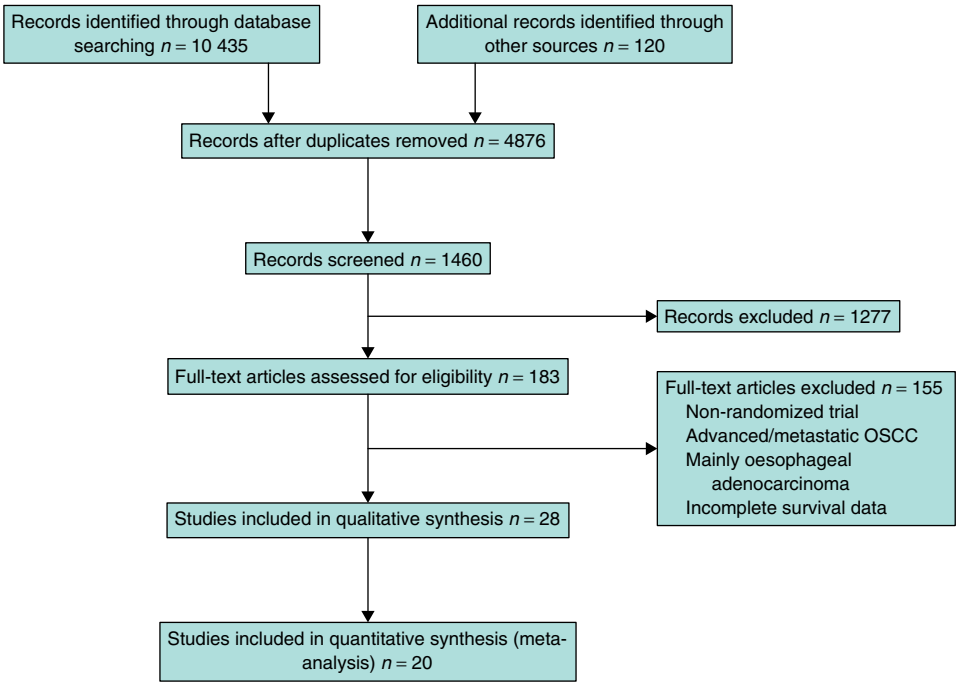

Fig. 1 Overview of data extraction for meta-analysis and review of the literature according to the PRISMA statement[39]. OSCC, oesophageal squamous cell carcinoma

Table 1 Trials of neoadjuvant chemoradiotherapy plus surgery *versus* surgery alone

Reference	Accrual period	No. of patients	Histology	Stage	Radiation dose	Chemotherapy	Interval to surgery (weeks)	Median follow-up (months)
Apinop *et al.*[12]	1986–1992	69	OSCC	–	40 Gy 2 Gy/fraction 4 weeks	Cisplatin 100 mg/m^2 5-FU 1000 mg/m^2 2 cycles, concurrent	–	12 (e)
Bosset *et al.*[13]	1989–1995	282	OSCC	T1–3 N0–1 M0	37 Gy 3.7 Gy/fraction 2 weeks	Cisplatin 80 mg/m^2 2 cycles, sequential	3	55
Burmeister *et al.*[14]	1994–2000	256	OSCC AC	T1–3 N0–1 M0	35 Gy 2.3 Gy/fraction 3 weeks	Cisplatin 80 mg/m^2 5-FU 800 mg/m^2 Concurrent	3–6	65
Lee *et al.*[17]	1993–1996	101	OSCC	T1–3 N0–1 M0	45.6 Gy 1.2 Gy/fraction 28 days	Cisplatin 60 mg/m^2 5-FU 1000 mg/m^2 Concurrent	3–4	25
Le Prise *et al.*[16]	1988–1991	86	OSCC	T1–3 N0 M0	20 Gy 2 Gy/fraction 12 days	Cisplatin 100 mg/m^2 5-FU 600 mg/m^2 2 cycles, sequential	2	12 (e)
Nygaard *et al.*[18]	1983–1988	88	OSCC	T1–2 N0–1 M0	35 Gy 1.75 Gy/fraction 4 weeks	Cisplatin 20 mg/m^2 Bleomycin 5 mg/m^2 2 cycles, sequential	3	18 (e)
Tepper *et al.*[19]	1997–2000	56	OSCC AC	T1–3 N0–1 M0	50.4 Gy 1.8 Gy/fraction 5–6 weeks	Cisplatin 60 mg/m^2 5-FU 1000 mg/m^2 2 cycles, concurrent	3–8	60
Urba *et al.*[20]	1989–1994	100	OSCC AC	T1–3 N0–1 M0	45 Gy 1.5 Gy/fraction 3 weeks	Cisplatin 20 mg/m^2 Vinblastine 1 mg/m^2 5-FU 300 mg/m^2 2 cycles, concurrent	3	98
Walsh[21]	1990–1995	61	OSCC	T1–3 N0–1 M0	40 Gy 2.7 Gy/fraction 3 weeks	Cisplatin 75 mg/m^2 5-FU 15 mg/kg 2 cycles, concurrent	2	10
Cao *et al.*[15]*	1991–2000	236	OSCC	T1–4 N0–1 M0	40 Gy 2 Gy/fraction 4 weeks	Cisplatin 20 mg/m^2 5-FU 500 mg/m^2 Mitomycin 10 mg/m^2 2 cycles, concurrent	2–3	60
Natsugoe *et al.*[22]*	1997–2001	45	OSCC	T2–3 N0–1 M0–1 (ly)	40 Gy 2 Gy/fraction 4 weeks	Cisplatin 7 mg in 2 h 5-FU 350 mg in 24 h	–	24

*Trial excluded from meta-analysis as survival data incomplete. OSCC, oesophageal squamous cell carcinoma; –, not stated; 5-FU, 5-fluorouracil; e, estimated; TNM, tumour node metastasis; AC, oesophageal adenocarcinoma; ly, lymphatic invasion.

status was distributed homogeneously between treatment and control groups.

There was marked variation in radiotherapy dose and scheduling as well as different neoadjuvant chemotherapy regimens (*Table 1*). Total doses ranged from 20 Gy[16] to 50·4 Gy[19]. Daily doses varied from 1·2 Gy[17] to 3·7 Gy[13], including a final boost treatment of 5·4 Gy in one trial[19]. The number of fractions given ranged from ten[13] to 38[17]. According to the chemotherapy protocol, cisplatin was administered as monotherapy[13], or in combination with either 5-fluorouracil (5-FU)[12,14,16,17,19–21] and vinblastine[20] or bleomycin[18] in variable doses and schedules. In 453 (82 per cent) of 554 patients, neoadjuvant treatment was completed according to the study protocol and dose reduction was necessary in approximately 10 per cent.

Surgery was performed between 2 weeks[16,21] and 8 weeks[19] after completion of neoadjuvant treatment (mean 3 weeks[13,14,17,18,20]). The preferred approach was through abdominal and right thoracotomy incisions together with two-field lymphadenectomy and gastric conduit formation in two trials[19,20], and some transhiatal resections in patients with limited cardiopulmonary reserve.

Postoperative pathological tumour stage was reported in seven RCTs[13–17,20,22] with a pathological complete response (pCR) in 11 per cent[16] to 43 per cent[17] of patients (*Table 4*).

The overall resection rate (curative and palliative) ranged from 80 per cent[18] to 98 per cent[13]. R0 resection rates were reported in seven RCTs[13–18,20], ranging from 55 per cent[18] to 100 per cent[17] with combined

Table 2 Trials of neoadjuvant chemotherapy plus surgery *versus* surgery alone

Reference	Accrual period	No. of patients	Histology	Stage	Chemotherapy	Interval to surgery (weeks)	Median follow-up (months)
Ancona *et al.*[30]	1992–1997	96	OSCC	T1–3 N0–1 M0	Cisplatin 100 mg/m^2 5-FU 1000 mg/m^2 2 cycles	3–4	24
Kelsen *et al.*[25]	1990–1995	440	OSCC AC	T1–3 N0–1 M0	Cisplatin 100 mg/m^2 5-FU 1000 mg/m^2 3 cycles	2–4	56
Law *et al.*[26]	1989–1995	147	OSCC	T1–3 N0–1 M0	Cisplatin 100 mg/m^2 5-FU 500 mg/m^2 2 cycles	2	17
Maipang *et al.*[27]	1988–1990	46	OSCC	T1–2 N0 M0	Cisplatin 100 mg/m^2 Vinblastine 3 mg/m^2 Bleomycin 10 mg/m^2 2 cycles	2	17 (e)
MRC[23] Allum *et al.*[24]	1992–1998	802	OSCC AC	T1–3 N0–1 M0	Cisplatin 80 mg/m^2 5-FU 1000 mg/m^2 2 cycles	3–5	37
Nygaard *et al.*[18]	1983–1988	91	OSCC	T1–2 N0–1 M0	Cisplatin 20 mg/m^2 Bleomycin 10 mg/m^2 2 cycles	3	18
Roth *et al.*[28]	1982–1986	39	OSCC	–	Cisplatin 120 mg/m^2 Vindesine 3 mg/m^2 Bleomycin 10 U/m^2 2 cycles	–	20
Schlag[29]	1992	46	OSCC	–	Cisplatin 20 mg/m^2 5-FU 1000 mg/m^2 3 cycles	–	75
Cao *et al.*[15]*	1991–2000	237	OSCC	T1–4 N0–1 M0	Cisplatin 20 mg/m^2 5-FU 500 mg/m^2 Mitomycin 10 mg/m^2 2 cycles	2–3	60
Baba *et al.*[41]*	1993–1995	42	OSCC	T1–3 N0–1 M0	Cisplatin 70 mg/m^2 5-FU 700 mg/m^2 Leucovorin 20 mg/m^2 2 cycles	3–4	–

*Trial excluded from meta-analysis as survival data incomplete. OSCC, oesophageal squamous cell carcinoma; TNM, tumour node metastasis; 5-FU, 5-fluorouracil; AC, oesophageal adenocarcinoma; e, estimated; MRC, Medical Research Council; –, not stated.

Table 3 Trials of definitive chemoradiotherapy *versus* neoadjuvant treatment followed by surgery or surgery alone

Reference	Accrual period	Histology	Stage	No. of patients	Intervention	R0 resection (%)	Median survival (months)	Survival (%)		*P**
								2 years	3 years	
Bedenne *et al.*[3]	1993–2000	OSCC	T1–3 N0–1 M0	129	Cisplatin, 5-FU, 46 Gy + oesophagectomy	75	18	34	–	NS
				130	Cisplatin, 5-FU, 66 Gy	–	19	40	–	
Stahl *et al.*[4]	1994–2002	OSCC	T3–4 N0–1 M0	86	Cisplatin, 5-FU, leucovorin, etoposide, 40 Gy + oesophagectomy	82	16	40	31	NS
				86	Cisplatin, 5-FU, leucovorin, etoposide, 65 Gy	–	15	35	24	NS
Chiu *et al.*[31]	2000–2004	OSCC	T2–3 N1 M0	45	Oesophagectomy		24	55	–	
				36	Cisplatin, 5-FU, 50–60 Gy		21	58	–	

OSCC, oesophageal squamous cell carcinoma; TNM, tumour node metastasis; 5-FU, 5-flurouracil; –not stated. *Comparison of survival; NS, not significant.

Table 4 Overview of tumour node metastasis category, and pathological complete response rates after neoadjuvant chemoradiotherapy compared with surgery alone

Reference	TNM category	Neoadjuvant CRT (%)	Surgery (%)	*P*	pCR (%)
Bosset *et al.*[13]	T0	26	0	0·001 (T)	26
	T1	24	28		
	T2	21	18		
	T3	28	50		
	T4	2	4		
	N0	59	44	0·03 (N)	
	N1	38	55		
Burmeister *et al.*[14]	N1	43	67	0.003	27
Lee *et al.*[17]	T0	49	0	0·001 (T)	43
	T1	11	7		
	T2	17	17		
	T3	23	72		
	T4	0	4		
	N0	63	22	0·001 (N)	
	N1	37	78		
Le Prise *et al.*[16]	T0 N0	11	0	NS (T/N)	11
	T0 N1	3	0		
	T1 N0	3	7		
	T3 N0	11	17		
	T3 N1	17	29		
Urba *et al.*[20]	—	—	—	—	38
Cao *et al.*[15]	T2–3 N0	54	0	0·005 (T2–3 N0)	23
	T1–2 N1	14	5		
	T3 N1	31	92		
	T1–4 N0–1 M1	1	3		
Natsugoe *et al.*[22]	Ly−	55	13	0·003 (Ly)	—
	Ly+	45	87		
	V−	60	22	0·01 (V)	
	V+	40	78		

TNM, tumour node metastasis; CRT, chemoradiotherapy; pCR, pathological complete response rate; NS, not significant; –, not stated; Ly−, lymphatic invasion-negative; Ly+, lymphatic invasion-positive; V−, venous invasion-negative; V+, venous invasion-positive.

treatment and from 37 per cent[18] to 100 per cent[16] in the surgery-alone group. The likelihood of R0 resection was significantly greater after neoadjuvant CRT (HR 1·15, 1·00 to 1·32; $P = 0·043$) (*Fig. 2*).

Complications during or after neoadjuvant therapy were reported in seven trials[13–17,19,20], with rates ranging from 2 to 78 per cent[14,20] (mainly World Health Organization (WHO) grade 3–4 toxicities). Postoperative morbidity rates were 5–80 per cent with combined treatment and 3–92 per cent in the surgery-alone group. The most frequent adverse events were cardiopulmonary complications (14 per cent in the CRT and 12 per cent in the surgery-alone group) and anastomotic leakage (7 *versus* 6 per cent). Neither cardiopulmonary complication nor anastomotic leakage rates differed significantly between the two groups. Postoperative morbidity rates after neoadjuvant treatment were not increased compared with those after surgery alone (HR 0·94, 0·82 to 1·07; $P = 0·363$) (*Fig. 3*). There were no clear descriptions of cumulative morbidity in relation to all phases of treatment.

In contrast, the postoperative 30-day mortality rate was higher with combined treatment (8 *versus* 5 per cent), reaching statistical significance in one RCT[13] but not in the meta-analysis (HR 1·46, 0·91 to 2·33; $P = 0·116$) (*Fig. 4*). In some trials, chemotherapy and radiotherapy were not delivered concurrently[13,16,18]. However, no significant difference in 30-day mortality rate was noted between concurrent and sequential treatment methods.

Overall postoperative hospital stay (mean(s.d.) 20·2(7·3) days) was reported in five trials[13,14,16,17,19]. Only two studies provided detailed data on duration of hospital stay for both treatment groups separately[17,19]. There was no significant correlation between length of hospital stay and morbidity rates between the groups.

Hazard ratios for overall survival after CRT followed by surgery *versus* surgery alone, together with the pooled estimate, are shown in *Fig. 5*. In total, the estimates of effect significantly favoured neoadjuvant CRT (HR 0·81, 0·70 to

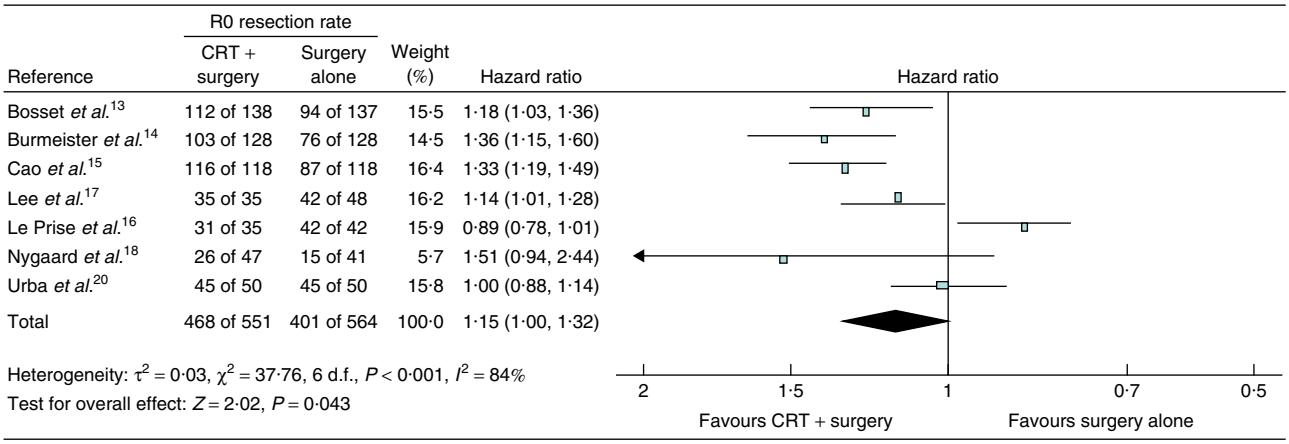

Fig. 2 Meta-analysis of probability of R0 resection with neoadjuvant chemoradiotherapy (CRT) plus surgery *versus* surgery alone. A Mantel–Haenszel random-effects model was used. Hazard ratios are shown with 95 per cent confidence intervals

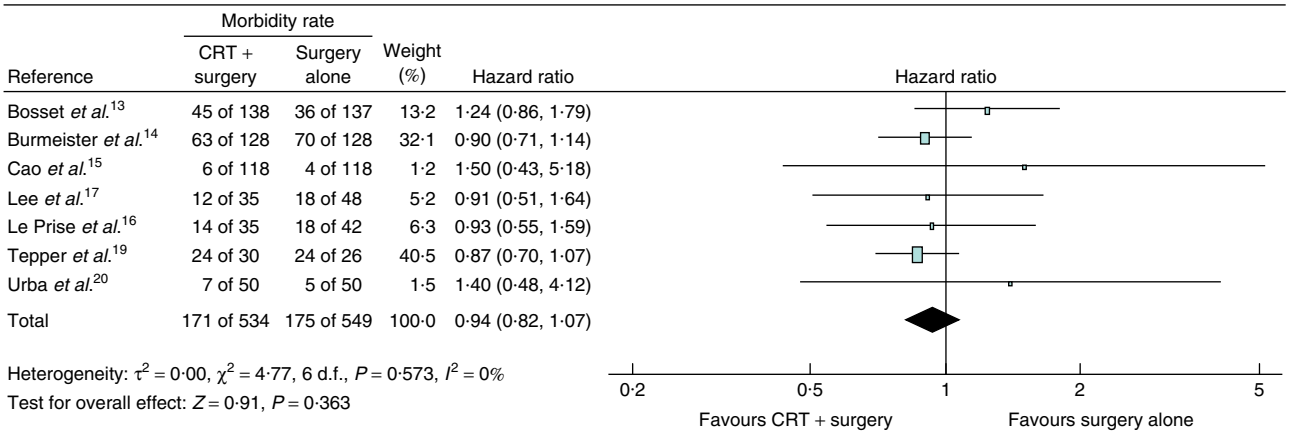

Fig. 3 Meta-analysis of postoperative morbidity after neoadjuvant chemoradiotherapy (CRT) plus surgery *versus* surgery alone. A Mantel–Haenszel random-effects model was used. Hazard ratios are shown with 95 per cent confidence intervals

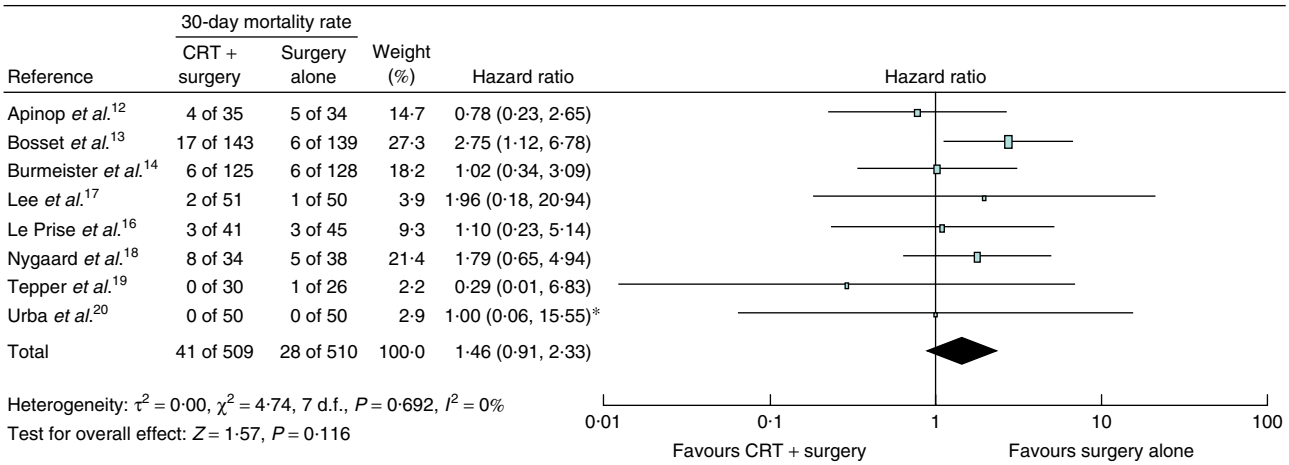

Fig. 4 Meta-analysis of 30-day mortality after neoadjuvant chemoradiotherapy (CRT) plus surgery *versus* surgery alone. A Mantel–Haenszel random-effects model was used. *Estimated by adding one ancillary pseudo-event to each event-free study group. The pseudo-events have been included in the total events. Hazard ratios are shown with 95 per cent confidence intervals

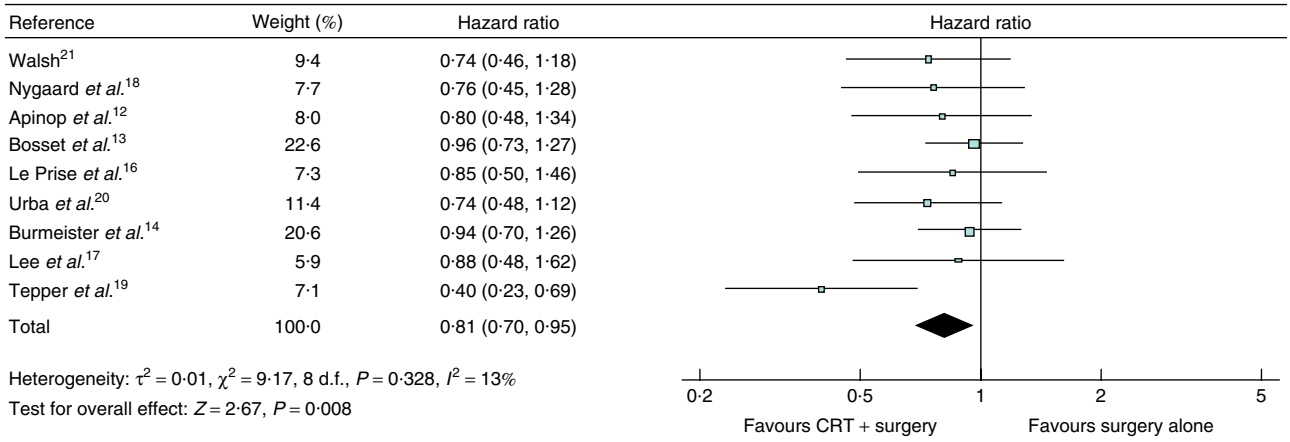

Fig. 5 Meta-analysis of overall survival estimates after neoadjuvant chemoradiotherapy (CRT) plus surgery *versus* surgery alone. The combined estimate (all published studies) was based on 554 patients receiving radiation and 545 receiving surgery alone. Hazard ratio estimates were calculated by the inverse variance method in a random-effects model; the size of each filled square is proportionate to the inverse variance (sample size). Hazard ratios are shown with 95 per cent confidence intervals

0·95; $P = 0·008$). There was no evidence of heterogeneity between the trials or any temporal effect ($P = 0·328$).

Two studies were not eligible for meta-analysis as their survival data were incomplete. In one trial, 45 patients (International Union Against Cancer (UICC) II–IV) were randomized to either neoadjuvant CRT (22 patients; 40 Gy, cisplatin and 5-FU) or surgery alone (23 patients)[22]. The frequency of lymphatic ($P = 0·003$) and venous ($P = 0·01$) invasion was significantly lower in the CRT group, but 5-year survival was the same (57 *versus* 41 per cent; $P = 0·58$). In a recently published trial[15], 473 patients were randomized into four groups: neoadjuvant chemotherapy, radiotherapy or CRT and surgery alone (control group). The R0 resection rate in the CRT group was significantly higher than after surgery alone ($P < 0·001$), as was the 3-year survival probability (73 *versus* 53 per cent; $P < 0·005$). There was no significant difference in treatment-related complications between neoadjuvant treatment and the control group.

Neoadjuvant chemotherapy followed by surgery *versus* surgery alone

The eight RCTs comparing neoadjuvant chemotherapy followed by surgery *versus* surgery alone[18,23–30] included 1707 patients, 757 of whom received chemotherapy before surgery (*Table 2*). Of these, two trials[23,25] also enrolled patients with oesophageal adenocarcinoma.

The mean(s.d.) age was 62·5(2·2) years and 79 per cent of the patients were men. The sample size varied between 39 and 802 patients. Inclusion criteria were uniform in all RCTs with advanced but resectable oesophageal carcinoma. For preoperative tumour staging, all patients underwent endoscopy with biopsy. CT was routine in four studies[23,25,27,30], but EUS was used in only one[30]. No study used PET–CT for staging. There were no differences in tumour stages between treatment and control groups.

The therapeutic regimens are summarized in *Table 2*. Again there was marked heterogeneity between the protocols. Cisplatin was administered in combination with either 5-FU[23,25,26,29,30] or bleomycin[18,27,28] in variable doses and schedules. In two trials vinblastine and vindesine were combined with cisplatin[27,28]. About two-thirds of patients completed the planned protocol. Dose reduction was necessary in approximately 10 per cent.

Surgery was performed between 2 weeks[25–27] and 5 weeks[23] weeks after completion of neoadjuvant treatment (mean 3 weeks[18,23,25,30]). The preferred approach was through abdominal and right thoracotomy incisions together with two-field lymphadenectomy and gastric conduit. In one trial, transhiatal resections in patients with limited cardiopulmonary reserves were also used[26].

Postoperative pathological tumour stage was assessed in all but two RCTs[18,27]. A pCR after neoadjuvant treatment was reported in 3 per cent[25] to 50 per cent[29] of patients (*Table 5*).

The overall resection rate (curative and palliative) was between 70 per cent[29] and 95 per cent[30]. R0 resection rates were reported in six RCTs[15,18,23,25,26,30], ranging from 44 per cent[18] to 87 per cent[15] with combined treatment and from 35 per cent[26] to 74 per cent[30] in the surgery-alone group. Patients treated with neoadjuvant chemotherapy had a significantly higher R0 resection

Table 5 Overview of tumour node metastasis category, and pathological complete response rates after neoadjuvant chemotherapy compared with surgery alone

Reference	TNM category	Neoadjuvant chemotherapy (%)	Surgery (%)	*P*	pCR (%)
Ancona *et al.*[30]	–	–	–	–	13
Kelsen *et al.*[25]	–	–	–	–	3
Law *et al.*[26]	T0	7	0	< 0·001 (T)	7
	T1	13	3		
	T2	13	6		
	T3	45	35		
	T4	22	57		
	N0	30	12	0·009 (N)	
	N1	70	88		
MRC[23]	N1	58	68	0·009	–
Roth *et al.*[28]	–	–	–	–	–
Schlag[29]	–	–	–	–	50
Cao *et al.*[15]	T2–3 N0	3	0	NS (T/N)	–
	T1–2 N1	13	5		
	T3 N1	82	92		
	T1–4 N0–1 M1	3	3		
Baba *et al.*[41]	T1	29	33	NS (T/N)	–
	T2	14	5		
	T3	38	48		
	T4	19	14		
	N0	38	43		
	N1	62	57		

TNM, tumour node metastasis; pCR, pathological complete response rate; –, not stated; MRC, Medical Research Council; NS, not significant.

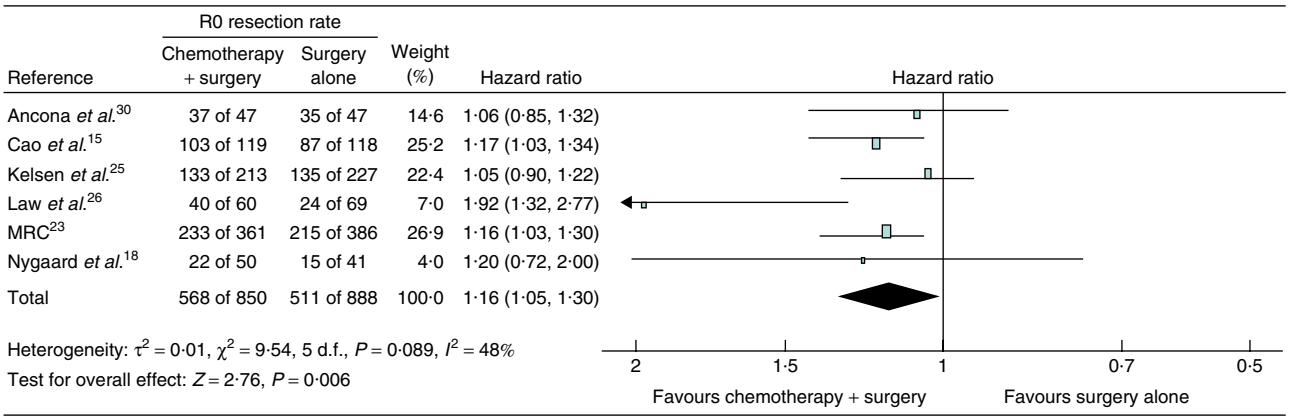

Fig. 6 Meta-analysis of probability of R0 resection with neoadjuvant chemotherapy plus surgery *versus* surgery alone. A Mantel–Haenszel random-effects model was used. Hazard ratios are shown with 95 per cent confidence intervals. MRC, Medical Research Council

probability than those who had surgery alone (HR 1·16, 1·05 to 1·30; $P = 0·006$) (*Fig. 6*).

Overall postoperative morbidity rates were 1–50 per cent with combined treatment and 3–47 per cent in the surgery-alone group. The most frequent adverse events were cardiopulmonary complications (30 per cent) and anastomotic leakage (6 per cent). Morbidity rates after neoadjuvant chemotherapy (HR 1·03, 0·90 to 1·19; $P = 0·638$) (*Fig. 7*) and postoperative 30-day mortality (HR 1·04, 0·76 to 1·43; $P = 0·810$) (*Fig. 8*) did not differ between the treatment groups. None of the trials provided detailed data about postoperative hospital stay.

Hazard ratios for overall survival after chemotherapy followed by surgery *versus* surgery alone, with the pooled estimate, are shown in *Fig. 9*. In total, the estimates of effect favoured neoadjuvant chemotherapy (HR 0·93, 0·81 to

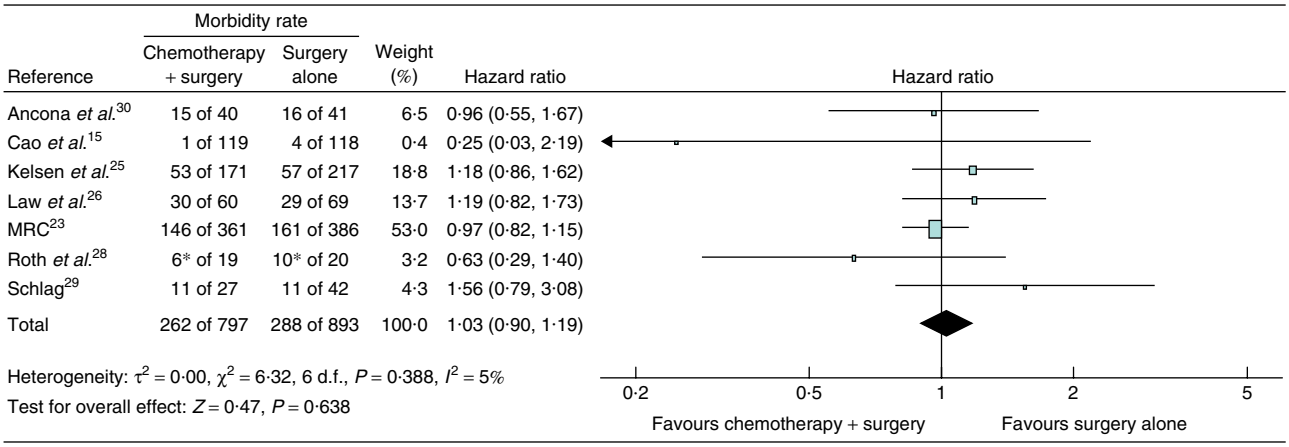

Fig. 7 Meta-analysis of postoperative morbidity after neoadjuvant chemotherapy plus surgery *versus* surgery alone. A Mantel–Haenszel random-effects model was used. *Estimated from group sample size and reported morbidity rate. Hazard ratios are shown with 95 per cent confidence intervals. MRC, Medical Research Council

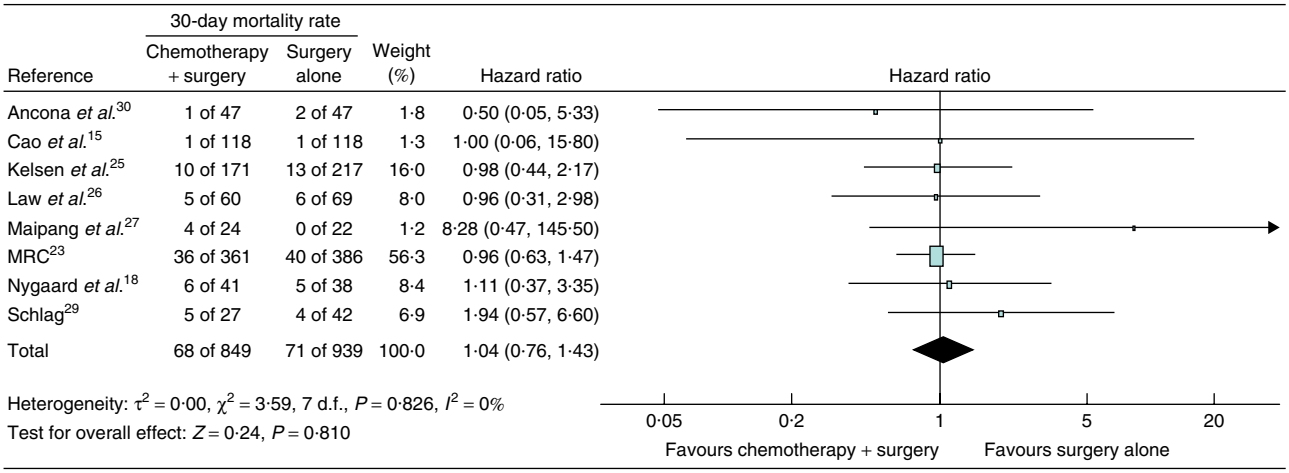

Fig. 8 Meta-analysis of 30-day mortality after neoadjuvant chemotherapy plus surgery *versus* surgery alone. A Mantel–Haenszel random-effects model was used. Hazard ratios are shown with 95 per cent confidence intervals. MRC, Medical Research Council

1·08, $P = 0·368$), although only one of the individual trials showed statistical significance[23]. There was no evidence of heterogeneity between the trials or any temporal effect ($P = 0·167$).

Two studies were not eligible for meta-analysis as survival data were incomplete. In one trial[15], neither the 3-year survival rate nor treatment-related complications related to neoadjuvant treatment differed from those in the control group. In another trial[41], 42 eligible patients (UICC II–IV) were randomized to either neoadjuvant chemotherapy (21 patients; cisplatin, 5-FU and leucovorin) or surgery (21 patients). Multivariable analysis identified a partial response to the first course of chemotherapy to be a favourable prognostic indicator.

Definitive chemoradiation *versus* neoadjuvant treatment followed by surgery or surgery alone

Three RCTs involving patients with operable squamous cell carcinoma, involving 512 patients, compared outcome after dCRT with neoadjuvant treatment followed by surgery[3,4] or surgery alone[31] (*Table 3*). The mean(s.d.) age was 59·1(2·4) years, and 87 per cent were men. The sample size ranged from 81 to 259 patients. Inclusion criteria were uniform in all RCTs with locally advanced but potentially resectable oesophageal cancers. Staging included endoscopy with biopsy[3,4,31], CT[3,4,31] and EUS[4,31]. No trial used PET–CT. Preoperative TNM status was distributed homogeneously between treatment and control groups.

Reference	Weight (%)	Hazard ratio
Roth *et al.*[28]	4·2	0·71 (0·36, 1·42)
Nygaard *et al.*[18]	10·6	1·22 (0·82, 1·81)
Schlag[29]	7·8	0·97 (0·60, 1·57)
Maipang *et al.*[27]	4·0	1·61 (0·79, 3·27)
Law *et al.*[26]	14·4	0·73 (0·53, 1·00)
Kelsen *et al.*[25]	23·3	1·07 (0·87, 1·32)
Ancona *et al.*[30]	6·6	0·85 (0·50, 1·44)
MRC[23]	29·2	0·84 (0·72, 0·98)
Total	100·0	0·93 (0·81, 1·08)

Heterogeneity: $\tau^2 = 0{\cdot}01$, $\chi^2 = 10{\cdot}41$, 7 d.f., $P = 0{\cdot}167$, $I^2 = 33\%$
Test for overall effect: $Z = 0{\cdot}90$, $P = 0{\cdot}368$

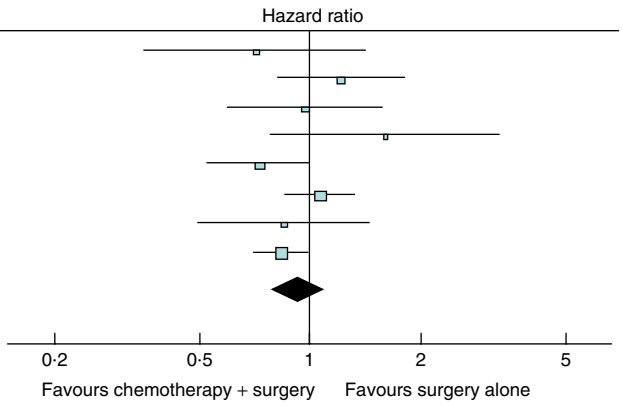

Fig. 9 Meta-analysis of overall survival estimates after neoadjuvant chemotherapy plus surgery *versus* surgery alone. The combined estimate (all published studies) was based on 850 patients receiving chemotherapy and 857 having surgery alone. Hazard ratio estimates were calculated by the inverse variance method in a random-effects model; the size of each filled square is proportionate to the inverse variance (sample size). Hazard ratios are shown with 95 per cent confidence intervals. MRC, Medical Research Council

	Morbidity rate			
Reference	Neoadjuvant therapy/surgery	dCRT	Weight (%)	Hazard ratio
Chiu *et al.*[31]	17 of 44	24 of 36	42·7	0·58 (0·37, 0·90)
Stahl *et al.*[4]	60 of 86	62 of 86	57·3	0·97 (0·80, 1·17)
Total	77 of 130	86 of 122	100·0	0·78 (0·47, 1·30)

Heterogeneity: $\tau^2 = 0{\cdot}11$, $\chi^2 = 4{\cdot}67$, 1 d.f., $P = 0{\cdot}031$, $I^2 = 79\%$
Test for overall effect: $Z = 0{\cdot}97$, $P = 0{\cdot}332$

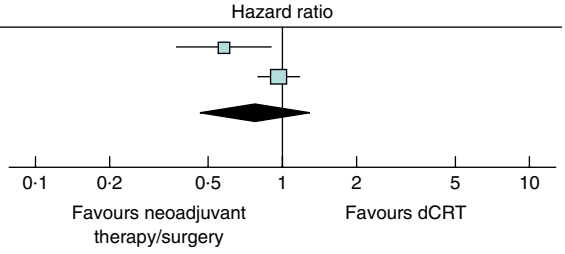

Fig. 10 Meta-analysis of morbidity for definitive chemoradiotherapy (dCRT) *versus* neoadjuvant treatment followed by surgery or surgery alone. A Mantel–Haenszel random-effects model was used. Hazard ratios are shown with 95 per cent confidence intervals

	Mortality rate			
Reference	Neoadjuvant therapy/surgery	dCRT	Weight (%)	Hazard ratio
Bedenne *et al.*[3]	6 of 129	1 of 130	48·5	6·05 (0·74, 49·52)
Chiu *et al.*[31]	3 of 44	0 of 36	25·0	5·76 (0·31, 107·91)
Stahl *et al.*[4]	7 of 86	0 of 86	26·5	15·00 (0·87, 258·60)
Total	16 of 259	1 of 252	100·0	7·60 (1·76, 32·88)

Heterogeneity: $\tau^2 = 0{\cdot}00$, $\chi^2 = 0{\cdot}31$, 2 d.f., $P = 0{\cdot}856$, $I^2 = 0\%$
Test for overall effect: $Z = 2{\cdot}71$, $P = 0{\cdot}007$

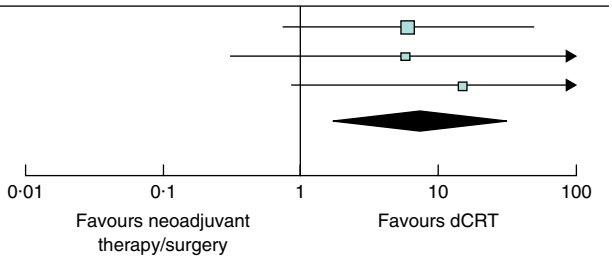

Fig. 11 Meta-analysis of mortality for definitive chemoradiotherapy (dCRT) *versus* neoadjuvant treatment followed by surgery or surgery alone. A Mantel–Haenszel random-effects model was used. Hazard ratios are shown with 95 per cent confidence intervals

There was marked variation in radiotherapy dose and scheduling as well as different neoadjuvant chemotherapy regimens (*Table 3*). Total doses ranged from 40 Gy[4] to 46 Gy[3] in the neoadjuvant therapy/surgery group and from 50 Gy[31] to 66 Gy[3] in the dCRT group. According to the chemotherapy protocol, cisplatin was administered in combination with 5-FU in all trials[3,4,31] and supplemented by leucovorin and etoposide in one[4].

dCRT was completed according to the study protocol in 224 (89 per cent) of 252 patients. Compliance with

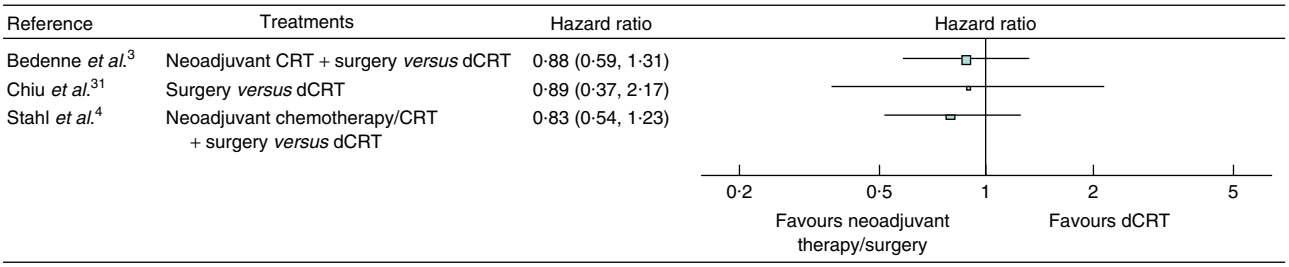

Fig. 12 Overall survival probabilities for definitive chemoradiotherapy (dCRT) *versus* neoadjuvant treatment followed by surgery or surgery alone. Hazard ratios are shown with 95 per cent confidence intervals. As very different treatment schemes were compared within the considered studies, any estimate of a pooled hazard ratio would have no meaningful interpretation. Furthermore, an imbalanced and possibly non-representative sample distribution of the treatment alternatives could lead to a biased overall effect estimate

the neoadjuvant chemotherapy protocol was 80 per cent[4] and 85 per cent[3]. Surgery was performed 2–5 weeks after completion of neoadjuvant treatment (mean 3 weeks). The preferred approach was through abdominal and right thoracotomy incisions together with two-field lymphadenectomy and gastric conduit formation. Two RCTs assessed postoperative pathological tumour stage[4,31].

The overall resection rate (curative and palliative) was between 66 per cent[4] and 93 per cent[31]. R0 resection rates were reported in two RCTs ranging from 75 per cent[3] to 82 per cent[4].

Postoperative morbidity rates were given in two RCTs, ranging from 39 per cent[31] to 70 per cent[4]. The most frequent adverse events were cardiopulmonary complications and anastomotic leakage. Morbidity rates in the dCRT group ranged between 31 per cent[3] and 70 per cent[4] (WHO grade 3–4 toxicities). Overall morbidity rates favoured neoadjuvant treatment followed by surgery (HR 0·78, 0·47 to 1·30; $P = 0·332$) (*Fig. 10*).

In contrast, mortality rates (30-day mortality in two trials[4,31] and 3-month mortality in one[3]) were significantly higher in the surgery (5 per cent[3] to 8 per cent[4]) compared with the dCRT group (0 per cent[4,31] to 1 per cent[3]). Overall the mortality risk was lower with dCRT (HR 7·60, 1·76 to 32·88; $P = 0·007$) (*Fig. 11*). Hospital stay (therapy period) was reported in two RCTs[3,31] (surgery group: mean(s.d.) 32·8(8·2) days; dCRT group: 32·9(11·5) days).

Fig. 12 provides an overview of overall survival probabilities for dCRT. None of the trials demonstrated a significant survival benefit of dCRT compared with neoadjuvant treatment followed by surgery[3,4] or surgery alone[31].

Discussion

Diagnostic and therapeutic approaches to oesophageal squamous cell carcinoma have changed markedly in the past 20 years[43]. More accurate staging has improved selection of candidates for surgery and who may benefit from multimodal treatments. Only 40–50 per cent of patients, however, respond to neoadjuvant treatment[44]. In consequence, non-responders might be compromised by side-effects and delay to surgery, although it is acknowledged that failure to respond might be associated with biologically more aggressive tumours.

Surgical resection is a well established curative treatment for patients with non-metastatic resectable squamous cell cancer[45]. In up to a third of patients, however, resection margins are positive[25] and this large number of non-curative resections strengthened the case for preoperative therapy to increase the likelihood of curative resection.

The concept of preoperative therapy for these patients has been analysed in several RCTs and meta-analyses[2,5–7,9–11,46–49], but most trials were contaminated by patients with oesophageal adenocarcinoma (*Table 6*). Many were underpowered to show a difference for the individual hypothesis tested, and some of the earliest studies lacked staging accuracy as CT and EUS were not available routinely[16,18,21,26,28,29].

The value of neoadjuvant chemotherapy compared with surgery alone has remained unclear. The meta-analysis by Urschel and Vasan[6] suggested no survival benefit for the combined treatment[6], whereas an earlier Cochrane review reported improved 5-year survival[50]. Neither meta-analysis was restricted to squamous cell cancer. A meta-analysis of preoperative radiotherapy compared with surgery alone included five randomized trials with 1147 patients; there was no survival benefit after neoadjuvant radiotherapy[51].

The first two meta-analyses examining neoadjuvant CRT reported improved 3-year survival[3,10]. Subsequent analyses demonstrated a survival benefit and reduced locoregional recurrence after neoadjuvant CRT but not after neoadjuvant chemotherapy[2,47].

From a surgical point of view these promising developments are often criticized on the basis that

Table 6 Overview of published meta-analyses for resectable oesophageal cancer

Reference	Year	No. of RCTs (patients)	Histology	Meta-analysis variable	Result*	*P*
Neoadjuvant CRT + surgery *versus* surgery alone						
Urschel and Vassan[6]	2003	9 (1116)	OSCC	1-year survival	OR 0·79 (0·59, 1·06)	0·12
			AC	2-year survival	OR 0·77 (0·56, 1·05)	0·1
				3-year survival	OR 0·66 (0·47, 0·92)	0·016
Kaklamanos *et al*.[5]	2003	5 (669)	OSCC AC	2-year survival difference	6·4 (−1·2, 14)%	
Malthaner *et al*.[11]	2004	6 (753)	OSCC AC	1-year mortality	OR 0·89 (0·76, 1·03)	0·12
Fiorica *et al*.[9]	2004	6 (764)	OSCC AC	3-year survival	OR 0·53 (0·31, 0·92) Significantly higher mortality in CRT group	0·003
Greer *et al*.[10]	2005	6 (738)	OSCC AC	Deaths/patient month of follow-up	RR 0·86 (0·74, 1·01)	0·07
Graham *et al*.[7]	2007	6 (733)	OSCC AC	1-year survival	RR 0·87 (0·75, 1·02)	> 0·05
Gebski *et al*.[2]	2007	10 (1209)	OSCC AC	Mortality HR	HR 0·81 (0·7, 0·93) 13% absolute survival difference at 2 years	0·002
Jin *et al*.[47]	2009	14 (1737)	OSCC AC	1-year survival	OR 1·19 (0·94, 1·48)	0·28
				2-year survival	OR 1·33 (1·07, 1·65)	0·69
				3-year survival	OR 1·76 (1·42, 2·19)	0·11
				4-year survival	OR 1·41 (1·06, 1·87)	0·11
				5-year survival	OR 1·64 (1·28, 2·12)	0·40
Neoadjuvant chemotherapy + surgery *versus* surgery alone						
Bhansali *et al*.[46]	1996	12 (1454)	OSCC AC	Reduction in odds of death	Mean(s.d.) 4·2(23·7)% OR 0·96 (0·75, 1·22)	
Urschel *et al*.[49]	2002	11 (1976)	OSCC AC	1-year mortality	OR 1·00 (0·76, 1·30)	0·98
				2-year mortality	OR 0·88 (0·62, 1·24)	0·45
				3-year mortality	OR 0·77 (0·37, 1·59)	0·48
Kaklamanos *et al*.[5]	2003	7 (1638)	OSCC AC	2-year survival difference	4·4 (0·3, 8·5)%	
Malthaner *et al*.[48]	2006	8 (1729)	OSCC AC	Mortality HR	HR 0·88 (0·75, 1·04)	0·15
Gebski *et al*.[2]	2007	8 (1724)	OSCC AC	Mortality HR	HR 0·90 (0·81, 1·00)	0·05
Graham *et al*.[7]	2007	6 (1460)	OSCC AC	1-year mortality	RR 0·94 (0·82, 1·08)	0·05

*Values in parentheses are 95 per cent confidence intervals unless indicated otherwise. RCT, randomized controlled trial; CRT, chemoradiotherapy; OSCC, oesophageal squamous cell carcinoma; AC, oesophageal adenocarcinoma; OR, odds ratio; RR, relative risk; HR, hazard ratio.

neoadjuvant therapy may increase postoperative morbidity and mortality. The present meta-analysis did not, however, provide evidence for increased morbidity as a result of neoadjuvant CRT, although two individual RCTs did describe increased postoperative mortality rates[13,50]. Morbidity and mortality rates were not increased after neoadjuvant chemotherapy.

Nonetheless, R0 resection rates were significantly increased by both neoadjuvant CRT and neoadjuvant chemotherapy compared with surgery alone. An important proviso here is that there is currently a worldwide discrepancy in the reporting of resection margins for oesophageal cancer. Circumferential resection margins have been related to prognosis[52], but the definition currently differs between the College of American Pathologists, which considers circumferential microscopic margins positive (R1) if tumour is found at the 'cut margin of resection'[53], and the Royal College of Pathologists in the UK, which considers circumferential margins positive when tumour is located within 1 mm of the cut margin[54]. As no detailed differentiation was reported in most of the included RCTs, the R0 resection margin range in this meta-analysis was fairly broad.

Because of the frequent co-morbidities among patients suffering from oesophageal squamous cell carcinoma, the question has been raised whether surgery can be replaced by

dCRT. The results of three RCTs comparing neoadjuvant CRT followed by surgery or surgery alone *versus* dCRT have been published recently. Bedenne and colleagues[3] reported similar survival probabilities and concluded that, for responders to CRT, there was no advantage of adding surgery after neoadjuvant treatment compared with the continuation of additional CRT, with respect to overall survival. The trial, however, included only responders to neoadjuvant therapy and there were long treatment breaks in the dCRT arm. In the trial by Stahl and co-workers[4] median and 3-year survival rates were again comparable between the surgical and dCRT arms. These authors concluded that adding surgery to neoadjuvant CRT improved local tumour control but not survival. The trial has been criticized for inadequate radiosensitization in the dCRT arm and may not have included enough patients to demonstrate a survival benefit for surgery. According to Chiu and colleagues[31] dCRT and surgery achieved equal survival rates.

Meta-analysis revealed no difference in treatment-related morbidity between neoadjuvant treatment followed by surgery or surgery alone and dCRT. However, mortality rates were significantly increased in the surgery group. None of the trials demonstrated a significant survival benefit of dCRT compared with neoadjuvant treatment followed by surgery[3,4] or surgery alone[31].

There is evidence of significant benefit in terms of overall survival with neoadjuvant CRT compared with surgery alone for patients with locally advanced resectable squamous cell cancer of the oesophagus. With neoadjuvant chemotherapy, no statistically significant difference was found. Both treatment regimens significantly increased the R0 resection rate. No Western trial has compared neoadjuvant CRT and surgery with chemotherapy and surgery. There is still a need to incorporate dCRT into future trials.

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