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SCIENTIFIC REVIEW

Definitive Chemoradiotherapy Versus Trimodality Therapy for Resectable Oesophageal Carcinoma: Meta-analyses and Systematic Review of Literature

Daan M. Voeten[1] · Chantal M. den Bakker[1] · David J. Heineman[1] · Johannes C. F. Ket[2] · Freek Daams[1] · Donald L. van der Peet[1]

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Abstract

Background Standard therapy for loco-regionally advanced, resectable oesophageal carcinoma is trimodality therapy (TMT) consisting of neoadjuvant chemoradiotherapy and oesophagectomy. Evidence of survival advantage of TMT over organ-preserving definitive chemoradiotherapy (dCRT) is inconclusive. The aim of this study is to compare survival between TMT and dCRT.

Methods A systematic review and meta-analyses were conducted. Randomised controlled trials and observational studies on resectable, curatively treated, oesophageal carcinoma patients above 18 years were included. Three online databases were searched for studies comparing TMT with dCRT. Primary outcomes were 1-, 2-, 3- and 5-year overall survival rates. Risk of bias was assessed using the Cochrane risk of bias tools for RCTs and cohort studies. Quality of evidence was evaluated according to Grading of Recommendation Assessment, Development and Evaluation.

Results Thirty-two studies described in 35 articles were included in this systematic review, and 33 were included in the meta-analyses. Two-, three- and five-year overall survival was significantly lower in dCRT compared to TMT, with relative risks (RRs) of 0.69 (95% CI 0.57–0.83), 0.76 (95% CI 0.63–0.92) and 0.57 (95% CI 0.47–0.71), respectively. When only analysing studies with equal patient groups at baseline, no significant differences for 2-, 3- and 5-year overall survival were found with RRs of 0.83 (95% CI 0.62–1.10), 0.81 (95% CI 0.57–1.14) and 0.63 (95% CI 0.36–1.12).

Conclusion These meta-analyses do not show clear survival advantage for TMT over dCRT. Only a non-significant trend towards better survival was seen, assuming comparable patient groups at baseline. Non-operative management of oesophageal carcinoma patients might be part of a personalised and tailored treatment approach in future. However, to date hard evidence proving its non-inferiority compared to operative management is lacking.

Introduction

Oesophageal carcinoma is the eighth most common and the sixth most lethal malignancy worldwide [1]. Surgical resection has long been standard treatment [2]. The addition of neoadjuvant chemoradiotherapy was proposed since many clinicians considered oesophageal carcinoma to be a systemic disease. Chemoradiotherapy was supposed to reduce micrometastases and increase resectability and radicality of surgery, thus reducing the chance of local recurrence [3]. The benefit of trimodality therapy (TMT),

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✉ Daan M. Voeten
d.voeten@vumc.nl

[1] Department of Gastrointestinal Surgery, VU University Medical Center, De Boelelaan 1117, 7F020, 1081 HV Amsterdam, The Netherlands

[2] Medical Library, Vrije Universiteit, Amsterdam, The Netherlands

consisting of neoadjuvant chemoradiotherapy followed by oesophagectomy and lymph node dissection, was confirmed by the "Chemoradiotherapy for Oesophageal cancer followed by Surgery Study" (CROSS). Median overall survival after TMT was 49.4 months, whereas overall survival after surgery alone was 24.0 months [4]. Since then, TMT is the standard therapy for loco-regionally advanced, resectable oesophageal cancer [5].

Surgery in TMT is, however, not considered feasible in all resectable patients [6–8]. In addition, up to 34% of patients eligible for TMT do not proceed to oesophagectomy after chemoradiotherapy due to deteriorating clinical status, disease progression or patient's choice [7, 9]. For inoperable patients, definitive chemoradiotherapy (dCRT) was established as non-surgical treatment modality with curative intent [10–12]. Two randomised controlled trials (RCTs) compared dCRT with TMT. Both studies concluded equal oncological outcome in terms of survival. Higher treatment-related mortality was reported in the TMT group by both studies [13, 14]. These trials suggest non-inferiority of organ-preserving dCRT but were not methodologically flawless. At this moment, a systematic review and meta-analysis of all existing literature (i.e. not only on RCTs) comparing TMT with dCRT do not exist. The aim of this meta-analysis is to compare overall survival in patients with resectable oesophageal carcinoma, treated with curative intent with either dCRT or TMT.

Materials and methods

Criteria for study eligibility

RCTs, longitudinal retrospective and prospective observational studies and case–control studies were included. There was no limit as to the length of the follow-up period. Case reports were excluded. Only full-text articles written in English or Dutch were included. No restrictions on publication status were applied. In case of overlapping cohorts, the study reporting the highest number of relevant outcome measures was included and marked as primary study. If another article on the same study mentioned a new outcome measure, it was also included. The remainder was excluded.

Participants

All studies reporting on patients older than 18 years with stages I through IVa histologically proven oesophageal carcinoma [adenocarcinoma (AC) or squamous cell carcinoma (SCC)] treated with curative intent were considered for inclusion. Studies were excluded if they included (1) patients with irresectable disease and (2) patients with Tis or M1b carcinoma.

Interventions

Studies comparing dCRT with TMT were considered eligible, irrespective of type of surgery and chemoradiotherapy regimen. Studies on adjuvant (chemo)radiotherapy, neoadjuvant chemotherapy or neoadjuvant radiotherapy were excluded. Studies mixing the former groups with TMT were also excluded. If studies performed adjuvant/salvage therapy in case of recurrence, the study was included.

Outcome measures

The primary outcomes of this study were (1) 1-, 2-, 3- and 5-year overall survival rates and (2) 1-, 2-, 3- and 5-year overall survival rates in equal patient populations at baseline.

Secondary outcome measures were (1) mean/median overall survival in months; (2) loco-regional recurrence rates; (3) distant failure rates; and (4) short-term mortality rates in the first 3 months of treatment.

Search methods for the identification of studies

A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (www.prisma-statement.org). The protocol was not published, but can be found in Online Resource 1. PubMed, Embase.com and Wiley/Cochrane Library were searched from inception up to 27 November 2017 (by DV and JCFK). The following terms were used (including synonyms and closely related words) as index terms or free-text words: 'esophageal neoplasms' and 'chemoradiation' and 'alone' or 'salvage therapy' or 'surgery' or 'chemoradiotherapy'. The full search strategies for all databases can be found in the Online Resource 2. Duplicate articles were excluded. In case of missing full texts, authors were contacted where possible.

Study selection

Two reviewers (DV and CdB) individually evaluated search results for eligibility. Disagreement was resolved by discussion, with DvdP acting as arbitrator where necessary. After the initial title and abstract screening, full texts of relevant articles were retrieved and screened by two authors independently (DV and CdB). DvdP acted as arbitrator in case of disagreement. Reasons for exclusion were documented. Covidence and Endnote were used in the selection process.

Data extraction

Data were extracted by DV and checked by CdB. Discrepancies were resolved by consensus, and DvdP was consulted in case of disagreement. A predefined data extraction sheet was used in Excel and was piloted in at least one included study. If possible, data were entered into RevMan. In case of missing outcome data, authors were contacted by e-mail where possible. Correspondence did not lead to additional data. The following data were extracted: (1) general information (author, year, methodology, patient characteristics, treatment regimens); (2) survival rates at reported follow-up; and (3) mean/median overall survival in months including standard errors (SE), standard deviations (SD) or 95% confidence intervals (CI). If available, survival data for (propensity score) matched cohorts were extracted. Local recurrence, distant failure and short-term mortality rates were extracted as well. When both per-protocol and intention to treat analyses were reported, the per-protocol based data were extracted.

Risk of bias

Risk of bias for randomised controlled trials was assessed at study level by DV and checked by CdB, using the Cochrane risk of bias tool for trials [15]. Discrepancies were resolved by consensus or referral to DvdP. Risk of bias was assessed according the following domains: selection bias, detection bias, attrition bias, reporting bias and other bias. Performance bias was not assessed as blinding is impossible due to the invasive character of the interventions. Each domain was graded as high, low or unclear.

Risk of bias in cohort studies was assessed at study level using the Cochrane tool for cohort studies. Quotes and a justification of our assessment were documented for every domain in every article.

Data analyses

If survival rates were given, the number of survivors was calculated using total sample sizes, unless authors reported on separate sample sizes for 1-, 2-, 3- or 5-year follow-up. All numbers were rounded down. If SD of mean overall survival was not reported, it was calculated from the SE or 95% CI according the Cochrane Handbook for Systematic Reviews of Intervention [16].

Homogeneity between included studies was assessed at outcome level using the Higgins I^2 statistic. When I^2 was more than 50%, studies were considered heterogeneous. A random-effect model was used since heterogeneity was expected. The Mantel–Haenszel method was used to compute relative risks (RR) in overall survival, recurrence and morbidity rates. For continuous data the inverse variance method was used, computing differences in means. Data of overlapping cohorts were added only once to each individual analysis (i.e. only the primary study data).

Separate analysis of overall survival rates and mean survival was performed including only studies with equal patient populations at baseline. Equal populations were created through randomisation, matching or coincidence.

The following subgroup analyses on 5-year overall survival were performed: (1) studies including only thoracic oesophageal carcinomas; (2) studies including only SCC or AC; (3) studies including only patients with relatively good performance status (Karnofsky score $\geq$70 or WHO/Eastern Cooperative Oncology Group (ECOG) scores $\leq$2); and (4) studies originating from Asia and the West.

A sensitivity analysis was performed on 5-year survival rates. In studies performing salvage oesophagectomy after dCRT, the number of patients receiving salvage surgery was deducted from both the total dCRT group size and the number of survivors.

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

The GRADE method was used to analyse the risk of bias across studies and evaluate the level of evidence of the conclusions. Results are presented in a Summary of Findings table using the GRADEpro software.

Results

Study selection and characteristics

The literature search produced a total of 7272 hits. After duplicate removal, 4089 hits were screened on title and abstract. This resulted in 126 full-text articles that were assessed for eligibility. The inclusion criteria were met by 35 articles describing 32 studies (21 Western and 11 Asian; Fig. 1) [7, 13, 14, 17–48]. Of the 35 articles included, two were RCTs and 33 were observational. In total 26,917 patients were included, of whom 17,513 received dCRT and 9404 received TMT. Nine studies included only patients with thoracic oesophageal carcinoma, while the other 23 did not mention excluding cervical carcinomas. Eleven studies included only patients with SCCs and three only patients with ACs. The remainder included both SCCs and ACs. Ten studies described by 11 articles had similar patient populations at baseline or performed propensity score matching. The main characteristics of included articles are presented in Table 1.

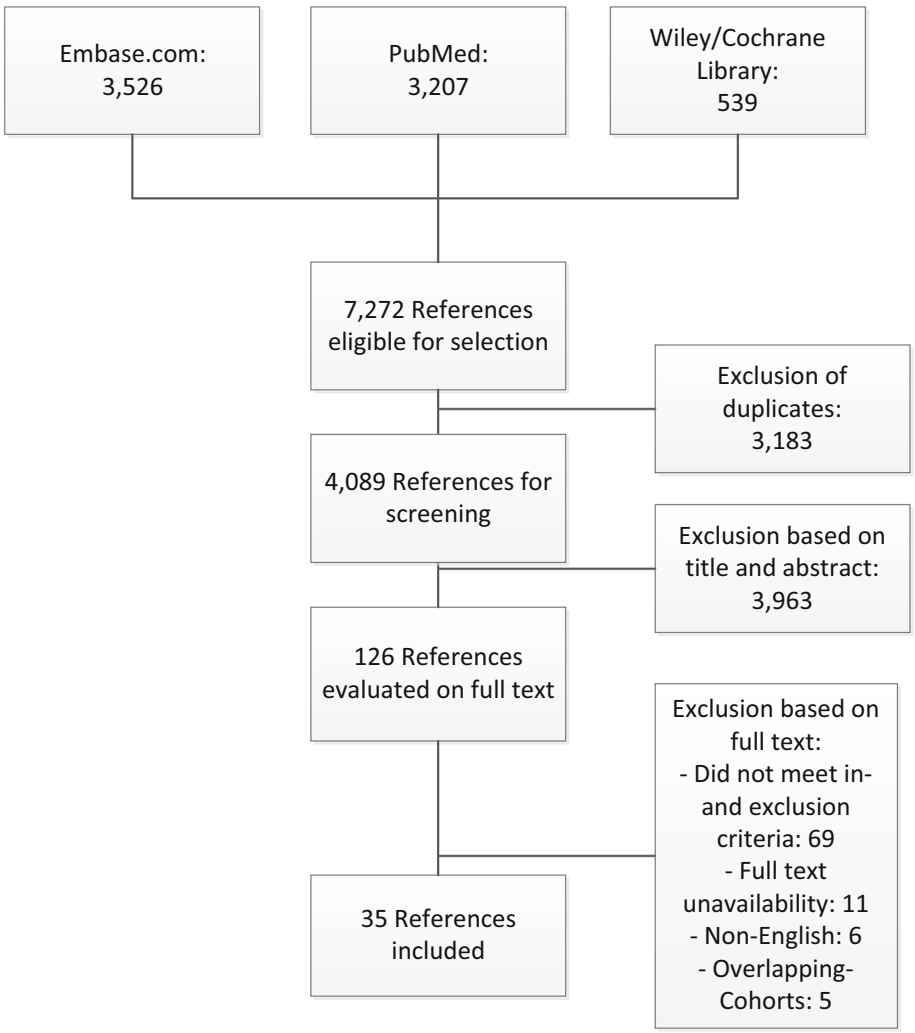


Fig. 1 Flowchart of the selection process

Risk of bias

Both RCTs had high risk of bias in the "selective reporting" domain since no trial protocols were published. One of the studies did not blind outcome assessment, while one other study did not report on outcome assessment blinding at all. No risk of bias was identified in other domains. The risk of bias in RCTs table is presented in Online Resource 3.

Risk of bias in the observational studies was high. In 42% of the observational studies, risk of bias in patient selection was high because dCRT patients were older and had more comorbidities, lower performance status and more advanced disease. Only eight studies tried to minimise this difference by matching the cohorts. In addition, 36% of the observational studies did not identify prognostic factors, and 42% did not have similar co-interventions in the two treatment groups, causing major bias. The risk of bias table in observational studies is presented in Online Resource 4.

One-year overall survival

One-year overall survival rates were reported in eight studies and were significantly lower in the dCRT group with a RR of 0.80 (95% CI 0.74–0.88; $P < 0.00001$). One study reported 1-year overall survival rates of 85.9% for dCRT and 97.8% for TMT in matched cohorts [32]. The forest plot of 1-year overall survival is presented in Fig. 2.

Two-year overall survival

Two-year overall survival rates were reported in 14 studies and were significantly lower in the dCRT group with a RR of 0.69 (95% CI 0.57–0.83; $P < 0.00001$). Four studies with equal patient groups at baseline reported 2-year overall survival rates. No statistical significant difference

Table 1 Baseline characteristics of included studies

Author (year)	Country	Study type	Inclusion period	Age[a]	% Females[a]	Stages	Upper third/ middle third/ lower third (dCRT)	Upper third/ middle third/ lower third (TMT)	Histology	Performance status of all included patients	MI[b]	Main chemotherapy regimen	Radiation dose[a]
Cervical + thoracic													
Adams (2007) [17]	United Kingdom	Observational	1998–2003	64 years/ 56 years[c]	43%/ 21%	T1-4N0-1M0-1a	5%/37%/58%	0%/25%/75%	SCC + AC	NRO[e]	–	Cis + 5-FU[f]	50 Gy
Algan (1995) [18]	USA	Observational	1981–1992	66 years/ 62 years[c]	0%/8.3%	Stage I–II	All lower third	All lower third	AC	NRO	–	5-FU + Mitomycin C	60 Gy
Berger (2012) [19]	Germany	Observational	1999–2009	63 years/ 60 years[c]	13%/ 16%	T1-4N0-1M0-1a	24%/41%/27%	18%/41%/27%	SCC + AC	NRO	–	Cis + (5-FU/etoposide/ leucovorin)	50 Gy/ 30–40 Gy
Gemici (2016) [20]	Turkey	Observational	NRO	58.6 years/ 53.0 years[c]	57.1%/ 68%	T3-4N0-1M0	8%/37%/41%	0%/52%/48%	SCC + AC	NRO	–	Varying	50–60 Gy/ 46 Gy
Haefner (2017) [21]	Germany	Observational	2000–2012	63.6 years/ 63.3 years[d]	16.1%/ 18.9%	T1-4N0-3M0	31%/19%/33%	5%/30%/60%	SCC + AC	Karnofsky score > 70	–	Cis + 5-FU	>50 Gy/ >41 Gy
Hainsworth (2007) [22]	USA	Started as RCT, became observational	1999–2004	60 years[c]	19%	Stage I–III	Upper + mid: 14% Distal: 86%	Upper + mid: 13% Distal: 87%	SCC + AC	ECOG score ≤ 2[g]	–	Cis + 5-FU + paclitaxel	64.8 Gy/ 45 Gy
Hategan (2014) [23]	United Kingdom	Observational	2004–2012	64 years/ 57 years[c]	34.0%/ 43.6%	T1-4N0-2M0	17%/30%/53%	0%/26%/75%	SCC + AC	WHO 0–1	–	Cis + 5-FU	50 Gy/45 Gy
Hennequin (2001) [24]	France	Observational	1988–1997	60 years/ 58 years[c]	18.9%/ 23.7%	T2-3N0-1M1a	43%/41%/12%	39%/41%/15%	SCC + AC	Karnofsky score > 60	–	Cis + 5-FU	60–66 Gy/ 40–43.2 Gy
Hofheinz (2004) [25]	Germany	Observational	1996–2001	59 years[c]	13.0%	T2-4N0-3M0	37%/54%/9%		SCC	NRO	–	Cis + 5-FU	40–50 Gy/ 40 Gy
Hsu (2008) [26]	Taiwan	Observational	1999–2004	64.1 years/ 57.7 years[d]	11%/4%	T2-4N0-1M0	30%/52%/16%	17%/50%/31%	SCC	NRO	–	Cis + 5-FU or Cis + paclitaxel	50–64 Gy/ 36–40 Gy
Javle (2006) [27]	USA	Observational	1990–2002	68 years/ 62 years[c]	31%/ 10%	Stage IIb–III	12%/34%/43%	4%/19%/73%	SCC + AC	NRO	–	NRO	NRO
Kim (2001) [30]	South-Korea	Observational	1993–1997	NRO	7.4%	Stage I–III	6%/59%/34%		SCC + AC	ECOG score ≤ 2	–	Cis + 5-FU	60 Gy/ 45.6–48 Gy
Lin (2017) [31]	Taiwan	Observational	2007–2013	55.3 years/ 54.0 years[c]	6.7%/ 1.5%	T2-4N0-3M0	NRO	12%/58%/35%	SCC	NRO	+	Cis + 5-FU	50–50.4 Gy
Morita (2012) [33]	Japan	Observational	2003–2009	62.7 years/ 62.3 years[d]	21.1%/ 9.9%	T4N0-3M0	7%/47%/27%	0%/58%/42%	SCC	NRO	–	Cis + 5-FU	60 Gy/40 Gy
Nakamura (2011) [37]	Japan	Observational	1992–2007	63 years/ 62 years[c]	17.1%/ 10.3%	T3-4N0-1M0-1a	23%/64%/13%	13%/64%/23%	SCC	WHO 0–1	–	(Cis/nedaplatin) + 5-FU	50–70 Gy/ 30–50 Gy

Table 1 continued

Author (year)	Country	Study type	Inclusion period	Age[a]	% Females[a]	Stages	Upper third/ middle third/ lower third (dCRT)	Upper third/ middle third/ lower third (TMT)	Histology	Performance status of all included patients	MI[b]	Main chemotherapy regimen	Radiation dose[a]
Sheil (2017) [39]	Ireland	Observational	2000–2014	67.3 years/ 59.2 years[d]	NRO	T1-4N0-3M0	19%/50%/25%	0%/61%/24%	SCC	NRO	–	Cis + 5-FU From 2012 onwards: CROSS[h]	40–44 Gy
Shridhar (2012)[i] [40]	USA	Observational	2006–2011	64.9 years[c]	16.7%	T1-4N0-3M0	5%/7%/43%		SCC + AC	NRO	+	Cis + 5-FU	45–60 Gy
Shridhar (2014) [41]	USA	Observational	2000–2011	69.8 years/ 63.4 years[c]	10.0%/ 9.6%	T1-4N1-1M0-1a	Mid: 2% Lower: 58%	Mid: 4% Lower: 48%	AC	NRO	+	Cis + 5-FU	40–66 Gy
Smith (2009) [42]	USA	Observational	1992–2002	76 years/ 72 years[d]	34%/ 20%	T1-4N0-1M0	14%/33%/44%	3%/21%/70%	SCC + AC	NRO	–	NRO	NRO
Stahl (2005) [13]	Germany	RCT	1994–2002	57 years/ 57 years[c]	20%/ 20%	T3-4N0-1M0	All upper + mid	All upper + mid	SCC	WHO 0–1	–	Cis + etoposide	50–65 Gy/ 40 Gy
Taketa (2013)[j] [44]	USA	Observational	2002–2011	68.5 years/ 68.5 years[c]	2.7%/ 13.9%	T1-4N0-3M0	Siewert 1: 43% Siewert 2: 31%	Siewert 1: 54% Siewert 2: 39%	SCC + AC	NRO	+	Fluoropyrimidine + (taxane or platinum)	38–66 Gy
Wang (2007) [43]	USA	Observational	NRO	60 years[d]	12%	Stage II–IV	NRO	NRO	SCC + AC	ECOG score ≤ 2	–	carboplatin + paclitaxel	50.4 Gy/ 45 Gy
Yap (2017) [46]	Taiwan	Observational	2009–2015	56 years[c]	2%/0%	T1-4N0-1M0	NRO	NRO	SCC + AC	NRO	+	(Cis + 5-FU) or (carboplatin + paclitaxel)	40–60 Gy
Zhongxing (2002) [48]	USA	Observational	1990–1998	66 years/ 59 years[c]	27.4%/ 15.0%	Stage II–III	34%/31%/33%	2%/25%72%	SCC + AC	NRO	–	Cis + 5-FU	50 Gy/45 Gy
Thoracic only													
Bedenne (2007) [14]	France	RCT	1993–2000	59.3 years/ 57.3 years[d]	6.2%/ 7.0%	T3N0-1-M0	NRO	NRO	SCC + AC	NRO	–	Cis + 5-FU	45–60 Gy/ 30–46 Gy
Jingu (2012) [28]	Japan	Observational	2000–2008	69.4 years/ 65.2 years[d]	6.7%/ 16.7%	T1b-2N0M0	NRO	NRO	SCC	ECOG score ≤ 2	–	Nedaplatin + 5-FU or Cis + 5-FU	60–70 Gy/ 60 Gy
Kapoor (2016) [29]	India	Observational	2008–2012	60 years[c]	44%	T3-4N0-3M0	All mid	All mid	SCC + AC	NRO	–	Cis + 5-FU	60 Gy/30 Gy
Liu (2017) [32]	China	Observational	2002–2012	60 years/ 55 years[c]	23.9%/ 20.0%	T1-4N0-1M0	NRO	NRO	SCC	ECOG score ≤ 2	–	Cis + (5-FU/ vinorelbine/docetaxel)	44–60 Gy/ 40 Gy
Myslivecek (2011) [34]	Czech Republic	Observational	2006–2010	60.7 years/ 57.0 years[c]	19.9%/ 11.8%	Stage I–IVa	All mid + lower	All mid + lower	SCC + AC	NRO	+	Cis + 5-FU	50 Gy
Nagata (2006) [35]	Japan	Observational	2000–2005	66.5 years/ 63.0 years[d]	8.7%/ 7.8%	T2-3N0-1M0	9%/56%/35%	16%/59%/25%	SCC	ECOG score 0–1	–	Cis + nedaplatin	60 Gy/30 Gy

Table 1 continued

Author (year)	Country	Study type	Inclusion period	Age[a]	% Females[a]	Stages	Upper third/ middle third/ lower third (dCRT)	Upper third/ middle third/ lower third (TMT)	Histology	Performance status of all included patients	MI[b]	Main chemotherapy regimen	Radiation dose[a]
Naik (2017) [36]	USA	Observational	2003–2011	NRO	23.9%/ 13.9%	T1-4N0-3M0	8%/24%/56%	1%/11%/79%	SCC + AC	NRO	–	NRO	50.4 Gy
Piessen (2013) [38]	France	Observational	1995–2012	NRO	6.8%/ 8.5%	Stage II–III	27%/46%/27%	30%/34%/36%	SCC + AC	NRO	–	Cis + 5-FU	50.4 Gy/ 45 Gy
Shao (2016)[k] [7]	USA	Observational	2004–2011	67 years/ 61 years[c]	23.2%/ 14.6%	T1-3N0-3M0	NRO	NRO	SCC + AC	NRO	–	NRO	41.6–64.8 Gy
Xi (2017) [45]	USA	Observational	2003–2015	61 years[c]	11.6%/ 6.7%	T1-4N0-3M0	Upper + mid: 2% Lower: 98%	Upper + mid: 2% Lower: 99%	AC	NRO	+	Fluoropyrimidine + (taxane or platinum)	50.4 Gy
Yen (2017) [47]	Taiwan	Observational	2006–2014	57.9 years/ 54.6 years[d]	4.83%/ 5.29%	Stage I–III	NRO	NRO	SCC	NRO	–	Cis based regimen	54 Gy/52 Gy

[a]If reported for both groups: dCRT group/TMT group

[b]MI = authors reported on performing minimally invasive oesophagectomy

[c]Median

[d]Mean

[e]NRO = not reported on

[f]Cis + 5-FU = cisplatin + 5 fluorouracil

[g] ECOG = Eastern Cooperative Oncology Group performance score

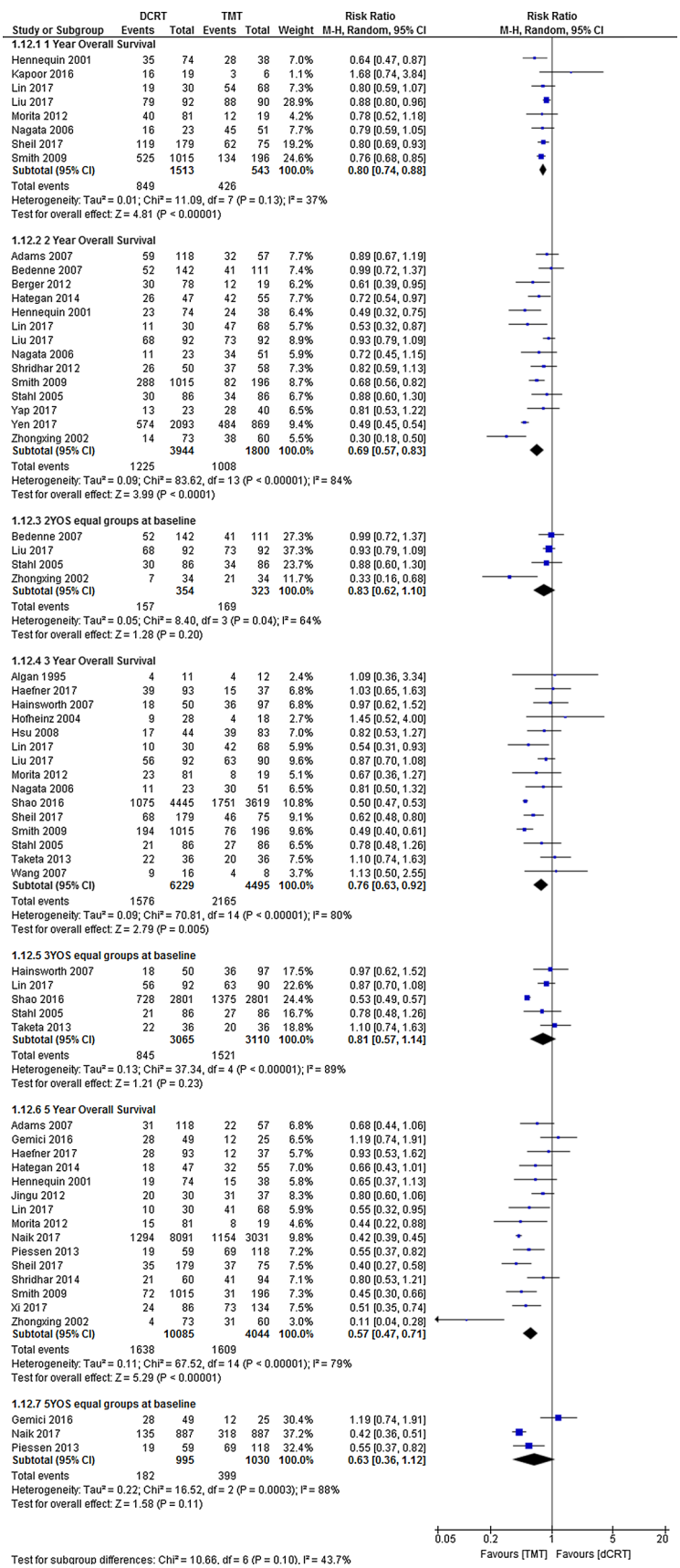
[h]CROSS = carboplatin + paclitaxel

[i]Overlapping cohorts with Shridhar 2014

[j]Overlapping cohorts with Xi 2017

[k]Overlapping cohorts with Naik 2017

Fig. 2 Forest plots of 1-, 2-, 3- and 5-year overall survival



was observed in overall survival in these four studies with a RR of 0.83 (95% CI 0.62–1.10; $P = 0.20$). Forest plots of 2-year overall survival rates for both (1) all included studies and (2) equal patient population studies are presented in Fig. 2.

Three-year overall survival

Three-year overall survival rates were reported in 15 studies and were significantly lower in the dCRT group with a RR of 0.76 (95% CI 0.63–0.92; $P = 0.005$). Five studies with equal patient groups at baseline reported 3-year overall survival rates. No statistical significant difference was observed in overall survival in these five studies with a RR of 0.81 (95% CI 0.57–1.14; $P = 0.23$). Forest plots of 3-year overall survival rates for both (1) all included studies and (2) equal patient population studies are presented in Fig. 2.

Five-year overall survival

Five-year overall survival rates were reported in 15 studies and were significantly lower in the dCRT group with a RR of 0.5 (95% CI 0.47–0.71; $P < 0.00001$). Three studies with equal patient groups at baseline reported 5-year overall survival rates. No statistical significant difference was observed in overall survival in these three studies with a RR of 0.63 (95% CI 0.36–1.12; $P = 0.11$). Forest plots of 5-year overall survival rates for both (1) all included studies and (2) equal patient population studies are presented in Fig. 2.

Mean/median overall survival

None of the studies reported the mean overall survival, and meta-analysis was therefore not possible. Sixteen studies reported the median overall survival, which ranged from 11.8 to 95 months in the dCRT group and from 16.4 to 83 months in the TMT group. Five studies with equal patient groups at baseline reported the median overall survival, ranging from 14.2 to 57.9 months in the dCRT group and from 17.7 to 59.4 months in the TMT group.

Local recurrence

Local recurrence rates were reported in 18 studies. Significantly more local recurrence was observed in the dCRT group compared to the TMT group with a RR of 2.18 (95% CI 1.79–2.66; $P < 0.00001$). The forest plot is presented in Fig. 3.

Distant failure rate

Distant failure rates were reported in 14 studies. No difference in distant failure rates between dCRT and TMT was observed with a RR of 0.84 (95% CI 0.65–1.09; $P = 0.20$). The forest plot is presented in Fig. 3.

Short-term mortality (90 days)

Short-term mortality rates were reported in eight studies. Significantly less short-term mortality was observed in patients treated with dCRT compared to TMT with a RR of 0.20 (95% CI 0.10–0.43; $P < 0.0001$). The forest plot is presented in Fig. 3.

Subgroup analyses

Subgroup analyses were performed on 5-year overall survival rates. All subgroup analyses showed significant survival advantage of TMT compared to dCRT.

The RRs on 5-year overall survival in dCRT compared to TMT for cervical and thoracic carcinomas and only thoracic carcinomas were 0.58 (95% CI 0.44–0.77; $P = 0.0001$) and 0.55 (95% CI 0.39–0.76; $P = 0.0004$), respectively. There was no difference between the two subgroups (I^2 statistic 0%, $P = 0.77$).

Subgroup analysis on studies including only SCC resulted in a RR of 0.54 (95% CI 0.36–0.82; $P = 0.003$). Performing a meta-analysis of studies including both SCC and AC resulted in a RR of 0.57 (95% CI 0.43–0.77; $P = 0.0002$). There was no difference between the two subgroups (I^2 statistic 0%, $P = 0.83$). A separate meta-analysis of studies including only AC could not be performed. Two studies only including ACs reported on 5-year overall survival rates. One author reported 5-year overall survival rates in dCRT and TMT groups of 35.6% and 43.6%, respectively [41]. The other reported 5-year survival rates of 28.1% and 54.7%, respectively [45]. One author reported 3-year overall survival rates in AC patients of 36% and 33%, respectively. Only 23 patients were included in this study. [18].

A meta-analysis of studies with only good performance status patients resulted in a RR of 5-year survival after dCRT compared to TMT of 0.77 (95% CI 0.62–0.97; $P = 0.02$).

The RR of 5-year survival in dCRT compared to TMT was 0.60 (95% CI 0.44–0.81; $P = 0.0009$) in Asian studies and 0.57 (95% CI 0.44–0.73; $P < 0.00001$) in Western studies. There was no difference between the two subgroups (I^2 statistic 0%, $P = 0.82$). The forest plots of these subgroup analyses are presented in Online Resource 5.

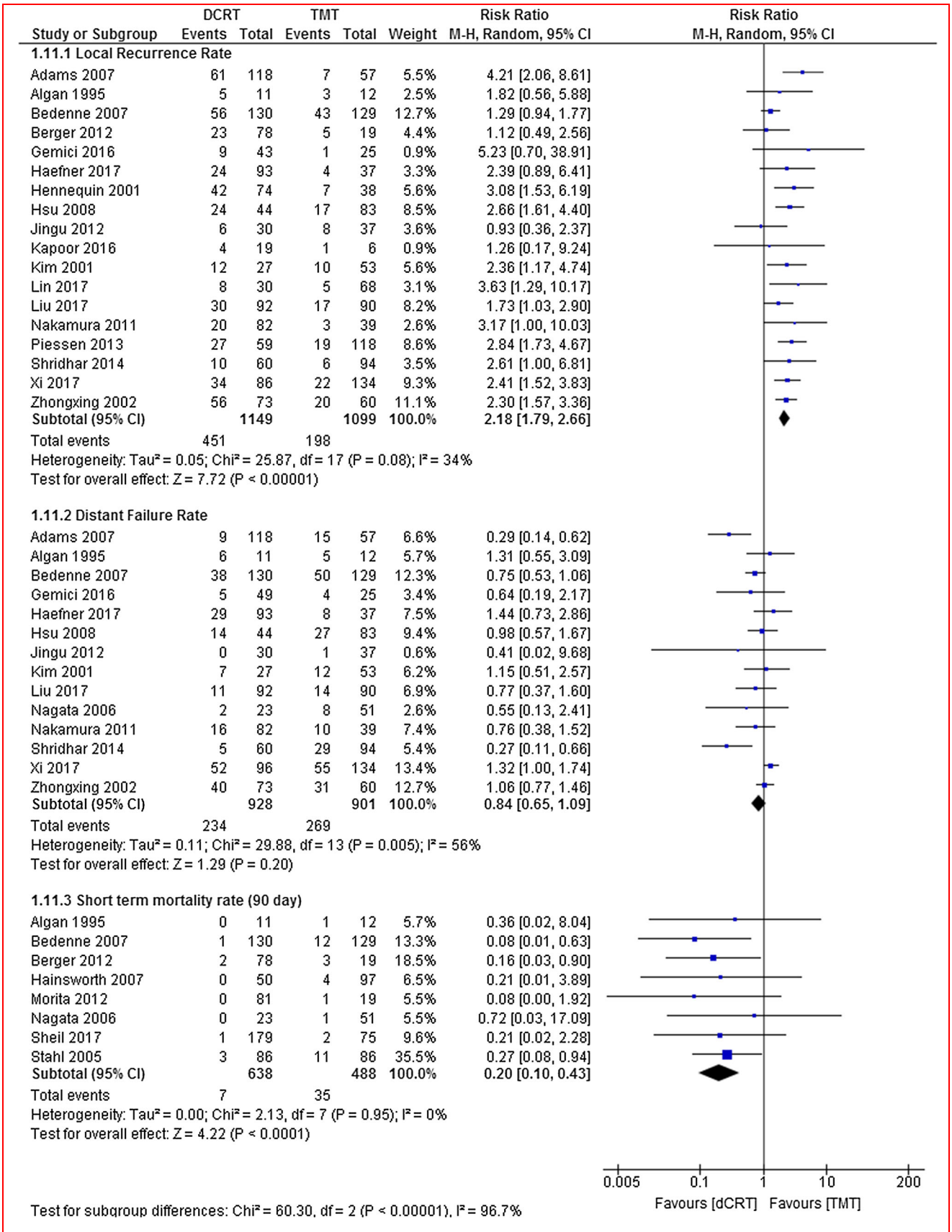


Fig. 3 Forest plot of local recurrence, distant failure and short-term mortality rates

Sensitivity analysis

A sensitivity analysis was performed in which patients in the dCRT group receiving salvage surgery were excluded. The RR of 5-year overall survival was 0.56 (95% CI 0.46–0.69) for dCRT compared to TMT. There was no difference between the sensitivity analysis and the original analysis (I^2 statistic 0%, $P = 0.87$). The forest plot of the sensitivity analysis is presented in Online Resource 6.

Grade

Risk of bias across studies and a summary of the results of these meta-analyses are presented in Summary of Findings of Table 2. The level of evidence was 'low', 'very low' or "moderate" since most included studies were observational. The level of evidence was downgraded due to (1) high risk of bias in the selection domain; (2) heterogeneity in the outcome measures; and (3) imprecision of the evidence.

Discussion

TMT is standard therapy for primary resectable, loco-regionally advanced oesophageal carcinoma. However, two RCTs by Bedenne and Stahl suggested comparable overall survival after dCRT and TMT [13, 14]. The results of this

Table 2 Summary of findings table

dCRT compared to TMT for locally advanced, resectable, non-metastatic oesophageal carcinoma					
Patient or population: locally advanced, resectable, non-metastatic, oesophageal carcinoma Intervention: dCRT Comparison: TMT					
Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with TMT	Risk with dCRT			
5-Year overall survival—total	398 per 1.000	227 per 1.000 (187–282)	RR 0.57 (0.47–0.71)	14,129 (15 observational studies)	⊕◯◯◯ very low[b,c,d]
5-Year overall survival—equal groups at baseline	387 per 1.000	244 per 1.000 (139–434)	RR 0.63 (0.36–1.12)	2025 (3 observational studies)	⊕◯◯◯ very low[c,d]
Local recurrence rate—total	180 per 1.000	393 per 1.000 (322–479)	RR 2.18 (1.79–2.66)	2248 (17 observational studies, 1 RCT)	⊕⊕◯◯ low[e]
Distant failure rate—total	299 per 1.000	251 per 1.000 (194–325)	RR 0.84 (0.65–1.09)	1829 (13 observational studies, 1 RCT)	⊕◯◯◯ very low[e,f]
Short-term mortality rate—total	72 per 1.000	14 per 1.000 (7–31)	RR 0.20 (0.10–0.43)	1126 (6 observational studies, 2 RCT's)	⊕⊕⊕◯ moderate

CI confidence interval, *RR* risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

[b]Risk of bias in selection of patients for both treatment groups in most studies. Older patients with higher disease stage and worse performance status or higher comorbidity index were shifted to the dCRT group

[c]Most studies found better overall survival rates in TMT groups (see meta-analyses); there was, however, large heterogeneity in outcomes (measured with I^2 statistic)

[d]Most authors reported on overall survival rates but did not report on the number of censored patients. Number of events (survival) at reported follow-up had to be calculated using the total patient groups

[e]Risk of bias in selection of patients for both treatment groups in some studies. Patients with more advanced disease stages were shifted to dCRT group

[f]Large heterogeneity in observed outcomes measured by the I^2 statistic

current meta-analysis show survival advantage for TMT over dCRT is not certain. However, there is a trend towards better survival after TMT. Analyses of equal patient groups at baseline were performed to counter the selection bias of observational studies. The results of this meta-analysis are supported by two Cochrane reviews that also did not find clear survival advantage for TMT over dCRT [49, 50]. These reviews included only randomised patients, creating equal patient groups at baseline. An overall survival hazard ratio (HR) of 0.99 (95% CI 0.79–1.24) for TMT compared to dCRT was reported.

The results from this study support the general consensus of TMT being standard therapy for resectable oesophageal carcinoma. However, the results suggest that dCRT is an acceptable treatment option in terms of survival as well, supporting clinicians in their decision to diverge from the best clinical care in certain specific situations. In terms of more personalised and tailored care, clinicians should be able to diverge from clinical practice guidelines. Multidisciplinary workup in which surgeons, oncologists, nurse practitioners, psychologists and radiotherapists consider the patient's condition and wishes should be the cornerstone of decision-making.

Most clinicians recognise cervical oesophageal carcinoma as different entities, preferably treated with dCRT alone [51, 52]. They are often advanced at presentation and tend to invade nearby structures. They are therefore especially difficult to treat and often deemed irresectable. It was decided not to exclude cervical carcinomas from this review because most authors comparing dCRT with TMT did not mention excluding cervical tumours. However, they often do only form a small proportion of total cohorts. It could possibly bias our results; this was, however, minimised by including only studies that did not mention inclusion of irresectable patients. In addition, subgroup analysis of studies with solely thoracic carcinomas showed this potential bias did not influence our results. Including cervical as well as junctional tumours contributed to the large heterogeneity at outcome level.

Analogous to gastric carcinoma, differences in patients and outcomes are expected in Asia and the West reflected in Asian and Western studies [53]. The predominant histology is SCC in Asia and AC in the West with different chemoradiotherapy regimen standards [54]. The preferred regimen is carboplatin and paclitaxel in the West and cisplatin and 5-fluorouracil in Asia [4, 55]. Subgroup analysis of Asian and Western studies was conducted to evaluate the effect of these differences on our results. In addition, subgroup analysis of only SCCs was conducted since SCCs are supposed to respond better to chemoradiotherapy [4]. A recent large cohort study showed better survival after multimodal therapy compared to dCRT in ACs but comparable survival in SCCs [56].

Study location and histologic subtype did not seem to influence our results. However, it has to be noted that most studies were conducted before the introduction of the CROSS regimen in 2012. In addition, it was not possible to perform subgroup analyses on ACs only since studies that only included ACs are lacking. Most studies included SCCs as well as ACs. To present a broad overview of literature and to strengthen external validity of these analyses in the Western World, it was decided to include those studies.

In this review, some studies included patients who received salvage surgery or chemotherapy after initial therapy. Most studies did not report on treatment of (local) recurrences. This is essential as it influences survival and therefore our results. To make sure salvage surgery did not influence the results, a sensitivity analysis excluding patients receiving salvage surgery after dCRT was performed. Some studies suggest that chemoradiotherapy, close monitoring and salvage oesophagectomy in case of recurrence increase overall survival. A systematic review by Jamel in 2017 included 11 studies comparing salvage oesophagectomy with planned oesophagectomy after chemoradiotherapy. They found no survival benefit for either [HR 1.17 (95% CI 0.94–1.46)]. However, higher postoperative morbidity rates in the salvage group were reported [odds ratio (OR) 1.30 (95% CI 1.00–1.67] probably due to the scarring effects of radiotherapy on the operation field. Authors suggest that these complex salvage oesophagectomies should only be performed in specialised high-volume centres [57]. Swisher et al. stated that 49% of patients in their trial were spared surgery by this approach [58]. Salvage surgery in case of recurrence and dCRT should be seen as different treatment entities, both are justified.

These meta-analyses show dCRT is associated with higher local recurrence rates as supported by the review by Vellayapan. No review reported on distant failure rates yet. In line with the two reviews, higher treatment-related mortality in the TMT group was found, which is logical as it displays the risk of operation [49, 50].

Our results suggest the addition of surgery to neoadjuvant chemoradiotherapy does not necessarily lead to survival benefit in comparable patient groups. A trend towards better survival after TMT was seen; it was, however, not significant. One strength of this review is its novelty, as no review of all literature comparing dCRT with TMT has been published to date. However, the broad overview of all existing literature is also a limitation of this study. In order to enable this broad overview, a wide variety of study was included. These studies were very heterogeneous in terms of patient characteristics, disease specificities, chemoradiation regimen and types of surgery. In addition, patient populations differ between Eastern and Western studies.

Most studies were published before the introduction of the CROSS protocol, which might influence our results. Another limitation relates to the selection bias of the included studies. This bias was tackled by subgroup analyses of equal patient groups at baseline. These subgroups are, however, small, and outcomes are very heterogeneous even among the subgroups. Many studies mixed up both SCCs and ACs creating possible bias as SCCs are supposed to show better response to chemoradiotherapy. Subgroup analyses including only SCCs did, however, not show different results. A direct comparison with studies including only ACs was not possible due to a lack of such studies in literature.

Given the limitations of this meta-analysis, it is difficult to formulate a clear conclusion on the comparison of dCRT and TMT. In order to draw definite conclusions on the benefit of TMT over dCRT, more randomised studies comparing both modalities should be conducted in future. However, our results, in accordance with those of other reviews, show randomisation is justified [49, 50, 57]. In addition, this review suggests that not all patients might benefit from surgery. Future research should focus on patient selection in order to identify which patients can be spared surgery. Finding a diagnostic modality able to predict complete pathologic response after neoadjuvant chemoradiotherapy might be a key in the process of patient selection. Even though the results of the PET-CT are promising, a diagnostic modality able to predict pathologic response has not been found yet [59]. Currently, trials on organ-preserving therapies in oesophageal carcinoma are being conducted [60].

Conclusion

Despite limitations of the available evidence, these meta-analyses comparing survival after dCRT and TMT in resectable oesophageal carcinoma do not show clear survival advantage for the one over the other. Only a non-significant trend towards better survival after TMT was seen assuming comparable groups at baseline. Evidence was mainly based on studies including SCCs. Results are in line with other studies comparing dCRT and TMT in equal patient groups at baseline. Non-operative management of oesophageal carcinoma patients might be part of a personalised and tailored treatment approach in future. However, to date hard evidence proving its non-inferiority compared to operative management is lacking.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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