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Treatment strategies for elderly patients with locally advanced esophageal cancer: a systematic review and meta-analysis

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Abstract

Background Neoadjuvant chemoradiotherapy (nCRT) followed by surgery remains a standard of care for resectable esophageal cancer (EC), and definitive chemoradiotherapy (dCRT) is an alternative for unresectable diseases. However, it is controversial for the use of the two aggressive regimens in elderly patients.

Methods We systematically searched multiple databases for studies comparing overall survival (OS) and/or progression-free survival (PFS) between dCRT and surgery (nCRT + surgery or surgery alone) or between dCRT and radiotherapy (RT) alone in elderly patients (age ≥ 65 years) until March 28, 2024. Statistical analysis was performed using random-effects model.

Results Fourty-five studies with 33,729 patients were included. dCRT significantly prolonged OS (hazard ratio [HR] = 0.64, 95% confidence interval [CI]: 0.58–0.70) and PFS (HR = 0.67, 95% CI: 0.60–0.76) compared to RT alone for unresectable EC, and resulted in a worse OS compared to surgery for resectable cases (HR = 1.34, 95% CI: 1.23–1.45). Similar results of OS were also observed when the multivariate-adjusted HRs were used as the measure of effect (dCRT vs. RT alone: HR = 0.65, 95% CI: 0.58–0.73; dCRT vs. surgery: HR = 1.49, 95% CI: 1.28–1.74). Subgroup analyses according to age group (≥ 70, ≥ 75, or ≥ 80 years), study design, study region, histological type, radiation field, chemotherapy regimen revealed comparable results.

Conclusions nCRT + surgery is likely a preferred strategy for elderly patients with good physiological conditions; and dCRT is a better alternative for unresectable cases. Advanced age alone does not appear to be a key predictor for the tolerability of the two aggressive treatments.

Keywords Surgery, Chemoradiotherapy, Elderly, Esophageal cancer, Meta-analysis

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Introduction

Esophageal cancer (EC) is the seventh most frequently diagnosed cancer and the sixth leading cause of cancer-related deaths in the world [1], and approximately 30% of all newly diagnosed patients are older than 70 years [2]. Neoadjuvant chemoradiotherapy (nCRT) followed by surgery remains a standard of care for resectable, locally advanced EC, and definitive chemoradiotherapy (dCRT) is the standard therapeutic modality for unresectable or medically inoperable cases [1]. However, either dCRT or surgery is associated with relatively high toxicity. Therefore, it is controversial whether the two aggressive strategies are suitable for elderly patients.

A series of studies [3–47] including several randomized controlled trials (RCTs) [17, 19, 20, 26] have assessed efficacy and/or safety of definitive dCRT vs. radiotherapy (RT) alone or dCRT vs. surgery in elderly patients with EC, while the results are conflicting. In fact, elderly patients are a heterogeneous group, with different definitions from age ≥ 65 to ≥ 80 years in individual studies. In addition, the physiological conditions among elderly patients (such as baseline comorbidity and performance status) are different, which may affect the tolerance to treatments. Thus, treatment selection for elderly patients should be based on individualized assessments.

In light of current issues, we performed a systematic review and meta-analysis, aiming to explore the optimal treatment strategy for elderly patient with locally advanced EC.

Methods

Literature search

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement [48] was followed for this study (Supplementary material: Table S1). Two authors (JY and XZ) independently searched PubMed, Embase, Cochrane Library, and Web of Science for publications until March 28, 2024. Search terms mainly included: "esophageal neoplasms", "esophageal cancer", "esophageal carcinoma", "esophagectomy", "surgery", "radiotherapy", "chemoradiotherapy", "aged", "geriatric", "elderly", and "older". The detailed strategies are presented in Supplementary material: Table S2.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) studies assessing dCRT vs. RT alone or dCRT vs. surgery (nCRT + surgery or surgery alone) in elderly patients (age ≥ 65 years) with locally advanced EC; (2) reported at least overall survival (OS) or progression-free survival (PFS); and (3) published in English. Non-comparative studies, case reports, letters, reviews, and meta-analysis were excluded.

Data extraction

Two authors (JY and XZ) independently collected the following information from the included studies: (1) study characteristics including name of the first author, year of publication, study design, study region, sample size, and median follow-up time; (2) patient characteristics including median age, sex, Eastern Cooperative Oncology Group [ECOG] score, histological type, and stage; (3) treatment characteristics including surgery method, RT technique and dose, radiation field, and chemotherapy (CT) regimen; and (4) data of OS, PFS, and grade ≥ 3 adverse events (AEs).

Quality assessment

The quality of each study was independently assessed by two authors (JY and XZ). Risk of bias of RCTs were assessed using Cochrane Risk of Bias Tool [49], and the quality of retrospective studies were assessed using the Newcastle-Ottawa Scale (NOS) [50]. The quality of the evidences were evaluated using the Grading of Recommendations Assessment, Development, and Evaluations (GRADE) [51].

Statistical analysis

The outcomes of interest included OS, PFS, and grade ≥ 3 AEs. A random-effects model was used for statistical analysis, using the software Review Manager 5.4 (Cochrane Collaboration, Oxford, UK). Hazard ratios (HRs) or odds ratios (ORs) with their 95% confidence intervals (CIs) were used as summary statistics. When not directly described in the studies, HRs with 95% CIs were calculated according to Tierney's method [52]. The heterogeneity was evaluated with I-square (I^2) test. A random-effects model was used when $I^2 \geq 50\%$, and a fixed-effects model was used when $I^2 < 50\%$. Univariate and multivariable meta-regression analysis were performed to search for the sources of heterogeneity. Subgroup analyses were performed according to multivariate-adjusted HRs, study design, study region, histological type, stage, radiation field, CT regimen, and age. The stability of the results were assessed by sensitivity analysis. Publication bias was evaluated using the funnel plot and the Egger's linear regression test [53].

Results

Eligible studies

The initial search retrieved 6232 records. After screening abstract and/or full text, 3007 duplicates and 3180 articles which did not meet the inclusion criteria were excluded. Finally, 45 studies [3–47] with 33,729 patients were eligible. The study selection process are shown in Fig. 1. Among the 45 studies, 26 studies involving 9105 patients examined dCRT vs. RT alone [3–28], and 19 studies involving 24,624 patients examined dCRT vs.

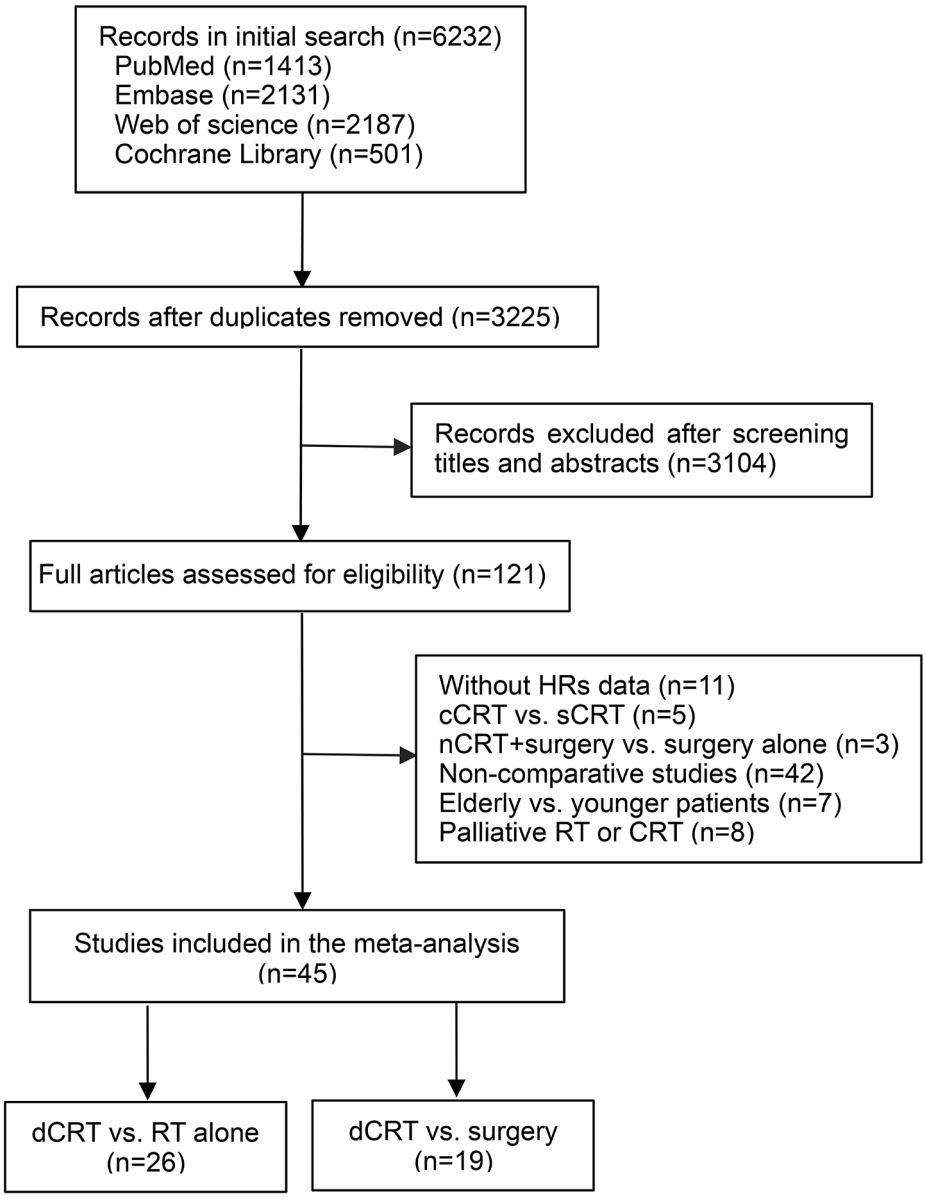

Fig. 1 Literature search and selection. HR, hazard ratio; cCRT, concurrent chemoradiotherapy; sCRT, sequential chemoradiotherapy; nCRT, neoadjuvant chemoradiotherapy; dCRT, definitive chemoradiotherapy; RT, radiotherapy

surgery (nCRT+surgery or surgery alone) [29–47]. Tumor stages were based on the criteria of the 6-8th edition of the American Joint Committee on Cancer (AJCC). Regarding dCRT vs. RT alone, the majority of patients had esophageal squamous cell carcinoma (ESCC) and received three-dimensional radiotherapy (3D-RT) or intensity modulated radiotherapy (IMRT) technique with a total dose of 50–70 Gy. Concurrent chemoradiotherapy (cCRT) was the common regimen used in dCRT group. The detailed characteristics of studies are presented in Table 1.

OS and PFS for dCRT vs. RT

Compared to RT alone, dCRT significantly improved OS (HR=0.64, 95% CI: 0.58–0.70, I^2=59%) (Fig. 2) and PFS (HR=0.67, 95% CI: 0.60–0.76, I^2=41%) (Supplementary material: Figure S1).

Considering the possibility of patient selection bias which might affect the results, we further compared the two treatments using adjusted HRs as the measure of effect. There were 15 and 11 studies reported multivariate-adjusted HRs for OS and PFS, respectively. Similar results were observed when these adjusted HRs were used as the measure of effect (OS: HR=0.65, 95% CI:

Table 1 Characteristics of included studies

First author/ year	Region	Study design	Treatment (Sample size)	SCC (%)	age (median)	Male (%)	ECOG	Stage	Stage criteria	RT dose (Gy)	RT field	RT technique	Median follow-up (m)
dCRT vs. RT													
Zhang/2014 [3]	China	retrospective	CCRT/RT(73/55)	100	≥ 65(72)	70	0–2	1–4	AJCC-6	60/1.8-2.0	IFI	3D/IMRT	18
Li/2015 [4]	China	retrospective	CCRT/RT(56/60)	100	≥ 70(76)	72	0–2	1–4	AJCC-6	60/1.8-2.0	ENI	3D/IMRT	17
Zhao/2017 [5]	China	retrospective	CCRT/RT(52/70)	100	>75(78)	71	0–2	2–3	AJCC-7	54–66/1.8-2.0	IFI	3D	40
Zhao/2017 [6]	China	retrospective	CCRT/RT(86/98)	100	≥ 70(76)	64	0–3	1–3	AJCC-7	61.6/NR	Mixed	IMRT/VMAT	15.5
Chen/2018 [7]	China	retrospective	CCRT/RT(49/41)	100	≥ 65(71)	58	0–2	2–3	AJCC-7	56-59.4/1.8-2.0	IFI	3D	NR
Huang/2019 [8]	China	retrospective	CCRT/RT(153/118)	100	≥ 65(72)	72	0–2	1–4	AJCC-6	58.4/NR	NR	2D/3D/IMRT	NR
Suzuki/2019 [9]	Japan	retrospective	CCRT/RT(38/12)	100	≥ 75(NR)	82	0–2	1–4	AJCC-7	60/1.8-2.0	Mixed	3D	21
Jingu/2019 [10]	Japan	retrospective	CCRT/RT(51/51)	96	≥ 80(83)	78	0–2	1–4	AJCC-6	60/2.0	Mixed	3D	NR
Chen/2020 [11]	China	retrospective	CCRT/RT(133/133)	100	>70(74)	NR	0–3	1–4	AJCC-7	61/1.8–2.2	ENI	3D/IMRT	21.7
Jingu/2020 [12]	Japan	retrospective	CCRT/RT(196/162)	96	≥ 80(NR)	85	NR	1–4	AJCC-7	NR	NR	NR	NR
Xia/2021 [13]	USA	retrospective	CRT/RT(1510/1510)	46	>65(75)	71	NR	1–4	AJCC-6	NR	NR	NR	NR
Derby/2021 [14]	UK	retrospective	CCRT/RT(62/21)	100	>65(74)	47	0–2	1–3	AJCC-7	50–55/2.0-2.75	NR	IMRT/VMAT	NR
Wu/2021 [15]	China	retrospective	CRT/RT(317/264)	100	≥ 65(74)	64	0–2	2–4	AJCC-8	50–70/1.8-2.0	IFI	IMRT	23.2
Li/2021 [16]	China	retrospective	CCRT/RT(45/45)	100	≥ 70(NR)	NR	NR	3–4	AJCC-6	60(40–70)/2.0	ENI	IMRT/VMAT	47.9
Ji/2021 [17]	China	phase 3	CCRT/RT(149/149)	99	≥ 70(77)	60	0–1	2–4	AJCC-6	54–60/1.8-2.0	Mixed	IMRT	33.9
Wang/2021 [18]	China	retrospective	CCRT/RT(149/157)	100	≥ 70(NR)	NR	NR	1–4	AJCC-8	50–70/2.0-2.3	NR	3D/IMRT	NR
Liu/2022 [19]	China	phase 2	CCRT/RT(78/79)	100	>70(77)	61	0–2	2–4	AJCC-6	50.4–59.4/1.8	IFI	3D/IMRT	38
Liu/2022 [20]	China	prospective	CCRT/RT(17/17)	100	≥ 70(76)	85	NR	2–3	NR	50.4–60/1.8-2.0	IFI	IMRT	24.5
Yan/2022 [21]	China	retrospective	CCRT/RT(93/99)	100	≥ 65(73)	58	0–2	2–3	AJCC-6	50.4–66/1.8-2.0	IFI	IMRT	21.3
Liu/2022 [22]	China	retrospective	CCRT/RT(32/29)	100	≥ 70(76)	85	0–2	2–3	AJCC-7	60/2.0	NR	3D	NR
Watanabe/2022 [23]	Japan	retrospective	CCRT/RT(15/25)	100	≥ 75(80)	75	0–3	3–4	AJCC-8	50.4–63/1.8	ENI	3D	NR
Jingu/2022 [24]	USA	retrospective	CRT/RT(714/714)	44	≥ 80(85)	65	NR	1–4	AJCC-6	NR	NR	NR	57
Saito/2023 [25]	Japan	retrospective	CCRT/RT(35/19)	100	≥ 65(72)	86	0–1	1b-3	AJCC-7	NR	NR	NR	61.2
Wang/2023 [26]	China	phase 3	CCRT/RT(184/146)	100	≥ 70(76)	70	0–1	2–4	AJCC-6	60/1.8	ENI	IMRT/VMAT	44
Qiu/2023 [27]	China	retrospective	CRT/RT(299/161)	100	≥ 65(NR)	66	NR	2-4a	AJCC-8	50–70/1.8-2.0	NR	3D/IMRT	24.7
Huang/2023 [28]	China	retrospective	CCRT/RT(103/63)	100	≥ 65(NR)	71	0–2	1–4	AJCC-6	NR	NR	NR	NR
dCRT vs. surgery													
Grace/2009 [29]	USA	retrospective	CRT/nCRT + S(1015/196)	52	≥ 65(76)	70	NR	1–3	NR	NR	NR	NR	9.6
Julian/2019 [30]	USA	retrospective	CRT/S(389/341)	42	≥ 65(NR)	71	NR	1–2	AJCC	NR	NR	NR	NR
Jing/2016 [31]	China	retrospective	CRT/S(100/88)	100	≥ 70(74)	64	91	1–3	AJCC-7	50.4–66/1.8-2.0	NR	3D/IMRT	28.5
Vlacich/2017 [32]	USA	retrospective	CCRT/nCRT + S(955/955)	NR	≥ 70(77)	NR	NR	2–3	NR	NR	NR	NR	NR
			CCRT/S(697/697)	NR	≥ 70(77)	NR	NR	2–3	NR	NR	NR	NR	NR
Amy/2017 [33]	USA	retrospective	CCRT/S(206/94)	22	≥ 80(84)	66	NR	1	AJCC-6/7	NR	NR	NR	13.9
Koëter/2018 [34]	Netherlands	retrospective	CRT/nCRT + S(405/309)	36	≥ 75(NR)	NR	NR	2-4a	AJCC-6/7	NR	NR	NR	NR
Verma/2019 [35]	USA	retrospective	CRT/nCRT + S(488/488)	NR	>75(NR)	NR	NR	2–3	AJCC-6/7	NR	NR	NR	NR
			CRT/S(457/457)	NR	>75(NR)	NR	NR	2–3	AJCC-6/7	NR	NR	NR	NR

Table 1 (continued)

First author/ year	Region	Study design	Treatment (Sample size)	SCC (%)	age (median)	Male (%)	ECOG	Stage	Stage criteria	RT dose (Gy)	RT field	RT technique	Median follow-up (m)
Faiz/2019 [36]	Netherlands	retrospective	CRT/nCRT + S(78)	0	≥ 75(NR)	NR	NR	2–3	AJCC-6/7	NR	NR	NR	NR
			CRT/nCRT + S(33)	100	≥ 75(NR)	NR	NR	2–3	AJCC-6/7	NR	NR	NR	NR
Rahimy/2020 [37]	USA	retrospective	CRT/nCRT + S(68/21)	40	≥ 75(80)	78	NR	1–4	AJCC-8	≥ 45	NR	3D/IMRT	16
Hao/2021 [38]	USA	retrospective	CRT/CRT + S(1595/1592)	NR	≥ 75(NR)	NR	NR	2–3	AJCC-6	NR	NR	NR	NR
Kato/2021 [39]	Japan	prospective	CCRT/CRT + S(83/78)	100	≥ 65(NR)	NR	0–1	1	AJCC-7	60/2.0	NR	NR	NR
Gaber/2022 [40]	USA	retrospective	CCRT/ nCRT + S(1240/1240)	0	≥ 65(72)	88	NR	1–3	AJCC-7	NR	NR	NR	NR
			CCRT/nCRT + S(661/661)	100	≥ 65(72)	55	NR	1–3	AJCC-7	NR	NR	NR	NR
Jensen/2022 [41]	USA	retrospective	CRT/ nCRT + S(1899/1674)	0	≥ 70(NR)	NR	NR	1–4	NR	NR	NR	NR	NR
			CRT/nCRT + S(1026/310)	100	≥ 70(NR)	NR	NR	1–4	NR	NR	NR	NR	NR
Yang/2022 [42]	USA	retrospective	CRT/CRT + S(1510/524)	56	≥ 70(NR)	74	NR	2–3	AJCC-7	NR	NR	NR	NR
			CRT/S(1510/194)	56	≥ 70(NR)	74	NR	2–3	AJCC-7	NR	NR	NR	NR
Motoyama/2022 [43]	Japan	retrospective	CRT/CRT + S or S (720/683)	95	≥ 75(77)	NR	NR	2–3	AJCC-6	NR	NR	NR	NR
Sawada/2022 [44]	Japan	retrospective	CCRT/S(11/21)	100	≥ 75(78)	80	0–1	1	AJCC-7	50–60	NR	3D/IMRT	72
Shimonosono/2022 [45]	Japan	retrospective	CRT/S(37/23)	NR	≥ 80(82)	83	0–3	1–4	AJCC-8	50.4	NR	NR	NR
Bostel/2023 [46]	Germany	retrospective	CRT/nCRT + S(133/42)	100	≥ 65(73)	74	0–2	1–4	AJCC-6/8	NR	NR	NR	NR
Ahmed/2023 [47]	Canada	retrospective	CRT/nCRT + S (12/16)	35	≥ 80(83)	67	NR	2–3	AJCC-8	41.4–50.4/1.8	NR	NR	NR

SCC, squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; m, month; dCRT, definitive chemoradiotherapy; CCRT, concurrent chemoradiotherapy; nCRT, neoadjuvant chemoradiotherapy; S, surgery; NR, not reported; IFI, involved-field irradiation; ENI, elective nodal irradiation; 2D, two-dimensional; 3D, three-dimensional; IMRT, intensity modulated radiotherapy

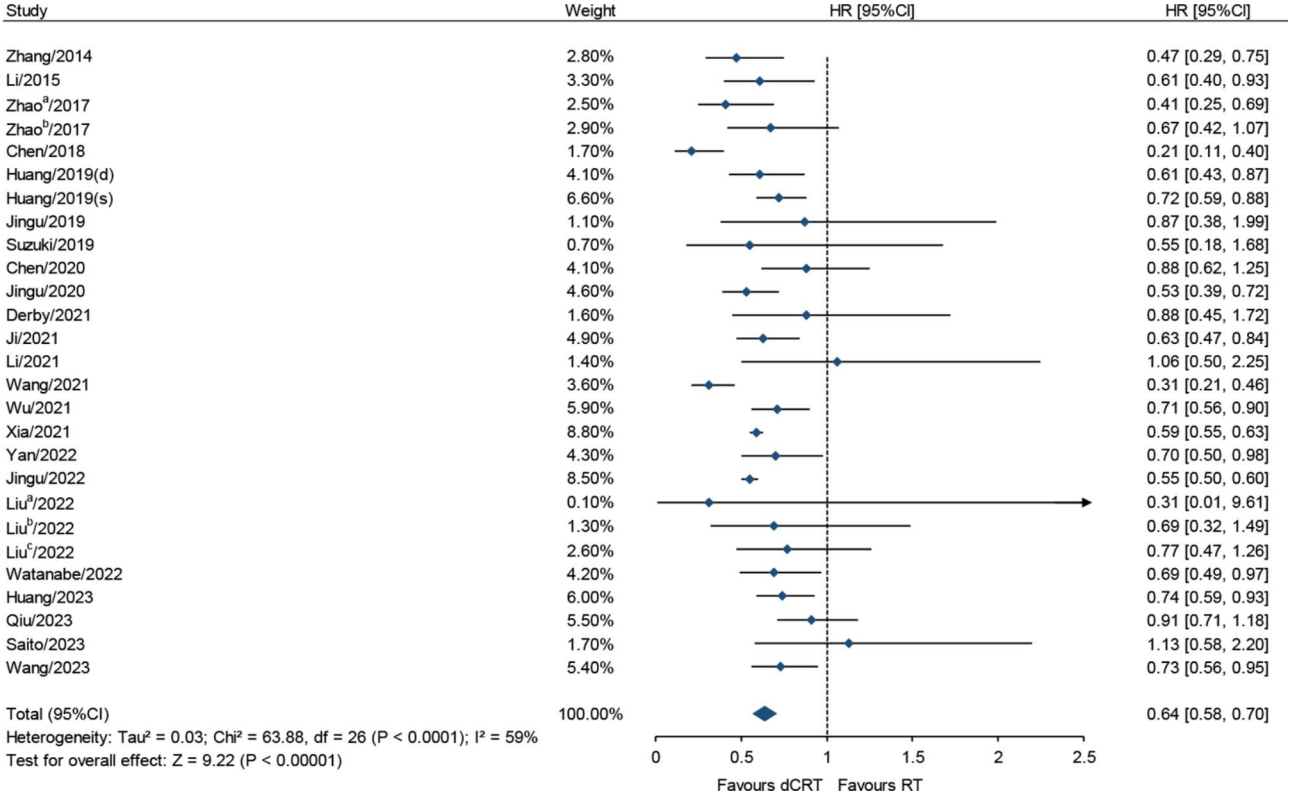

Fig. 2 Forest plot of HRs comparing OS between dCRT and RT. OS, overall survival; dCRT, definitive chemoradiotherapy; RT, radiotherapy; HR, hazard ratio; CI, confidence interval; Zhao[a], Qian Zhao; Zhao[b], Lina Zhao; Liu[a], Yanxiao Liu; Liu[b], Li-Hua Liu; Liu[c], Junqing Liu

0.58–0.73, I^2=47%; PFS: HR=0.69, 95% CI: 0.60–0.78, I^2=37%) (Supplementary material: Figure S2 and S3).

In subgroup analyses, significantly longer OS with dCRT was observed in each subgroup, including Asia (HR=0.65, 95% CI: 0.58–0.73, I^2=55%), non-Asia (HR=0.58, 95% CI: 0.53–0.62, I^2=31%), prospective studies (HR=0.69, 95% CI: 0.58–0.83, I^2=0%), retrospective studies (HR=0.63, 95% CI: 0.57–0.70, I^2=64%), involved-field irradiation (IFI) (HR=0.58, 95% CI: 0.44–0.76, I^2=61%), elective nodal irradiation (ENI) (HR=0.74, 95% CI: 0.63–0.87, I^2=0%), dCRT using S-1 regimen (HR=0.69, 95% CI: 0.58–0.83, I^2=0%), dCRT using other CT regimens (HR=0.63, 95% CI: 0.57–0.70, I^2=64%), stage 2–3 disease (HR=0.66, 95% CI: 0.54–0.81, I^2=60%), ESCC (HR=0.64, 95% CI: 0.58–0.72, I^2=57%), age≥70 years (HR=0.62, 95% CI: 0.55–0.70, I^2=53%), age≥75 years (HR=0.60, 95% CI: 0.53–0.67, I^2=29%), and age≥80 years (HR=0.55, 95% CI: 0.50–0.59, I^2=0%) (Fig. 3). dCRT also significantly prolonged PFS in all subgroups, except subgroup of ENI (Supplementary material: Figure S4).

OS for dCRT vs. surgery

Compared to surgery, dCRT resulted in a significantly worse OS (HR=1.34, 95% CI: 1.23–1.45, I^2=76%) (Fig. 4). Similar results were also observed when the multivariate-adjusted HRs were used as the measure of effect (HR=1.49, 95% CI: 1.28–1.74, I^2=65%) (Supplementary material: Figure S5). PFS was not assessed because most of studies did not reported the data.

In subgroup analyses, significantly decreased OS with dCRT was observed in the majority of subgroups, including Asia (HR=1.21, 95% CI: 1.02–1.44, I^2=68%), non-Asia (HR=1.36, 95% CI: 1.23–1.50, I^2=80%), stage 2–3 disease (HR=1.25, 95% CI: 1.13–1.37, I^2=75%), ESCC (HR=1.32, 95% CI: 1.15–1.52, I^2=45%), esophageal adenocarcinoma (EAC) (HR=1.56, 95% CI: 1.24–1.97, I^2=91%), nCRT+surgery (HR=1.37, 95% CI: 1.25–1.50, I^2=72%), age≥70 years (HR=1.35, 95% CI: 1.23–1.48, I^2=73%), and age≥75 years (HR=1.33, 95% CI: 1.19–1.49, I^2=54%), but not in subgroups of stage 1 disease (HR=1.17, 95% CI: 0.88–1.56, I^2=0%) and age≥80 years (HR=1.08, 95% CI: 0.86–1.36, I^2=25%) (Fig. 5); dCRT was associated with a trend of worse OS compared to surgery alone (HR=1.22, 95% CI: 0.97–1.54, I^2=84%) (Fig. 5).

Grade ≥ 3 AEs

Twelve studies assessing dCRT vs. RT alone [3–5, 7, 8, 10, 15, 17, 19, 20, 23, 26] reported data of the overall or individual grade≥3 AEs. Compared to RT alone, dCRT was associated with a significantly higher risk of

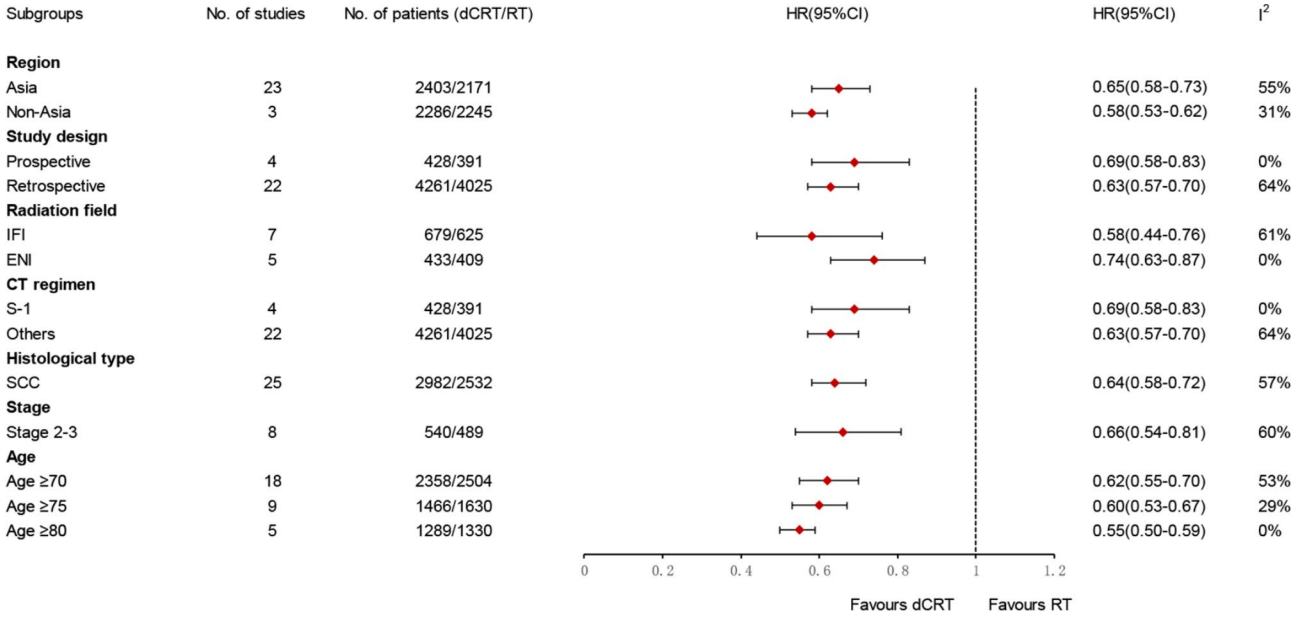

Fig. 3 Subgroup analyses for OS in dCRT vs. RT group. OS, overall survival; dCRT, definitive chemoradiotherapy; RT, radiotherapy; CT, chemotherapy; IFI, involved-field irradiation; ENI, elective nodal irradiation; SCC, squamous cell carcinoma; HR, hazard ratio; CI, confidence interval

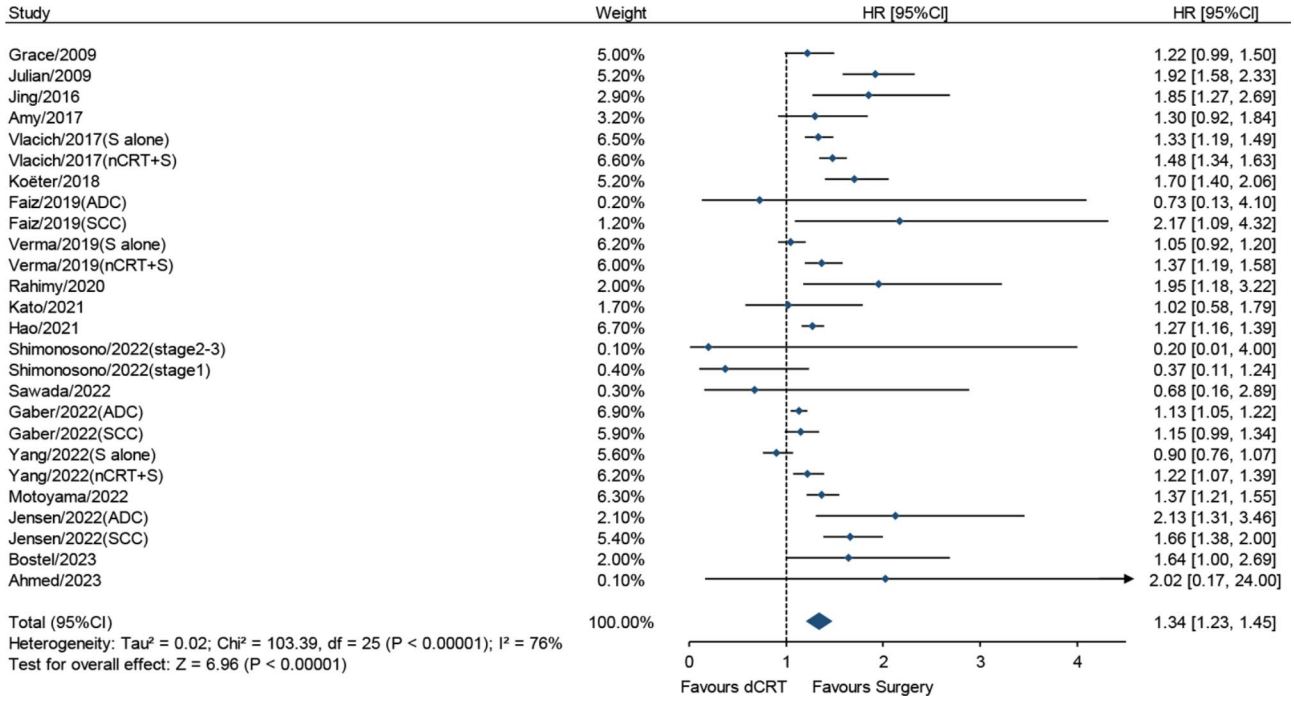

Fig. 4 Forest plot of HRs comparing OS between dCRT and surgery. OS, overall survival; dCRT, definitive chemoradiotherapy; HR, hazard ratio; CI, confidence interval; ADC, adenocarcinoma; SCC, squamous cell carcinoma; nCRT, neoadjuvant chemoradiotherapy; S, surgery

the overall AEs (OR=2.55, 95% CI: 1.60–4.06, I^2=34%), leukocytopenia (OR=2.42, 95% CI: 1.51–3.90, I^2=0%), thrombopenia (OR=3.93, 95% CI: 1.75–8.81, I^2=0%), and nausea/vomiting (OR=3.89, 95% CI: 2.12–7.13, I^2=4%); risk of pneumonitis (OR=1.04, 95% CI: 0.68–1.59, I^2=0%), esophagitis (OR=1.30, 95% CI: 0.93–1.82, I^2=19%), and anemia (OR=1.50, 95% CI: 0.67–3.36, I^2=0%) were comparable between the two groups (Fig. 6).

We further compared individual grade≥3 AEs between dCRT using S-1 regimen [17, 19, 20, 26] and other CT regimens [3–5, 7, 8, 10, 15, 23]. The pooled rate of pneumonitis (3.5 vs. 3.0%) was similar between the two regimens, while the incidence of esophagitis (6.0% vs. 9.2%),

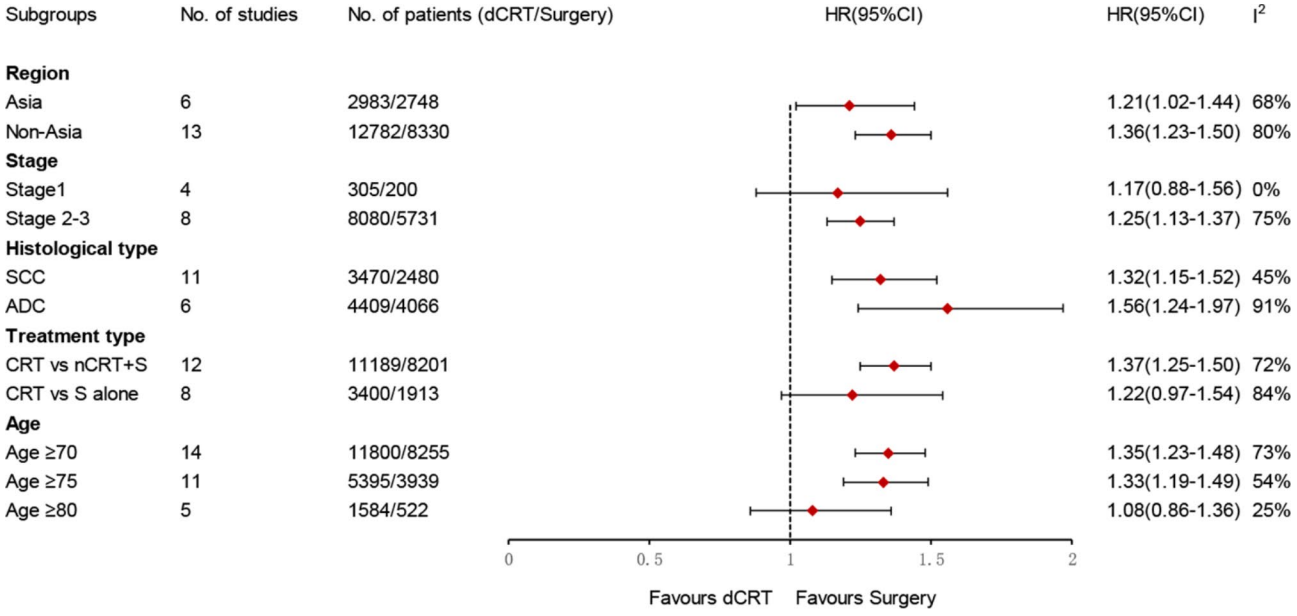

Fig. 5 Subgroup analyses for OS in dCRT vs. surgery group. OS, overall survival; dCRT, definitive chemoradiotherapy; nCRT, neoadjuvant chemoradiotherapy; S, surgery; SCC, squamous cell carcinoma; ADC, adenocarcinoma; HR, hazard ratio; CI, confidence interval

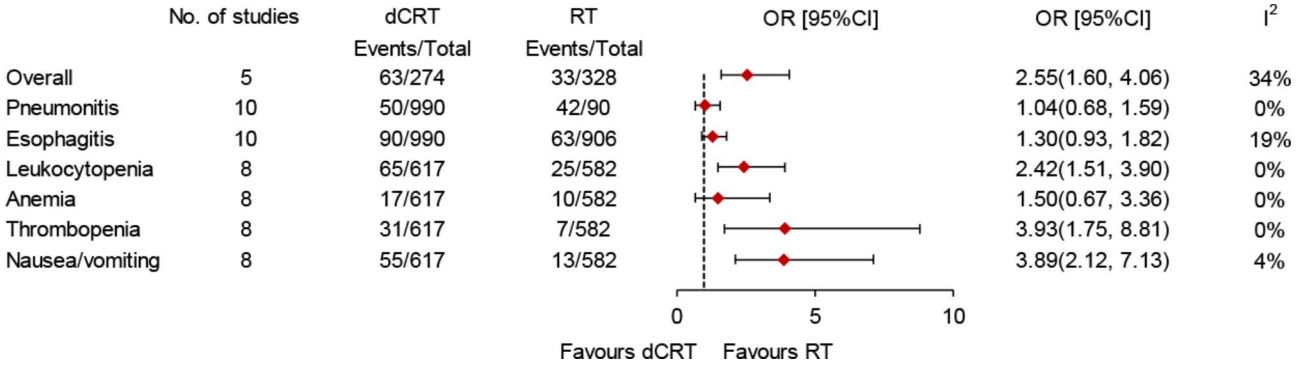

Fig. 6 Grade ≥ 3 AEs for dCRT vs. RT. AEs, adverse events; dCRT, definitive chemoradiotherapy; RT, radiotherapy

leukocytopenia (7.5% vs. 11.6%), anemia (0.9% vs. 3.5%), thrombopenia (2.4% vs. 5.5%), and nausea/vomiting (2.0% vs. 14.4%) were relatively low in S-1 group compared to that in the other regimens group (Supplementary material: Figure S6).

The GRADE assessment

Results of the GRADE assessment can be seen in Supplementary material: Table S3. Most of the evidences had low GRADE ratings, except the evidences for subgroups of prospective studies and dCRT using S-1 regimen which had moderate GRADE ratings.

Meta-regression analysis

Multivariable meta-regression analysis showed that study region, study design, stage, histological type, radiation field, and chemotherapy regimen were not significantly associated with the heterogeneity for either OS or PFS ($P>0.05$ for each comparison) (Supplementary material: Table S4).

Sensitivity analysis

When omitting one study at a time, the results for OS and PFS were not significantly altered (Supplementary material: Figure S7).

Assessment of studies and publication bias

There were 4 RCTs [17, 19, 20, 26] which were rated with low or unclear risk of bias (Supplementary material: Figure S8). All observational studies had a score of ≥6 (Supplementary material: Table S5). The Egger's test results indicated no publication bias ($P>0.05$ for each result). The funnel plots are shown in Supplementary material: Figure S9.

The forest plots for the results of subgroup analyses

The forest plots for the results of subgroup analyses in dCRT vs. RT alone group and dCRT vs. surgery group are presented in Supplementary material: Figures S10–S33.

Discussion

This is a comprehensive meta-analysis to assess the optimal treatment strategy for elderly patients with locally advanced EC. It showed that dCRT significantly improved OS and PFS compared to RT alone in patients with unresectable EC. As for resectable cases, dCRT resulted in worse OS and PFS compared to surgery. Comparable results were observed when the multivariate-adjusted HRs were used as the measure of effect. Regarding safety of dCRT vs. RT alone, dCRT was associated with higher risk of the overall grade≥3 AEs, and grade≥3 thrombopenia and nausea/vomiting, without increased risk of grade≥3 pneumonitis and esophagitis.

It should be noted that the definitions for elderly patients in individual studies were inconsistent (age≥65, ≥70, ≥75, or ≥80 years). In theory, comorbidity should increase and physiological reserves should decrease with age, leading to reduced tolerability to the aggressive treatments with age. In a large retrospective study assessing safety of esophagectomy in elderly patients, operative mortality substantially increased with age (8.8% for aged 65–69, 13.4% for aged 70–79, and 19.9% for age≥80) [54]. In our meta-analysis, dCRT significantly prolonged OS compared to RT alone in each age group (age≥70, ≥75, or ≥80 years); and surgery was associated with a better OS in age≥70 and ≥75 years groups compared to dCRT. These results suggest that surgery or dCRT can provide survival benefits in selected elderly patients, and advanced age alone is not a key factor associated with the benefits. Nevertheless, the tolerability should be carefully evaluated before selecting these aggressive treatments in elderly patients.

The common CT regimens used with dCRT in individual studies were platinum-based double-agent regimens. It has been reported that intravenous CT has high risk of treatment-related AEs in elder patients [55]. As an orally administered drug, S-1 is generally considered to have less toxicities. However, there is still lack of studies comparing dCRT using platinum-based regimens with single-S-1 regimen in elderly patients with EC. In our meta-analysis, both the two regimens with dCRT significantly improved OS and PFS compared to RT alone. In addition, we found that single-S-1 was associated with low grade≥3 AEs compared to platinum-based regimen. Thus, dCRT using single-S-1 is likely a reasonable alternative selection in elderly patients with EC.

Regarding radiation field, current NCCN clinical practice guidelines recommends using ENI in patients with locally advanced EC receiving cCRT [1]. However, given the relatively high toxicity, whether ENI is necessary in elder patients needs further investigation. In a retrospective study of 137 elderly patients with EC treated with cCRT, IFI was associated with reduced toxicities without decreased OS compared to ENI [56]. In our meta-analysis, either dCRT using ENI or IFI gained better OS compared to RT alone, which supported the use of IFI in elderly patients. In addition, results from a retrospective study in EC [57] showed that cCRT using IMRT had lower cardiac mortality and overall mortality compared to 3D-CRT in patients with age>65 years. More prospective trials are needed to confirm the superiority of IMRT.

The CROSS [58] and NEOCRTEC5010 [59] trials have demonstrated that nCRT followed by surgery improves survival compared with surgery alone in patients with resectable, locally advanced EC. However, the NEOCRTEC5010 trial excluded patients with age ˃70 years, and the median age was 60 years (range, 18–75 years) in the CROSS trial. There are still lack of RCTs examining nCRT plus surgery vs. surgery alone specifically in elderly patients. In our study, surgery alone also gained a trend of improved OS compared to dCRT. This finding suggests that surgery alone can be used as an alternative regimen when there is a concern for the tolerability of the trimodality therapy in elderly patients. In addition, esophagectomy has been a standard of care for stage 1 (cT1-2N0) EC, and dCRT is only recommended for patients who are medically inoperable or decline surgery [1]. However, whether surgery can be avoid in elderly patients with stage 1 disease remain uncertain. Several retrospective studies [33, 44, 45] have demonstrated a comparable efficacy between esophagectomy and dCRT in patients with stage 1 and age≥75 years. In our meta-analysis, OS was similar between surgery and dCRT in subgroup of stage 1 disease. Nevertheless, this finding needs to be validated in large RCTs.

Several studies reported that histological type was associated with the efficacy of nCRT. Results from two population-based studies showed that nCRT followed by surgery achieved longer OS than dCRT in elderly patients (≥75 years) with EAC but not in those with ESCC [34, 36]. The authors explained that different tumor aggressiveness and carcinogenesis might be one of the reasons for the difference in survival benefits with nCRT between patients with EAC and ESCC [36]. However, there are also studies demonstrating a superior OS of nCRT+surgery vs. dCRT in elderly patients with ESCC [31, 40, 46]. In our meta-analysis, significantly improved OS with nCRT was observed both for patients with EAC and ESCC. Based on current evidences, it is difficult to conclude the less efficacy of nCRT in elderly patients with ESCC.

Recently, a series of phase 1 or 2 trials have examined the role of nCRT or nCT combined with immune

checkpoint inhibitor (nICRT or nICT) in resectable EC. A meta-analysis including 27 trials with 809 patients showed that both nICRT and nICT achieved promising pathologic complete response rates with acceptable tolerability [60]. However, most of the trials excluded patients with age > 70 years. Further large trials are needed to evaluate the efficacy and safety of the immunotherapy in elderly patients with locally advanced EC.

There are several limitations in this study. First, due to retrospective nature of the included studies, there is likely patient selection bias between dCRT and RT alone groups or between dCRT and surgery groups. For example, patients receiving surgery might have better physical condition than those receiving non-surgery treatment. However, we found the consistent results when the multivariate-adjusted HRs instead of crude HRs were used as the measure of effect, which would be helpful to increase statistical power of our analyses. Second, several included studies were with relatively small sample size, which might affect the overall results. However, in sensitivity analysis, the OS and PFS results were not significantly altered when these studies were removed one by one, suggesting the small influence of them. In addition, high heterogeneity was observed, especially in group of dCRT vs. surgery. Although meta-regression analyses were performed, no significant heterogeneity source could be identified. Third, surgical method and surgery related toxicity could not be assessed in this meta-analysis because most of the studies did not report the related data. Fourth, the majority of patients in dCRT vs. RT alone group had ESCC, and therefore, the findings in this group might not be generalizable to EAC. Finally, some HRs were calculated using the Kaplan Meier curve, which might have error compared to the direct calculation using the raw data.

Conclusions

nCRT followed by surgery appears to be a preferred strategy for elderly patients with good physiological conditions; and dCRT is a better alternative for unresectable cases. Advanced age alone is not likely a key predictor for the tolerability of the two aggressive treatments.

Abbreviations

nCRT	neoadjuvant chemoradiotherapy
EC	Esophageal cancer
dCRT	definitive chemoradiotherapy
OS	Overall survival
PFS	Progression-free survival
RT	Radiotherapy
HR	Hazard ratios
CI	Confidence intervals
RCTs	Randomized controlled trials
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
ECOG	Eastern Cooperative Oncology Group
CT	Chemotherapy
AEs	Adverse events
NOS	Newcastle-Ottawa Scale
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
AJCC	American Joint Committee on Cancer
ESCC	Esophageal squamous cell carcinoma
3D-RT	Three-dimensional radiotherapy
IMRT	Intensity modulated radiotherapy
cCRT	concurrent chemoradiotherapy
IFI	Involved-field irradiation
ENI	Elective nodal irradiation
EAC	Esophageal adenocarcinoma

Supplementary Information

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Supplementary Material 1

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Author contributions

J.D. and Y.S. contributed to conception and design of the study, and reviewed and revised the article. J.Y. and X.Z. performed the literature search and data extraction. T.L., J.Y., and J.C. performed statistical analysis and prepared Figs. 1, 2, 3, 4, 5 and 6; Table 1. J.Y. and X.Z. drafted the article. All authors read and approved the final version.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

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Competing interests

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