

REVIEW

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# The impact of radiation dose on the efficacy of definitive chemoradiotherapy in patients with locally advanced esophageal carcinoma: a systematic review and meta-analysis

Danjing Luo<sup>a,b</sup>, Qiulu Zhong<sup>a,b</sup>, and Xiaodong Zhu<sup>a,c</sup>

<sup>a</sup>Department of Radiation Oncology, Guangxi Medical University Cancer Hospital, Nanning, P.R.China; <sup>b</sup>Department of Radiation Oncology, Second Affiliated Hospital of Guangxi Medical University, Nanning, China; <sup>c</sup>Department of Oncology, Wuming Hospital of Guangxi Medical University, Nanning, China

## ABSTRACT

To investigate the impact of radiation dose on the efficacy of definitive chemoradiotherapy (dCCRT) in patients with locally advanced esophageal carcinoma. PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) were searched for eligible studies. Studies that compared high-dose radiation (HD-RT) group with low-dose radiation (LD-RT) group using modern radiotherapy techniques for locally advanced esophageal carcinoma patients in dCCRT were identified. The hazard ratios (HR) for overall survival (OS), progression-free survival (PFS), and the odds ratios (OR) for clinical complete response (cCR), local-regional failure (LRF), distant metastasis (DM), and grade  $\geq 3$  AEs. Meta-analysis was performed when relevant data were available. Eleven studies involving 1943 patients were included for analyses. The results showed that the HD-RT group had better OS (pooled HR 0.78 [0.70, 0.87],  $p < .00001$ ), PFS (pooled HR 0.72 [0.55, 0.94],  $p = .01$ ), cCR (OR 1.52 [1.13, 2.05],  $p = .005$ ), and LRF (OR 0.60 [0.45, 0.80],  $p = .0004$ ). In addition, there were no significant differences between the two groups in terms of DM (OR 1.43 [1.00, 2.04],  $p = .05$ ), grade 3–5 radiation pneumonitis (OR 1.38 [0.71, 2.68],  $p = .35$ ), grade 3–5 radiation esophagitis (OR 1.36 [0.88, 2.10],  $p = .17$ ), grade 3–5 other esophageal toxicities (stenosis/fistula/hemorrhage) (OR 1.22 [0.75, 2.00],  $p = .43$ ), and treatment-related death (OR 1.40 [0.73, 2.68],  $p = .31$ ). High-dose radiotherapy in definitive CCRT for patients with locally advanced esophageal carcinoma is associated with improved PFS, OS, cCR, and LC with no increase of grade  $\geq 3$  AEs. Simultaneously, we await the preliminary and final results of several ongoing dose-escalation randomized trials. Furthermore, future studies should provide personalized radiotherapy doses for these patients.

## ARTICLE HISTORY

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## Introduction

Patients with locally advanced esophageal carcinoma (LAEC) account for approximately 50% of the total,<sup>1</sup> and the majority of them have lost the opportunity for surgery at the time of diagnosis. The currently recommended treatment modality for these unresectable patients is platinum-based definitive concurrent chemoradiotherapy (CCRT) based on the result of the Intergroup Radiation Therapy Oncology Group (RTOG)-8501.<sup>2</sup> The recommended dose by National Comprehensive Cancer Network (NCCN) was 50–50.4 Gy<sup>3</sup> based on the results of Intergroup Radiation Therapy Oncology Group (RTOG)90–12<sup>4</sup> and INT-0123 (also known as RTOG 94–05).<sup>5</sup> Although even with this modality therapy, survival remains disappointing and with 5-year overall survival (OS) rate of approximately 20%, and the most common mode of treatment failure is locoregional recurrence within the gross tumor volume, which was as high as 50%,<sup>6</sup> especially in patients with LAEC.<sup>7,8</sup> Simultaneously, dose escalation has been shown in numerous clinical trials and meta-analyses to improve local control (LC) and OS with no increase in serious side effects,

raising the possibility that this factor may be advantageous in CCRT.<sup>9–13</sup> Nevertheless, the ARTDECO study<sup>14</sup> and the study undertaken by Xu et al<sup>15</sup> came to oppose, indicating that dose escalation has no benefit on OS. Hence, the recommended radiation dose remains controversial. However, many studies included patients at all stages, which may have impacted the findings and reduced the effect of current clinical evidence. Hence, we performed this up-to-date meta-analysis to determine whether dose escalation of CCRT could improve the survival of patients with LAEC.

## Patients and methods

### Search strategy

This study was registered on the PROSPERO database (number CRD42022330871). The following keywords were used to search PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) for literature published before June 2022:

((“esophageal” [Title]) or (“oesophageal” [Title]) or (“esophagus” [Title])) and ((“tumor” [Title]) or (“cancer” [Title]) or (“carcinoma” [Title]) or (“neoplasm” [Title]) or (“neoplasms” [Title])) and ((“chemoradiation” [Title]) or (“chemoradiotherapy” [Title]) or (“radiochemotherapy” [Title]) or (“chemo-irradiation” [Title]) or (“chemo-radiotherapy” [Title])) and ((“dose” [Abstract]) or (“dose escalation”

[Abstract]) or (“dose-escalated” [Abstract]) or (“high dose” [Abstract])). Manual searches of reference lists were also performed.

### Study election

Inclusion criteria included: 1) Studies on patients with LAEC (AJCC 6<sup>th</sup>: stage II–IVA; AJCC 7<sup>th</sup>: stage IB–IIIC; AJCC 8<sup>th</sup>: stage IB–IVA). 2) Studies comparing the curative efficacy in LAEC patients with HD-RT or LD-RT. 3) OS must be reported. 4) The most recent and informative publication from the same trial. 5) The language limit to English and Chinese.

The following studies were excluded: 1) Studies on patients with distant metastasis or with other cancers. 2) Only 2D radiotherapy techniques or Co-60. 3) single-arm trial, letters, review, case report, meta-analysis, or abstract of meeting.

### Data extraction

The following information was gathered from all included studies: 1) information and characteristics: first name of author, nation, year of publication, study period, sort of research, clinical stage, gender, histology, groups, patient number, location, radiation dose, regimens, radiation technology, quality. 2) primary data: HR and 95% CI of OS and PFS; incidence rate for cCR, LRF, and DM, and grade  $\geq 3$  adverse events (AEs). Engauge Digitizer version 4.1 (available from: <http://digitizer.sourceforge.net/>) was applied to read the survival rates from Kaplan-Meier curves, and then the spreadsheet attached to Tierney’s paper was used to calculate HR.

### Quality assessment

The quality of all included studies was rated separately by two evaluators. The 9-star Newcastle-Ottawa Scale (Available from: [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.htm](http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm)) was used to assess non-RCTs, with high quality scoring 7–9, medium quality scoring 4–6, and low quality scoring 1–3. The 7-point JADAD scale was used to assess RCTs, with high quality scoring 4–7 and poor quality scoring 1–3.

### Statistical analysis

This meta-analysis was carried out using the software of the Review Manager (Rev Man) (version 5.3) and STATA v12.0.  $I^2$  was used to assess statistical heterogeneity. If  $I^2 \leq 50\%$ , a fixed-effects model was conducted to synthesize HR and OR; otherwise, a random-effects model was used. The tests were considered statistically significant if  $P < .05$ . All the P values were two-sided. Begg’s and Egger’s tests were used to examine the

publication bias of PFS and OS. Sensitivity analysis was used to determine the effect of any individual study on the final results.

## Results

Eleven studies met the criteria and were incorporated into the meta-analysis (Figure 1 outlines the selection process flow). The eleven studies consisted of four randomized controlled trials (RCTs), three population-based propensity-score-matched analyses, and four retrospective studies. There was a total of 1943 LAEC patients, of whom 962 received LD-RT while 981 received HD-RT. The detailed information of all studies is reported in Table 1.<sup>14–24</sup>

All articles reported overall survival in groups. Patients in the HD-RT group had significant survival benefits compared to patients in the LD-RT group (pooled HR 0.78 [0.70, 0.87],  $p < .00001$ , Figure 2a). A fixed model was employed because  $I^2 < 50\%$  ( $I^2 = 45\%$ ).

Five studies analyzed the PFS of the two groups. HD-RT group had a significant advantage over LD-RT group (HR 0.72 [0.55, 0.94],  $p = .01$ , Figure 2b). A random model was employed because  $I^2 > 50\%$  ( $I^2 = 57\%$ ).

Six studies compared the cCR and LRF rates of the two groups, with the HD-RT group outperforming the LD-RT group in both cCR (OR 1.52 [1.13, 2.05];  $P = .005$ , Figure 3a) and LRF (OR 0.60 [0.45, 0.80],  $p = .0004$ , Figure 3b). A fixed model was employed because  $I^2 < 50\%$ .

Five articles analyzed the DM rates of the two groups. There was no difference between the two groups in this respect (OR 1.43 [1.00, 2.04];  $P = .05$ , Figure 3c). A fixed model was employed because  $I^2 < 50\%$ .

Eight articles reported grade  $\geq 3$  AEs (Table 2). No significant difference was demonstrated between the two arms in terms of grade 3–5 radiation pneumonitis (OR 1.38 [0.71, 2.68],  $p = .35$ , Figure 4a), grade 3–5 radiation esophagitis (OR 1.36 [0.88, 2.10],  $p = .17$ , Figure 4b), grade 3–5 radiation other esophageal toxicities (stenosis/ fistula/ hemorrhage) (OR 1.22 [0.75, 2.00],  $p = .43$ , Figure 4c), treatment-related death (OR 1.40 [0.73, 2.68],  $p = .31$ , Figure 4d). A fixed model was employed because  $I^2 < 50\%$ .

### Sensitivity analysis

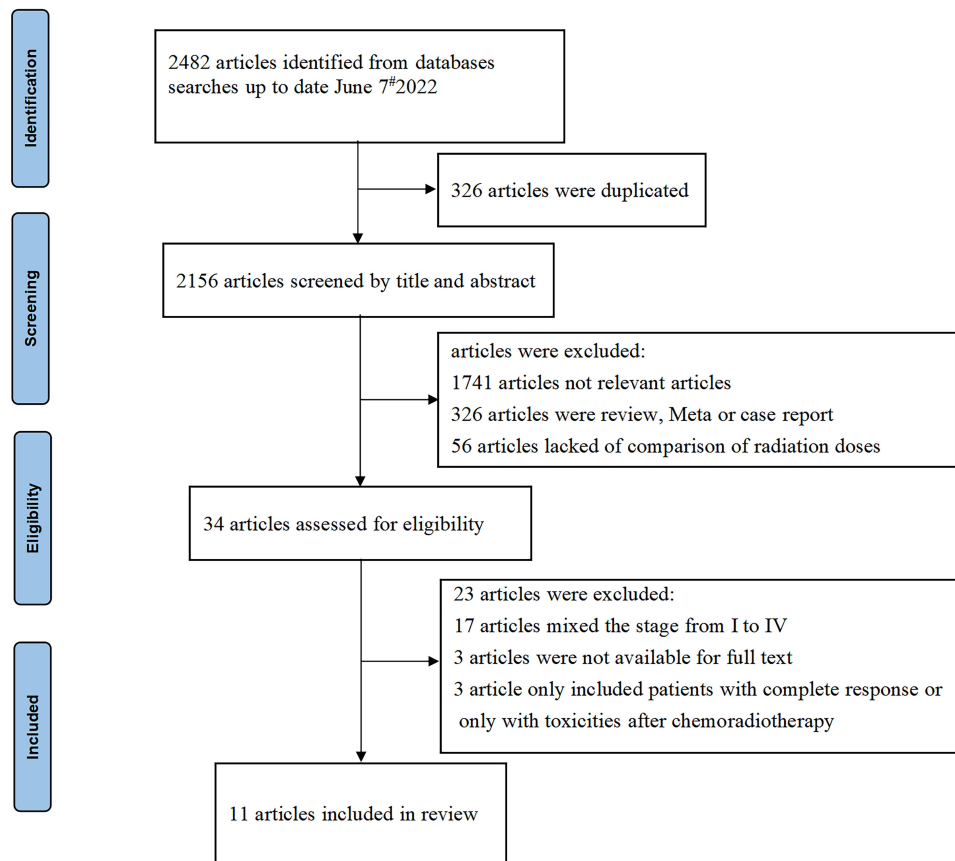
Sensitivity analysis revealed that the new HRs for OS (Figure 5a) and PFS (Figure 5b) were identical to the original HRs, demonstrating that no single study may have significantly influenced the meta-analysis results.

### Publication bias

No significant publication bias was found between HD-RT group and LD-RT group among all studies on OS (Figure 5c, Begg’s test,  $P = .533$ ; Figure 5d, Egger’s test,  $p = .325[-2.6350, 0.9731]$ ) and PFS (Figure 5e, Begg’s test,  $P = .086$ ; Figure 5f, Egger’s test,  $p = .148[-9.7395, 2.3638]$ ), all P-values were  $> 0.05$ .

## Discussion

Does dose escalation of CCRT improve the survival of patients with LAEC? In our study, we focus on patients with locally



**Figure 1.** Flow chart of studies selection procedure.

advanced esophageal carcinoma and summarize the current clinical evidence of dose escalation. The findings demonstrated a higher dose utilizing modern radiation techniques for definitive CCRT of LAEC might reduce LRF and improve PFS, OS, and cCR of patients without increasing toxicity rates compared to low-dose radiotherapy. There have been numerous studies on esophageal cancer dose escalation, but no conclusion has been reached. Based on the findings of the INT0123 study,<sup>5</sup> the dose recommendation for definitive radiotherapy is 50–50.4 Gy. Minsky et al compared the high radiation dose group (64.8 Gy) to the low-dose group (50.4 Gy) with conventional radiotherapy techniques (2D-RT), and no benefit in local control rate or survival rate was observed, but treatment-related mortality increased. It was worth noting that the enrolled population contains a higher proportion of patients in the early stages (I–IIB). Moreover, only the primary tumor was treated up to 64.8 Gy, with no dose escalation for involved nodes. Furthermore, HD group radiotherapy treated patients with squamous cell carcinoma (85.8%) and adenocarcinoma (14.2%). In addition, the radiation dose did not meet 50.4 Gy in 7 of the 11 treatment-related deaths in the high-dose group. As a result, the study spurred controversy in its aftermath. Similar results were in other studies even with modern radiotherapy techniques (3D-RT).<sup>25,26</sup> Brower et al<sup>25</sup> conducted a population-based retrospective analysis of 6854 patients from the National Cancer Data Base (NCDB) of America, of which 3821 received doses of 50 to 50.4 Gy and 3033 received doses higher than 50.4 Gy, and three matched groups were generated for the

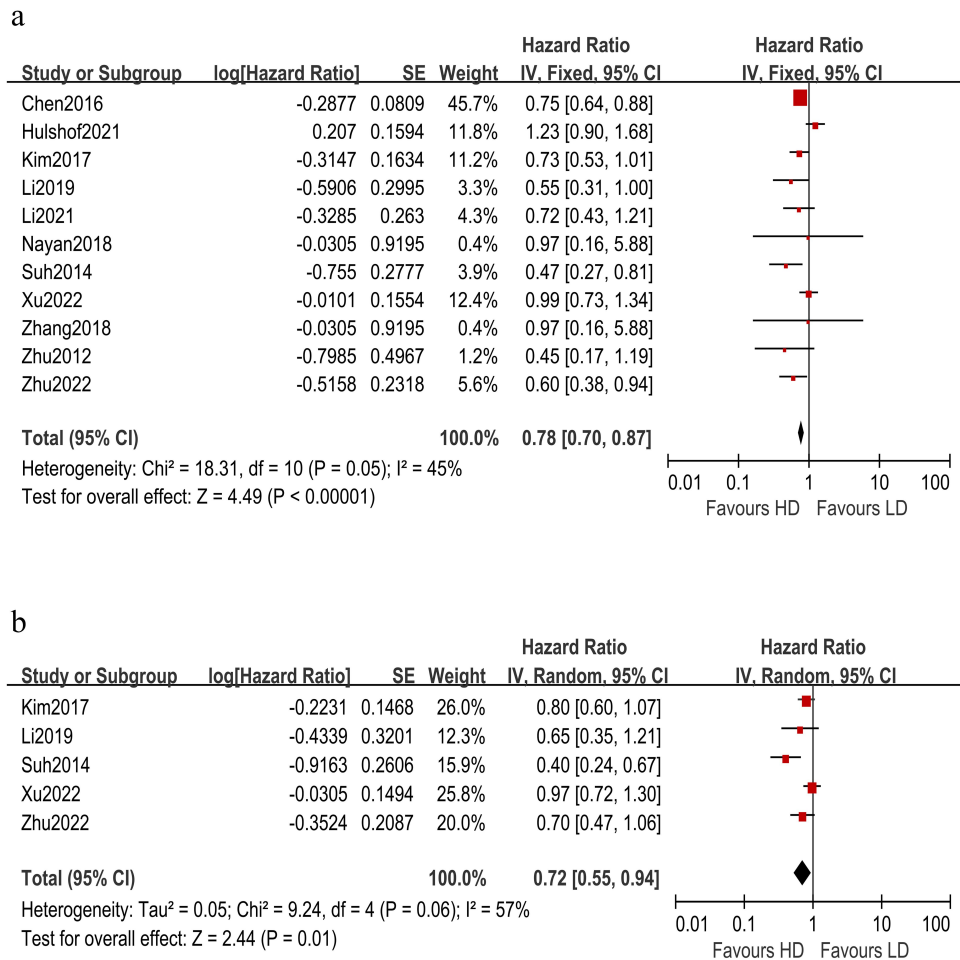
comparisons of 50 to 50.4 Gy versus 51 to 54 Gy, 50 to 50.4 Gy versus 55 to 60 Gy, and 50 to 50.4 Gy versus >60 Gy, there were no survival differences between the two groups. Unfortunately, the same outcome was achieved when propensity-score-matched comparisons were attempted to investigate the effect of dose escalation on OS stratified by histologic type and IMRT use. This was a retrospective database-based study, and conclusions were limited by lacking radiotherapy technique and planning, staging and chemotherapy regimens, and salvage regimens for recurrence and metastasis. In another study,<sup>26</sup> twelve patients were assigned to receive a radiation dose of 61.2 Gy and 30 patients to receive 50.4 Gy; dose-related toxicities were encountered in two out of twelve patients in the high-dose group, including grade 3 esophagomediastinal fistula and grade 4 pericardial effusion. However, it might be limited by the unbalanced sample size and the increased toxicity of chemoradiation therapy, which combines three cytotoxic agents.

However, several studies showed that higher radiation doses resulted in effective local control of locally advanced esophageal cancer. Suh et al<sup>17</sup> suggested that dose escalation in stage II–III locally advanced esophageal carcinoma improved the 2-year local control rate (69% versus 32%,  $P < .01$ ) and PFS (47% versus 20%,  $P = .01$ ), with no increase in treatment-related toxicity. Squamous cell carcinoma and adenocarcinoma were among the patients. Finally, high-dose radiotherapy of 60 Gy or more combined with concurrent chemotherapy is an effective therapeutic option for Stage II–III esophageal cancer. In another study,<sup>16</sup> 44 patients with

**Table 1.** Basic characteristics of the included studies.

Author	Nation	Year	Study period	Study design	Clinical stage	Gender (M/F)	Histology types (SCC/Other)	Groups	Patients number	Location(Cervical/upper/middle/lower/other)	Radiation Dose groups	Chemotherapy regimens	Radiation technology	Studies Quality
Zhu <sup>16</sup>	China	2012	1/2007-12/2007	prospective	II-III (AJCC6 <sup>th</sup> )	-	44/0	Low dose High dose	24 20	44(c + u)/0/0/0	60 Gy 63.9 Gy (SIB)	PF	IMRT	5
Suh <sup>17</sup>	Korea	2014	1/1998-2/2008	retrospective	II-III (AJCC6 <sup>th</sup> )	117/9	117/9	Low dose High dose	49 77	1/10/24/14/0 9/14/41/13/0	54 Gy (45-59.4) 63 Gy (60-75.6)	PF/5-Fu	3D-CRT	7
Chen <sup>18</sup>	China, Taiwan	2016	2008-2013	retrospective	II-IV (AJCC6/7 <sup>th</sup> )	619/29	648/0	Low dose High dose	324 324	-	50- 50.4 Gy ≥60 Gy	CCRT	3D-CRT, IMRT	5
Kim <sup>19</sup>	Korea	2017	1994-2013	retrospective	II-III (AJCC6/7 <sup>th</sup> )	226/10	230/6	Low dose High dose	120 116	5/27/55/33/0 11/31/58/16/0	50.4 Gy (45-59.4) 63 Gy (60-66.6)	PF /other	3D-CRT, IMRT	6
Nayan <sup>20</sup>	India	2018	-	Prospective	IIB-IIIB (AJCC7 <sup>th</sup> )	18/10	28/0	Low dose High dose	14 14	-	50.4 Gy 64.8 Gy	PF	3D-CRT, IMRT	5
Zhang <sup>21</sup>	China	2018	2010-2014	retrospective	II-III (AJCC7 <sup>th</sup> )	47/33	80/0	Low dose High dose	43 37	0/8/16/19/0 0/6/15/16/0	52 Gy (50.4-56) 62 Gy (59.4-64.8)	TP /PF /PS	3D-CRT, IMRT	6
Li <sup>22</sup>	China, Taiwan	2019	2011-2015	retrospective	II-III (AJCC7 <sup>th</sup> )	36/0	36/0	Low dose High dose	18 18	-	50 Gy (47.5-52.5) 60 Gy (57-63)	CCRT	IMRT, IGRT	6
Li <sup>23</sup>	China, Taiwan	2021	2011-2017	retrospective	II-III (AJCC7 <sup>th</sup> )	52/2	54/0	Standard dose High dose	27 27	27/0/0/0 27/0/0/0	50 Gy 60-70 Gy	CCRT	IMRT, IGRT	6
Hulshof <sup>14</sup>	Netherlands	2021	9/2012-6/2018	Prospective (Phase III)	II-IVA (AJCC7 <sup>th</sup> )	179/78	159/98	Low dose High dose	130 130	9/33/27/50/0 4/27/40/50/0	50.4 Gy 61.6 Gy (SIB)	TC	3D-CRT	5
Xu <sup>15</sup>	China	2022	10/5/2013 - 16/5/2017	Prospective (Phase III)	IIA-IVA (AJCC6 <sup>th</sup> )	251/68	319/0	Low dose High dose	159 160	96(c + U)/63(M + L)/0 89(c + U)/71(M + L)/0	50 Gy 60 Gy	DP	IMRT, IGRT	5
Zhu <sup>24</sup>	China	2022	1/2015-12/2019	retrospective	II-III (AJCC7 <sup>th</sup> )	85/27	112/0	Low dose High dose	54 58	0/15/25/14 0/19/27/12	50.4 Gy 60 Gy	NS ND	IMRT	7

M Male, F Female, SCC Squamous cell cancer, 3D-CRT Three dimensional conformal radiotherapy, IMRT Intensity-modulated radiotherapy, IGRT Imaging Guided radiation therapy, CCRT Concurrent chemo-radiotherapy, PF Cisplatin + 5-fluorouracil, DCF docetaxel+displatin+ 5-fluorouracil, TP dislatin +paclitaxel,PS Cisplatin +S-1,DP docetaxel + cisplatin,NS Nedaplatin+S-1,ND Nedaplatin+ docetaxel. AJCC 6/7<sup>th</sup> American Joint Committee on Cancer staging 6/7<sup>th</sup>.



**Figure 2.** Forest plots for relationship between HD-RT and LD-RT;(a) pooled analyses for OS;(b)pooled analyses for PFS.

squamous cell carcinoma were divided into two groups, with the high-dose group receiving 63.9 Gy (boosted in primary lesion) and the low-dose group receiving 60 Gy, boosted high dose can increase relapse-free survival. Furthermore, He et al<sup>27</sup> included patients who were treated with doses of 50.4 Gy or more; HD-RT group had a considerably reduced local failure rate (17.9% versus 34.3%,  $p = .024$ ) and a somewhat higher 5-year local-regional failure-free survival (68.7% versus 55.9%,  $p = .052$ ) than the low-dose group.

More encouragingly, dose escalation will be a viable option for improving OS rather than just local control. Chen et al analyzed the results of 691 patients with esophageal squamous cell carcinoma after matching the general clinical data, HR of death was 0.75 (95% CI 0.64–0.88) when high-dose compared to standard dose. It concluded that higher radiotherapy dose led to better survival for locally advanced squamous cell carcinoma. Similarly, Kim et al<sup>19</sup> retrospectively analyzed the clinical data of 236 patients with stage II–III esophageal cancer and compared 120 patients with radiotherapy doses <60 Gy to 116 patients with  $\geq 60$  Gy. The results showed that there was a significant local control advantage (69.1% versus 50.3%,  $P = .002$ ) and survival advantage (35.1 months versus 22.3 months,  $P = .043$ ) in high doses and the incidence of treatment-related adverse reactions was similar. In another study,<sup>21</sup>

higher doses than that used for standard radiotherapy resulted in higher 5-year OS rates (42.8% versus 21%). Similar findings were in other studies.<sup>22–24</sup> According to the mentioned research, the benefit of OS and LC in the HD-RT group may base on the biological behavior of solid tumors and squamous cell carcinomas<sup>28,29</sup> and attributed to advancements in radiotherapy technology and imaging technology, which allow for more precise target delineation. And the selection bias of retrospective studies cannot be ignored.

Undoubtedly, the findings of three recent randomized controlled trials must be discussed. This study included the ARTDECO study<sup>14</sup> and the study conducted by Xu et al,<sup>15</sup> whereas the CONCORDE study<sup>30</sup> only reported the results of conference abstracts, which could not be included in this study. According to the ARTDECO study, there was no significant difference in PFS, OS, and Locoregional progression-free survival (LRPFS) between the HD-RT (61.6 Gy) group and LD-RT (50.4 Gy) group. The results may be related to the fact that dose escalation was only delivered to the primary tumor, and 39% of adenocarcinoma patients show different risk factors and biological characteristics from squamous carcinoma. In addition, an excess of fatal bleeding in grade 4 and 5 toxicities in the HD arm occurred. Similarly, Xu et al found no difference toward 3y-OS or PFS or LRPFS between the HD-RT (60 Gy) and LD-RT (50 Gy) groups, but grade 3



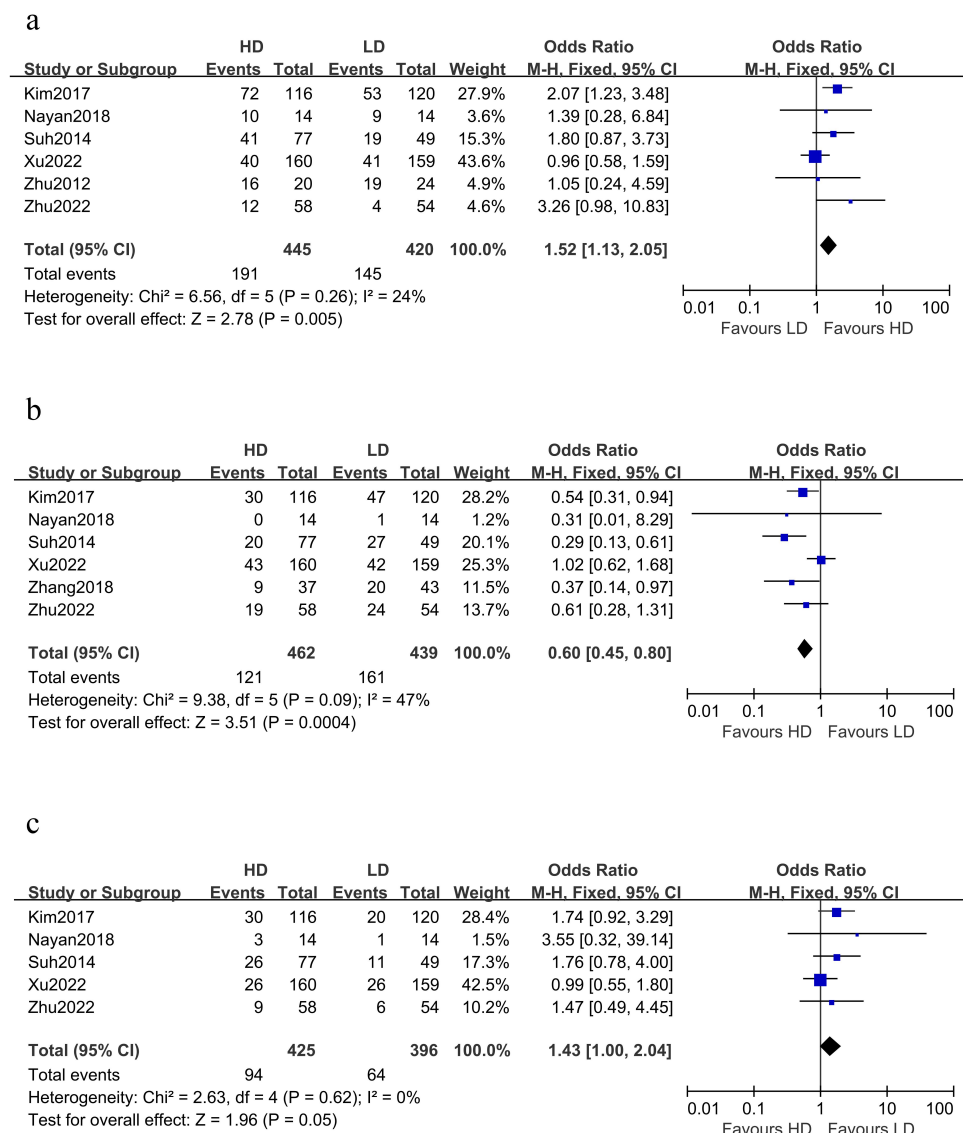
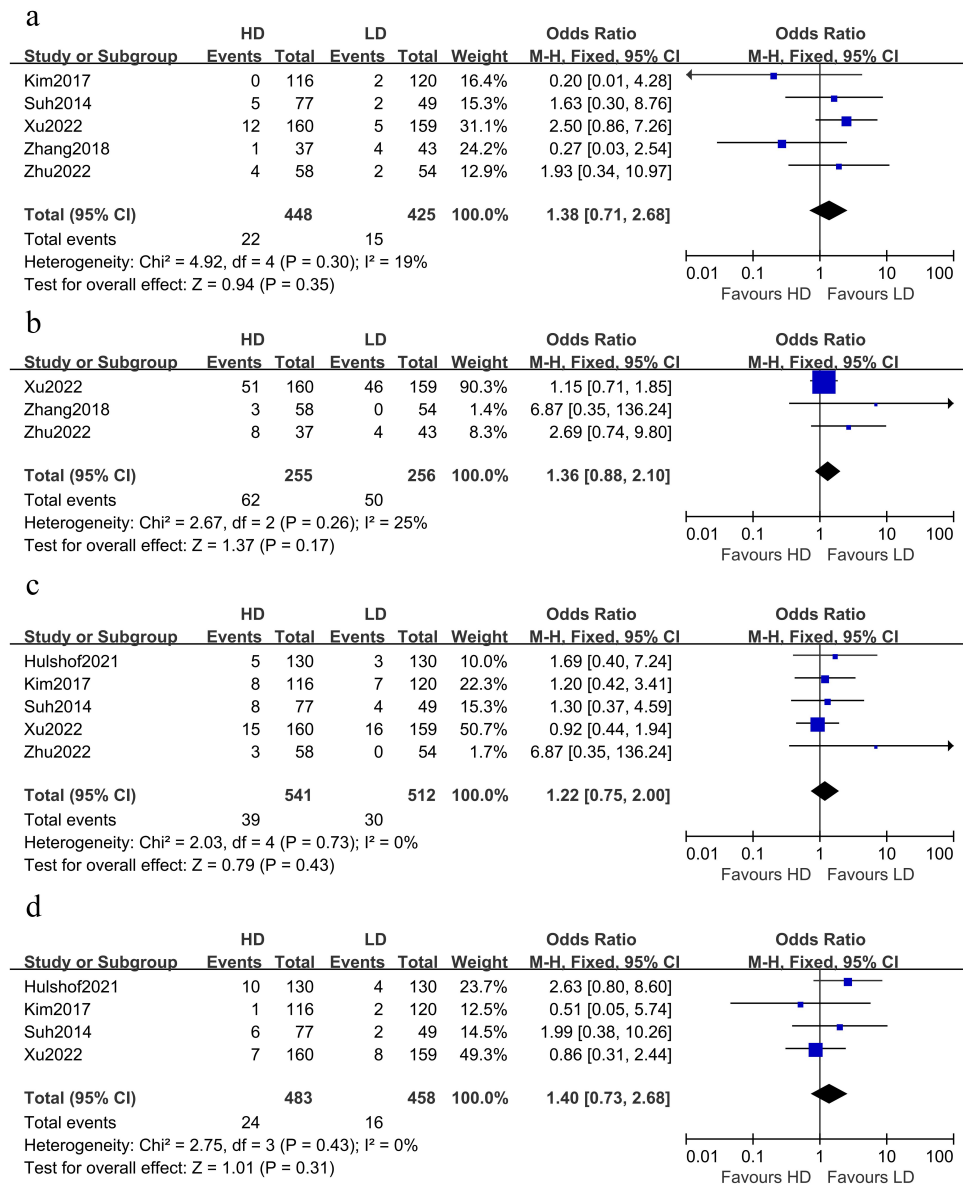


Figure 3. Forest plot for relationship between HD-RT and LD-RT.(a) odds ratio for cCR;(b) odds ratio for LRF;(c) odds ratio for DM.

Table 2. Adverse events of grades 3–5.

Studies	Patients Number (LD/HD)	Radiation technology	Radiotherapy dose		Pneumonitis	Esophagitis	Other Esophageal toxicities (stenosis/fistula/ hemorrhage)	Treatment- Related Death	Evaluation Criterion for toxicities
			LD-RT	HD-RT					
Zhu <sup>16</sup>	24/20	IMRT	60 Gy/2 Gy	63.9 Gy/2.13 Gy	0 vs 0	0 vs 0	0 vs 0	0 vs 0	CTCAE 3.0
Suh <sup>17</sup>	49/77	2D/	45–	60–75.6 Gy/1.8–	4% vs 6%	-	8.2% vs 10.4%	4% vs	CTCAE 3.0
		3D-CRT	59.4 Gy/1.8– 2 Gy	2 Gy				7.8%	
Kim <sup>19</sup>	120/ 116	3D-CRT, IMRT	45–	60–66.6 Gy/1.8–	1.7% vs 0	-	5.8% vs 6.9%	1.7% vs 0.9%	CTCAE 4.0
			59.4 Gy/1.8– 2 Gy	2 Gy					
Nayan <sup>20</sup>	14/14	3D-CRT, IMRT	50.4 Gy/1.8 Gy	64.8 Gy/1.8 Gy	0 vs 0	0 vs 0	0 vs 0	0 vs 0	CTCAE 4.0
Zhang <sup>21</sup>	43/37	3D-CRT, IMRT	50.4–	59.4–	9.3% vs 27%	9.3% vs	-	0 vs 0	CTCAE 4.0
			56 Gy/1.8– 2 Gy	64.8 Gy/1.8– 2 Gy		21.6%			
Hulshof <sup>14</sup>	130/ 130	3D-CRT	50.4 Gy/1.8 Gy	61.6 Gy/2.2 Gy	-	-	2.3% vs 3.8%	3.3% vs 7.6%	CTCAE 4.0
Xu <sup>15</sup>	159/ 160	IMRT, IGRT	50 Gy/2 Gy	60 Gy/2 Gy	3.1% vs	28.8%	9.9% vs 9.3%	5.0% vs	CTCAE 4.0
					7.5%	vs 31.7%		4.4%	
Zhu <sup>24</sup>	54/58	IMRT	50.4 Gy/1.8 Gy	60 Gy/2.0 Gy	1.9% vs 6.9%	0 vs 5.2%	0 vs 5.1%	0 vs 0	CTCAE 4.0

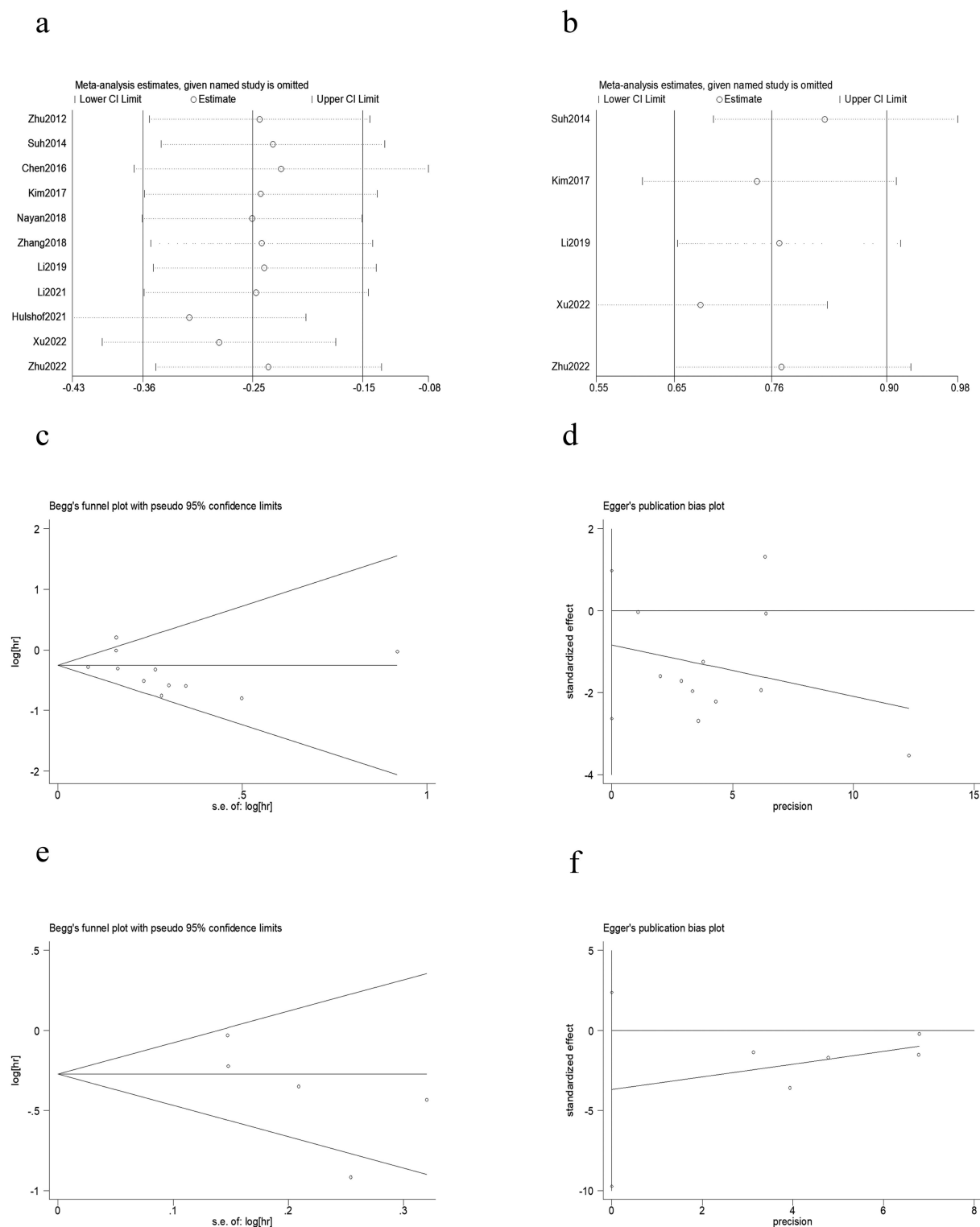
RT radiotherapy, IMRT Intensity-modulated radiotherapy, 3D-CRT Three dimensional conformal radiotherapy, IGRT Imaging Guided radiation therapy, LD low dose, HD high dose; CTCAE Common Terminology Criteria for Adverse Events.



**Figure 4.** Effect of HD-RT and LD-RT on grade $\geq 3$  AEs. Odds ratio for (a) pneumonitis; (b) esophagitis; (c) other esophageal toxicities: stenosis/fistula/hemorrhage; (d) treatment-related death.

+ radiation pneumonitis (7.5% versus 3.1%, nominal  $P = .03$ ) increased. It should be noted that there was a difference in the RT completion rates (88.2% versus 96.9%,  $P < .01$ ), poor implementation of the PET/CT scan may result in the improper stage, and a dose of 60 Gy may still be insufficient for LAEC, particularly for ESCC. Correspondingly, the results of the CONCORDE study reported at the 2021 American Society for Radiation Oncology (ASTRO) annual meeting showed no statistically significant difference in the primary endpoint 2y-LRPFS (43.8% versus 42.7%,  $p = .88$ ) between the HD-RT (66 Gy) and LD-RT (50 Gy) groups. And this outcome could be attributed to 3D conformal radiotherapy technology. Conclusions cannot be drawn before the publication of the detailed data. Simultaneously, we should note that these three studies used radiotherapy with elective lymph nodal irradiation. And there is no discernible difference in

treatment failure mode compared to previous involved field irradiation reports. The ESO-Shanghai 1 study<sup>31</sup> also found that involved field irradiation (IFI) resulted in lower irradiation toxicities without sacrificing OS in patients with LAEC. The preliminary findings from a multicenter, phase III clinical trial (NROG 001-Northern Radiation Oncology Group of China)<sup>32</sup> also supported this claim, with a better PFS and LRRFS in the high-dose IFI group. The final result lives up to our expectations. We are also looking forward to the SCOPE2 study (NCT 02741856),<sup>33</sup> which will compare the effects of conventional dosages (50 Gy) to higher doses (60 Gy), as well as the impact of alternative chemotherapy regimens in patients who do not respond to standard drugs early in treatment. Furthermore, the ongoing NCT02556762 study, which compares 66 Gy (SIB) to 50 Gy, may determine whether higher doses than 60 Gy is beneficial.



**Figure 5.** Sensitivity analyses for (a) OS and (b) PFS. Publication bias funnel plot: Beggs test and Eggers test for (c and d) OS and (e and f) PFS.

Given the contradictory findings of the above studies, we conducted this meta-analysis and indicated that higher doses can benefit patients with LAEC in survival. Inevitably, there are some limitations in this study. At first, the quality of the included studies varied, with four retrospective studies. Second, a small patient population enrolled in some studies, including two RCTs. The studies conducted by Zhu et al and Nayan et al

found no lung or esophageal side effects (grade  $\geq 3$ ), which could be attributed to the small sample size and individual differences in radiation sensitivity. Another reason that Zhu et al. chose patients with neck and upper thoracic esophageal cancer was doubtless. Third, the stages of patients were based on different versions instead of individual patient data. Finally, some studies lacked critical information such as radiation field, dosage distribution,



and chemotherapy regimens. These limitations may have an impact on the actual value of our research. More RCTs are needed to back up our findings.

## Conclusion

High-dose radiotherapy in definitive CCRT for patients with locally advanced esophageal carcinoma is associated with improved PFS, OS, cCR, and LC with no increase of grade $\geq$ 3AEs. Simultaneously, we await the preliminary and final results of several ongoing dose-escalation randomized trials. Furthermore, future studies should provide personalized radiotherapy doses for these patients.

## Disclosure statement

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## ORCID

Xiaodong Zhu  <http://orcid.org/0000-0002-7997-8268>

## Data availability statement

All data, models, and code generated or used during the study appear in the submitted article.

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