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Is Escalated Radiation Dose in Definitive Chemoradiotherapy Better for Inoperable Esophageal Carcinoma? A Meta-Analysis and Systematic Review

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Abstract

Purpose: This study aimed to compare the survival benefits between different total radiation doses in definitive chemoradiotherapy (dCRT) for inoperable esophageal carcinoma (EC) based on modern radiotherapy techniques. **Methods:** A systematic review was performed by searching the databases of PubMed, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science. All studies published prior to November 30, 2022, comparing radiation dose and disease-related outcomes in EC patients. The hazard ratio (HR) and odds ratio (OR) were used to describe the risk of outcomes and toxicities. **Results:** Seven prospective trials involving 1124EC patients were enrolled for analyses. The results revealed that the effect on overall survival (HR = 0.99, 95% CI = 0.85 - 1.16, P = 0.94), local progression-free survival (HR = 0.83, 95% CI = 0.58 - 1.17, P = 0.29), local regional progression-free survival (HR = 0.94, 95% CI = 0.76 - 1.17, P = 0.61), progression-free survival (HR = 0.90, 95% CI = 0.71 - 1.13, P = 0.35) was similar in the high-dose and standard-dose groups. Additionally, a high radiation dose exhibited a potential disadvantage in respiratory toxicities when compared with a standard dose (4.8% vs 2.2%, OR 2.11, P = 0.06). **Conclusions:** The efficacy of the HD group (≥60 Gy) and the SD group (approximately 50 Gy) for inoperable local advanced EC was similar. However, the HD group exhibited a high radiation dose exhibited a potential disadvantage in respiratory toxicities when compared with a standard dose. Simultaneously, the final results of several ongoing prospective trials regarding the optimal radiation dose in dCRT are awaited.

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Keywords

Esophageal Carcinoma, Chemoradiotherapy, High-Dose, Low-Dose, Meta-Analysis

1. Introduction

Globally, esophageal cancer (EC) ranks sixth cause of disease-related deaths with about 544,000 deaths and seventh with regard to incidence with a rate of 604,000 new cases every year [1], and the majority of them have lost the opportunity for surgery at the time of diagnosis. For this part of the patients, the landmark RTOG 85-01 and RTOG 94-05/INT 0123 trials [2] [3] established a dose of 50 - 50.4 Gy conventional fractionated radiotherapy as the standard regimen in definitive chemoradiotherapy (dCRT) for non-surgical locally advanced esophageal carcinoma. However, more than 50% of EC patients failed loco-regionally, even in patients with clinical complete response (cCR) after definitive chemoradiation [4] [5] [6], inducing the investigation of radiotherapy dose escalation as a theoretic solution. Thus, radiation dose escalation has been proposed as a more effective substitute to improve local-regional and survival rates, especially in Asian population [7] [8] [9]. Additionally, two-dimensional radiotherapy (2D-RT) technology, which has apparent dosage deficiency and cold spots compared with modern radiotherapy techniques [10], thus questions have been raised as to whether dose escalation utilizing computerized tomography (CT)-based radiotherapy approaches could bring about survival benefits with less treatment-related toxicity in the 3D-RT era. In recent years, numerous studies or pooled meta-analyses showed that escalated radiation dose could improve local control (LC) and OS with no increase in serious adverse radiation-related toxicities, raising the possibility that this factor may be advantageous in dCRT [7] [8] [9] [11]-[17]. However, several recently published clinical trials [18] [19] [20] opposed that dose escalation did not result in significant benefits in survival. Hence, the question of optimal radiation dose remained unclear.

Multiple meta-analyses regarding the optimal dCRT dose have revealed that receiving escalated dCRT dose brought about better disease-related outcomes (including locoregional control and OS) in patients with inoperable EC without an increase in severe toxicities compared with conventional-dose radiotherapy. However, most of the included studies in these meta-analyses were retrospective, which might influence the findings and reduced the sufficient effect of a standard radiation dose due to inevitable retrospective bias. Based on the above, we carried out this meta-analysis, which only enrolled prospective trials, to explore what is the optimal dCRT dose utilizing CT-based radiotherapy techniques.

2. Materials and Methods

2.1. Search Strategy and Studies Selection

Randomized controlled trials (RCTs) published prior to November 30, 2022,

comparing radiation dose and disease-related outcomes in inoperable Esophageal Cancer (EC) patients were targeted. A literature search was carried out the following databases: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science. The following retrieval keywords included "esophagealoroesophagealor esophagus" and "tumor* orcancer* or carcinoma* or neoplasm*" and "radiation* orradiotherapy" and "chemoradiation or chemoradiotherapyor radiochemotherapyor chemo-irradiation or chemo-radiotherapy" and "dose*". Then, we manually filtered the articles by title, abstract and/or full text review. Inclusion criteria in our analyses included: 1) Clinical trials must compare high-dose radiotherapy (≥60 Gy) with low-dose radiotherapy (approximately 50 Gy) groups, with comparative data provided; 2) Studies utilized PET-CT/CT-based radiotherapy techniques, such as 3D-RT, IMRT, image-guided radiotherapy (IGRT) or proton beam therapy; 3) Studies on EC patients treated with definitive CCRT; 4) Dataon overall survival (OS) had to be reported; 5) The language of publication abstract was limited to English; 6) Only prospective trials (all the randomized controlled trials and nonrandomized controlled trials)were eligible; 7) hazard ratio (HR) and 95% confidence intervals (CI) were provided or could be calculated. Studies were excluded as following: a) Duplicate studies; b) Review, meta-analysis, case report, manual research, basic research, retrospective study, and ongoing clinical trial; c) Not relevant records; d) Hazard ratio (HR) or unknown; e) Phase I trials; f) Radiotherapy delivered by 2D-CRT or brachytherapy; g) Studies mixed radiotherapy dose or unclear; and h) Single-arm trial. The selection process was shown in **Figure 1**.

2.2. Assessment of Methodological Quality

The quality of RCT was evaluated according to the modified Jaded scale [21]. Two point each was awarded for the presence of randomization, random sequences concealment, and double blinding, while one point each was awarded for an appropriate description of withdrawals and dropouts. If the trial had been described as randomized and/or double blind, but there was no description of the methods used to fulfill the procedure of randomization or the double-blind conditions, one point was awarded in each item. Total scores ranged from 1 to 3 present poor quality while scores from 4 to 7 stand for high quality. The Newcastle-Ottawa Scale (NOS) (available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was used for assessment of the NRCT. The quality grades were defined as follows: high quality (score 7 - 9), medium quality (score 4 - 6) and low quality (score less than 4). This scale evaluated studies on three major sections: selection, comparability, and the ascertainment of outcome of interest. High-quality choices in each section were identified by answering "Yes" to the questions. The more Yeses allocated to a study (to a maximum of nine Yeses), the better the quality it was. Two reviewers independently screened each of the potential studies, abstracts, and/or full texts to determine whether they were eligible for inclusion and cross-checked the results. If there were some different opinions, a third author

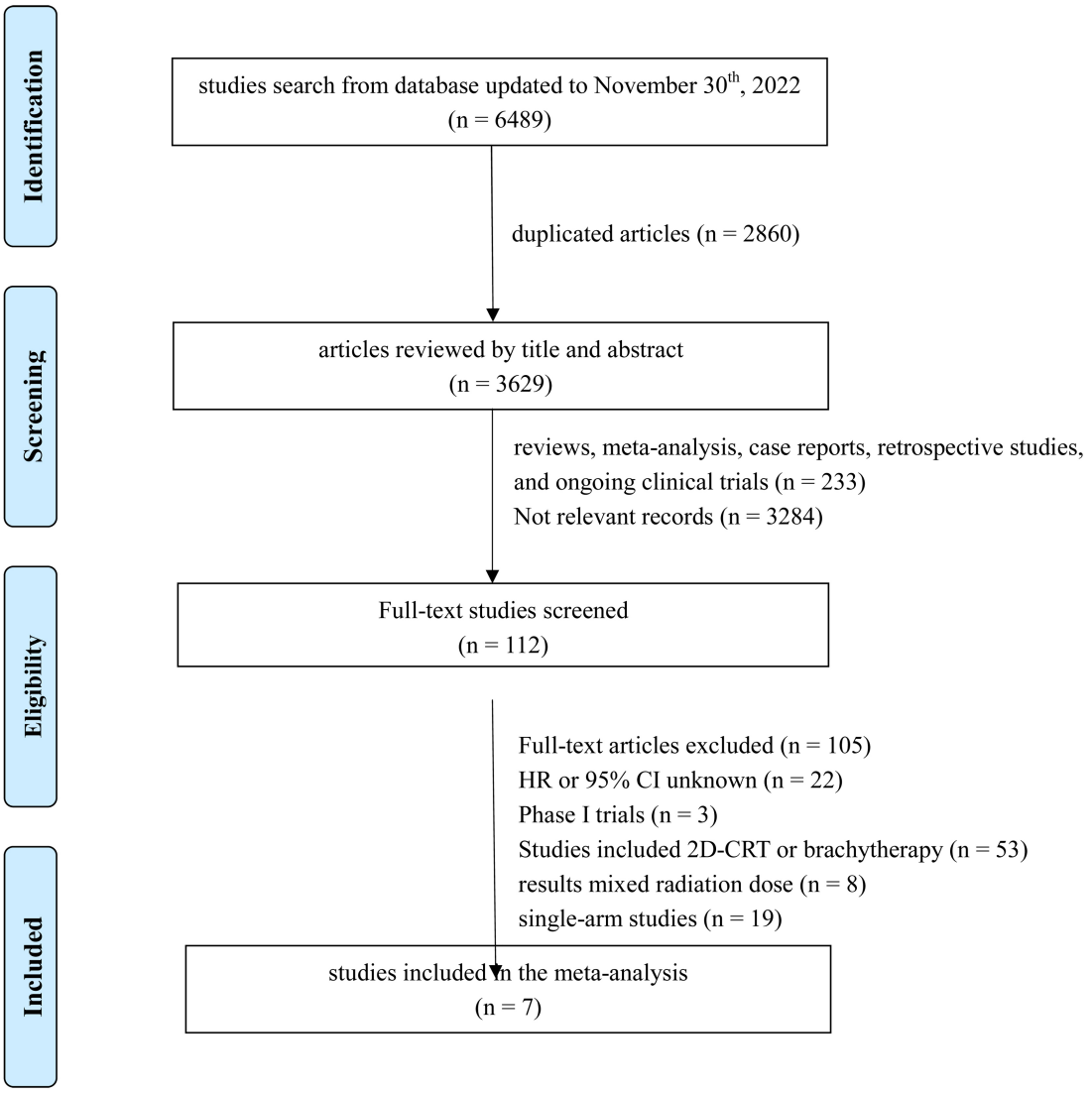


Figure 1. Flow chart showing studies selection workflow.

would be invited to deal with the disagreement.

2.3. Detail Data Extraction

The detailed information in HD-RT and SD-RT groups of each study was extracted by two investigators (XC Gan and QT Gou) independently. The evaluation results were compared and re-reviewed until the two authors reached a consensus on all variables. The following data were extracted and synthesized: first author's name, country, inclusion period, type of study, histology, tumor location, TNM stage, sample size, radiation dose, radiation technique, chemotherapy regimens, and outcome data, which included HR of OS, the local progression-free survival (LPFS), the locoregional progression-free survival (LRPFS), progression-free survival (PFS), and incidence of locoregional failure (LRF), distant metastasis (DM), short-term outcomes, treatment-related deaths as well as toxicities. Detailed data on all eligible prospective studies was presented in **Table 1**.

Table 1. Characteristics of trials included in the meta-analysis.

Author	Country	Inclusion period	Study type	Histology (SCC/ AC/ Other)	Tumor location (Cervical/ Upper/ Mid/ Lower/ Junction)	stage	sample size (SD/HD)	radiation dose	radiation technique	Concurrent chemotherapy	Adjuvant chemotherapy	Follow-up time (median, range)	3-year OS rate (SD/HD)
Zhu *et al.* [25]	China	2007.01-2007.12	RCT	44/0/0	44 (cervical and upper)	II-III^{+}	44 (24/20)	60 Gy/30 Fx 63.9 Gy/30 Fx	sIMRT	PF × 2	PF × 2	36 m, -	25.0%/ 35.0%
Ma *et al.* [23]	China	2005.05-2010.12	NRCT	112/0/0	0/21/79/ 12/0	T2-4, N0-1, M0$^{\#}$	112 (60/52)	50.4 Gy/28 Fx 66 (63-70) Gy	IMRT	PF/3 weeks	-	18 m, 5 - 40 m	0/ 21.3%
Nayan *et al.* [24]	India	not reported	RCT	28/0/0	0/4/24/0/0	II-III^{++}	28 (14/14)	50.4 Gy/28 Fx 64.8 Gy/36 Fx	3D-RT and IMRT	PF × 2	-	21 m, 18 - 26 m	-
Crehange *et al.* [22]	France	2011.06-2019.10	RCT II/III	191/25/1	unknown	I-III^{++}	217 (109/ 108)	50.0 Gy/25 Fx 66.0 Gy/33 Fx	3D-RT and IMRT	FOLFOX-4 × 3	FOLFOX-4 × 3	35.4 m, 1.3 - 65.7 m	-
You *et al.* [18]	China	2016.04-2019.04	RCT III	144/0/0	144 (thoracic)	T1-4 N0-1 M0-1a$^{+\#\#}$	144 (73/71)	50.4 Gy/28 Fx 59.4 Gy/33 Fx	IMRT	TC × 6	TC × 2 (max)	36 m, -	38.1%/ 43.5%
Hulshof *et al.* [20]	Dutch	2012.09-2018.06	RCT III	159/95/6	13/60/67/ 100/17	II-IVA^{++}	260 (130/ 130)	50.4 Gy/28 Fx 61.6 Gy/28 Fx	IMRT	TC × 6	-	50 m, -	42.0%/ 39.0%
Xu *et al.* [19]	China	2013.05-2017.05	RCT III	319/0/0	185 (cervical and upper) 134 (middle and lower)	IIA-IVA^{+}	319 (160/ 159)	50.0 Gy/25 Fx 60.0 Gy/30 Fx	IMRT and IGRT	DP/week	DP × 2	34 m, -	53.1%/ 52.7%

SCC, squamous cell cancer; AC, adenocarcinoma; SD, standard-dose; HD, high-dose; 3D-RT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; sIMRT, simplified intensity-modulated radiotherapy; 5-FU, 5-fluorouracil; PF, cisplatin + 5-fluorouracil; FOLFOX-4, oxaliplatin + folinic aci + 5-fluorouracil; TC, paclitaxel + carboplatin; DP docetaxel + cisplatin; $^{\#}$staged according to the TNM staging system of the 2007 International Union against cancer on cancer staging system; $^{\#\#}$M1a, Patients with enlarged (1.5 cm) retroperitoneal or celiac lymph nodes; $^{\#\#\#}$staged on the basis of supraclavicular lymph node spread; $^{+}$staged according to the sixth version American Joint Committee on Cancer (AJCC) staging manual for esophageal carcinoma; $^{++}$staged according to the seventh version AJCC staging manual for esophageal carcinoma; m, month; OS, overall survival.

2.4. Statistical Analysis

Data were analyzed with Review Manager Version 5.4.1. The statistical heterogeneity, which indicates the variation among eligible studies, was evaluated using I^2-statistic. The fixed-effect model was used for statistical consolidation if there was no statistical heterogeneity (I^2 < 50%) after testing, otherwise random-effects model should be required. Survival rates were extracted from Kaplan-Meier curves by the software of Engauge Digitizer version 11.3. The estimated values of Hazard ratio (HR) and its upper limit and lower limit of 95% confidence intervals (95% CI) were calculated by using the calculation spreadsheet according to Tierney's report if a figure for survival data was not available. Funnel plots were made to assess the potential of publication bias. The estimated HR, odds ratio (OR) and their 95% CIs on survival outcomes, which described the theoretical benefits in OS, LPFS, LRPFS, and PFS, or measured effect size of LPF and DM rates, were shown by forest plots. The tests were defined statistically significant if two-sided P values were less than 0.05.

3. Results

3.1. Eligible Studies Description

We screened 6489 potential eligible articles initially with the defined search strategy. After Careful examination and discreet exclusion, seven prospective trials [18] [19] [20] [22] [23] [24] [25] were included in the meta-analysis ultimately (**Table 1**; exclusion reasons were shown in **Figure 1**), which consisted of6 randomized clinical trials and 1 non-randomized study. The sample size in each study included in the meta-analysis ranged from 28 to 319, with the publication year range of 2012-2022. Most studies came from Asian countries (including four from China and one from India), and two studies from western countries (including one from France and the other one from Dutch). 1124 patients were diagnosed with esophageal cancer, including 997 (88.7%) squamous cell carcinoma (SCC), 120 (10.7%) adenocarcinoma (AC), and 7 (0.6%) other histologic classifications. All included studies used PET-CT/CT-based radiotherapy techniques, including 3D-RT, IMRT, image-guided radiotherapy (IGRT) or proton beam therapy. The total radiation doses ranged from 50.0 to 60.0 Gy, and 59.4 to 70.0 Gy were carried out for the standard-dose (SD) group and the high-dose (HD) group, respectively. All eligible studies implemented radiotherapy with concurrent chemotherapy and four studies complicated further 2 - 3 circles adjuvant chemotherapy.

3.2. Quality Assessment

Six RCTs and one NRCT were evaluated using The Jadad scale and The Newcastle-Ottawa Scale, respectively, and assessed quality score was listed in **Table 2**. The Newcastle-Ottawa Scale of the only NRCT was 9 of 9, indicating that the quality was high. The mean score of the six RCTs was 4. All RCTs were described as randomized, while three trials described an appropriate method of randomization. All trails had a description of withdrawals and dropouts. No study was a double-blinded trial.

3.3. Effect of Radiation Dose on Survival

All studies evaluated the OS of the two groups [18] [19] [20] [22] [23] [24] [25]. There was no statistically significant difference in OS between the two groups (pooled HR 0.99, 95% CI 0.85 - 1.16; P = 0.94; **Figure 2(a)**). The 3-year OS rates were presented in **Table 1**.

The LPFS of the two groups were analyzed in three articles including 516 patients [18] [20] [23]. The high-dose group did not show a significant benefit when compared with the standard-dose group in this respect (HR 0.83, 95% CI 0.58 - 1.17; P = 0.29; **Figure 2(b)**). Considering approximately 90% of squamous cell EC patients in these three studies, we conducted a further subgroup analysis of LPFS in the patients with esophageal squamous cell carcinoma in the two radiation dose groups in order to decrease the influence of tumor histology on LPFS, and similar results were found (HR 0.73, 95% CI 0.48 - 1.11; P = 0.15).

Table 2. Quality assessment of included studies.

Randomized Clinical Trials*									
	Was the study described as randomized?	Was the method used to generate the sequence of randomization described and appropriate?	Was there a description of random sequences concealment?	Was the method of random sequences concealment described and appropriate?	Was the study described as double-blind?	Was the method of double-blinding described and appropriate?	Was there a description of withdrawals and dropouts?	Total
Zhu *et al.* [25]	1	0	1	0	0	0	1	3
Nayan *et al.* [24]	1	0	1	0	0	0	1	3
Crehange *et al.* [22]	1	0	1	0	0	0	1	3
You *et al.* [18]	1	1	1	1	0	0	1	5
Hulshof *et al.* [20]	1	1	1	1	0	0	1	5
Xu *et al.* [19]	1	1	1	1	0	0	1	5

Non-randomized clinical trial**										
	Representative of Exposed Cohort	Selection of Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Control for Important Factors	Additional Factors	Assessment of Outcome	Follow-Up	Adequacy of Follow-Up	
Ma *et al.* [23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9

*assessed by the modified JADAD scale; **assessed by the 9-star Newcastle-Ottawa Scale.

Three trials assessed the LRPFS of the two groups [18] [19] [20], indicating no significant difference between the HD and SD groups (HR 0.94, 95% CI 0.76 - 0.17; P = 0.61; **Figure 2(c)**).

Three studies analyzed the PFS of the two groups [18] [19] [25]. Pooled analysis of PFS indicated that there was no significant advantage in PFS for the HD group over the SD group (HR 0.90, 95% CI 0.71 - 1.13; P = 0.35; **Figure 2(d)**).

Funnel plots were created to evaluate the risk of bias in the above results (**Figure 3**).

3.4. Effect of Radiation Dose on Patterns of Failure

The LRF rate data were available from five studies [18] [19] [20] [23] [24]. The LRF rate was 113 (26.5%) of 426 in the high-dose radiation group and 125 (28.6%) of 437 in the standard-dose radiation group, representing no significant difference (OR 0.87, 95% CI 0.64 - 1.19; P = 0.39; **Figure 4(a)**). Similar results

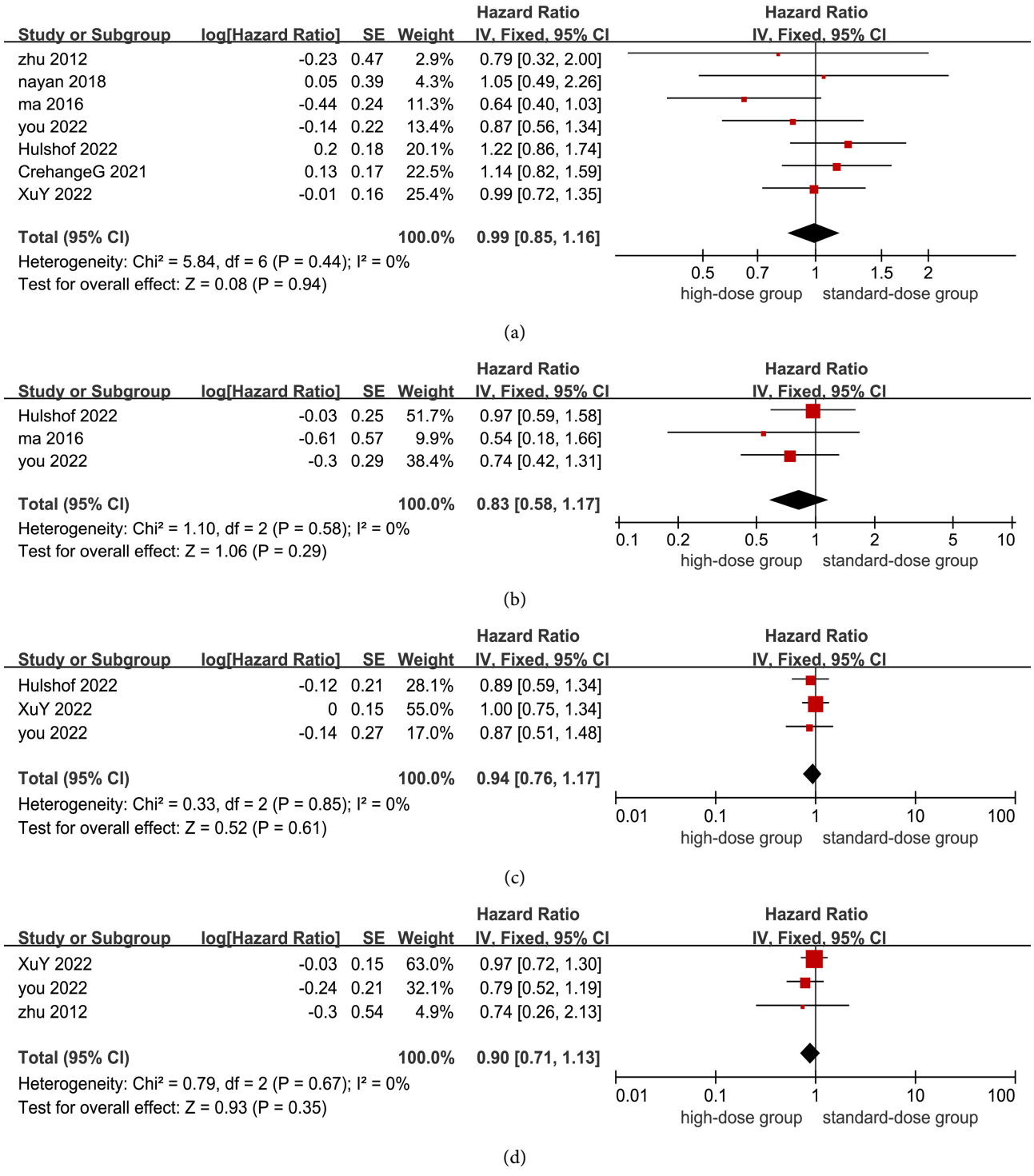


Figure 2. Comparisons of (a) OS, (b) LPFS, (c) LRPFS, (d) PFS between HD-RT arms and SD-RT arms in trials included in this analysis. HD, high-dose; LD, low-dose; RT, radiotherapy; OS, overall survival; LPFS, local progression-free survival; LRPFS, loco-regional progression-free survival; PFS, progression-free survival.

were observed in the DM rate of the two groups analyzed by four articles [18] [19] [23] [24] (OR 1.06, 95% CI 0.72 - 1.58; P = 0.76; **Figure 4(b)**). There was no visible heterogeneity among individual trials (P = 0.78, I^2 = 0%).

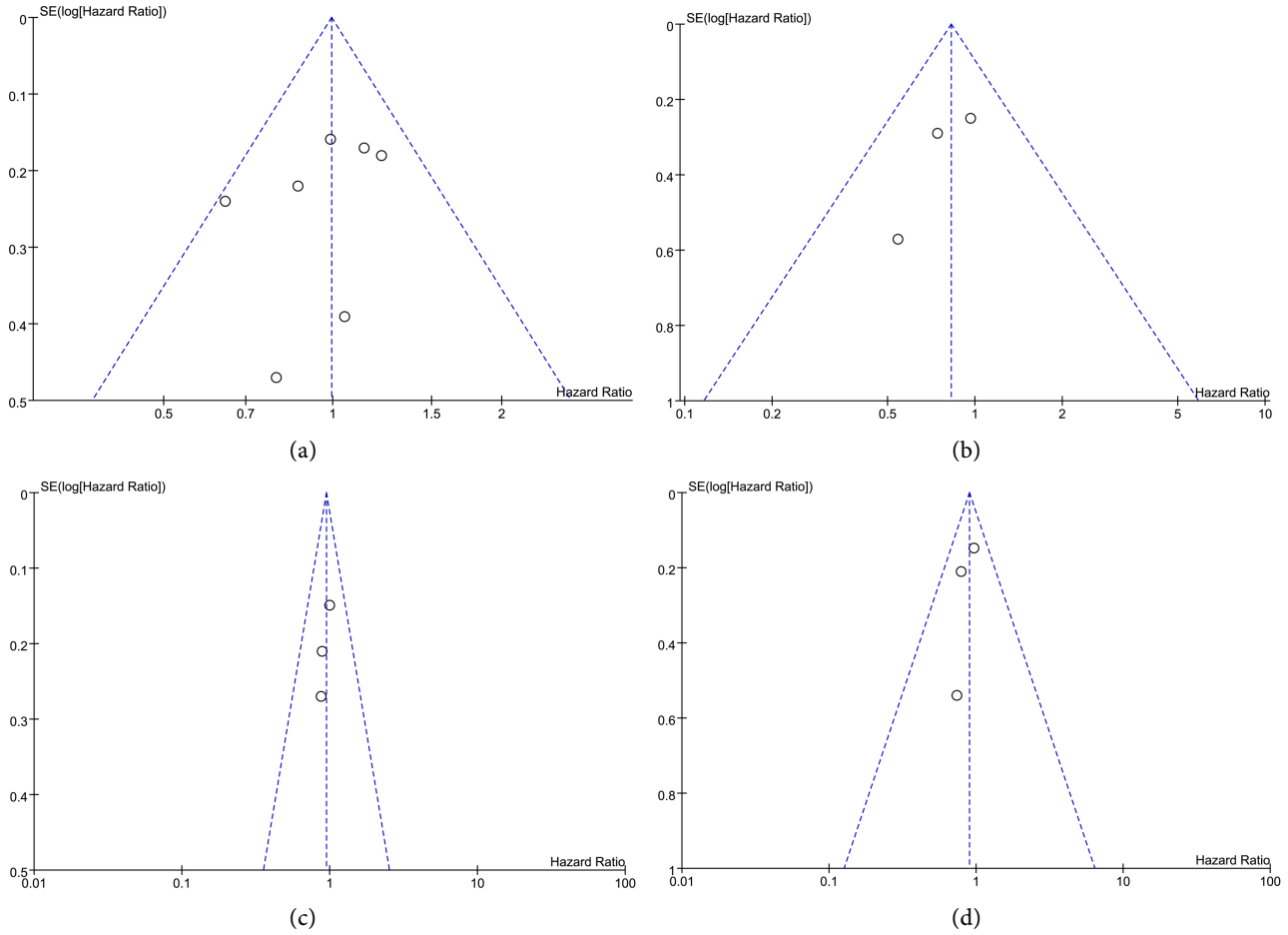


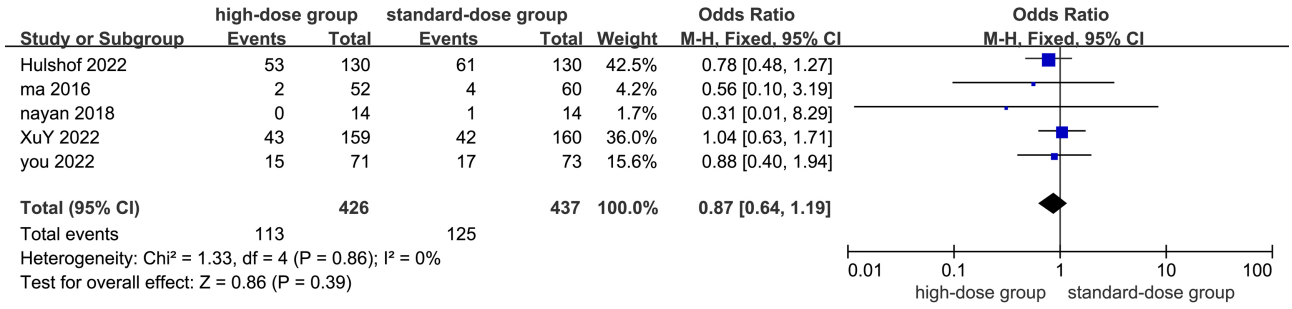
Figure 3. Funnel plot for publication bias in (a) OS, (b) LPFS, (c) LRPFS, (d) PFS. The two oblique lines indicate the pseudo 95% confidence limits. OS, overall survival; LPFS, local progression-free survival; LRPFS, locoregional progression-free survival; PFS, progression-free survival.

3.5. Effect of Radiation Dose on Short-Term Effect

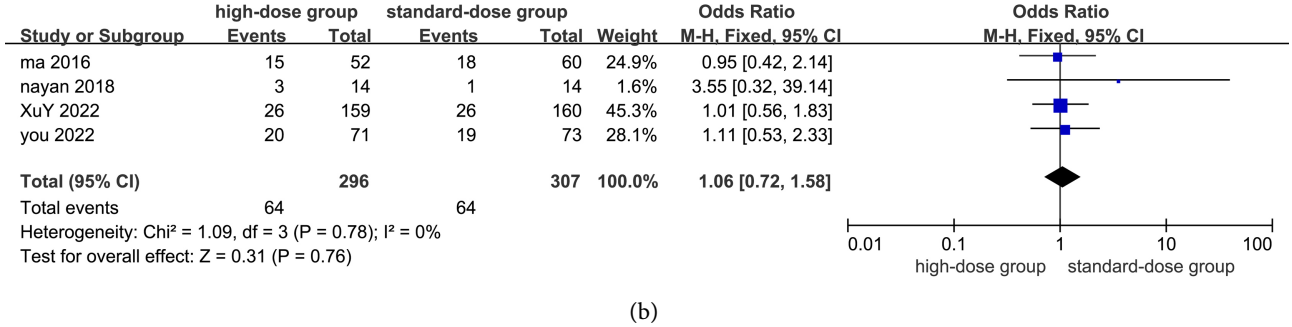
Two studies analyzed the (complete response) CR and (partial response) PR rates of the two groups [24] [25], noting that there was no significant difference in CR (HR 1.20, 95% CI 0.41 - 3.53; P = 0.75; **Figure 4(c)**), nor was any difference observed for PR (HR 0.66, 95% CI 0.19 - 2.25; P = 0.51; **Figure 4(d)**).

3.6. Treatment-Related Toxicities

Six of seven studies reported specific radiation-induced toxicities, while all articles calculated treatment-related deaths (**Table 3**). The most common adverse events of grades 3 - 5 induced by CCRT for EC patients were esophagitis and hematological toxicities. Acute treatment-related toxicities in Zhu *et al*. [25] were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [26], while toxicities in other articles were graded using the CTCAE 4 (available from: http://www.cancer.gov and search for CTCAE v 4). The results of the final pooled analysis showed that high-dose radiotherapy did not increase the risk of treatment-related death compared with the standard-dose group (OR



(a)



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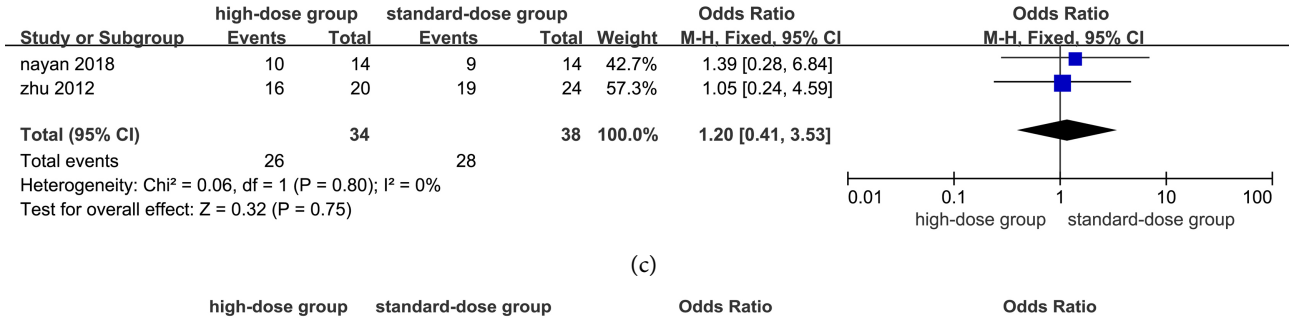
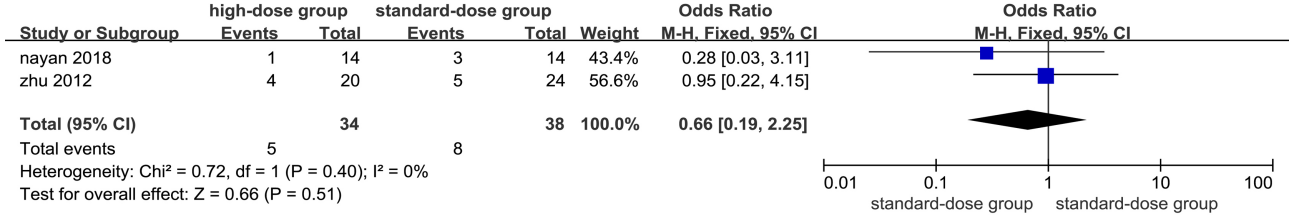


(c)



(d)

Figure 4. Comparisons of the rates of (a) LRF, (b) DM, (c) CR, (d) PR between HD-RT arms and SD-RT arms in trials included in this analysis. HD, high-dose; LD, low-dose; RT, radiotherapy; LRF, locoregional failure; DM, distant metastasis; CR, complete response; PR, partial response.

1.06, 95% CI 0.62 - 1.83, P = 0.83). Furthermore, no significant difference was observed between the two groups in radiation-induced esophagitis (OR 1.12, 95% CI 0.72 - 1.77; P = 0.61), other esophageal toxicities (including stenosis/fistula/bleeding/dysphagia) (OR 1.20, 95% CI 0.67 - 2.16; P = 0.53), and neutropenia/leukopenia (OR 0.94, 95% CI 0.65 - 1.35; P = 0.74). However, the HD-RT group had a potential risk of respiratory toxicities (including pneumonitis/bronchitis/respiratory failure/bronchopulmonary bleeding) compared with the SD-RT group (OR 2.11, 95% CI 0.97 - 4.58; P = 0.06), although no significant

Table 3. Treatment-related deaths and grade ≥3 toxicities according to CTCAE 3/4.

Adverse events (grade ≥ 3)	Availability			Effect		Heterogeneity		Model
	Trials (N)	HD (events/total)	SD (events/total)	OR (95% CI)	P value	I^2	P value	
Treatment-related deaths	7	28/555	27/569	1.06 (0.62 - 1.83)	0.83	0%	0.94	FE
Esophagitis	4	55/264	51/271	1.12 (0.72 - 1.77)	0.61	0%	0.90	FE
Other esophageal toxicities*	6	26/502	22/510	1.20 (0.67 - 2.16)	0.53	0%	0.58	FE
Neutropenia/Leukopenia	4	107/264	112/271	0.94 (0.65 - 1.35)	0.74	1%	0.32	FE
Respiratory toxicities**	5	19/394	9/401	2.11 (0.97 - 4.58)	0.06	0%	0.46	FE

HD, high-dose; SD, standard-dose; CTCAE, Common Terminology Criteria for Adverse Events; OR, odds ratio; CI, confidence interval; FE, fixed-effects mode; *including stenosis/fistula/bleeding/dysphagia; **including pneumonitis/bronchitis/respiratory failure/bronchopulmonary bleeding.

difference was observed in this respect. From the above results, we revealed that most EC patients could tolerate the toxicities of radiation, and escalated radiation dose did not increase the risk of toxicities and treatment-related death.

4. Discussion

This meta-analysis analyzed seven relevant trials, which involved data on the efficacy and safety of 554 patients in the HD radiation group and 570 patients in the SD radiation group. The final analysis evaluated efficacy with respect to OS, LPFS, LRPFS, and PFS, demonstrating that an escalated dCRT radiation dose (approximately 60 Gy) utilizing modern radiation techniques did not contribute to the improvement of local control rates or survival outcomes. Additionally, a high radiation dose exhibited a potential disadvantage in respiratory toxicities when compared with a standard dose (4.8% vs 2.2%, OR 2.11, P = 0.06), and a larger sample size was required to confirm the conclusion. Only two studies [24] [25] provided definite data on clinical complete response (cCR) and partial response (PR), showing that the short-term effect of the high-dose regimen is similar to that of standard-dose as well. However, considering the relatively small sample sizes of the two studies, further research will be required to confirm these results. Several meta-analyses regarding the optimal dCRT dose for esophageal carcinoma have revealed that receiving escalated dCRT dose brought about better disease-related outcomes (including locoregional control and OS) in patients with inoperable EC without an increase in severe toxicities compared with conventional-dose radiotherapy. Their results were inconsistent with our conclusion, which may be attributed to that most of the included studies in these me-

ta-analyses were retrospective, inducing inevitable retrospective bias.

Three ongoing prospective trials reported the preliminary results, which could not be enrolled in this meta-analysis. At the 2022 American Society for Therapeutic Radiology and Oncology (ASTRO), a multicenter phase III randomized clinical trial (NROG-001) [27] reported that the HD arm (59.4 Gy) did not present significantly prolonged OS (HR = 0.93, P = 0.54) but exhibited improved PFS (29.1 months to 20.0 months, HR = 0.77, P = 0.023) when compared with the SD arm (50.4 Gy) for local advanced thoracic ESCC. The ongoing Chinese ESO-Shanghai 12 study [28] and British SCOPE2 study [29] are making an earnest endeavor to compare the effects of standard-dose and high-dose radiation treatments. The final results of these clinical studies are awaited.

A dose of 50 - 50.4 Gy was established as the standard treatment for inoperable EC, but almost 50% of these patients suffered locoregional recurrence after dCRT [4] [5] [6], suggesting a need for local control improvement. According to a subgroup analysis with regard to different cutoffs of RT doses in a published meta-analysis [15], ≥60 Gy can significantly improve the OS (HR = 0.73, P < 0.0001) as well as the local-regional control (OR = 0.54, P < 0.0001) as compared with <60 Gy, while >50.4 Gy showed no significant advantages for OS or local-regional control as compared with ≤50.4 Gy, suggesting that 45 - 50 Gy radiation dose was sufficient to control microscopic diseases, and at least 60 Gy was required for gross tumors. Similar results were also noted by some previous studies [30] [31]. However, in consistent with the RTOG 94-05/INT 0123 trial [2], the Dutch ARTDECO trial [20] demonstrated that a dose escalation from 50.4 Gy to 61.6 Gy at the primary tumor site did not contribute to an improvement in local control or survival. Hulshof *et al*. [20] considered the reason may be that the dose of 61.6 Gy was still insufficient to engender a visible effect. However, doses above 66 Gy are generally not considered in esophageal cancer because of the expected severe esophageal toxicity, which will induce a sharp decline in the life quality of patients. Improvement of locoregional control is still a challenge to thrive for. Future molecular/genetic studies on the heterogeneity of the esophageal carcinoma are necessary for the development of individualized treatment. Selecting patients who would benefit the most from dCRT can be based on patients who demonstrate a clinical response with PET/CT [32] [33] during CRT or on biomarkers that could identify tumors sensitive to CRT [34].

In these enrolled studies in this meta-analysis, as there was no identical standard in the patient treatment regime, which may influence the statistical outcome of the final analysis, additional subgroup analyses were conducted. Four studies employing adjuvant chemotherapy plans (including one using PF, one using FOLFOX-4, one using TC and one using DP) after dCRT [18] [19] [22] [25] and three studies delivered dCRT without adjuvant chemotherapy [20] [23] [24] were included for subgroup analysis, respectively. OS in the HD-RT group revealed no statistical significance compared to the SD-RT group for patients treated with dCRT followed by adjuvant chemotherapy (HR 1.00, 95% CI 0.82 -

1.22, P = 0.99), nor was any difference observed for patients treated with only dCRT (HR 0.98, 95% CI 0.75 - 1.28, P = 0.88). For both subgroup analyses, no significant heterogeneity was observed between the results when comparing the two treatment plans. Because of the limitation of the complete high-quality evidence, we cannot analyze the effects of the different chemotherapy regimens. According to the published data, the concurrent chemotherapy regimens used were not significantly different between the two arms, respectively, in most enrolled studies. Several decades ago, exclusive chemoradiation delivering 50 Gy of external beam radiotherapy (EBRT) combined with PF (cisplatinum and 5-FU) represented the standard of therapy for locally advanced EC patients. The French PRODIGE 5/ACCORD 17 phase III trial [35] has revealed the safety and the efficacy of FOLFOX-4 combined with exclusive 50 Gy EBRT, while the Dutch CROSS phase III trial [36] demonstrated an advantage in OS with carboplatin and paclitaxel in the preoperative radiation dose at 41.4 Gy. Then, Crehange *et al*. [37] reported that exclusive chemoradiation with TC (carboplatin and paclitaxel) regime seemed feasible with similar toxicity and efficacy than FOLFOX-4 regime. As previous researches noted [29] [37] [38] [40], various chemotherapy regimens utilized in the definitive concurrent chemoradiotherapy may not influence the survival outcomes of local advanced EC patients.

Judging from the pooled analysis of seven studies with different results, the efficacy of escalated radiation dose was equal to that of standard radiation dose, but the final results were not without caveats. Due to malignancy of tumors and adverse events, a diversity of changes in actual received radiation doses occurred even though the patient compliance was statistically acceptable, which may dilute the therapeutic benefit of the 60 Gy group. Especially, according to Xu *et al.* [19], the total radiotherapy completion rates were 88.2% and 96.9% in the HD and SD groups (P < 0.01), respectively. Nevertheless, the authors then performed additional analyses for the patients who had completed the prescribed radiotherapy dose in both arms, and no significant difference was seen in these values as well.

Inevitably, there are some limitations in our meta-analysis. Firstly, due to some absent outcome data in the included studies, we can only include part of the studies when comparing certain outcomes between the two groups. It was difficult for us to evaluate the influence of this absent information. Secondly, no study included in the meta-analysis reported the Quality-of-life (QOL) in the two arms. Many factors, such as radiation machine maintenance and regional economic differences, affected the costs, which were compared by a few studies. As a result, little related high-quality literature was available. Comparison of cost-effectiveness is often difficult because medical systems and nursing emphasis vary greatly among countries. In the RTOG 94-05 phase III trial [2], CD-CRT (50.4 Gy) had a similar QOL profile compared with HD-CRT (64.8 Gy). However, this study used a radiation technique largely based on historical 2D-RT, as well as utilized fields larger than that used in modern radiation application,

which may increase toxicity rates and not be well suited for dose-escalation. This may no longer be suitable for the assessment of quality of life in the contemporary radiotherapy era. Patients in the HD-RT group reported significantly less treatment convenience, including patients in the high-dose group who underwent a visible longer treatment period as well as a greater expenditure for adverse events recovery, resulting in poorer care satisfaction, than did the patients in the CD-RT group. So more high-quality trials with quantized results on cost-effectiveness of the two regimes were required to provide additional high-quality evidence for the final conclusion and clinical application.

5. Conclusion

In summary, this study noted that the efficacy of the HD group (≥60 Gy) and the SD group (approximately 50 Gy) for inoperable local advanced EC was similar. However, the HD group exhibited a high radiation dose exhibited a potential disadvantage in respiratory toxicities when compared with a standard dose. In clinical application, 50 - 50.4 Gy should be considered as the recommended dose in dCCRT for inoperable local-advanced EC.

Authors' Contributions

All authors read and approved the final manuscript prior to submission. HS Luo and HC Huang: conceived and designed the experiments; HC Huang and LX Lin: performed the experiments; HS Luo: analyzed the data; HS Luo: wrote the paper.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Competing Interests

The authors declare that they have no competing interests.

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