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Heart dose linked with cardiac events and overall survival in lung cancer radiotherapy

A meta-analysis

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Abstract

Background: The aim of this study was to investigate the link between heart dose and overall survival, the link between heart dose and cardiac events and whether radiation-induced heart diseases were associated with overall survival in lung cancer radiotherapy.

Methods: We performed a literature search by using Pubmed, Embase, China National Knowledge Infrastructure (CNKI) databases. Pairs of reviewers independently screened literature according to the inclusion criteria, extracted data, assessed methodological quality, and publication bias. The primary end points included overall survival and cardiac events. I^2 was calculated in a heterogeneity assessment. Publication bias was evaluated by using Begg funnel plot and Egger test.

Results: Ten studies including 1 randomized controlled trial, 3 post hoc analysis of prospective trials, and 6 cohort studies were identified. The meta-analysis showed that heart volume receiving ≥5 Gy (HV5) (hazard ratio [HR] = 1.01; 95% confidence interval [CI]: 1.00–1.01), heart volume receiving ≥30 Gy (HV30) (HR = 1.01; 95% CI: 1.00–1.02), heart volume receiving ≥50 Gy (HV50) (HR = 1.05; 95%CI: 1.00–1.10), and mean heart dose (MHD) (HR = 1.01; 95%CI:1.00–1.02) all were associated with worse overall survival. In addition, the MHD (HR = 1.03; 95% CI: 1.02–1.05), HV5 (HR = 1.02; 95% CI: 1.01–1.03), and HV30 (HR = 1.02; 95% CI: 1.01–1.03) were significantly associated with all grade cardiac events. Meanwhile, compared with those who did not receive radiotherapy, the radiotherapy group experienced a significantly increased risk for cardiac-specific mortality (HR = 1.297; 95% CI: 1.213–1.387). However, the results did not show that cardiac events were associated with overall survival in lung cancer radiotherapy (HR = 1.472; 95% CI: 0.988–2.193).

Conclusion: Exposure of the heart to radiation increased the risk of cardiac events during radiotherapy for lung cancer. Meanwhile, heart dose including HV5 and HV30 were predictors of overall survival in lung cancer radiotherapy. It is necessary to constrain the heart dose when perform thoracic radiation therapy to decrease the incidence of cardiac events and improve the overall survival.

Abbreviations: CI = confidence interval, CNKI = China National Knowledge Infrastructure, HRs = hazard ratio, HV30 = heart volume receiving >30 Gy, HV5 = heart volume receiving >5 Gy, HV50 = heart volume receiving >50 Gy, MHD = mean heart dose, RIHD = radiation-induced heart disease, RTOG = Radiation Therapy Oncology Group.

Keywords: heart dose, lung cancer, overall survival, radiation-induced heart disease

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide[1,2] and the optimal treatment is according to the type and the stage of lung cancer. Radiochemotherapy is the recommended therapy for locally advanced non-small cell cancer.[3] It has been shown to increase the control of tumor and improve survival outcomes. Unfortunately, radiation to the lung and chest has been associated with radiation-related disease

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LP and DL are both the first author, they contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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that may offset some of the benefit of radiation. Radiation-induced heart disease (RIHD) has long been recognized in breast cancer,[4,5] Hodgkin lymphoma[6] and childhood cancer[7] patients, but studies of RIHD in lung cancer radiotherapy, are limited. The conventional view is that the breast cancer and lymphoma have higher survival rates than lung cancer, so they are more possible to experience the late cardiac toxicity. However, the lung cancer patients are more prone to have smoking statue and comorbidities such as vascular diseases, COPD, and diabetes which might accelerate the happen of RIHD.[8] So the RIHD in lung cancer should not be overlooked and it might have great impact on the long-term survival of lung cancer. Many promising phase II trials showed that radiation dose escalation may be associated with longer survival.[9,10] However, the phase 3 trial (Radiation Therapy Oncology Group [RTOG] 0617) founded the high-dose arm (74 Gy) had worse overall survival (OS) compared with standard-dose arm (60 Gy) and more remarkable, the study also showed that heart V5 (heart volume receiving ≥5 Gy) and (heart V30 heart volume receiving ≥30 Gy) were important predictors of overall survival on multivariate models.[11] Subsequently, some studies also founded the association of heart dose with survival,[12,13] but there also were some studies did not find the association.[14–17] Therefore, it is uncertain that whether dose escalation can bring better survival; however, it is also controversial that whether heart dose is really predictor of survival and how heart dose links to inferior survival. Some secondary analyses of trials or prospective studies were conducted to explore the issue and put forward different hypothesis.[18] We hypothesize that the higher heart dose may increase the incidence of cardiac event; subsequently, the RIHD contributed to the worse survival. Therefore, we conducted the meta-analysis to investigate the relationship between heart dose, cardiac events and overall survival to give some enlightenment to the future radiotherapy for lung cancer.

2. Materials and methods

2.1. Search strategy

We searched the publications listed in Pubmed, Embase, China Knowledge Resource Integrated Database, and Wangfang database from their inception to May 2019 using the following words: radiotherapy or irradiation or radiation, cardiac events or cardiactoxity, heart dose or cardiac dose, survival or mortality, lung cancer or lung neoplasm. Additionally, we scrutinized references from included articles to identify other relevant studies. The ethical approval was not necessary for this study did not involve any patients and their privacy.

2.2. Outcomes

The primary study end points were overall survival, cardiac events (Common Terminology Criteria for Adverse Events including acute coronary syndrome, cardiac arrest, systolic and diastolic dysfunction, congestive heart failure, pericardial disease, Valvular disease, and arrhythmia), and cardiac-specific mortality.

2.3. Selection criteria

We imposed the following restrictions for the inclusion criteria: studies were published in journals with full-text; the participants of included studies were biopsy-confirmed lung cancer patients and treated with radiotherapy; studies contained hazard ratio (HRs) with 95% confidence interval (CI) associated with heart dose or there were sufficient published data to estimate HRs with a 95% CI; cardiac dosimetry was analyzed as a continuous variable or several studies used the same cutoff when analyzed the cardiac dosimetry; if the studies were post hoc analysis of prospective trials, the original RCTs should not be included. Consequently, there was no overlap participant in analyzing every cardiac dosimetric variable.

2.4. Data extraction and quality assessment

According to the inclusion criteria to access to the full text, every study was extracted by one author and reviewed by another author for accuracy. Any disagreement was resolved by consensus. For each study, the following information was extracted: first author's name, year of publication, geographical location, mean age, sample size, length of follow-up, study design, end points, HRs with their 95% CIs of different variables. If possible, we extracted the most comprehensively adjusted HR. Otherwise, we used the HR of unavailable analysis.

To evaluate the quality of the included studies, we used the Newcastle-Ottawa scale for the cohort studies and the Modified Jadad Score for the randomized control trials. For cohort studies, the highest score was 9 and studies with a cumulative score ≥7 were viewed of high quality.[19] As for RCT, the score ranged from 0 to 6 points.

2.5. Statistical analyses

Pooled HRs with 95% CI were analyzed by published methods. We assessed heterogeneity across studies by calculating the I^2 and Cochran Q estimates.[20] Statistical significance for heterogeneity was considered if $P < .05$ or $I^2 > 50\%$. Pooled HRs with 95% CI were analyzed using a fixed-effects model when there was no conspicuous heterogeneity, otherwise a random-effects model was performed. In order to assess the effect of study quality, we conducted sensitivity analysis that omitted one study at one time. Publication bias was evaluated by the Begg adjusted rank correlation test and the Egger regression asymmetry test.[21,22]

3. Results

3.1. Study selection

Initially, a total of 1072 articles were identified. Of these, 64 articles were considered of interest by reading the titles and abstracts. An additional 52 studies were excluded due to no relevant data or overlap of participants. Finally, 12 studies met the inclusion criteria and were included in our meta-analysis by reading full text. The flow diagram for study selection was shown in Figure 1.

3.2. Study characteristics

A total of 12 studies met our inclusion criteria including 1 randomized controlled trials,[11] 3 post hoc analysis of prospective trials,[14,16,17] 8 cohort studies.[12,13,15,23–27] Among the studies, 6 studies discussed the relationship between heart dose and overall survival, 3 studies discussed the relationship between heart dose and cardiac events, and 3 studies discussed both outcomes including cardiac events and overall survival in lung cancer radiation therapy. Age and follow-up time varied across

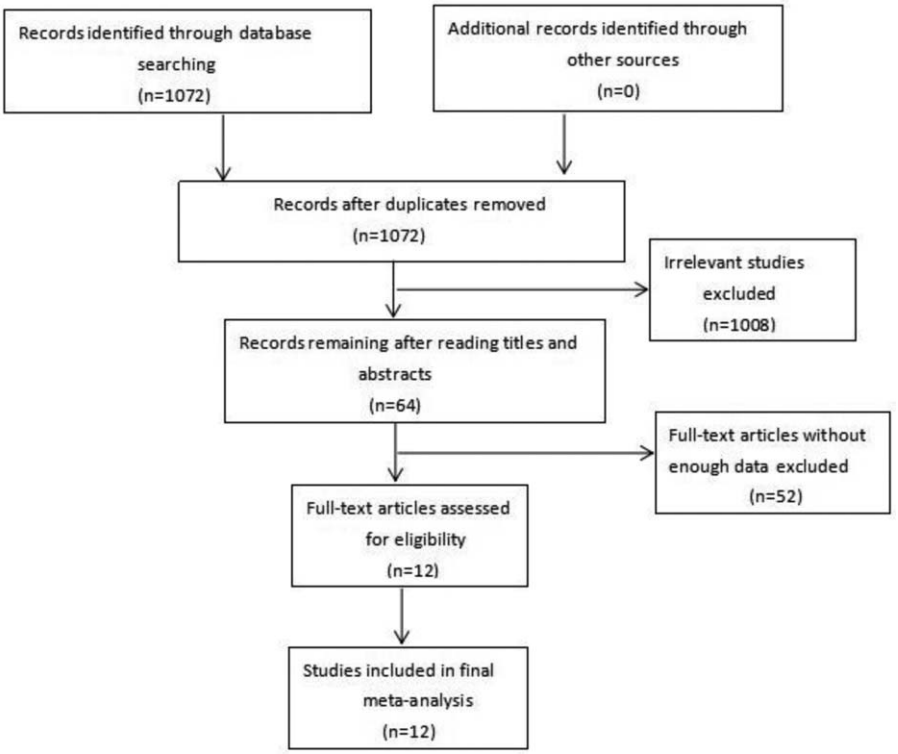


Figure 1. Flow diagram of the studies included and excluded in the meta-analysis.

studies. The sizes of the studies ranged from 86 to 6148 and the study of Abdel-Rahman [23] did not show the size of lung cancer patients with radiation therapy. Of the 8 cohort studies, the scores of the Newcastle-Ottawa scale ranged from 6 to 8. In addition, the Modified Jadad scores of randomized controlled trials and post hoc analysis of randomized controlled trials were ≥3. The characteristics and quality scores of the 12 studies included were shown in Table 1.

3.3. Heart dose and overall survival

Nine studies were included for the relationship between heart dose and overall survival in lung cancer, involving 2823 participants [11–17,26,27]. The heart dose was analyzed as continuous variable. Pooled HRs and corresponding 95% CIs were shown in Figure 2. Our results suggested that radiation heart dosimetric parameters, including HV5 (HR = 1.01; 95% CI: 1.00–1.01 by fixed effect; $P = .716$ for heterogeneity; $I^2 = 0.0\%$), HV30 (HR = 1.01; 95% CI: 1.00–1.02 by fixed effect; $P = .949$ for heterogeneity; $I^2 = 0.0\%$), and mean heart dose (MHD) (HR = 1.01; 95% CI: 1.00–1.02 by fixed effect; $P = .952$ for heterogeneity; $I^2 = 0.0\%$), all were associated with worse OS. Meanwhile, HV50 also was associated with worse OS (HR = 1.05; 95% CI: 1.00–1.10 by random effect) with high heterogeneity ($-^2 = 81.2\%$, $P = .001$) (Fig. 2A–D).

We performed sensitivity analyses by omitting 1 study at 1 time. There was no study affecting the pooled HRs of HV5 group (1.0036–1.0059) and HV50 group (1.019–1.028). The pooled HRs of MHD (keep 1.010) and HV30 (keep 1.011) also stayed stable.

To evaluate the possibility of publication bias among the studies of HV5 group, funnel plots were performed. The Begg rank correlation test ($P = .189$) and Egger linear regression test (0.317) all indicated that there were no publication bias.

3.4. Heart dose and cardiac events

There were 3 studies with 5 estimates for the cardiac events.[14,17,27] The heart dose was analyzed as continuous variable. Our results showed that MHD (HR = 1.03; 95% CI: 1.02–1.05 by fixed effect; $P = .316$ for heterogeneity; $I^2 = 15.4\%$), HV5 (HR = 1.02; 95% CI: 1.01–1.03 by fixed effect; $P = .624$ for heterogeneity; $I^2 = 0.0\%$), HV30 (HR = 1.02; 95% CI: 1.01–1.03 by fixed effect; $P = .562$ for heterogeneity; $I^2 = 0.0\%$) all were significantly associated with all grade cardiac events (Fig. 3). However, our result did not show that HV50 independently associated with cardiac events (HR = 1.04; 95% CI: 0.98–1.10 by random effect; $P = .116$ for heterogeneity; $I^2 = 59.6\%$). In addition, our results showed that preexisting cardiac disease was not associated with all grade cardiac events in lung cancer radiotherapy (HR = 1.42; 95% CI: 0.76–2.66 by random effect; $P = .005$ for heterogeneity; $I^2 = 81.2\%$) (Fig. 4).

There were 3 studies compared radiotherapy with non-radiotherapy for cardiac-specific mortality.[23–25] Compared with those who did not receive radiotherapy, the radiotherapy group experienced an increased risk for cardiac-specific mortality (HR = 1.297; 95% CI: 1.213–1.387 by fixed effect; $P = .984$ for heterogeneity; $I^2 = 0.0\%$) (Fig. 5).

We also performed sensitivity analyses by omitting 1 estimate at 1 time. The results showed that the pooled HRs all were robust. The pooled HRs of MHD group ranged from 1.030 to 1.040, HV5 group ranged from 1.017 to 1.021, HV30 group ranged from 1.019 to 1.024, and HV50 group ranged from 1.00 to 1.06.

Table 1

Characteristics of the studies included in the meta-analysis.

Study (year)	Country	Mean age	Follow-up time	Sample	Study type	End points[variables:HR (95%CI)]		score
						Overall survival	Cardiac Events	
Contreras et al (2018)[26]	USA	64 (36-88)	17 mo	207	Retrospective cohort	HV50:1.02 (1.01–1.03)	NR	7
Lee et al (2018)[27]	Singapore	65.5 (58.5–73.2)	17.6 mo	120	Retrospective cohort	MHD: 1.15 (0.74–1.77) HV5: 1.00 (0.66–1.53) HV30: 0.91 (0.58–1.41) HV50: 1.10 (0.71–1.69)	Acute myocardial infarct: MHD:1.03 (1.01–1.06) HV5:1.01 (1.00–1.03) HV30:1.01 (0.99–1.03) HV50:1.00 (0.94–1.07)	6
Dess et al (2017)[14]	USA	66 (40–92)	51 mo	125	Post hoc analysis of prospective trials	MHD: 1.01 (0.98–1.03) HV5: 1.00 (0.99–1.01) HV30: 1.01 (0.99–1.02) HV50: 1.01 (0.98–1.04) Grade ≥3cardiac events: 1.76 (1.04–2.99)	Grade ≥2 cardiac event: MHD: 1.07 (1.03–1.11)+ HV5: 1.02 (1.01–1.03) HV30: 1.03 (1.02–1.05) HV50: 1.06 (1.03–1.10) Preexisting cardiac disease: 2.34 (1.23–4.45)	4
McWilliam et al (2017)[15]	UK	73 (38–95)	2010–2013	1101	Retrospective cohort	MHD: 1.010 (0.99–1.03) HV5: 1.00 (0.99–1.01) HV30: 1.01 (0.99–1.02) Induction chemotherapy: 0.92 (0.74–1.15)+	NR	7
Guberina et al (2017)[16]	Germany	58 (33–74)	2004–2013	161	Post hoc analysis of prospective trials	HV5: 1.005 (0.995–1.015)	NR	4
Wang et al (2017)[17]	USA	58 (36–82)	8.8 y	112	Post hoc analysis of prospective trials	MHD: 1.01 (0.995, 1.03) Symptomatic cardiac event: 1.16 (0.63, 2.13)	Pericardial events: MHD: 1.04 (1.01, 1.07) HV5: 1.02 (1.001, 1.04) HV30: 1.02 (1.003, 1.04) Ischemic events: MHD: 1.04 (0.996, 1.08) HV5: 1.03 (1.01, 1.05) HV30: 1.03 (1.00, 1.05) Arrhythmic events: MHD: 1.02 (1.00, 1.05) HV5: 1.02 (1.001, 1.04) HV30: 1.02 (1.00, 1.03)	4
Johnson et al (2016)[12]	USA	72 (49–85)	16.8 mo	86	Retrospective cohort	HV5: 1.007 (0.999–1.014) HV30: 1.013 (1.001–1.024) MLD: 1.028 (0.978–1.080)	NR	7
Speirs et al (2016)[13]	Italy	64 (36–88)	14.5m	416	Retrospective cohort	HV50: 1.23 (1.12–1.35)	NR	8
Bradley et al (2015)[11]	USA	64 (38–83)	22.9 m	495	RCT	HV5: 1.007 (1.002–1.011)	NR	6
Abdel-Rahman (2017)[23]	Egypt	N	1988–2008	N	SEER database retrospective cohort	NR	cardiac-specific mortality: Radiation (no vs yes):0.771 (0.718–0.827)+	8
Hardy et al (2010)[24]	USA	65–89	1991–2002	34,209	SEER database retrospective cohort	NR	Ischemic heart disease: 0.85 (0.76–0.95) Cardiomyopathy: 0.46 (0.25–0.82) Conduction disorders: 1.01 (0.76–1.35) Cardiac dysfunction:1.54 (1.29–1.83) Heart failure: 1.06 (0.96–1.18)	6
Lally et al (2007)[25]	USA	64 (24–88)	2.1y	6148	SEER database retrospective cohort	NR	Heart disease mortality: 1.30 (1.04–1.61)	7

CI = confidence interval; HR = hazard ratio; HV30 = heart volume receiving ≥30 Gy; HV5 = heart volume receiving ≥5 Gy; HV50 = volume receiving ≥ 50 Gy; MHD = mean heart does; NR = not reported; OS = overall survival; UK = United Kingdom of Great Britain and Northern Ireland; USA = United States of America.

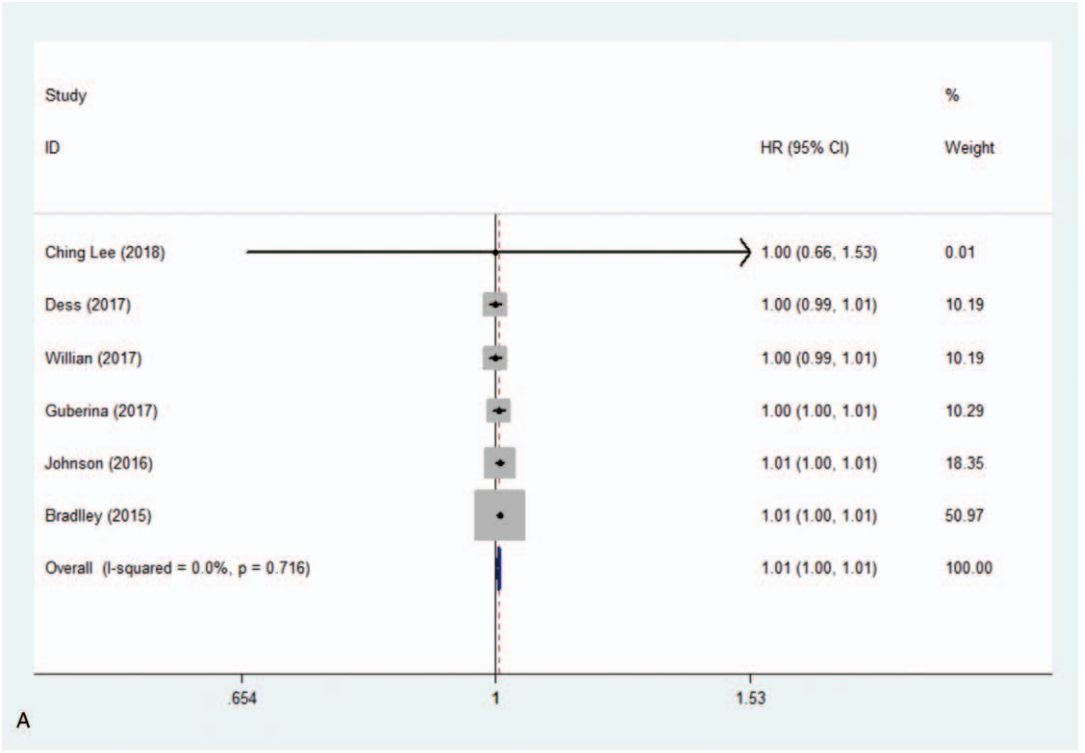
Because the included studies in this part were limited, we did not discuss the potential publication bias.

3.5. Cardiac events and overall survival

In the included studies, 2 studies reported risk estimates for the relationship between cardiac events and overall survival in lung cancer radiotherapy. Our results showed that cardiac events were not associated with overall survival in lung cancer radiotherapy (HR = 1.472; 95% CI: 0.988–2.193 by fixed effect; $P = .311$ for heterogeneity; $I^2 = 2.70\%$) (Fig. 6).

4. Discussion

Lung cancer is the most common cancer worldwide with high mortality which responsible for nearly one cancer death in



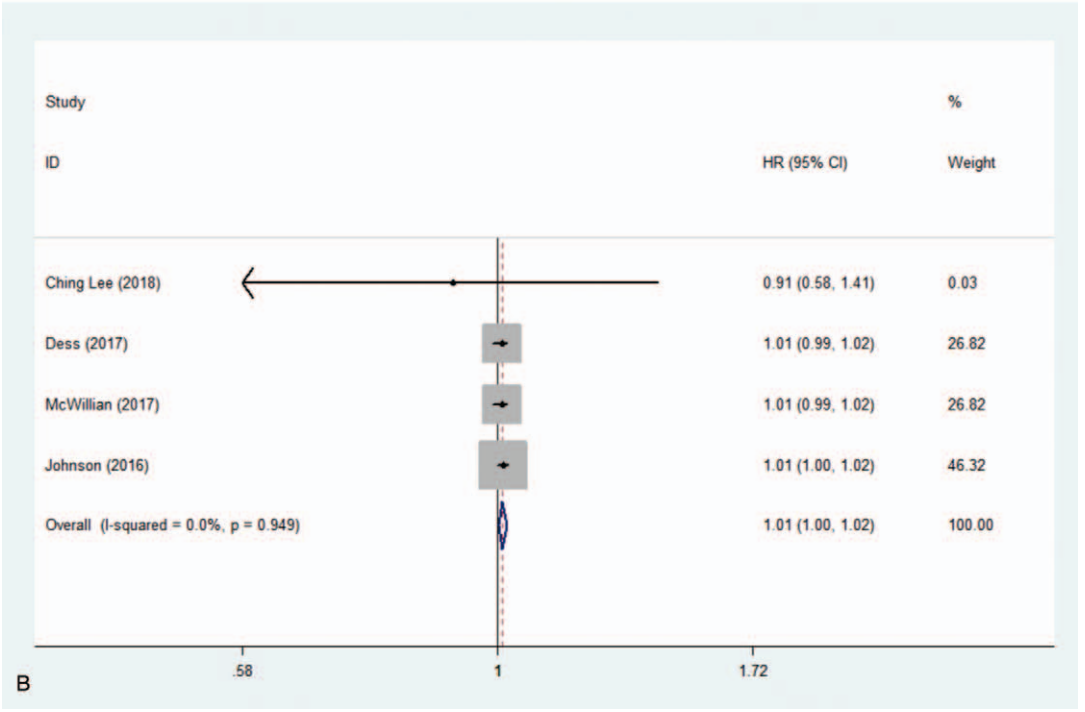
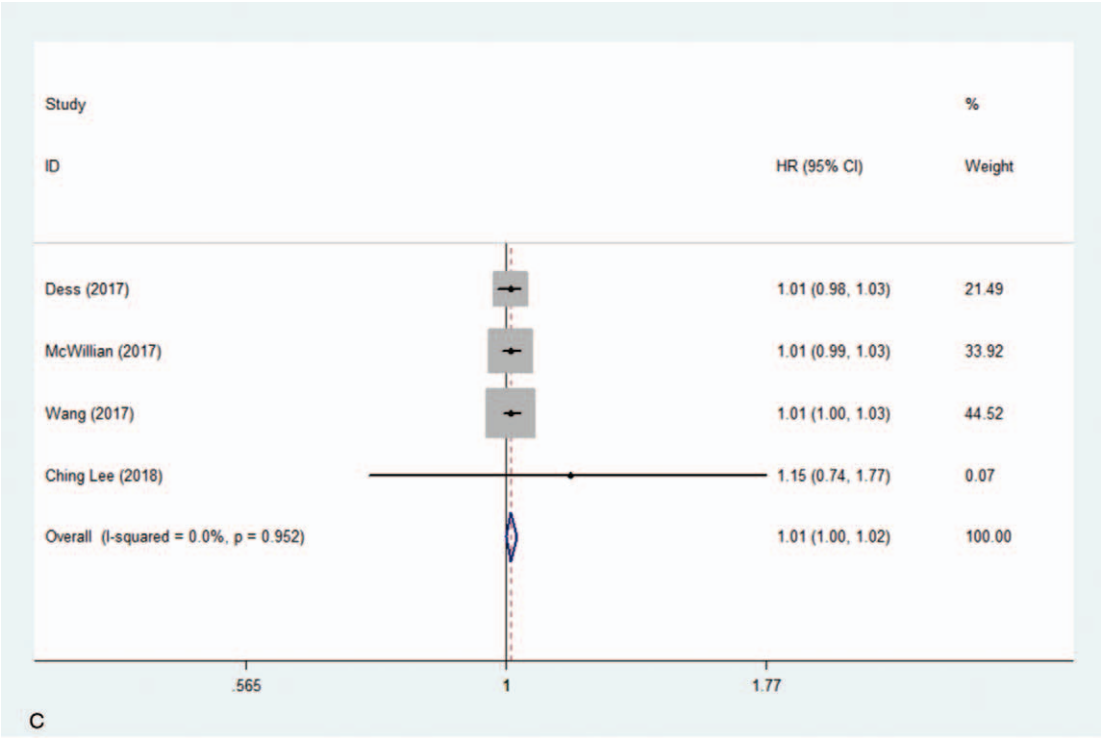


Figure 2. (A) Forest plot of the association between HV5 and overall survival in lung cancer radiotherapy. (B) Forest plot of the association between HV30 and overall survival in lung cancer radiotherapy. (C) Forest plot of the association between HV50 and overall survival in lung cancer radiotherapy. (D) Forest plot of the association between mean heart dose (MHD) and overall survival in lung cancer radiotherapy.

five.[28] The optimal treatment is decided according to the type and the stage of lung cancer.[29,30] Over 80% of all lung cancers are non-small cell lung cancer including squamous cell carcinoma, adenocarcinoma and large cell carcinoma. The other can be characterized as small cell lung cancer. Radiation combined with chemotherapy is usually the treatment for locally advanced non-small cell cancer.[3,31] The improvements of radiation technology and radiation accuracy offer dose escalation as well as normal tissue sparing.[32,33] However, the results of Radiation Therapy Oncology Group (RTOG) 0617, which compared 74 Gy with the standard 60 Gy both delivered with concurrent chemotherapy, founded the high-dose arm had worse OS compared with



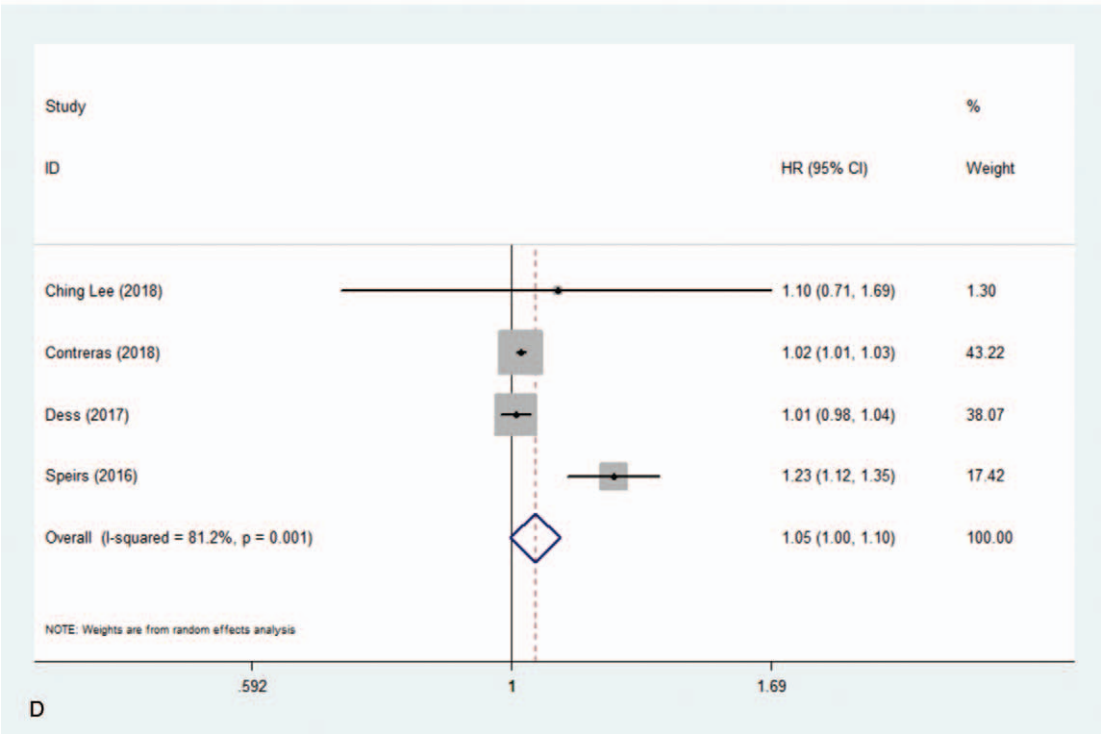


Figure 2. (Continued).

standard-dose arm.[11] Meanwhile, the RTOG0617 founded that heart V5 and heart V30 were predictors of overall survival on multivariate models. Because of the unexpected result of RTOG0617, many researches were conducted to assess the association between heart dosimetry and overall survival of lung cancer. Consistent with RTOG 0617, the study of Johnson et al[12] also found that HV30 was a significant predictor of survival in multivariate analysis. However, Dess et al[14] showed that cardiac dose including HV5, HV30, and HV50 was not significantly associated with OS and several studies[15,16] also did not observe the association. So it is still controversial that whether heart dose is really predictor of survival. In our study, the result showed that HV5 (HR = 1.01; 95% CI: 1.00–1.01), HV30 (HR = 1.01; 95% CI: 1.00–1.02), HV50 (HR = 1.05; 95% CI:

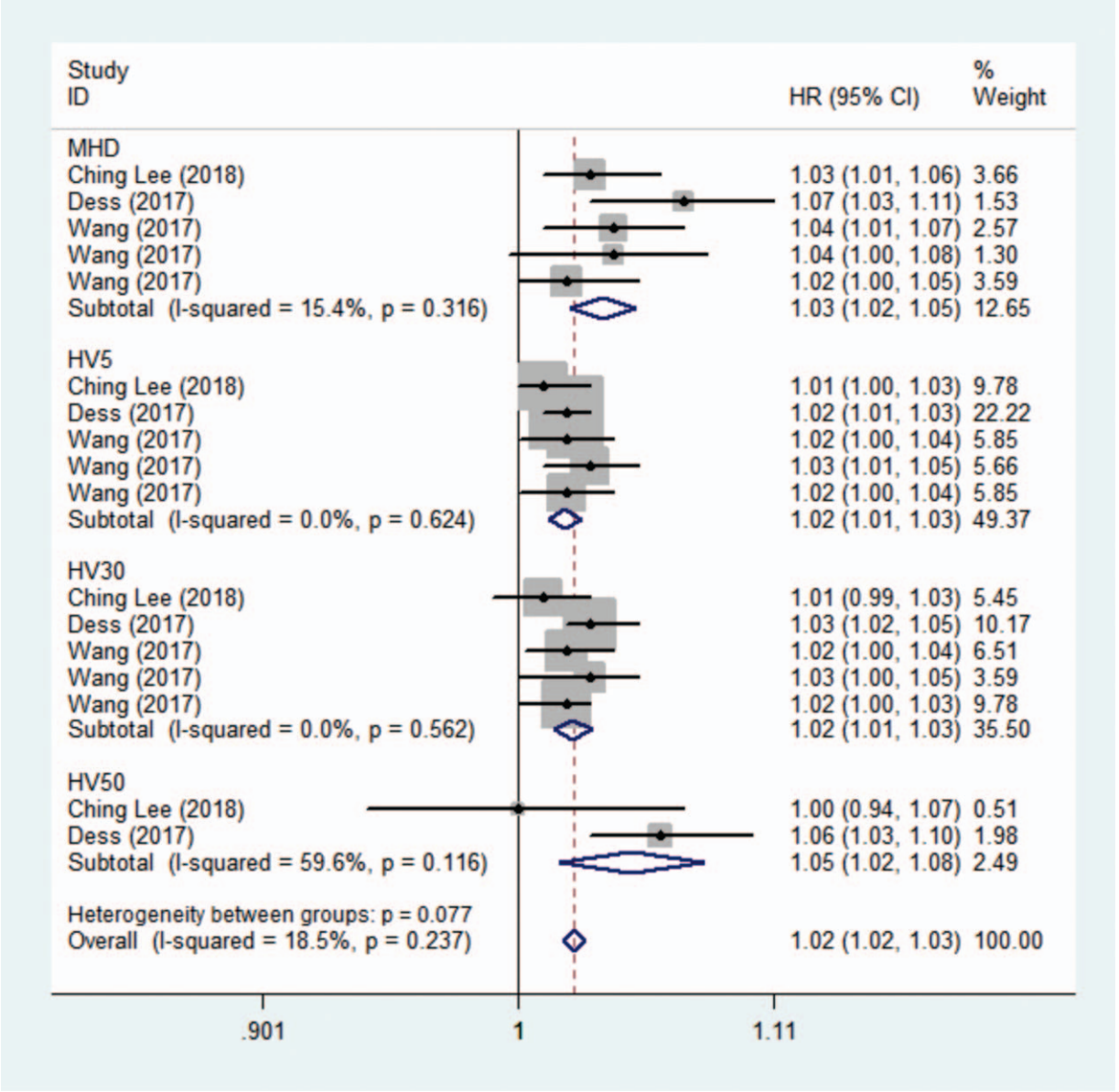


Figure 3. Forest plot of the association between heart dose and cardiac events in lung cancer radiotherapy.

1.00–1.10), and MHD (HR = 1.01; 95% CI: 1.00–1.02) all were associated with decreased OS.

So there is now great interest in exploring how heart dose links to survival. A study by McNew et al[18] found that both location and extent of mediastinal lymph node involvement correlates with heart dose, so they suggested heart dose may be a surrogate for mediastinal nodal involvement rather than an independent predictor of survival. On the other hand, there were more studies founded that heart dose also were associated with cardiac events.[14,17] So there may be association between heart dose, radiation-induced heart disease and survival in lung cancer radiotherapy.

Cardiovascular diseases and cancer are the 2 most common causes of death worldwide.[34] The survival outcomes of cancer patients improved with the appliance of modern therapeutic technology and the better understanding of tumor biology. However, there is treatment-related toxicity including cardiotoxic complications which may offset some of the benefit of effective therapy. Cardiotoxicity is a serious side effect which is already found in both cytostatic and molecularly targeted therapies.[35,36] Meanwhile, RIHD also has long been recognized. It usually includes pericardial disease, myocardial fibrosis, ischemic heart disease, valvular disease, arrhythmias, autonomic changes, and cardiomyopathy.[37] Previous studies had revealed the possible mechanism of RIHD.[38] It is usually thought that fibrosis is a key mediator in RIHD and fibrosis is both acute and late effect of heart irradiation. Acute changes majorly refer to that radiation damage endothelial cells and induce acute inflammatory response, subsequently, the recruited inflammatory cells secrete profibrotic cytokines including platelet-derived growth factor, transforming growth factor b, basic fibroblast growth factor, insulin-like growth factor, and connective tissue growth factor. Furthermore, the persistent fibrosis may associate with epigenetic changes, stem cell loss, and altered cell signaling.

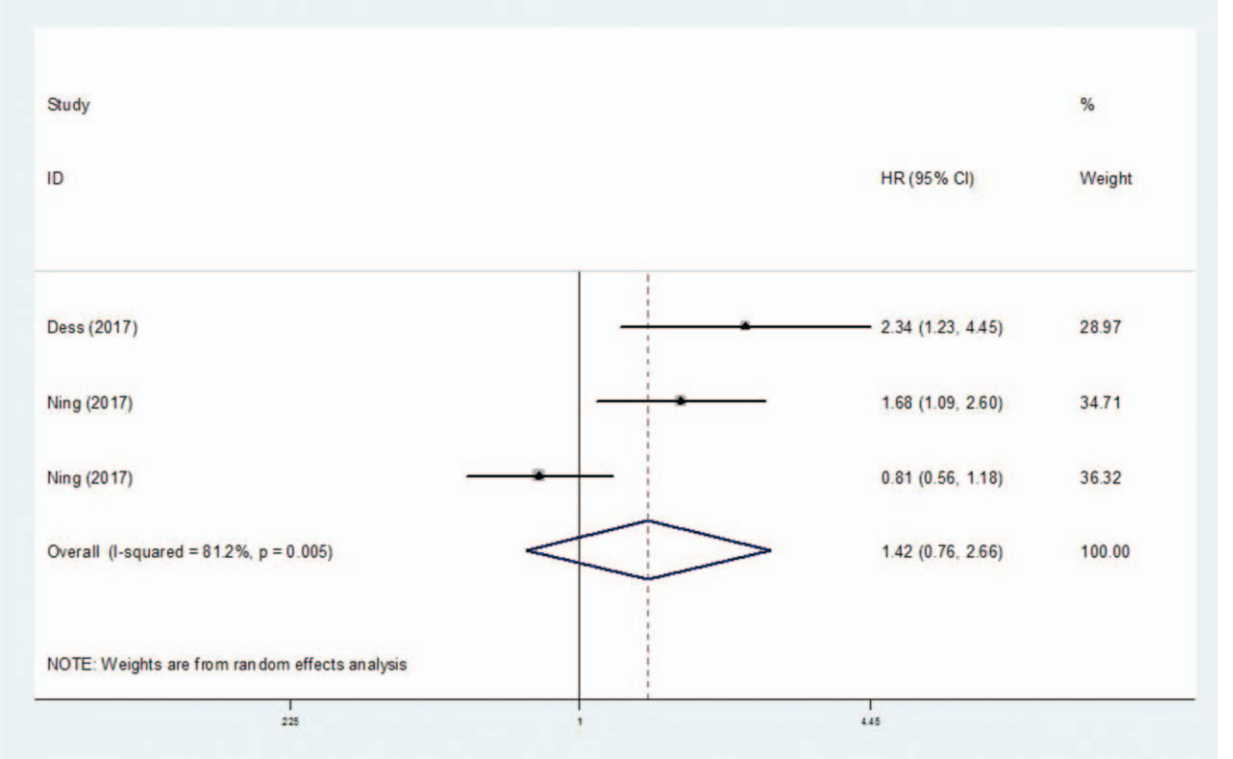


Figure 4. Forest plot of the association between preexisting cardiac disease and cardiac events in lung cancer radiotherapy.

Radiation-induced heart disease (RIHD) has been reported extensively in breast cancer, Hodgkin lymphoma, and childhood cancer patients,[4–7] but studies of RIHD in lung cancer radiotherapy are limited especially those with adequate data of dose–volume parameters. Ming et al[39] summarized the potential risk factors for lung cancer patients including the heart dose,

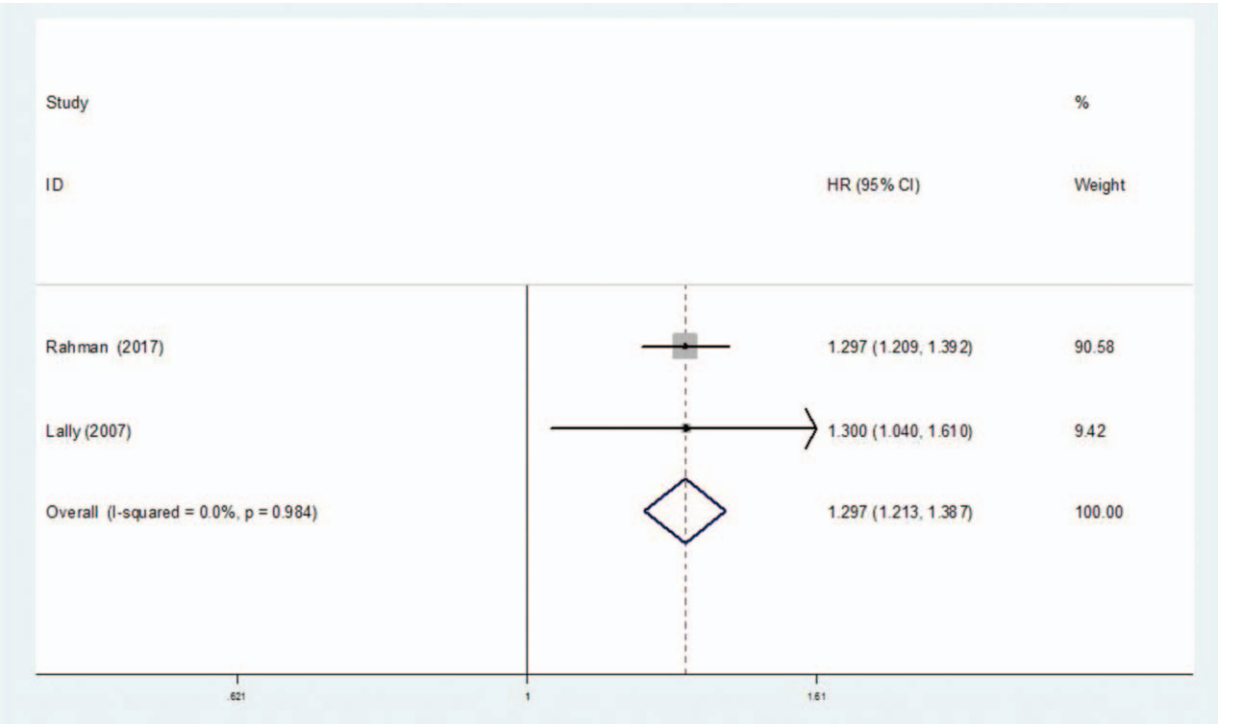


Figure 5. Forest plot of the association between radiotherapy and cardiac-specific mortality in lung cancer radiotherapy.

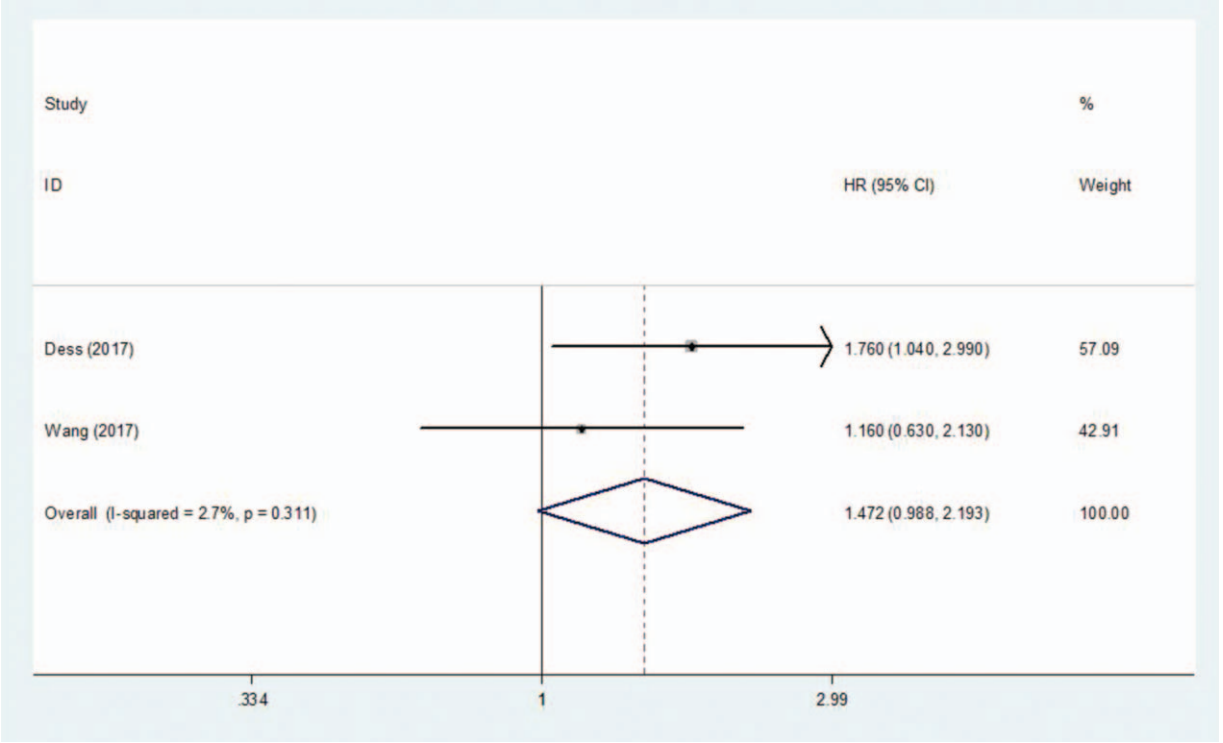


Figure 6. Forest plot of the association between cardiac events and overall survival in lung cancer radiotherapy.

tumor laterality, and the treatment modality, the history of heart and pulmonary disease, and smoking. However, they did not perform quantitative analysis for heart dose. Our study founded that the radiotherapy group had higher cardiac-specific mortality compared with nonradiotherapy group. Furthermore, in the analysis of continuous variable, we also found that the MHD (HR = 1.03; 95% CI: 1.02–1.05), HV5 (HR = 1.02; 95% CI: 1.01–1.03), and HV30 (HR = 1.02; 95% CI: 1.01–1.03) all were significantly associated with all grade cardiac events. However, in our study, the HV50 was not associated with cardiac events which may result from the limited included studies and sample size involving the parameter-HV50. In addition, we set the all grade cardiac events as ending points instead of focusing on the specific cardiac events, which also may influence the result. So future studies are expected to explore the relationship between HV50 and specific cardiac event. Furthermore, the preexisting cardiac disease did not affect the incidence of cardiac events (HR = 1.42; 95% CI: 0.76–2.66). In addition, some studies focused on the specific cardiac events. Ning et al[40] investigated the potential risk factors for pericardial effusion which is the most common complication in radiotherapy and they found that HV35 >10% (cutoff volume is 10%), adjuvant chemotherapy, and previous cardiac disease were predictors of pericardial effusion. Wang et al[17] also discussed 3 types of cardiac events including pericardial events, ischemic events, and arrhythmic events, respectively.

In our study, the result showed heart dose was predictor of OS and heart dose also was risk factor for cardiac events. So we hypothesize that high heart dose may increase the incidence of cardiac event; subsequently, the RIHD contributed to the worse overall survival. Indeed, the study of Dess et al[14] found the grade ≥3 cardiac events were associated with decreased OS, whereas Wang et al[17] showed that symptomatic cardiac events did not remain significantly associated with survival on multivariable analysis. However, our study showed that cardiac events were not associated with overall survival in lung cancer radiotherapy (HR = 1.472; 95% CI: 0.988–2.193). But there also were several studies that explored the issue in different perspective, which discussed the dose to heart substructures and contained other end points. The study by Stam et al[41] showed that the maximum dose on the left atrium and the dose to 90% of the superior vena cava were associated with noncancer death, and Wong et al[42] also found that bilateral ventricles max dose was associated with non–cancer-related death. The non—cancer-related death may be more accurate than OS to evaluate the relationship between heat dose and survival. Furthermore, the dose to heart substructures may further explain the relationship of heat does, cardiac events, and survival.

There were several limitations in our meta-analysis. Firstly, we did not include studies which used different cutoff when analyzing the cardiac dosimetry, because it is difficult to evaluate the result if these data were pooled. Secondly, we did not perform subgroup analysis because the included studies was limited. Thirdly, the cardiac events are not defined by the same standard, so we only discussed the all grade cardiac events instead of analyzing every specific cardiac event.

5. Conclusions

The relationship between heart dose, cardiotoxicity, and survival may not be explained by single reason. But the result from our meta-analysis suggested that higher MHD, HV5, HV30 were risk factors for RIHD. In addition, MHD, HV5, HV30, and HV50 all were predictors of OS in lung cancer. So it is necessary to

constrain the heart dose when performing thoracic radiation therapy to decrease the incidence of cardiac events. Meanwhile, it will bring better overall survival for lung cancer patients. However, in consideration of the limitations mentioned above, future studies are expected to explore that which cut-off of heart dose is best for prognosis of patients and to discuss that whether some heart substructures should take priority over others when performing thoracic radiation therapy.

Author contributions

Dan Wang designed the study, Li Pan, Dengshun Lei, Wenbing Wang and Yanqiu Luo conducted the data searching. Li Pan and Dengshun Lei drafted the manuscript. Dan Wang critically revised the manuscript. Li Pan and Dengshun Lei contributed equally to this work. All authors read and approved the final manuscript.

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