Dose-volume predictors of cardiac adverse events after high-dose thoracic radiation therapy for lung cancer

Locquet, Médéa; Jacob, Sophie; Geets, Xavier; Beaudart, Charlotte

Published in:
BMC Cancer

DOI:
10.1186/s12885-024-13281-8

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

BMC Cancer

SYSTEMATIC REVIEW

Open Access

Dose-volume predictors of cardiac adverse events after high-dose thoracic radiation therapy for lung cancer: a systematic review and meta-analysis

Médéa Locquet[1,2,5*], Sophie Jacob[3], Xavier Geets[4] and Charlotte Beaudart[1,2]

Abstract

Background Lung cancer is a leading cause of cancer mortality and may require high-dose thoracic radiation therapy (RT). However, RT significantly increases the risk of radiation-induced cardiac events, such as pericarditis, cardiomyopathy, and ischemic heart diseases. Despite evidence from clinical trials showing that higher RT doses are associated with poorer survival outcomes due to these cardiac effects, data on dose-volume predictors of such events in lung cancer remain sparse.

Objective To systematically synthesize the incidence of cardiac events following radiation therapy for lung cancer treatment and dose-volume metrics predictors of radiation therapy-induced cardiac events in lung cancer treatment.

Methods This systematic review, registered on PROSPERO (CRD42024565103), adhered to PRISMA guidelines to investigate cardiac events and its dose-volume predictors following high-dose radiation therapy in adults with lung cancer. Data were extracted from longitudinal observational studies and randomized controlled trials. A comprehensive literature search was conducted across MEDLINE, Cochrane CENTRAL, and Embase, with studies selected based on predefined criteria, focusing on clinical cardiac outcomes. Data extraction followed CHARMS guidelines, and study quality was reported using the PROBAST tool. Results were synthesized narratively, with meta-analyses performed where appropriate using R software to estimate pooled effect sizes, heterogeneity, and publication bias.

Results The systematic review included 21 studies and identified a significant association between high-dose thoracic radiation therapy (RT) and an increased incidence of cardiac adverse events in lung cancer patients. The review revealed that higher dose-volume parameters, notably higher mean heart doses (MHD), were predictive of major cardiac events such as pericardial effusion, arrhythmias, and acute coronary syndrome. The meta-analysis showed a significant 4% (95% confidence interval: 3%-6%) increased probability of the occurrence of cardiac events per additional Gray of MHD, with low heterogeneity among studies ($I^2 = 23\%$). No publication bias was evidenced.

Conclusion This study underscores the importance of dose-volume parameters as predictors of cardiac adverse events following high-dose thoracic RT in lung cancer treatment. The findings highlight the need for careful consideration of heart dose constraints in RT planning to mitigate the risk of radiation-induced cardiotoxicity, thereby

*Correspondence:
Médéa Locquet
medea.locquet@gmail.com; medea.locquet@inserm.fr
Full list of author information is available at the end of the article

improving the therapeutic ratio for lung cancer patients. Future research should focus on refining these dose constraints and exploring cardioprotective strategies during lung cancer radiotherapy.

Keywords Lung cancer, Cardiotoxicities, Radiotherapy, Meta-analysis, Review

Introduction

Lung cancer, which includes both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), remains the leading cause of cancer-related deaths globally, presenting a significant public health challenge [1]. Furthermore, the incidence of lung cancer is expected to rise by 65% by 2035 [2]. Prognosis and treatment options are widely determined by the stage of diagnosis, histological (sub)type, and molecular profile of the cancer. For patients with locally advanced, non-resectable NSCLC, as well as those with limited-stage SCLC, standard treatment typically involves high-dose thoracic radiation therapy, often in combination with chemotherapy.

However, RT is not without iatrogenic risk, the most life-threatening being the potential for radiation-induced cardiac events, which can occur due to the proximity of the heart to the tumor target within or near the radiation field. Significant evidence from three phase III randomized trials has demonstrated that high-dose thoracic RT increases the risk of cardiac events in lung cancer patients. In the RTOG 0617 trial for stage III NSCLC, patients receiving higher doses (74 Gray (Gy)) had a significantly lower median survival (20 months) compared to those receiving standard doses (60 Gy) (28 months). Moreover, the heart dose was also reported among the predictors of worse survival in this trial. In other words, the heart dose was associated with a worse survival at a median follow-up of 2 years, indicating a significant contribution to radiation-induced cardiac morbidity and still relatively soon after treatment. In the CALGB 30610/RTOG 0538 trial for limited-stage SCLC, no survival benefit was observed with 70-Gy compared to 45-Gy, potentially due to grade 5 adverse events such as sudden deaths or cardiac arrests (6 in the 70-Gy arm *versus* 2 in the 45-Gy arm). In the LungART trial for postoperative stage II NSCLC, postoperative RT improved local tumor control but did not confer a survival benefit due to cardiopulmonary toxicities (11% in the postoperative RT arm *versus* 5% in the control arm). In each of these trials, the benefit of RT was disadvantaged by excess harmful cardiac events. Since the initial randomized controlled trials, several observational studies have sought to identify the best dose-volume predictors of cardiotoxicity following RT for lung cancer. For example, a retrospective study demonstrated that a mean heart dose (MHD) above 10 Gy significantly increased the risk of major adverse cardiac events in patients without a history of cardiovascular diseases [3]. Another study found that a dose of 40 Gy received by at least 40% of the heart was strongly associated with reduced overall survival [4]. Given these divergent findings and the complexity of dose-volume interactions, this topic must be addressed in a systematic review to clarify the most relevant predictors and optimize cardiac protection for patients undergoing lung cancer treatment.

Many studies have shown that RT for breast cancer or lymphoma can increase the risk of cardiac events, and the spectrum of cardiac events following radiation exposure is broad, including acute pericarditis, pericardial effusion, constrictive pericarditis, cardiomyopathy, heart failure, ischemic heart diseases, valve regurgitation and stenosis, and new-onset arrhythmias. A notable study published in *The New England Journal of Medicine* (Darby et al*.,* 2013) found that the risk of major coronary events increased by 7.4% for each gray (Gy) of radiation delivered to the heart, with the risk becoming apparent within the first five years after treatment and continuing for at least 20 years [5]. Given the significantly higher doses of radiation delivered to the heart in lung cancer treatment compared to other malignancies such as breast cancer or lymphomas, the incidence of cardiac events following RT for lung cancer warrants separate consideration. Moreover, the current literature regarding radiation-induced cardiac events predominantly focuses on medium-term and long-term cardiac outcomes in breast cancer or lymphoma patients, given their long-term survival expectations, which contrasts with the more limited survival of lung cancer patients. Furthermore, lung cancer patients often present with more cardiovascular risk factors than other cancer populations, making them potentially more vulnerable to cardiac risk after cancer treatment. The question then becomes whether the cardiac risk is linked to the patient's baseline characteristics or the effect of RT, making the investigation of dose–response relationships crucial for refining our understanding of the causal relationship.

As survival rates improve due to advancements in therapy for lung cancer, clarifying the existence of a potential dose–response relationship between heart exposure during lung cancer RT and cardiac events and identifying the dose-volume predictors of cardiac

adverse events becomes crucial for optimizing treatment plans and minimizing long-term morbidity. However, data on dose-volume predictors of cardiac events in lung cancer patients remain sparse and heterogeneous. Several retrospective studies provided data on the incidence of cardiac events following RT and heart dose-volume metrics predictors of RT-induced cardiac events to evaluate the risk of cardiac events after RT for lung cancer. However, variability in studied dose-volume parameters and cardiac outcomes yielded various findings, and it would be relevant to synthesize results through a systematic literature review and identify key dose-volume parameters associated with cardiac toxicity following high-dose thoracic RT in lung cancer patients.

In this context, we aimed to systematically review and perform a meta-analysis of cardiac disease risk in patients treated with RT for lung cancer, providing critical insights for clinicians aiming to balance efficacy and safety in treatment protocols.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [6] ensure the quality and transparency of the present report. The PRISMA checklist is available in Supplementary Material 1. The protocol has been previously registered on the PROSPERO International Prospective Register of Systematic Reviews website (reference CRD42024565103). The issue of interest was defined using the following PICOS strategy: Population: Adults with a confirmed diagnosis of lung cancer—Intervention: High-dose radiation therapy and its cardiac dose-volume metrics—Comparator: Not applicable—Outcomes: Cardiac events (any type) following radiation therapy possibly combined with other cancer treatment—Study design: Longitudinal, prospective or retrospective, observational studies, and randomized controlled trials.

Literature search strategies

The literature search was launched on March 26, 2024, applying a specific search strategy on MEDLINE, Cochrane CENTRAL, and Embase (via Ovid), available in Supplementary Material 2. Additionally, we manually searched the reference lists of the included studies and the Google Scholar search engine. An update was conducted on August 26, 2024. The search strategy comprised four key concepts: (1) lung cancer, (2) radiation therapy, (3) cardiac events, and (4) cardiac dose-volume predictors.

Inclusion and exclusion criteria

We established predefined eligibility criteria to determine the inclusion of abstracts and articles. In summary, we included peer-reviewed original studies from MEDLINE indexation (1946) to 2024, involving at least 30 adults (≥ 18 years old) with a confirmed diagnosis of NSCLC or SCLC who received high-dose radiation therapy (≥ 45 Gy; the minimum prescribed dose for treating lung cancer considered higher than standard protocols for other thoracic radiotherapies such as for breast cancer) regardless of the modality. Studies had to report on cardiac events of any type, with the clinical manifestation of the cardiac event being mandatory for inclusion. Eligible study designs could include longitudinal, prospective, or retrospective observational studies published in the English language [7]. Comprehensive eligibility criteria are available in Table 1.

Table 1 Eligibility criteria of references to be included in the systematic review

Inclusion criteria
- Adults (≥ 18 years old) with confirmed diagnosis of non-small cell lung carcinoma or small-cell lung carcinoma
- High-dose of radiation therapy (≥ 45 Gy) (any technique, any modality, any dose-volume predictors)
- Cardiac events (any type) (clinical manifestation of the cardiac event is mandatory to be included)
- Original studies: Longitudinal, prospective or retrospective, observational studies, randomized controlled trials
Exclusion criteria
- Animal studies
- Dose-volume predictors not studied
- Original studies including less than 30 patients
- Case reports, reviews, systematic reviews, letters to the editors
- Non-English language studies
- Protocol of research study
- No report of dose-volume metrics as potential predictors of radiation therapy treatment
- Palliative radiation therapy

Selection of studies

Titles and abstracts of references identified by the search strategy were independently screened by two reviewers (ML and CB) according to the above eligibility criteria. The full-text review stage followed, and eligible studies were identified by the two reviewers (ML and CB). At each stage, disagreements were resolved by discussion between reviewers (ML and CB) with the intervention of a third peer (XG), if needed, to arbitrate in final inclusion. Clinicians and other experts were consulted to ensure the comprehensive inclusion of relevant references. This entire procedure was performed using the Covidence® systematic review management software suggested by the Cochrane Collaboration (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.).

Data extraction

A standardized data extraction form was developed. An initial pilot extraction of the first reference evaluated the form's relevance. Following this, ML extracted relevant data. The extraction was performed according to the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) [8]. Following the systematic review process, this checklist was selected a posteriori due to the final inclusion of only retrospective observational studies aiming to evaluate the predictive power of dose-volume metrics about the occurrence of cardiac events after radiotherapy for lung cancer treatment. The following data were extracted: information related to the reference included study design and main characteristics, patient and tumor characteristics, radiation therapy and other cancer treatment, cardiac events, dose-volume parameters, the magnitude of the association between dose-volume predictors of cardiac events after radiation therapy for lung cancer treatment.

Quality assessment and risk of bias

ML assessed each included study's quality and Risk of Bias (RoB) using the Prediction model study Risk Of Bias Assessment Tool (PROBAST), specifically designed for prediction modeling studies. This tool was selected as a posteriori because of the final inclusion, after the systematic review work, of only retrospective observational studies that tested the predictive power of dose-volume metrics on the occurrence of cardiac events after radiotherapy for lung cancer treatment. The RoB assessment involved questions regarding several domains: participants, predictors, outcomes, and analysis. The questions were answered with "high risk of bias" (0 points) or "low risk of bias." (1 point). Any issue was resolved through consensus, with the intervention of a second party (CB).

Data synthesis and statistical analyses

A descriptive analysis of the included studies was performed as a narrative report. The results were structured to provide an initial description of the general characteristics of the included studies, followed by details on the incidence of cardiac events and the dose-volume prediction model.

Several studies provide different cardiac dose parameters, and the mean heart dose is known to be a key metric in dose–response studies. Given the diversity of dose-volume parameters studied in the literature, only studies focusing on the MHD predictor were included in the meta-analysis because they were sufficiently numerous to pool the results. The other dose-volume parameters were each studied by less than three studies, not allowing a meta-analysis. The meta-analysis focused on included studies that provided results with this metric, and we pooled them using the meta-analysis, a random effects meta-analytical model assuming heterogeneity between studies was applied. The adjusted effect sizes of interest, specifically hazard ratios, were pooled using appropriate statistical packages in R (i.e., the 'meta' and 'risks' packages), resulting in an increased probability of cardiac events per additional Gy administered during RT. Heterogeneity among studies was assessed using the I^2 statistic. Leave-one-out (LOO) sensitivity analyses determined the stability of the results when omitting individual studies. Egger's regression asymmetry test detected any publication bias. No funnel plot asymmetry was applied because less than ten studies were included in the meta-analysis.

All results were considered statistically significant if they had a two-sided p-value of 0.05 or less. All analyses were conducted using R software and its relevant packages.

Results

Of the 1,630 abstracts reviewed, we selected 250 articles for full-text screening. The list of the references excluded is available at https://osf.io/3d4be/. As shown in Fig. 1, 21 studies finally met the eligibility criteria and were included in our review.

Description of the included studies

Table 2 gives the general characteristics of the 21 included studies. Most of the studies were performed in the USA on patients with NSCLC, except Kim et al., 2022 [9] which also included some SCLC. Retrospective cohort design was the most frequent, and only two studies had a prospective cohort design (Chen et al., 2019

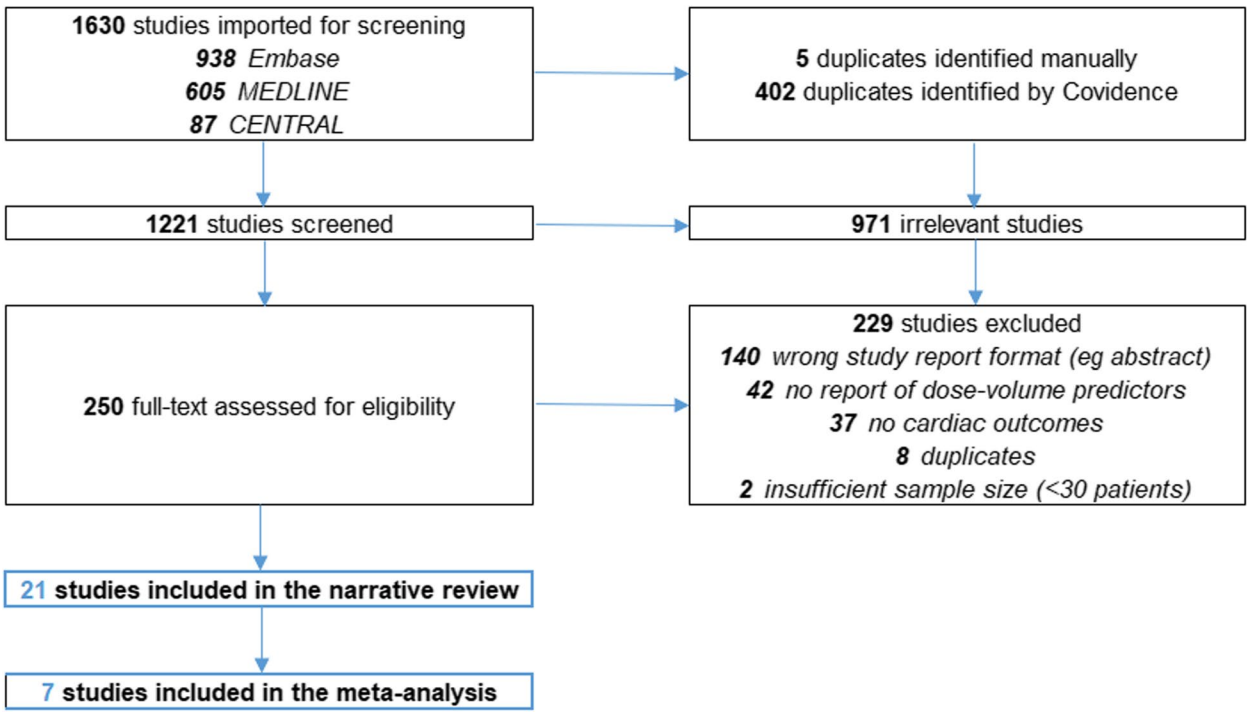

Fig. 1 PRISMA flow diagram for the inclusion of studies

[10] and Ning et al., 2017 [11]). Retrospective and prospective data collection was the study design applied in three references (Table 2). No randomized controlled trials matched our inclusion criteria. The different follow-ups varied between 20.4 months [12] and 8.8 years [3].

Table 3 describes the exposure and outcomes definitions of the 21 included studies regarding dose-volume predictors of radiation-induced cardiac events in lung cancer patients. The outcomes of the studies included various cardiac events and exposure measures (dose-volume predictors), including MHD (in all studies except one [21]). The exposure of specific cardiac substructures, such as cardiac chambers or coronary arteries, varied significantly between studies, with limited explanations for selecting these additional cardiac structures and the corresponding dose-volume parameters. Regarding cardiac outcomes, five studies focused on major adverse cardiac events (MACE) [12, 13, 17, 20, 27], 5 studies on grade 2, 3 or higher of "common terminology criteria for adverse events" (CTCAE) [10, 15, 16, 18, 19], and other focused on specific cardiac events.

Quality assessment

Figure 2 presents the evaluation of PROBAST signaling questions and the overall risk of bias across participants, predictors, outcomes, and analysis domains. Most studies presented medium to low quality and a high to moderate risk of bias. The studies demonstrated a low or unclear bias risk in the predictors and analysis domains. Indeed, the selection of predictors is mainly arbitrary, except for two studies that evaluated the best predictors using statistical principles [14, 27]. None of the studies reported the intercept of the prediction models or prediction model accuracy parameters, and only one assessed the model's discriminatory power in the area under the receiver operating characteristic curve [27].

Incidence of cardiac events after radiation therapy

Table 4 lists the incidence of post-RT cardiac events in patients treated for lung cancer, varying widely according to the studies, the cardiac outcome, and the respective follow-ups.

Overall, these cardiac events occur in up to 32% [15] in the cohort, followed by Cho et al. during a 36-month observation period. The smallest incidence was 10% [13] in Atkins et al. (b) during a 9-month observation period. The most frequent cardiac events were as follows:

- Pericardial effusion: 42.8% as observed over nine months follow-up by Ning et al. [11] (the smallest incidence was 6.2% as observed over 26 months follow-up by Wang et al. [23]).
- Arrhythmias: 17.0% as observed over 60 months follow-up by Banfill et al [4]. (the smallest incidence was

Table 2 Characteristics of the 21 studies regarding dose-volume predictors of cardiac events in lung cancer patients

Reference	Year	Country	Population	Study design	Number of patients	Follow-up
Atkins (a) [12]	2019	USA	Locally advanced NSCLC	Retrospective cohort analysis	748	20.4 months
Atkins (b) [13]	2021	USA	Locally advanced NSCLC	Retrospective cohort analysis	701	20.4 months
Banfill [4]	2022	UK	Stage I to III NSCLC	Retrospective cohort analysis	967	60 months
Borkenhagen [14]	2019	USA	NSCLC	Retrospective cohort analysis	76	1.2 years
Chen [10]	2019	China	Stage III NSCLC	Retrospective and prospective cohort analysis	112	29.5 months
Cho [15]	2022	Republic of Korea	NSCLC	Retrospective cohort analysis	133	45 months
Dess [16]	2017	USA	Stage II to stage III NSCLC	Retrospective and prospective cohort analysis	125	51 months
Jang [17]	2020	Republic of Korea	Stage III NSCLC	Retrospective cohort analysis	53 (low risk CVD) 205 (high risk CVD)	27.5 months
Kim [9]	2022	Republic of Korea	Limited-stage SCLC and locally advanced NSCLC	Retrospective cohort analysis	560	25.7 months
Koutroumpakis [18]	2022	USA	NSCLC	Retrospective cohort analysis	193	24.3 months
Ning [11]	2017	USA	Locally advanced NSCLC	Retrospective and prospective cohort analysis	201 (prospective) 301 (retrospective)	31 months
No [19]	2023	USA	Locally advanced NSCLC	Retrospective cohort analysis	233	73.7 months
Tjong [20]	2022	USA	Locally advanced NSCLC	Retrospective cohort analysis	701	19 months
Walls (a) [21]	2024	UK	NSCLC	Retrospective cohort analysis	420	21.8 months
Walls (b) [22]	2024	UK	NSCLC	Retrospective cohort analysis	478	21.1 months
Wang (a) [23]	2022	USA	Stage III NSCLC	Retrospective and prospective cohort analysis	109	26 months
Wang (b) [3]	2017	USA	Stage III NSCLC	Retrospective cohort analysis	112	8.8 years
Wang (c) [24]	2017	USA	Stage III NSCLC	Retrospective and prospective cohort analysis	112	8.8 years
Xue [25]	2019	USA	Inoperable/unresectable NSCLC	Retrospective cohort analysis	94	58 months
Yegya-Raman (a) [26]	2018	USA	Stage II-III NSCLC or stage IV oligometastatic NSCLC	Retrospective cohort analysis	165	47.4 months
Yegya-Raman (b) [27]	2024	USA	Locally advanced NSCLC	Retrospective cohort analysis	335	3.3 years

Abbreviations: *NSCLC* Non-small cell lung cancer, *SCLC* Small cell lung cancer, *USA* United States of America, *UK* United Kingdom, *CVD* Cardiovascular disease

0.7% as observed over 36 months by Cho et al [15].). Atrial fibrillation was also observed over 24 months follow-up with an incidence rate of around 6% [18, 21].

- Heart failure: 7.3% as observed over 17 months follow-up by Walls et al [21]. (the smallest incidence 0.9% as observed over 26 months follow-up by Wang et al [3].).
- Acute coronary syndrome: 6.0% as observed over 36 months follow-up by Cho et al [15]. (the smallest incidence was 0.7% as observed over 28 months follow-up by Jang et al [20].).

Moreover, cardiac death was also observed over a 60-month follow-up by Banfill et al. [4], with an incidence rate of 11.4%.

Dose-volume predictors of cardiac events

Table 4 summarizes all dose-volume predictors of cardiac events following RT observed in each included study. Overall heterogeneity was observed in both the predictors and cardiac events analyzed. However, whole heart exposure, characterized by MHD or heart volumes receiving a specific dose, was most frequently and significantly associated with cardiac events and was the best predictor of such events following RT for lung cancer. The likelihood of a cardiac event increased by 1% to 7% per Gray of MHD when adjusted for confounders such as age, sex, competing risks, comorbidities, and cardiovascular risk scores. In retrospective studies, seven references analyzed the relationship between MHD (exposure) and cardiac events (outcome) after RT for lung cancer. Figure 3 shows the results of the data meta-analysis regarding MHD as a predictor of cardiac events after RT for lung cancer.

This meta-analysis demonstrated a significant positive association between the MHD and the risk of cardiac events. The pooled HR across the studies was 1.04 [95% CI: 1.03, 1.06], indicating that each Gy increase in MHD corresponded to a 4% increase in the probability of

Table 3 Exposure and outcomes definitions of the 21 included studies

Reference	RT technique and dose prescribed	Dose prescribed	Heart structures delineated	Dose-volume parameters	Justification for the choice of dose-volume parameters	Cardiac events
Atkins (a) [12]	3D-CRT, IMRT	64,0 (54,9–66,0) Gy	Heart	Mean	No justification	AHA/ACC-defined MACE: cardiac death, unstable angina, myocardial infarction, heart failure hospitalization or urgent visit, and coronary revascularization
Atkins (b) [13]	3D-CRT, IMRT	60 Gy	Heart, coronary arteries (left main, LAD left circumflex, right, and posterior descending), LV, LA, RA, RV	Mean, DMax, V[5-Gy increments]	No justification	AHA/ACC-defined MACE: cardiac death, unstable angina, myocardial infarction, heart failure hospitalization or urgent visit, and coronary revascularization
Banfill [4]	Not reported	Not reported	Heart	Mean, V5, V30, V50	No justification	Death with a cardiac cause
Borkenhagen [14]	Not reported	60 (44–69) Gy	LV, RV, LA, RA, pericardium	Mean, Dmax, V30, V45	LASSO for predictors selection	Arrhythmias, pericardial effusion, valvular disease
Chen [10]	Not reported	Not reported	Heart, LV	Mean, V5, V30	No justification	≥Grade 3 cardiac event (CTCAE 4.0)
Cho [15]	3D-CRT, IMRT	Not reported	Heart, myocardium	Mean, V5, V30, V50	No justification	≥Grade 2 cardiac event (CTCAE)
Dess [16]	3D-CRT, IMRT	70 (45–88) Gy	Heart	Mean, V5, V30, V50	No justification	≥Grade 3 cardiac event (CTCAE 4.03)
Jang [17]	3D-CRT, IMRT	50 to 72 Gy	Heart, LV, RV, RA, LA	Mean, V5, V10, V20, V30, V40, V50, V60	No justification	AHA/ACC-defined MACE: cardiac death, unstable angina, myocardial infarction, heart failure hospitalization or urgent visit, and coronary revascularization
Kim [9]	3D-CRT (photon-based RT and proton therapy)	60 (54.0–60.8) Gy 63 (60.0–64.5) Gy	LV, RV, LA, RA, LAD, RCA, LCA	Mean, Dmax, V5, V60	No justification	Cardiac death, unstable anginas, myocardial infarction, coronary revascularization, heart failure, and atrial fibrillation
Koutroumpakis [18]	Proton therapy, IMRT	66 Gy: 16 patients (8%) 66–73 Gy: 64 patients (33%) 74 Gy: 113 patients (59%)	Heart	Mean	No justification	≥Grade 3 cardiac event (CTCAE 5.0)
Ning [11]	3D-CRT, IMRT, VMAT	Not reported	Heart	Mean, V20, V[increment 5 Gy to V65]	Increment 5 Gray (volume)	Pericardial effusion

Table 3 (continued)

Reference	RT technique and dose prescribed	Dose prescribed	Heart structures delineated	Dose-volume parameters	Justification for the choice of dose-volume parameters	Cardiac events
No [19]	3D-CRT, IMRT	Not reported	Heart, LV, LAD, LMCA, LCx, RCA, combined 3-vessel arteries (LAD, LMCA, and LCx, referred to as TotalLeft), and all combined coronary arteries (TotalCor)	Mean, V15	No justification	≥Grade 3 cardiac event (CTCAE 4.0)
Tjong [20]	3D-CRT, IMRT	Not reported	Heart, LAD	Mean, V15, V30	Based on prior studies	AHA/ACC-defined MACE: cardiac death, unstable angina, myocardial infarction, heart failure hospitalization or urgent visit, and coronary revascularization
Walls (a) [21]	3D-CRT, IMRT, VMAT	55 Gy	Right pulmonary vein (RPV), Left pulmonary vein (LPV)	Mean, Dmax, V10, V20, V55	Based on prior studies	Atrial fibrillation
Walls (b) [22]	3D-CRT, IMRT, VMAT	52–55 Gy: 461 patients (96%) 60–66 Gy: 14 patients (3%) 72–79 Gy: 14 patients (3%)	Heart base	Dmax	No justification	Atrial fibrillation, acute heart failure, and acute coronary syndrome
Wang (a) [23]	3D-CRT	70–74 Gy: 84 (77%) 78–90 Gy: 25 (23%)	Heart, LV	Mean, V5, V30	No justification	Symptomatic pericardial effusion, pericarditis, unstable angina, myocardial infarction, significant arrhythmia, and/or heart failure
Wang (b) [3]	3D-CRT	74,0 Gy	Heart, LV, LA, RA	Mean, V5, V30, V60	No justification	Symptomatic pericardial effusion, pericarditis, ischemic cardiac events, myocardial infarction, unstable angina, significant arrhythmia
Wang (c) [24]	3D-CRT	74,0 Gy	Heart, LV	Mean, V5, V30	No justification	Symptomatic pericardial effusion, myocardial infarction, unstable angina, pericarditis, significant arrhythmia, heart failure
Xue [25]	3D-CRT, others	Not reported	Heart, pericardium	Mean, V5, V30, V55	V5 and V30 were significant predictors in the trials	Pericardial effusion

Table 3 (continued)

Reference	RT technique and dose prescribed	Dose prescribed	Heart structures delineated	Dose-volume parameters	Justification for the choice of dose-volume parameters	Cardiac events
Yegya-Raman (a) [26]	3D-CRT, IMRT, both	61,2 (60–66)	Heart, LV, RV, LAD	Mean, V5, V30, V50	The metrics are based on RTOG 0617	Acute coronary syndrome, significant arrhythmia, symptomatic pericardial effusion, pericarditis, congestive heart failure
Yegya-Raman (b) [27]	Pencil beam scanning PBT Passive scatter PBT IMRT 3D-CRT	66.6 (66.6–70)	Heart, LV, LAD	Mean, Dmin, Dmax, V[increment 5 Gy to V95]	Based on statistical properties	AHA/ACC-defined MACE: cardiac death, unstable angina, myocardial infarction, heart failure hospitalization or urgent visit, and coronary revascularization

Abbreviations: *3D-CRT* 3-dimensional conformal radiation therapy, *IMRT* Intensity modulated radiation therapy, *Gy* Gray, *LV* Left ventricle, *RV* Right ventricle, *RA* Right atrium, *LA* Left atrium, *LAD* Left anterior descending artery, *MACE* Major adverse cardiac event, *PBT* Proton beam therapy

References	Participants /2 points	Predictors /3 points	Outcome /6 points	Analysis /9 points	Total /20 points
Atkins (a)	1	1	5	5	13
Atkins (b)	1	1	3	5	12
Banfill	2	3	4	6	15
Borkenhagen	2	3	3	8	17
Chen	1	3	3	5	13
Cho	2	2	4	7	15
Dess	2	2	5	5	15
Jang	0	2	5	6	14
Kim	1	1	4	7	14
Koutroumpakis	2	3	5	4	14
Ning	2	3	5	6	16
No	2	3	5	1	11
Tjong	2	2	4	5	14
Walls (a)	1	1	4	5	13
Walls (b)	2	2	5	5	15
Wang (a)	1	1	4	6	13
Wang (b)	2	3	5	6	16
Wang (c)	2	2	4	5	14
Xue	2	2	5	6	16
Yegya-Raman (a)	1	3	3	5	13
Yegya-Raman (b)	2	1	5	5	14

Low quality
Medium quality
High quality

Fig. 2 Signaling questions from the Prediction model Risk of Bias Assessment Tool (PROBAST)

cardiac events. There was a low heterogeneity across the studies ($I^2 = 23\%$).

The leave-one-out (LOO) analysis (Fig. 4) confirmed the robustness of the association. The HR remained consistent at 1.04 across all iterations, with a slight variation to 1.05 when the study by Yegya-Raman et al. (b) [27] was omitted but remained within the confidence interval [1.03, 1.06]. Furthermore, the I^2 statistic varied slightly across the iterations, ranging from 0% (when omitting Koutroumpakis et al. [18]) to 35% (when omitting Atkins et al. [28] or Wang et al. (b) [24]). Sensitivity analysis confirmed the observation of the association when omitting the study, potentially duplicating the study population from the works of Wang et al. (b) (2022) [16] (Supplementary Material 3).

Egger's test for asymmetry did not reveal statistically significant evidence of publication bias ($t = -0.10$, p-value = 0.93), which was unlikely.

Discussion

This systematic review and meta-analysis provide new insights into the relationship between cardiac exposure and the incidence of radiation-induced cardiac events in patients undergoing high-dose thoracic RT for lung cancer. Throughout all these studies, significant dose–response relationships between cardiac exposure (characterized by heart exposure or cardiac structure exposure metrics) and cardiac events were observed, with higher doses to cardiac structures inducing significantly increased risk of cardiac adverse events, such as pericardial effusion, arrhythmias, congestive heart failure, and acute coronary syndromes.

A strong predictor identified across studies was the MHD. Our meta-analysis revealed that for each additional Gy of MHD, the risk of cardiac events increased by approximately 4% (95% CI: 3% to 6%). This finding aligns with existing literature, such as the study by Darby et al., which reported a 7.4% increase in major coronary events per Gy in breast cancer patients undergoing RT [5]. However, the slightly lower risk observed in our analysis could be explained by differences in patient populations (i.e., the lung cancer population is already at higher risk of cardiac events, mainly due to tobacco exposure), treatment protocols, and shorter follow-up periods.

Furthermore, our review identified that while MHD is a significant predictor, doses to specific cardiac substructures, particularly the left ventricle and the left anterior descending (LAD) artery, also play a crucial role. Some studies included in our review reported that exceeding 20 Gy to the LAD was associated with a marked increase in the incidence of ischemic heart disease, corroborating findings from the RTOG 0617 trial, which highlighted the importance of limiting cardiac doses to reduce cardiotoxicity [29]. However, the variability in dose metrics across studies indicates the need for more standardized reporting and a deeper understanding of the dose–response relationship for these substructures.

Our findings are consistent with previous studies on radiation-induced cardiotoxicity in lung and breast cancer populations. For example, Gagliardi et al. found that patients receiving doses exceeding 25 Gy to the heart had a significantly higher incidence of pericarditis than those receiving lower doses [30]. Similarly, the CHARTED trial demonstrated that patients with MHD above 15 Gy had a nearly two-fold increase in cardiac mortality compared to those with lower MHD [31].

Table 4 Incidence of cardiac events after radiation therapy for lung cancer

	Incidence	Event	Time for the CE to occur or FU period*	Risk	Predictor	Adjusted HR and 95%CI	*p*-value
Atkins (a) [12]	10.3%	MACE	18,5 (5,4–33,6) months	Increased risk of MACE	Mean heart dose	1.05 (1.02–1.08)	< 0.001
Atkins (b) [13]	10.0%	MACE	20,6 (8,8–43,3) months	Increased risk of MACE	LAD coronary artery V15 Gy ≥ 10%	13.90 (1.23–157.21)	0.03
Banfill [4]	21.9% 17.0% 11.4% 3.1% 1.0%	Ischemic heart disease Arrhythmias Cardiac death Valve disease Peri/myocardial disease	60 months*	Increased risk of death with a cardiac cause	Mean heart dose Heart V5 Heart V30	1.07 (1.01–1.13) 1.01 (1.00–1.03) 1.04 (1.00–1.07)	0.02 0.05 0.04
Borkenhagen [14]	21.0% 6.6% 1.3%	Pericardial effusion Arrhythmia Valve disease	14 months*	Increased risk of cardiotoxicity (PE, arrhythmias, valve disease)	LV V45	1.50	0.03
Chen [10]	5.3% 3.6% 0.9%	Acute coronary syndrome Heart failure Myocardial infarction	29.5 months*	Increased risk of cardiac events (CTCA)	Heart V30	3.73 (1.06–6.90)	0.04
Cho [15]	32.0% 26.3% 6.0% 3.0% 0.7%	Cardiac events Pericardial effusion Acute coronary syndrome Congestive heart failure Arrhythmia	36 (9–119) months	Increased risk of cardiac events (CTCA)	Mean heart dose > 11.1 Gy	3.65 (1.79–7.42)	< 0.001
Dess [16]	15.2%	≥ Grade 3 cardiac events	11.0 (0.4–63.0) months	Increased risk of cardiac events (CTCA)	Mean heart dose	1.07 (1.02–1.13)	0.01
Jang [17]	10.5% 1.8% 1.1% 0.7%	Cardiac events MACE Heart failure Acute coronary syndrome	27.5 months*	Increased risk of acute coronary syndrome	LV V60 > 0	9.49 (1.28–70.53)	0.03
Kim [9]	SCLC cohort/ NSCLC cohort 3.8%/ 5.3% 2.1%/ 1.9%	Arrhythmia Non-arrhythmia cardiac events	SCLC cohort/ NSCLC cohort 25.7 (16.5–47.2) months/ 36.2 (26.9–60.2) months	Increased risk of arrhythmias	SAN Dmax > 53.5 Gy	14.91 (4.00–55.56)	< 0.001
Koutroumpakis [18]	15.0% 5.7% 6.2% 3.1%	≥ Grade 2 cardiac event (CTCA) Coronary/vascular event Atrial fibrillation Heart failure	24.3 months*	Increased risk of cardiac events (CTCA)	Mean heart dose	1.00 (0.96–1.05)	0.95
Ning [11]	42.8%	Pericardial effusion	8.9 (0.7–40.2) months	Increased risk of pericardial effusion	Heart V20 > 21% Heart V25 > 21.7% Heart V30 > 18.9% Heart V35 > 10.2% Heart V40 > 9.2% Heart V45 > 8.0% Heart V50 > 7.0% Heart V55 > 5.4% Heart V60 > 4.9% Heart V65 > 3.0% Mean heart dose > 12 Gy	1.72 (1.17–2.65) 1.72 (1.13–2.62) 1.77 (1.16–2.71) 2.02 (1.26–3.23) 1.88 (1.19–2.97) 1.95 (1.23–3.10) 1.93 (1.23–3.02) 1.98 (1.25–3.14) 1.74 (1.13–2.68) 1.76 (1.14–2.73) 1.79 (1.16–2.77)	0.01 0.01 0.009 0.004 0.007 0.005 0.004 0.01 0.01 0.01 0.008

Table 4 (continued)

	Incidence	Event	Time for the CE to occur or FU period*	Risk	Predictor	Adjusted HR and 95%CI	*p*-value
No [19]	22.3% 11.6% 8.1% 1.3% 1.3%	Cardiac events Conduction events Myocardial events Constrictive events Valvular events	21.5 (1.7–118.9) months	Increased risk of cardiac events	Total left heart V15	1.38 (1.11–1.72)	0.004
Tjong [20]	13.7%	MACE	21.8 months*	Increased risk of MACE	LAD V15	1.04 (1.03–1.06)	< 0.001
Walls (a) [21]	6.0%	Atrial fibrillation	21.1 months*	Increased risk of atrial fibrillation	Left pulmonary dose Right pulmonary dose	1.02 (1.00–1.03) 1.01 (1.00–1.02)	0.005 0.03
Walls (b) [22]	17.0% 7.3% 6.1% 3.1%	Cardiac events Heart failure Atrial fibrillation Acute coronary syndrome	16.3 (9.5–33.9) months	Increased risk of cardiac events	Heart base DMax	1.75 (1.03–2.97)	0.04
Wang (a) [23]	11.0% 6.4% 4.6% 2.7% 1.8% 0.9%	Arrhythmia Pericardial effusion Myocardial infarction Unstable angina Pericarditis Heart failure	26.0 (1.0–84.0) months	Increased risk of cardiac events	Mean heart dose	1.05	< 0.001
Wang (b) [3]	10.7% 8.0% 6.2%	Arrhythmic events Pericardial events Ischemic events	Arrhythmic: 23 (1–190) months Pericardial: 28 (7–58) months Ischemic: 26 (9–68) months	Increased risk of: Arrhythmic events Pericardial events Ischemic events	LA V30 LA Mean dose Heart V60 RA V60 LV V5 LV V30 LV Mean Heart V5 Heart V5 RA V60 Heart V30 Mean heart dose	1.03 1.04 1.04 1.02 1.03 1.03 1.05 1.03 1.02 1.02 1.02 1.02	0.001 0.002 0.004 0.005 0.008 0.012 0.014 0.014 0.042 0.047 0.014 0.054
Wang (c) [24]	23.0% 10.7% 6.2% 4.4% 2.7% 1.8% 0.9%	Cardiac events Arrhythmia Pericardial effusion Myocardial infarction Unstable angina Pericarditis Heart failure	26.0 (1.0–84.0) months	Increased risk of cardiac events	Mean heart dose Heart V5 Heart V30 LV mean dose LV V5 LV V30	1.04 1.02 1.02 1.03 1.02 1.02	0.001 0.001 0.01 0.08 0.001 0.01
Xue [25]	40.4%	Pericardial effusion	5.4 (1.0–24.7) months	Increased risk of pericardial effusion	Pericardial V30 Pericardial V35	1.02 (1.00–1.03) 1.03 (1.01–1.05)	0.01 0.01
Yegya-Raman (a) [26]	28.6%	Cardiac events	15.3 (1.0–75.3) months	Increased risk of cardiac events	Mean heart dose LV Mean dose RV Mean dose LAD Mean dose	1.07 (1.03–1.10) 1.04 (1.02–1.07) 1.06 (1.03–1.10) 1.04 (1.02–1.07)	0.0003 0.0013 0.003 0.0005
Yegya-Raman (b) [27]	10.4%	MACE	3.3 (3.1–3.5) years	Increased risk of MACE	LAD V15 Mean heart dose	%1.%2 (1.00–1.02) 1.03 (1.01–1.06)	0.01 0.03

Abbreviations: *MACE* Major adverse cardiac event, *FU* Follow-up, *HR* Hazard ratio, *CI* confidence interval, *LV* Left ventricle, *Gy* Gray, *SAN* Sino-atrial node, *LAD* Left anterior descending artery, *LV* Left ventricle, *PE* Pericardial effusion

* FU period

The consistency of these findings across different cancer types and treatment protocols underscores the critical importance of cardiac dose constraints in RT planning. However, the heterogeneity in the definitions of cardiac events and the varying follow-up durations across studies

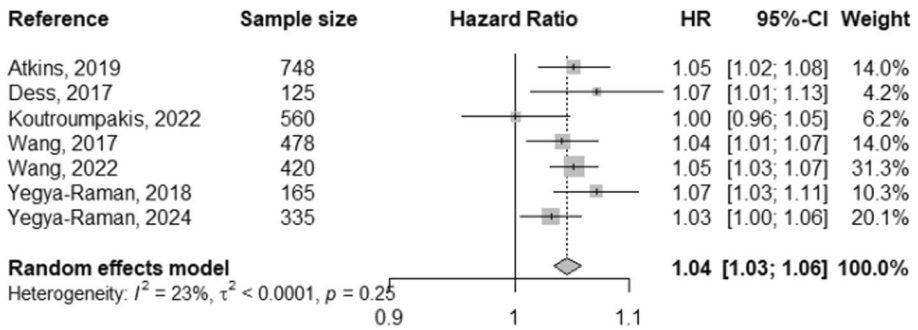

Fig. 3 Forest plot pooling the results of 7 seven studies regarding the impact of mean heart dose on cardiac events risk after radiation therapy for lung cancer

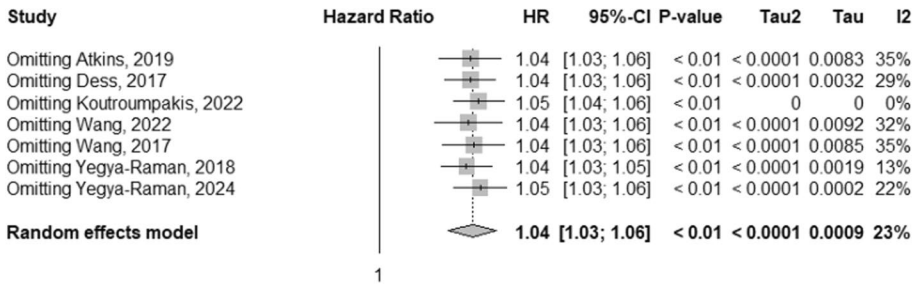

Fig. 4 Leave-one-out analysis when considering the 7 seven studies regarding the impact of mean heart dose on cardiac events risk after radiation therapy for lung cancer

complicate direct comparisons and highlight the need for more uniform criteria in future research.

Several limitations must be acknowledged. First, the methodological differences of the included studies implied a significant challenge. The variability in RT techniques, protocol intent, and the definition of cardiac events did not allow for pool estimates. For instance, some studies used three-dimensional conformal RT (3D-CRT). In contrast, others employed intensity-modulated RT (IMRT) or proton therapy, each with different implications for cardiac dose distribution, therefore not reflected in the MHD metric.

Additionally, the varied definitions of cardiac events across studies could impact the conclusions drawn regarding the dose-volume parameter, potentially introducing inconsistencies or biases in interpreting results; each type of cardiac event likely has distinct prognostic implications. However, there was no heterogeneity in pooled studies, yielding a robust HR. Moreover, the LOO analysis showed consistency, suggesting that no single research overly influences the overall result, indicating the robustness of the findings despite different follow-up periods, number of cardiac events, or sample size. Finally, our results suggested that publication bias was unlikely in this meta-analysis, supporting the reliability of the conclusions regarding the association between MHD and the risk of cardiac events following radiotherapy in patients with lung cancer.

A second limitation could be residual confounding. Notably, there was little or no information in the included studies about CV risk factors such as age, smoking status, and pre-existing cardiovascular conditions. However, our conclusions would probably not have been impacted. Indeed, in 2013, Darby et al. demonstrated that the proportional increase in the rate of major coronary events per Gy was similar in women with and women without cardiac risk factors at the time of RT for breast cancer, which was further demonstrated in other breast cancer and Hodgkin lymphoma survivors treated with RT [5].

The third limitation of this meta-analysis is the inclusion of only retrospective studies. Retrospective studies, while valuable for providing comprehensive data, are more prone to biases, which can affect the reliability of the findings. Additionally, they limit the ability to establish causality. Future research incorporating prospective studies would help validate and strengthen our conclusions. Residual confounding could also arise from the lack of information in the references about radiation dose fractionation concurrent with chemotherapy. Without detailed data on these aspects, it becomes difficult to control the effects of these variables on the results thoroughly, leading to incomplete conclusions.

The findings of this review have significant clinical implications. Given the apparent association between cardiac dose and radiation-induced cardiac events, it is essential that clinicians carefully warrant heart exposure as low as possible during RT planning for lung cancer patients. Advanced RT techniques, such as proton therapy, which can more precisely target tumors while sparing surrounding cardiac tissue, should be explored to minimize cardiotoxicity [32].

Future research should focus on establishing a more precise dose–response association and possible thresholds for cardiac substructures, particularly the LAD and left ventricle, and developing predictive models incorporating patient-specific factors. Prospective studies with extended follow-up periods are also needed to understand better the long-term cardiac risks associated with thoracic RT (e.g., the RAPID-RT study) [33].

In conclusion, this systematic review and meta-analysis underscore the critical importance of dose-volume parameters in predicting radiation-induced cardiac events in lung cancer patients. While MHD remains a crucial predictor, the role of specific substructures warrants further investigation. Future research should standardize dose reporting and explore strategies to mitigate cardiotoxicity, ultimately improving patient outcomes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13281-8.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Authors' contributions

Conceptualization: ML; Methodology: CB; Software: CB; Validation: ML, CB, SJ, XG; Formal analysis: ML, CB, SJ; Investigation: ML, CB; Resources: CB; Data curation: ML, CB; Writing – Original Draft: ML, Writing – Review & Editing: ML, SJ, CB; Vizualization: ML, SJ, XG, CB; Supervision: CB; Project administration: ML.

Funding

None.

Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Biomedical Sciences, Namur Research Institute for Life Sciences, (NARILIS), Faculty of Medicine, University of Namur, Namur, Belgium. [2]Clinical Pharmacology and Toxicology Research Unit, Namur Research Institute for Life Sciences, Faculty of Medicine, University of Namur, 5000 Namur, Belgium. [3]Laboratory of Epidemiology (LEPID), Institut de Radioprotection Et de Sureté Nucléaire, Fontenay-Aux-Roses, France. [4]Radiation Oncology Department, Cliniques Universitaires Saint-Luc, 1200 Brussels, MIRO Lab. IREC – UCLouvain, Brussels, Belgium. [5]National Institute for Medical Research (Inserm), Unit 1018 Centre for Research in Epidemiology and Population Health, Laboratory of "Epidemiology of Radiations, Clinical Epidemiology and Cancer Survivorship", Paris–Saclay University, Gif-Sur-Yvette, France.

Received: 30 September 2024 Accepted: 2 December 2024
Published online: 20 December 2024

References

1. Didkowska J, Wojciechowska U, Mańczuk M, Łobaszewski J. Lung cancer epidemiology: contemporary and future challenges worldwide. Ann Transl Med. 2016;4(8):150–150. https://doi.org/10.21037/atm.2016.03.11.
2. Luo G, Zhang Y, Etxeberria J, et al. Projections of lung cancer incidence by 2035 in 40 countries worldwide: population-based study. JMIR Public Health Surveill. 2023;9:e43651. https://doi.org/10.2196/43651.
3. Wang K, Pearlstein KA, Patchett ND, et al. Heart dosimetric analysis of three types of cardiac toxicity in patients treated on dose-escalation trials for Stage III non-small-cell lung cancer. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2017;125(2):293–300. https://doi.org/10.1016/j.radonc.2017.10.001.
4. Banfill K, Abravan A, van Herk M, et al. Heart dose and cardiac comorbidities influence death with a cardiac cause following hypofractionated radiotherapy for lung cancer. Front Oncol. 2022;12:1007577. https://doi.org/10.3389/fonc.2022.1007577.
5. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368(11):987–98. https://doi.org/10.1056/NEJMoa1209825.
6. PRISMA 2020 checklist. PRISMA statement. https://www.prisma-statement.org/prisma-2020-checklist. Accessed 5 Aug 2024.
7. Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care. 2012;28(2):138–44. https://doi.org/10.1017/S0266462312000086.
8. Moons KGM, de Groot JAH, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: The CHARMS checklist. PLOS Med. 2014;11(10):e1001744. https://doi.org/10.1371/journal.pmed.1001744.
9. Kim KH, Oh J, Yang G, et al. Association of sinoatrial node radiation dose with atrial fibrillation and mortality in patients with lung cancer. JAMA Oncol. 2022;8(11):1624–34. https://doi.org/10.1001/jamaoncol.2022.4202.
10. Chen L, Ta S, Wu W, Wang C, Zhang Q. Prognostic and added value of echocardiographic strain for prediction of adverse outcomes in patients with locally advanced non-small cell lung cancer after radiotherapy. Ultrasound Med Biol. 2019;45(1):98–107. https://doi.org/10.1016/j.ultrasmedbio.2018.09.012.
11. Ning MS, Tang L, Gomez DR, et al. Incidence and predictors of pericardial effusion after chemoradiation therapy for locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2017;99(1):70–9. https://doi.org/10.1016/j.ijrobp.2017.05.022.
12. Atkins KM, Rawal B, Chaunzwa TL, et al. Cardiac radiation dose, cardiac disease, and mortality in patients with lung cancer. J Am Coll Cardiol. 2019;73(23):2976–87. https://doi.org/10.1016/j.jacc.2019.03.500.
13. Atkins KM, Chaunzwa TL, Lamba N, et al. Association of left anterior descending coronary artery radiation dose with major adverse cardiac events and mortality in patients with non-small cell lung cancer. JAMA Oncol. 2021;7(2):206–19. https://doi.org/10.1001/jamaoncol.2020.6332.
14. Borkenhagen JF, Bergom C, Rapp CT, Klawikowski SJ, Rein LE, Gore EM. Dosimetric predictors of cardiotoxicity in thoracic radiotherapy for lung cancer. Clin Lung Cancer. 2019;20(6):435–41. https://doi.org/10.1016/j.cllc.2019.05.014.

15. Cho SG, Kim YH, Park H, et al. Prediction of cardiac events following concurrent chemoradiation therapy for non-small-cell lung cancer using FDG PET. Ann Nucl Med. 2022;36(5):439–49. https://doi.org/10.1007/s12149-022-01724-w.
16. Dess RT, Sun Y, Matuszak MM, et al. cardiac events after radiation therapy: combined analysis of prospective multicenter trials for locally advanced non-small-cell lung cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35(13):1395–402. https://doi.org/10.1200/JCO.2016.71.6142.
17. Jang BS, Cha MJ, Kim HJ, et al. Heart substructural dosimetric parameters and risk of cardiac events after definitive chemoradiotherapy for stage III non-small cell lung cancer. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2020;152:126–32. https://doi.org/10.1016/j.radonc.2020.09.050.
18. Koutroumpakis E, Xu T, Lopez-Mattei J, et al. Coronary artery calcium score on standard of care oncologic CT scans for the prediction of adverse cardiovascular events in patients with non-small cell lung cancer treated with concurrent chemoradiotherapy. Front Cardiovasc Med. 2022;9:1071701. https://doi.org/10.3389/fcvm.2022.1071701.
19. No HJ, Guo FB, Park NJI, et al. Predicting adverse cardiac events after radiotherapy for locally advanced non-small cell lung cancer. JACC CardioOncology. 2023;5(6):775–87. https://doi.org/10.1016/j.jaccao.2023.08.007.
20. Tjong MC, Zhang SC, Gasho JO, et al. External validation of Cardiac disease, Hypertension, and Logarithmic Left anterior descending coronary artery radiation dose (CHyLL) for predicting major adverse cardiac events after lung cancer radiotherapy. Clin Transl Radiat Oncol. 2023;42:100660. https://doi.org/10.1016/j.ctro.2023.100660.
21. Walls GM, McCann C, O'Connor J, et al. Pulmonary vein dose and risk of atrial fibrillation in patients with non-small cell lung cancer following definitive radiotherapy: An NI-HEART analysis. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2024;192:110085. https://doi.org/10.1016/j.radonc.2024.110085.
22. Walls GM, O'Connor J, Harbinson M, et al. the association of incidental radiation dose to the heart base with overall survival and cardiac events after curative-intent radiotherapy for non-small cell lung cancer: results from the NI-HEART study. Clin Oncol. 2024;36(2):119–27. https://doi.org/10.1016/j.clon.2023.11.029.
23. Wang K, Malkin HE, Patchett ND, et al. Coronary artery calcifications and cardiac risk after radiation therapy for stage iii lung cancer. Int J Radiat Oncol Biol Phys. 2022;112(1):188–96. https://doi.org/10.1016/j.ijrobp.2021.08.017.
24. Wang K, Eblan MJ, Deal AM, et al. Cardiac toxicity after radiotherapy for stage III non-small-cell lung cancer: pooled analysis of dose-escalation trials delivering 70 to 90 Gy. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35(13):1387–94. https://doi.org/10.1200/JCO.2016.70.0229.
25. Xue J, Han C, Jackson A, et al. Doses of radiation to the pericardium, instead of heart, are significant for survival in patients with non-small cell lung cancer. Radiother Oncol. 2019;133:213–9. https://doi.org/10.1016/j.radonc.2018.10.029.
26. Yegya-Raman N, Wang K, Kim S, et al. dosimetric predictors of symptomatic cardiac events after conventional-dose chemoradiation therapy for inoperable NSCLC. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2018;13(10):1508–18. https://doi.org/10.1016/j.jtho.2018.05.028.
27. Yegya-Raman N, Ho Lee S, Friedes C, et al. Cardiac radiation dose is associated with inferior survival but not cardiac events in patients with locally advanced non-small cell lung cancer in the era of immune checkpoint inhibitor consolidation. Radiother Oncol. 2024;190:110005. https://doi.org/10.1016/j.radonc.2023.110005.
28. Atkins KM, Rawal B, Chaunzwa TL, et al. Cardiac radiation dose, cardiac disease, and mortality in patients with lung cancer. J Am Coll Cardiol. 2019;73(23):2976–87. https://doi.org/10.1016/j.jacc.2019.03.500.
29. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35(1):56–62. https://doi.org/10.1200/JCO.2016.69.1378.
30. Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. Int J Radiat Oncol Biol Phys. 2010;76(3):S77–85. https://doi.org/10.1016/j.ijrobp.2009.04.093.
31. Jacobse JN, Duane FK, Boekel NB, et al. Radiation dose-response for risk of myocardial infarction in breast cancer survivors. Int J Radiat Oncol Biol Phys. 2019;103(3):595–604. https://doi.org/10.1016/j.ijrobp.2018.10.025.
32. Teoh S, Fiorini F, George B, Vallis KA, Van den Heuvel F. Proton vs photon: A model-based approach to patient selection for reduction of cardiac toxicity in locally advanced lung cancer. Radiother Oncol. 2020;152:151–62. https://doi.org/10.1016/j.radonc.2019.06.032.
33. Price G, Devaney S, French DP, et al. Can real-world data and rapid learning drive improvements in lung cancer survival? The RAPID-RT study. Clin Oncol R Coll Radiol G B. 2022;34(6):407–10. https://doi.org/10.1016/j.clon.2021.12.017.

Publisher's Note