Advances in Radiation Oncology (2023) **8**, 101213

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Higher Lung and Heart Doses Decrease Early and Long-Term Survival, Respectively, in Patients With Non-Small Cell Lung Cancer Undergoing Postoperative Radiation

Zeliang Ma, MD,[a] Yunsong Liu, MD,[a] Yongxing Bao, MD,[a] Meng Yuan, MD,[a] Xu Yang, MD,[b] Yu Men, MD,[c] Jianyang Wang, MD,[a] Lei Deng, MD,[a] Yirui Zhai, MD,[a] Nan Bi, MD,[a] Luhua Wang, MD,[a] and Zhouguang Hui, MD[a,c,*]

[a]Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [b]Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; and [c]Department of VIP Medical Services, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Received 13 October 2022; accepted 25 February 2023

Abstract

Purpose: Cardiopulmonary toxic effects may reduce the efficacy of postoperative radiation therapy (PORT) in patients with non-small cell lung cancer (NSCLC). However, few studies have examined whether the heart and lung doses affect overall survival (OS). We investigated the correlation of heart and lung doses with OS in patients with NSCLC undergoing PORT.

Methods and Materials: This retrospective analysis included 307 patients with NSCLC undergoing PORT. The total dose was 50 Gy. Landmark analyses were performed at 36 months, with hazard ratios (HRs) calculated separately for events occurring up to 36 months (early survival) and after 36 months (long-term survival). Stabilized inverse probability of treatment weighting (sIPTW) was performed to balance the characteristics of the high- and low-dose groups. We performed sensitivity analyses at 24 and 48 months.

Results: The median follow-up period was 67.42 months. Heart doses were significantly correlated with long-term survival (HR, 1.14; $P = .015$) but not with early survival (HR, 0.97; $P = .41$) or whole survival (HR, 1.02; $P = .58$). Lung doses were marginally significantly correlated with early survival (HR, 1.03; $P = .07$) but not with long-term survival (HR, 1.00; $P = .85$) or whole survival (HR, 1.02; $P = .12$). Higher heart and lung doses were associated with decreased long-term and early survival, respectively, before and after sIPTW. Landmark analyses at 24 and 48 months showed consistent results.

Sources of support: This study was supported by the Non-profit Central Research Institute Fund of the Chinese Academy of Medical Sciences (2022-JKCS-18), Capital's Funds for Health Improvement and Research (2022-1-4022), and the Beijing Hope Run Special Fund of the Cancer Foundation of China (ZZ2021A02).

Disclosures: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Research data are stored in an institutional repository and will be shared upon appropriate request to the corresponding author for research only.

*Corresponding author: Zhouguang Hui, MD; E-mail: drhuizg@163.com

https://doi.org/10.1016/j.adro.2023.101213

Conclusions: For patients with NSCLC undergoing PORT, a higher heart dose was associated with decreased long-term survival, whereas a higher lung dose was associated with decreased early survival.

Introduction

Postoperative radiation therapy (PORT) for non-small cell lung cancer (NSCLC) is controversial.[1] Many retrospective and large public database studies have suggested that PORT confers survival benefits for patients with pathologic N2 NSCLC[2,3]; however, 2 recent randomized controlled trials showed that PORT does not improve progression-free survival (PFS) or overall survival (OS) in these patients.[4,5] Cardiopulmonary toxic effects may diminish the benefit of PORT. Moreover, owing to the short survival of patients with locally advanced NSCLC, the focus of treatment is primarily on disease control, and current surveillance strategies may underestimate heart and lung radiation injuries and their effect on survival.

Results of the Radiation Therapy Oncology Group (RTOG) 0617 trial[6] raise the question of whether the heart dose in definitive radiation therapy affects OS.[7] Many studies have shown that the radiation therapy heart dose is a prognostic factor for poor OS,[8-10] but some studies have shown that cardiac dose is not related to OS.[11-13] Moreover, to our knowledge, only 2 studies have investigated whether the heart dose in PORT affects OS. One study had a limited sample size of 43 patients,[14] and the other had 289 patients but included patients with incomplete resection (R1) who had nonuniform stages (I-III), and it used a heterogeneous radiation dose (45-70 Gy).[15] Therefore, the conclusions were not convincing. Regarding the lung dose, most studies have concentrated on its effect on radiation pneumonitis or fibrosis rather than survival. Moreover, few studies have investigated the effect of the lung dose on the survival of patients undergoing PORT.

Radiation heart injury develops over several years after radiation, whereas radiation pneumonitis and fibrosis peak at 1 to 3 months and 6 to 12 months after radiation therapy, respectively. Therefore, we hypothesized that the lung dose affects early survival, whereas the heart dose affects long-term survival. We investigated the effect of the heart and lung doses on OS and whether they had different effects on early and late survival.

Methods and Materials

Patients

This was a post hoc analysis of our recently published phase deanonymize randomized controlled trial[4] and a retrospective review of the deanonymize database in our institution. Patients diagnosed with pN2 NSCLC between January 2006 and June 2019 were analyzed. The eligibility criteria were as follows: age 18 to 70 years, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1, complete resection (R0) and systemic lymph node dissection, and 4 cycles of adjuvant chemotherapy followed by PORT. The exclusion criteria included a history of other cancers and receipt of neoadjuvant chemotherapy. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the ethics committee of the institutional review board of deanonymize. The requirement for informed consent was waived owing to the retrospective nature of the research.

Treatments

Surgery consisted of lobectomy, bilobectomy, or pneumonectomy with thorough dissection of the mediastinal lymph nodes. All patients received 4 cycles of platinum-based doublet adjuvant chemotherapy and PORT.

Experienced radiation therapists delineated the target volume and organs at risk. The clinical target volume included the ipsilateral hilum, subcarinal region, ipsilateral mediastinum, and stump of the central lesions. The lungs were delineated using automatic thresholding, excluding gross tumors. The heart was delineated as previously defined.[16] A total dose of 50 Gy was delivered in 25 fractions at 2 Gy per fraction, 5 days per week. The dose constraints for the heart were $V30 < 40\%$ and $V40 < 30\%$, and the dose constraint for the lung was $V20 < 30\%$ (where Vx equals the volume percentage of the organ receiving more than a specific dose in gray).

All patients received intensity modulated radiation therapy or 3-dimensional conformal radiation therapy using linear accelerators with a 6-MV beam. Simulation computed tomography (CT) images with a 5-mm slice thickness were obtained with the patient in the supine position using the Brilliance Big Bore scanner (Philips Healthcare, Andover, MA) with iodine-based intravenous contrast. Treatment plans were designed using the Pinnacle treatment planning system, version 9.0 (Philips, Fitchburg, WI). Individual radiation therapy dose distributions were manually reviewed.

Follow-up

Patients were followed up every 3 months for the first 2 years, every 6 months for 2 to 5 years, and annually

thereafter. During follow-up, all patients were evaluated by blood and imaging examinations (chest CT, abdominal CT, or B-ultrasonography) and any other necessary tests based on their symptoms. Disease progression was confirmed by clinical assessment, radiologic examination, and pathology reports.

Statistics

Continuous variables are presented as mean ± standard deviation for normally distributed data and median and interquartile range (IQR) for nonnormally distributed data. Categorical variables are presented as count and percentage. Continuous variables were compared using *t* tests or Wilcoxon rank sum tests; categorical variables were compared using χ^2 tests or Fisher exact tests as appropriate. The primary endpoint was OS, calculated from the date of diagnosis to the date of all-cause death or last day of follow-up. The median follow-up time was calculated using the reverse Kaplan-Meier method. OS was calculated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazards models were used to analyze the unadjusted and adjusted influences of the heart and lung doses on OS. Prognostic factors with a *P* value <.1 in the univariate analysis or of clinical importance were included in the multivariate analysis. Landmark analyses were performed at the landmark point of 36 months, with hazard ratios (HRs) calculated separately for events up to 36 months and after 36 months. For early survival (≤36 months), patients who survived more than 36 months were censored at 36 months; for long-term survival (>36 months), only patients who survived more than 36 months were included in the analysis. The mean dose was chosen as the cutoff value. We also categorized patients into low- and high-dose groups using an optimal cutoff threshold determined by maximizing the log-rank statistic between the 2 groups. Stabilized inverse probability of treatment weighting (sIPTW) was performed to balance the characteristics of the high- and low-dose groups. In addition, we performed sensitivity analyses of the landmark points at 24 and 48 months. A statistically significant difference was set at $P < .05$. All analyses were performed using R, version 4.2.0 (R Foundation, Vienna, Austria).

Results

Patient characteristics and survival

A total of 307 patients were eligible: 127 from the prospective database and 180 from the retrospective database. A total of 211 patients survived for >36 months. The median follow-up time was 67.42 months. The median age was 56 years (IQR, 49-62 years); 40.39% of patients were women, and 32.9% were current smokers. The median mean heart dose (MHD) was 8.98 Gy, and the heart V50 was 1.96%. The median mean lung dose was 9.82 Gy, and the lung V8 was 32.57% (Table 1). The median OS was not reached, and the median PFS was 25.76 months (95% confidence interval [CI], 12.68 months to not reached). The 3-year OS was 81.6%, and the 3-year PFS was 42.4%. Because PFS decreased dramatically within the first 36 months and tended to flatten after 36 months (Fig. 1), we chose 36 months as the landmark point of early and long-term survival. Sex, ECOG PS, smoking status, histology, tumor size, and positive lymph node ratio had *P* values <.1 in the univariate analysis or were clinically important and were included in the multivariate analysis (Table E1). We performed univariate Cox analysis for associations of the planning target volume (PTV) with overall survival (HR, 1.01; 95% CI, 1.00-1.01), early survival (HR, 1.01; 95% CI, 1.00-1.01), and long-term survival (HR, 1.01; 95% CI, 1.00-1.01). The PTV size was weakly associated with heart V50 (correlation coefficient = 0.20) or lung V8 (correlation coefficient = 0.34), whereas it was more associated with sex (correlation coefficient = 0.47) because men usually have bigger bodies than women. Because treatment target volume was delineated uniformly as described in the methods, the analysis did not include the PTV size.

Heart dose and survival

In the univariate analysis, most heart dose parameters were related to long-term survival, whereas no parameters were related to early survival (Table 2, Fig. 2A). The heart V50 was significantly correlated with whole and long-term survival but not early survival. Since the heart dose parameters were highly correlated, they could not all be included in the multivariate analysis. Because the heart V50 was significantly correlated with whole and long-term survival, it was included in the multivariate analysis, and it remained significant for long-term survival (HR, 1.14; $P = .015$) but not whole survival (HR, 1.02; $P = .58$) (Table 3). The heart V50 and lung V8 were not highly correlated (Pearson correlation coefficient = 0.23); therefore, they were both included in the multivariate analysis. In the multivariate analysis, the heart V50 and positive lymph node ratio were the only prognostic factors for long-term survival; sex, ECOG PS, smoking status, and tumor size were not correlated with long-term survival. Multivariate analysis showed consistent results for other heart dose parameters. Using the mean heart V50 as the cutoff, landmark analysis revealed that long-term survival, but not early survival, was significantly different between the low- and high-dose groups (Fig. 3A).

As for cardiac events, among the 127 patients in the prospective cohort, 1 patient (0.8%) developed a cardiac event (coronary heart disease) and 109 (85.8%) did not develop

Table 1 Patient characteristics (N = 307)

Characteristic	Patients*
Sex	
Male	183 (59.6)
Female	124 (40.4)
Age (y), median (IQR)	56.00 (49.00-62.00)
Smoking status	
Former or never†	206 (67.1)
Current	101 (32.9)
ECOG PS	
0	23 (7.5)
1	284 (92.5)
Tumor location	
Left lung	116 (37.8)
Right lung	191 (62.2)
Histology	
Non-SCC	244 (79.5)
SCC	63 (20.5)
pT	
1	66 (21.5)
2	194 (63.2)
3	40 (13.0)
4	7 (2.3)
Tumor size (cm), median (IQR)‡	3.20 (2.30-4.10)
Detected lymph nodes, median (IQR)	22.00 (16.00-28.00)
Positive lymph nodes, median (IQR)	5.00 (3.00-9.00)
MHD (Gy), median (IQR)	8.98 (5.01-13.96)
MLD (Gy), median (IQR)	9.82 (8.57-11.30)
Heart volume (cm^3), median (IQR)	619.33 (529.63-725.98)
Lung volume (cm^3), median (IQR)	2496.38 (2074.24-3079.10)
PTV volume (cm^3), median (IQR)	234.7 (197.1-287.4)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; MHD = mean heart dose; MLD = mean lung dose; PTV = planning target volume; SCC = squamous cell carcinoma.

* Data are presented as the number and percentage of patients unless otherwise indicated.

† Former smokers are those who had a smoking history and quit smoking before diagnosis.

‡ Tumor size refers to the maximum diameter of the tumor in the pathologic specimen.

cardiac events during follow-up; development of cardiac events was unknown for 17 patients (13.4%). The association between heart V50 and cardiac events could not be evaluated owing to the low incidence of cardiac events.

Lung dose and survival

In the univariate analysis, the lung V8 and V50 were significantly correlated with whole and early survival but not with long-term survival (Table 2, Fig. 2B). The lung V8 had the lowest *P* value in the univariate analysis; therefore, it was included in the multivariate analysis and remained marginally insignificant for early survival (HR, 1.03; $P = .07$) but was not correlated with long-term survival (HR, 1.00; $P = .85$) or whole survival (HR, 1.02; $P = .12$) (Table 3). Landmark analysis revealed that lung V8 was significantly correlated with early survival but not long-term survival (Fig. 3B). The incidence of radiation pneumonitis was 13.7%. We performed univariate logistic regression between lung dose and any grade of radiation pneumonitis (Common Terminology Criteria for Adverse Events, version 4.0). We found that a lung dose around V30 was associated with radiation pneumonitis (OR, 1.12; 95% CI, 1.01-1.24; $P = .04$); however, lung V8 was not associated with radiation pneumonitis (OR, 1.00; 95% CI, 0.97-1.04; $P = .81$).

sIPTW analysis

The optimal cutoff points for the heart V50 and lung V8 were 3.49% and 42.06%, respectively. A lower heart V50 was associated with better long-term survival ($P < .01$) (Fig. E1A), and a lower lung V8 was associated with better early survival ($P = .016$) (Fig. E2A). However, patient characteristics were not balanced between the high and low heart V50 groups in the long-term survival cohort. Therefore, we performed sIPTW to balance the characteristics between the 2 groups (Table E2). After sIPTW, the low-dose group had better long-term survival ($P < .01$) (Fig. E1B), which was consistent with the results of the multivariate analysis. Patient characteristics were balanced between the high and low lung V8 groups for early survival after sIPTW (Table 3). A low lung V8 was associated with better early survival ($P = .004$) (Fig. E2B), consistent with the results of the multivariate analysis.

Sensitivity analysis

When using a landmark time of 24 months, the results were consistent with those using a landmark time of 36 months. The heart V50 was significantly correlated with long-term survival but not with early survival, and the lung V8 was significantly correlated with early survival but not with long-term survival (Fig. E3). Similar results were observed using a landmark time of 48 months (Fig. E4).

Discussion

For patients with NSCLC undergoing PORT, a higher heart dose decreased long-term OS, whereas a higher lung dose decreased early OS. This partially explains the lack of efficacy of PORT in prolonging OS; therefore, the

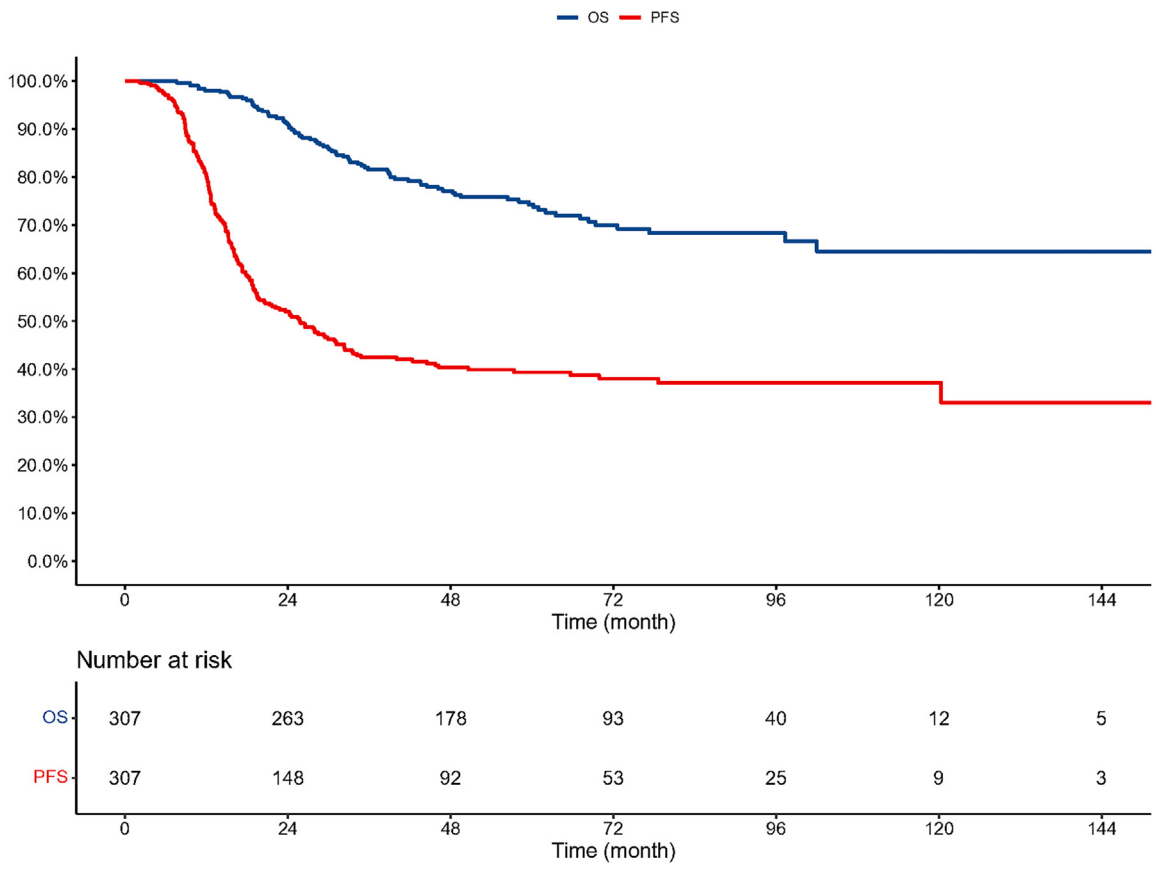

Figure 1 Kaplan-Meier curves of overall survival and progression-free survival.

cardiopulmonary toxic effects of PORT should not be neglected.

Heart dose and survival

We found that the heart dose was related to long-term survival but not OS or early survival. The heart dose has been confirmed to increase the risk of coronary heart disease (CHD) in patients undergoing radiation therapy for lymphoma[17] and breast cancer.[18] The increase in risk is proportional to the MHD, begins several years after radiation therapy, and continues for more than 20 years. In addition, subclinical heart radiation injury may worsen over time and diminish long-term survival. Because the secondary analysis of RTOG 0617 revealed that the heart V5 and V30 were associated with OS in patients with locally advanced NSCLC undergoing definitive chemoradiation therapy,[6] studies have investigated this issue and have drawn opposing conclusions. A systemic review including 22 studies found that for OS, associations with the heart V5 were significant in multivariate analysis in only 1 of 11 studies and the heart V30 in only 2 of 12 studies. The MHD was not significant in any of the 8 studies.[19] The reasons for these inconsistent results included varying heart contours, inconsistencies in the cardiac dosimetric parameters reported in different studies, and heterogeneous treatments. In addition, the latent period of radiation heart injury could have contributed to the mixed results of previous studies.

We found that the heart dose was related to long-term survival in patients with lung cancer undergoing PORT, whereas previous studies on definitive radiation therapy showed mixed results. Patients undergoing PORT had a relatively stable target volume, mainly containing the superior mediastinum, and fewer comorbidities (such as CHD) than did those undergoing definitive radiation therapy, which may explain the mixed results. In patients with breast cancer[18] or Hodgkin lymphoma[17] receiving radiation therapy, a linear relationship between MHD and cardiac events has been identified. However, there is no agreement on the relation between MHD and cardiac events in patients with lung cancer.[7] This may result from the dose distribution variability of the heart for patients with lung cancer, which contrasts with the uniform radiation volume of the heart in tangential radiation for breast cancer or mediastinal nodal radiation for lymphoma.[20] The target volume of PORT is relatively universal in the superior mediastinum, and the dose distribution in the heart is relatively stable compared with that in definitive radiation therapy. A higher radiation dose to the heart base was associated with poorer survival in patients with

Table 2 Univariate analysis of heart and lung dose parameters

	Whole survival		Long-term survival		Early survival	
Characteristic	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
MHD	1.03 (1-1.06)	.093	1.07 (1.01-1.13)	.017	1.01 (0.97-1.05)	.657
Heart Dmax	1.02 (1-1.04)	.093	1.07 (1.01-1.12)	.016	1 (0.98-1.02)	.781
Heart EUD	1.02 (1-1.05)	.081	1.08 (1.01-1.15)	.015	1 (0.98-1.03)	.751
Heart V5	1 (1-1.01)	.327	1.01 (1-1.03)	.107	1 (0.99-1.01)	.945
Heart V10	1.01 (1-1.02)	.142	1.02 (1-1.04)	.045	1 (0.99-1.02)	.676
Heart V20	1.01 (1-1.03)	.103	1.03 (1.01-1.06)	.017	1 (0.99-1.02)	.687
Heart V30	1.01 (1-1.03)	.134	1.05 (1.01-1.08)	.005	1 (0.98-1.02)	.998
Heart V40	1.03 (1-1.06)	.048	1.08 (1.03-1.13)	.001	1.01 (0.97-1.04)	.763
Heart V50	1.07 (1.02-1.12)	.008	1.13 (1.04-1.23)	.003	1.04 (0.98-1.11)	.198
Heart V60	1.17 (1.07-1.27)	.001	1.13 (0.92-1.39)	.259	1.18 (1.07-1.3)	.001
MLD	1.1 (1-1.21)	.056	1.08 (0.93-1.25)	.336	1.11 (0.98-1.25)	.094
Lung Dmax	1.06 (1.02-1.1)	.002	1.05 (1-1.12)	.067	1.06 (1.01-1.11)	.009
Lung EUD	1.06 (1.01-1.11)	.025	1.06 (0.98-1.15)	.119	1.05 (0.99-1.12)	.107
Lung V5	1.02 (1-1.03)	.086	1.01 (0.98-1.04)	.713	1.02 (1-1.04)	.06
Lung V8	1.03 (1.01-1.06)	.005	1.02 (0.98-1.06)	.261	1.04 (1.01-1.07)	.007
Lung V10	1.04 (1.01-1.07)	.008	1.03 (0.98-1.08)	.232	1.04 (1.01-1.08)	.016
Lung V20	1.05 (0.99-1.11)	.085	1.06 (0.97-1.16)	.213	1.04 (0.97-1.12)	.226
Lung V30	1.05 (0.98-1.12)	.159	1.05 (0.95-1.17)	.349	1.05 (0.96-1.13)	.291
Lung V40	1.02 (0.95-1.1)	.562	1.03 (0.92-1.16)	.606	1.02 (0.92-1.12)	.742
Lung V50	1.05 (0.95-1.16)	.354	1.04 (0.89-1.21)	.653	1.06 (0.93-1.2)	.403
Lung V60	1.14 (0.99-1.31)	.062	1.03 (0.8-1.34)	.805	1.21 (1.03-1.42)	.023

Abbreviations: Dmax = maximum dose; EUD = equivalent uniform dose; MHD = mean heart dose; MLD = mean lung dose; V*x* = volume percentage of the organ receiving more than a specific dose in gray.

lung cancer undergoing definitive radiation therapy.[21,22] The target volume of PORT mainly contains the superior mediastinum, which is near the heart base; therefore, heart V50 is mainly located at the heart base (Fig. E5). We found that heart V50 was associated with OS in patients undergoing PORT, consistent with previous studies.[8,15] Previous studies have shown that the effect of radiation therapy on the heart is more prominent in patients without CHD. One study of 748 patients with locally advanced NSCLC undergoing definitive radiation therapy or PORT found that a higher MHD was associated with a significantly increased risk of all-cause mortality in patients without CHD but not in patients with CHD.[9] Another study of 701 patients found that the left anterior descending coronary artery dose was an independent estimator of the probability of all-cause mortality in patients without CHD but not in patients with CHD.[23] Patients undergoing PORT had fewer cardiac comorbidities to tolerate surgery than did those undergoing definitive radiation therapy; therefore, it would be easier to observe the increased cardiac risk without preexisting CHD.

Two studies have investigated the relationship between the heart dose and OS in patients with pN2 NSCLC undergoing PORT. One study concluded that heart doses were not associated with OS (heart V50: HR, 1.01; $P = .868$); however, the small sample size (43 cases) limited the statistical power.[14] The other study included 284 cases and found a strong correlation between increasing heart dose and OS; however, this study included 55 patients (19.4%) with R1 resection, nonuniform stages (I-III), and a heterogeneous radiation dose (45-70 Gy).[15] Patients who underwent R1 resection had poor survival and tended to receive a high administrative dose, suggesting R1 resection may confound the relationship between the heart dose and OS. We included a homogeneous cohort with pN2 disease, R0 resection, and a PORT dose of 50 Gy, contoured the heart according to a published atlas, and reported detailed dose parameters to minimize these confounding factors. Our results showed that the heart dose was not related to whole or early survival but was related to long-term survival.

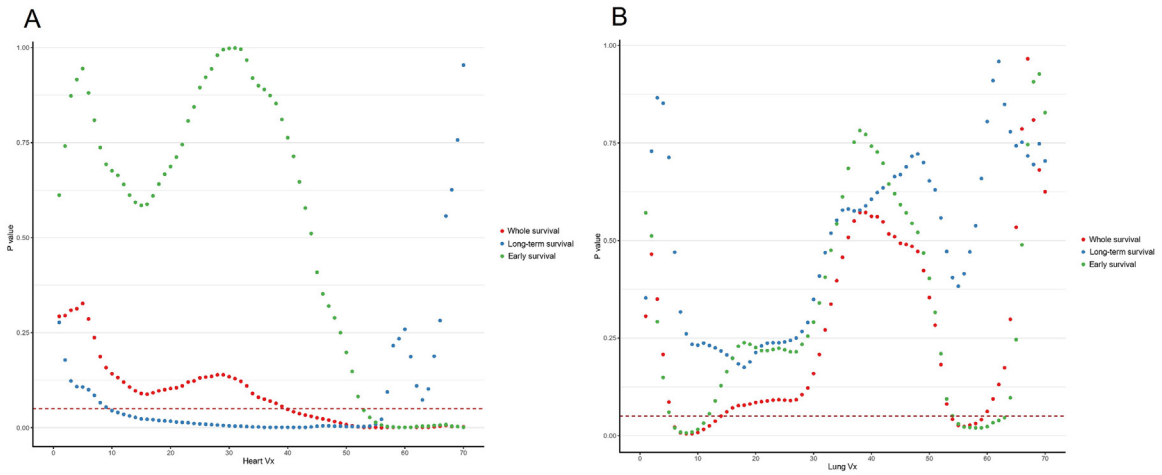

Figure 2 *P*-value distribution of (A) heart V*x* and (B) lung V*x* in the univariate analysis. The red dashed line indicates a *P* value of .05. *Abbreviation:* V*x* = volume percentage of the organ receiving more than a specific dose in gray.

Lung dose and survival

We found that a higher lung dose diminished early survival but was unrelated to long-term survival. Radiation pneumonia peaks 1 to 3 months after thoracic radiation therapy, whereas radiation lung fibrosis develops 4 to 12 months after radiation therapy and continues for several years. Subclinical lung injury mainly accumulates during the early term after radiation therapy. A correlation between pneumonitis and the lung volume exposed to low doses of radiation has been confirmed in previous studies,[24,25] and the most significant correlations were for lung V5 to V13.[26] The lung volume exposed to low doses (V5-V13) was associated with early survival in our study.

Table 3 Multivariate Cox regression analysis

	Whole survival		Long-term survival		Early survival	
	HR	*P* value	HR	*P* value	HR	*P* value
Heart V50	1.02 (0.96-1.08)	.557	1.14 (1.03-1.27)	.015	0.97 (0.90-1.05)	.411
Lung V8	1.02 (1.00-1.05)	.115	1.00 (0.96-1.05)	.851	1.03 (1.00-1.06)	.069
Sex						
Male	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-
Female	0.48 (0.26-0.88)	.017	0.57 (0.23-1.45)	.239	0.47 (0.21-1.01)	.054
Smoking status						
Former or never	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-
Current	1.06 (0.61-1.84)	.832	0.78 (0.29-2.11)	.626	1.23 (0.62-2.43)	.553
ECOG PS						
0	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-
1	1.87 (0.58-6.01)	.293	0.92 (0.21-4.02)	.912	3.47 (0.47-25.48)	.221
Histology						
Non-SCC	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-
SCC	0.77 (0.42-1.41)	.392	0.72 (0.23-2.25)	.567	0.81 (0.39-1.66)	.562
Tumor size	1.17 (1.06-1.30)	.003	0.99 (0.80-1.24)	.951	1.25 (1.11-1.41)	<.001
Positive lymph node ratio	3.04 (1.11-8.34)	.031	7.47 (1.53-36.42)	.013	1.64 (0.44-6.17)	.461

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; SCC = squamous cell carcinoma; V*x* = volume percentage of the organ receiving more than a specific dose in gray.

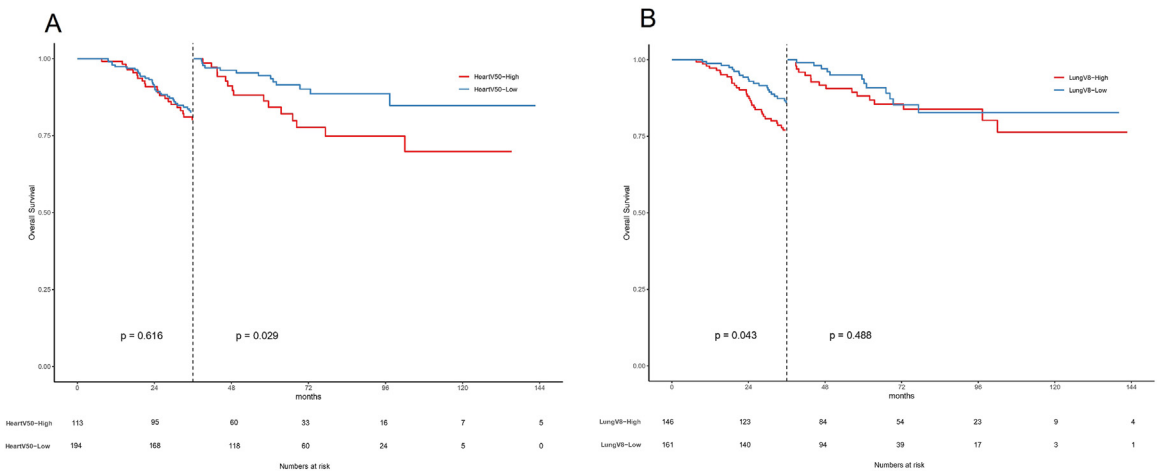

Figure 3 Landmark analysis of (A) heart V50 and (B) lung V8 at 36 months. *Abbreviation:* V*x* = volume percentage of the organ receiving more than a specific dose in gray.

Few studies have investigated the relationship between lung dose and OS, and RTOG 0617 did not find that the lung V5 was related to OS in definitive thoracic radiation therapy.[6] One study investigated the association between heart and lung doses and early survival up to 24 months in patients with locally advanced NSCLC undergoing chemoradiation therapy and found that the heart dose was not associated with early survival outcomes when the lung dose was taken into account, whereas the mean lung dose was associated with early survival.[12] In addition, one study of 216 patients with esophageal cancer undergoing curative radiation therapy found that lung dosimetric factors (lung V45) were more critical for OS than were heart dosimetric factors. One study analyzed 178 patients with NSCLC undergoing PORT and found that the lung dose significantly affected OS.[27] Our results showed that lung dose was associated with early survival but not long-term survival.

Our study has some limitations. First, our study did not include heart and lung events owing to their low incidence and the follow-up strategy. Subclinical heart and lung radiation injuries could affect survival but could not be recorded in the follow-up strategy in this study. Second, bias could not be avoided because this was a retrospective study. We performed multivariate analysis and sIPTW to minimize known bias and a sensitivity analysis to decrease biases. Finally, although we found that the heart dose was associated with long-term survival, we did not investigate the association between the heart substructure dose and survival. Whether the heart substructure dose is more associated with survival is still debated.[18,28] We aim to delineate the heart substructures in the future to better resolve this question.

Conclusion

For patients with pN2 NSCLC undergoing PORT, a higher heart dose decreased long-term OS, whereas a higher lung dose decreased early OS. Individualized PORT strategies should be further investigated to balance locoregional tumor control and cardiopulmonary toxic effects.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101213.

References

1. Levy A, Mercier O, Le Péchoux C. Indications and parameters around postoperative radiation therapy for lung cancer. *J Clin Oncol*. 2022;40:556-566.
2. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol*. 2006;24:2998-3006.
3. Robinson CG, Patel AP, Bradley JD, et al. Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: A review of the National Cancer Data Base. *J Clin Oncol*. 2015;33:870-876.
4. Hui Z, Men Y, Hu C, et al. Effect of postoperative radiotherapy for patients with pIIIA-N2 non-small cell lung cancer after complete resection and adjuvant chemotherapy: The phase 3 PORT-C randomized clinical trial. *JAMA Oncol*. 2021;7:1178-1185.
5. Le Pechoux C, Pourel N, Barlesi F, et al. Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): An open-label, randomised, phase 3 trial. *Lancet Oncol*. 2022;23:104-114.
6. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): A randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015;16:187-199.

7. Banfill K, Giuliani M, Aznar M, et al. Cardiac toxicity of thoracic radiotherapy: Existing evidence and future directions. *J Thorac Oncol*. 2021;16:216-227.
8. Speirs CK, DeWees TA, Rehman S, et al. Heart dose is an independent dosimetric predictor of overall survival in locally advanced non-small cell lung cancer. *J Thorac Oncol*. 2017;12:293-301.
9. 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;73:2976-2987.
10. 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*. 2017;35:1395-1402.
11. Guberina M, Eberhardt W, Stuschke M, et al. Heart dose exposure as prognostic marker after radiotherapy for resectable stage IIIA/B non-small-cell lung cancer: Secondary analysis of a randomized trial. *Ann Oncol*. 2017;28:1084-1089.
12. Tucker SL, Liu A, Gomez D, et al. Impact of heart and lung dose on early survival in patients with non-small cell lung cancer treated with chemoradiation. *Radiother Oncol*. 2016;119:495-500.
13. Beukema JC, Kawaguchi Y, Sijtsema NM, et al. Can we safely reduce the radiation dose to the heart while compromising the dose to the lungs in oesophageal cancer patients? *Radiother Oncol*. 2020;149:222-227.
14. Lee CC, Chua GWY, Zheng H, et al. Are heart doses associated with survival in patients with non-small cell lung cancer who received post-operative thoracic radiotherapy? A national population-based study. *Medicine (Baltimore)*. 2019;98:e17020.
15. Shepherd AF, Yu AF, Iocolano M, et al. Increasing heart dose reduces overall survival in patients undergoing postoperative radiation therapy for NSCLC. *JTO Clin Res Rep*. 2021;2: 100209.
16. Feng M, Moran JM, Koelling T, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. *Int J Radiat Oncol Biol Phys*. 2011;79:10-18.
17. van Nimwegen FA, Schaapveld M, Cutter DJ, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. *J Clin Oncol*. 2016;34:235-243.
18. 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;368:987-998.
19. Zhang TW, Snir J, Boldt RG, et al. Is the importance of heart dose overstated in the treatment of non-small cell lung cancer? A systematic review of the literature. *Int J Radiat Oncol Biol Phys*. 2019;104:582-589.
20. Bergom C, Bradley JA, Ng AK, et al. Past, present, and future of radiation-induced cardiotoxicity: Refinements in targeting, surveillance, and risk stratification. *JACC CardioOncol*. 2021;3: 343-359.
21. McWilliam A, Kennedy J, Hodgson C, Vasquez Osorio E, Faivre-Finn C, van Herk M. Radiation dose to heart base linked with poorer survival in lung cancer patients. *Eur J Cancer*. 2017;85:106-113.
22. Craddock M, Nestle U, Koenig J, et al. Cardiac function modifies the impact of heart base dose on survival: A voxel-wise analysis of lung cancer patients from the PET-Plan trial. *J Thorac Oncol*. 2023;18:57-66.
23. 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;7:206-219.
24. Jo IY, Kay CS, Kim JY, et al. Significance of low-dose radiation distribution in development of radiation pneumonitis after helical-tomotherapy-based hypofractionated radiotherapy for pulmonary metastases. *J Radiat Res*. 2014;55:105-112.
25. Tanabe S, Myojin M, Shimizu S, et al. Dose-volume analysis for respiratory toxicity in intrathoracic esophageal cancer patients treated with definitive chemoradiotherapy using extended fields. *J Radiat Res*. 2013;54:1085-1094.
26. Yorke ED, Jackson A, Rosenzweig KE, Braban L, Leibel SA, Ling CC. Correlation of dosimetric factors and radiation pneumonitis for non-small-cell lung cancer patients in a recently completed dose escalation study. *Int J Radiat Oncol Biol Phys*. 2005;63:672-682.
27. Heo J, Noh OK, Kim HI, et al. Lung dose and the potential risk of death in postoperative radiation therapy for non-small cell lung cancer: A study using the method of stratified grouping. *Radiother Oncol*. 2018;129:61-67.
28. Atkins KM, Bitterman DS, Chaunzwa TL, et al. Mean heart dose is an inadequate surrogate for left anterior descending coronary artery dose and the risk of major adverse cardiac events in lung cancer radiation therapy. *Int J Radiat Oncol Biol Phys*. 2021;110:1473-1479.