
# Higher lung and heart doses decrease early and long-term survival respectively in patients with non-small cell lung cancer undergoing postoperative radiotherapy

Zeliang Ma MD , Yunsong Liu MD , Yongxing Bao MD , Meng Yuan MD , Xu Yang MD , Yu Men MD , Jianyang Wang MD , Lei Deng MD , Yirui Zhai MD , Nan Bi MD , Luhua Wang MD , Zhouguang Hui MD

PII: S2452-1094(23)00042-8
DOI: https://doi.org/10.1016/j.adro.2023.101213
Reference: ADRO 101213

To appear in: *Advances in Radiation Oncology*

Received date: 13 October 2022
Accepted date: 25 February 2023

Please cite this article as: Zeliang Ma MD , Yunsong Liu MD , Yongxing Bao MD , Meng Yuan MD , Xu Yang MD , Yu Men MD , Jianyang Wang MD , Lei Deng MD , Yirui Zhai MD , Nan Bi MD , Luhua Wang MD , Zhouguang Hui MD , Higher lung and heart doses decrease early and long-term survival respectively in patients with non-small cell lung cancer undergoing postoperative radiotherapy, *Advances in Radiation Oncology* (2023), doi: https://doi.org/10.1016/j.adro.2023.101213

# Higher lung and heart doses decrease early and long-term survival respectively in patients with non-small cell lung cancer undergoing postoperative radiotherapy

**[Short Running Title]**

Heart and lung doses in NSCLC undergoing PORT

**[Author Names]**

*Zeliang Ma, MD1; Yunsong Liu, MD1; Yongxing Bao, MD1; Meng Yuan, MD1; Xu Yang, MD2; Yu Men, MD3, Jianyang Wang, MD1; Lei Deng, MD1; Yirui Zhai, MD1; Nan Bi, MD1; Luhua Wang, MD1; Zhouguang Hui, MD1,3*

**[Author Institutions]**

*1 Department of Radiation Oncology, 2 Department of Medical Oncology; 3 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*

**[Corresponding Author Name & Email Address]**

Zhouguang Hui, M.D. Professor, Department of Radiation Oncology, Director, Department of VIP Medical Services, National Cancer Center/ National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College.
Panjiayuan Nanli #17, Chaoyang District, Beijing (100021), China
Phone Number: +86-10-87787656
Email address: drhuizg@163.com

**[Author Responsible for Statistical Analysis Name & Email Address]**

Zeliang Ma, mzliang@mail2.sysu.edu.cn

**[Conflict of Interest Statement for All Authors]**

*Conflict of Interest: None*

**[Funding Statement]**

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

**[Data Availability Statement for this Work]**

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

**[Ethics approval and consent to participate]**

*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 National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academic of Medical Sciences and Peking Union Medical College. The requirement for informed consent was waived owing to the retrospective nature of the research.*



**Abstract**

**Purpose:** Cardiopulmonary toxicity may reduce the efficacy of postoperative radiotherapy (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 impact of heart and lung doses on OS in patients with NSCLC undergoing PORT.

**Methods:** 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 significantly correlated with long-term survival (HR = 1.14, P = 0.015) but not early survival (HR = 0.97, P = 0.41) or whole survival (HR = 1.02, P = 0.58). Lung doses marginally significantly

correlated with early survival (HR = 1.03, P = 0.07) but not long-term survival (HR = 1.00, P = 0.85) or whole survival (HR = 1.02, P = 0.12). 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.

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

**Keywords**

Non-small cell lung cancer, cardiopulmonary toxicity, postoperative radiotherapy, early survival, long-term survival

**Abbreviations List:**

CHD: coronary heart disease

CI: confidence interval

CT: computed tomography

ECOG PS: Eastern Cooperative Oncology Group performance status

HR: hazard ratio

IQR: interquartile range

MHD: mean heart dose

MLD: mean lung dose

NSCLC: non-small cell lung cancer

OS: overall survival

PFS: progression-free survival

PLNR: positive lymph node ratio

PORT: postoperative radiotherapy

RCT: randomized controlled trial

sIPTW: stabilized inverse probability of treatment weighting

**Introduction**

Postoperative radiotherapy (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, two recent randomized controlled trials (RCTs) showed that PORT does not improve progression-free survival (PFS) or overall survival (OS) in these patients. [4,5] Cardiopulmonary toxicity may diminish the benefit of PORT. Moreover, due 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 impact on survival.

The RTOG 0617 [6] results raise the question of whether the heart dose in definitive radiotherapy affects OS. [7] Many studies have shown that the radiotherapy 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, only two 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 non-uniform stages (I-III), and that 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 impact 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 1-3 months and 6-12 months after radiotherapy, respectively. Therefore, we hypothesized that the lung dose affects early survival, whereas the heart dose affects long-term survival. We investigated the impact 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 III XXXX RCT [4] and a retrospective review of the XXXX database in our institution. Patients diagnosed with pN2 NSCLC between January 2006 and June 2019 were analyzed. The eligibility criteria were as follows: age 18–70 years, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, complete resection (R0) and systemic lymph node dissection, and four 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 XXXX. 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 four cycles of platinum-based doublet adjuvant chemotherapy and PORT.

Experienced radiotherapists 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 Gy).

All patients received intensity-modulated radiation therapy or three-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, USA) with iodine-based intravenous contrast. Treatment plans were designed using the Pinnacle treatment planning system (v9.0, Philips, Fitchburg, WI, USA). Individual radiotherapy dose distributions were manually reviewed.

**Follow-up**

Patients were followed up every 3 months for the first 2 years, every 6 months for 2–5 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, radiological examination, and pathology reports.

**Statistics**

Continuous variables are presented as mean ± standard deviation for normally distributed data and median ± interquartile range (IQR) for non-normally 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 $\chi 2$ tests or Fisher's 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 < 0.1 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 over 36 months were censored at 36 months; for long-term survival (>36 months), only patients who survived over 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 two 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 $p < 0.05$. 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 (MLD) 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-not reached). The 3-year OS was 81.6%, and the 3-year PFS was 42.4%. PFS decreased dramatically within the first 36 months and tended to flatten after 36 months (Figure 1); therefore, 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 (PLNR) had P-values < 0.1 in the univariate analysis or were clinically important and were included in the multivariate analysis (Supplement Table 1). We performed univariate COX analysis for 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), while it was more associated with sex (correlation coefficient = 0.47) because males usually have bigger bodies than females. Since treatment target volume is delineated uniformly as described in the methods part, 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, figure 2A). 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 = 0.015) but not whole survival (HR = 1.02, P = 0.58) (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 PLNR 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 (Figure 3A). As for cardiac events, among the 127 patients in the prospective cohort, only 1 (0.8%) patient developed a cardiac event (coronary heart disease), 109 (85.8%) patients did not develop cardiac events during follow up, and it was unknown for 17 (13.4%) patients. The association between heart V50 and cardiac events cannot be evaluated due 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 long-term survival (Table 2, figure 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 = 0.07) but was not correlated with long-term survival (HR = 1.00, P = 0.85) or whole survival (HR = 1.02, P = 0.12) (Table 3). Landmark analysis revealed that lung V8 was significantly correlated with early survival but not long-term survival (Figure 3B). The incidence of radiation pneumonitis was 13.7%. We performed univariate logistic regression between lung dose and any grade radiation pneumonitis (CTCAE v4.0). We found that lung dose around V30 was associated with radiation pneumonitis (OR=1.12, 1.01–1.24, P=0.04); however, lung V8 was not associated with radiation pneumonitis (OR=1.00, 0.97–1.04, P=0.81).

**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 < 0.01) (Supplement Figure 1a), and a lower lung V8 was associated with better early survival (P = 0.016) (Supplement Figure 2a). 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 two groups (Supplement Table 2). After sIPTW, the low-dose group had better long-term survival (P < 0.01) (Supplement Figure 1b), 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 (Supplement Table 3). A low lung V8 was associated with better early survival (P = 0.004) (Supplement Figure 2b), 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 early survival, and the lung V8 was significantly correlated with early survival but not long-term survival (Supplement Figure 3). Similar results were observed using a landmark time of 48 months (Supplement Figure 4).

## 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 cardiopulmonary toxicities 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 radiotherapy for lymphoma [17] and breast cancer. [18] The increase in risk is proportional to the MHD, begins several years after radiotherapy, and continues for over 20 years. In addition, subclinical heart radiation injury may worsen over time and diminish long-term survival. Since the second analysis of RTOG 0617 revealed that the heart V5 and V30 were associated with OS in patients with locally advanced NSCLC undergoing definitive chemoradiotherapy, [6] studies have investigated this issue and drawn opposing conclusions. A systemic review including 22 studies found that, for OS, the heart V5 was significant in multivariate analysis in only 1 of 11 studies and the heart V30 in only 2 of 12 studies. MHD was not significant in any of the eight 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 radiotherapy showed mixed results. Patients undergoing PORT had a relatively stable target volume mainly containing the superior mediastinum and fewer comorbidities than definitive radiotherapy, such as CHD, which may explain the mixed results. In patients with breast cancer [18] or Hodgkin lymphoma [17] receiving radiotherapy, 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 radiotherapy. Higher radiation dose to the heart base was associated with poorer survival in lung cancer patients undergoing definitive radiotherapy. [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 (Supplement Figure 5). 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 radiotherapy on the heart is more prominent in patients without CHD. One study of 748 patients with locally advanced NSCLC undergoing definitive radiotherapy 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 those undergoing definitive radiotherapy; 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 = 0.868); however, the small sample size (43 cases) limited the statistical power. [14] The other study of 284 cases found a strong correlation between increasing heart dose and OS; however, this study included 55 (19.4%) patients with R1 resection, non-uniform 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 homogenous 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 long-term survival.

Lung dose and survival

We found that a higher lung dose diminished early survival but was unrelated to long-term survival. Radiation pneumonia peaks 1-3 months after thoracic radiotherapy, whereas radiation lung fibrosis develops 4-12 months after radiotherapy and continues for several years. Subclinical lung injury mainly accumulates during the early term after radiotherapy. A

correlation between the lung volume exposed to low doses of radiation and pneumonitis has been confirmed in previous studies, [24,25] and the most significant correlations were for the lung V5–V13. [26] The lung volume exposed to low doses (V5-V13) was associated with early survival in our study.

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 radiotherapy. [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 chemoradiotherapy and found that the heart dose was not associated with early survival outcomes when the lung dose was taken into account, whereas the MLD was associated with early survival. [12] In addition, one study of 216 esophageal cancer patients undergoing curative radiotherapy found that lung dosimetric factors (lung V45) were more critical for OS than heart dosimetric factors. One study analyzed 178 patients with NSCLC undergoing PORT and found that the lung dose significantly impacted 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 due to their low incidence and the follow-up strategy. Subclinical heart and lung radiation injuries could impact 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 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 resolve this question better.

**Conclusions**

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 toxicities.

# References


1. Levy A, Mercier O, Le Péchoux C. Indications and Parameters Around Postoperative Radiation Therapy for Lung Cancer. *J Clin Oncol*. 2022;40(6):556-566. doi:10.1200/JCO.21.01774.
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(19):2998-3006. doi:10.1200/JCO.2005.04.6110.
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(8):870-876. doi:10.1200/JCO.2014.58.5380.
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(8):1178-1185. doi:10.1001/jamaoncol.2021.1910.
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. *The Lancet Oncology*. 2022;23(1):104-114. doi:10.1016/S1470-2045(21)00606-9.

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. *The Lancet Oncology*. 2015;16(2):187-199. doi:10.1016/S1470-2045(14)71207-0.
7. Banfill K, Giuliani M, Aznar M, et al. Cardiac Toxicity of Thoracic Radiotherapy: Existing Evidence and Future Directions. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2021;16(2):216-227. doi:10.1016/j.jtho.2020.11.002.
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. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2017;12(2):293-301. doi:10.1016/j.jtho.2016.09.134.
9. Atkins KM, Rawal B, Chaunzwa TL, et al. Cardiac Radiation Dose, Cardiac Disease, and Mortality in Patients With Lung Cancer. *Journal of the American College of Cardiology*. 2019;73(23):2976-2987. doi:10.1016/j.jacc.2019.03.500.
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. *Journal of Clinical Oncology*. 2017;35(13):1395-1402. doi:10.1200/JCO.2016.71.6142.

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(5):1084-1089. doi:10.1093/annonc/mdx069.
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(3):495-500. doi:10.1016/j.radonc.2016.04.025.
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. doi:10.1016/j.radonc.2020.05.033.
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(35):e17020. doi:10.1097/MD.0000000000017020.
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(8):100209. doi:10.1016/j.jtocrr.2021.100209.
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(1):10-18. doi:10.1016/j.ijrobp.2009.10.058.

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(3):235-243. doi:10.1200/JCO.2015.63.4444.

18. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *New England Journal of Medicine*. 2013;368(11):987-998. doi:10.1056/NEJMoa1209825.

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(3):582-589. doi:10.1016/j.ijrobp.2018.12.044.

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(3):343-359. doi:10.1016/j.jaccao.2021.06.007.

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. *European Journal of Cancer*. 2017;85:106-113. doi:10.1016/j.ejca.2017.07.053.

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. *Journal of Thoracic Oncology*. 2022. doi:10.1016/j.jtho.2022.09.004.

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(2):206-219. doi:10.1001/jamaoncol.2020.6332.

24. Jo I-Y, Kay C-S, Kim J-Y, 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(1):105-112. doi:10.1093/jrr/rrt080.

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(6):1085-1094. doi:10.1093/jrr/rrt047.

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. *International Journal of Radiation Oncology, Biology, Physics*. 2005;63(3):672-682. doi:10.1016/j.ijrobp.2005.03.026.

27. Heo J, Noh OK, Kim H-I, 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(1):61-67. doi:10.1016/j.radonc.2018.03.018.

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(5):1473-1479. doi:10.1016/j.ijrobp.2021.03.005.

**Figure Captions**

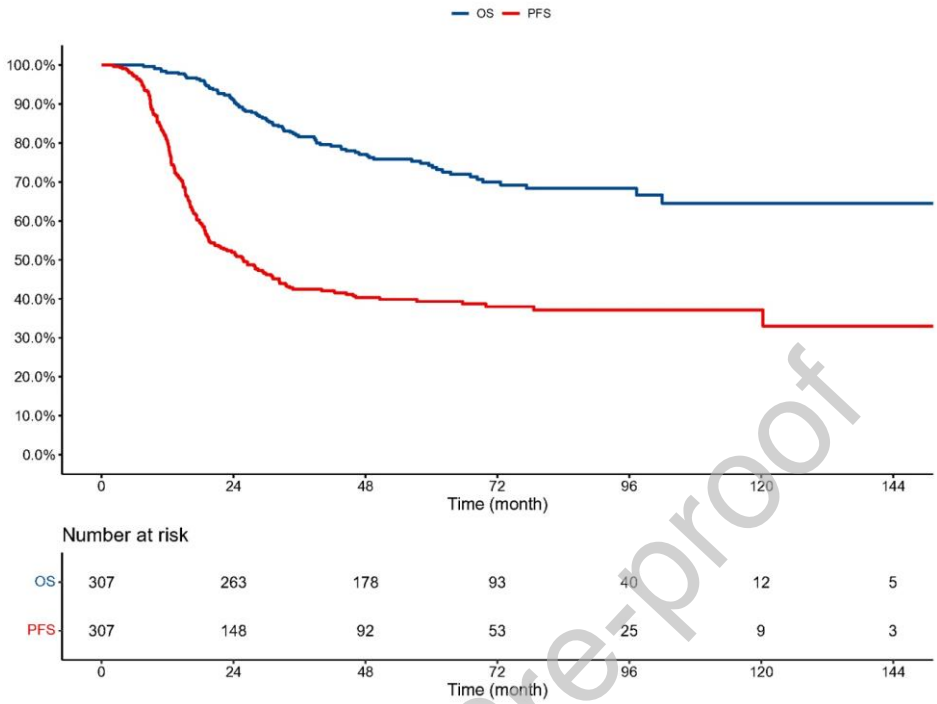


Figure 1. Kaplan-Meier Curves of overall survival and progression-free survival.

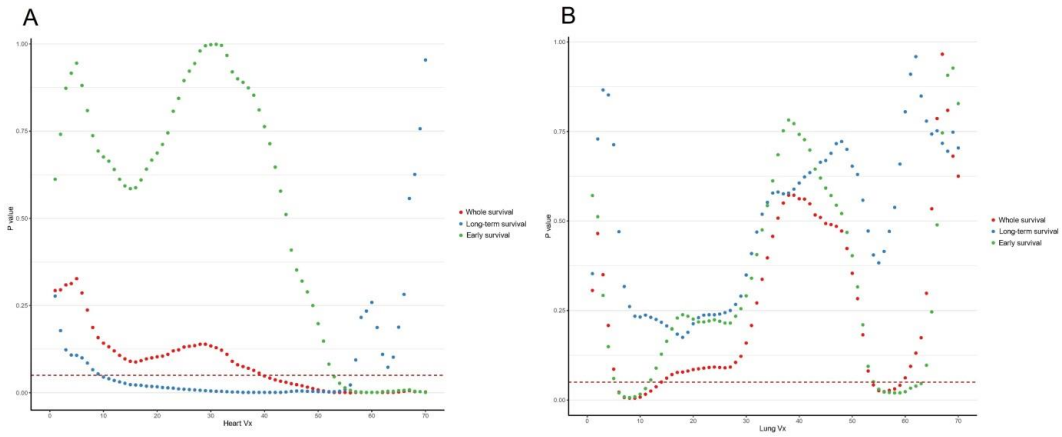


Figure 2. P-value distribution of heart Vx (Figure 2A) and lung Vx (Figure 2B) in the univariate analysis. The red dashed line referred to a P-value of 0.05.

Figure 3. Landmark analysis of heart V50 (Figure 3A) and lung V8 (Figure 3B) at 36 months.

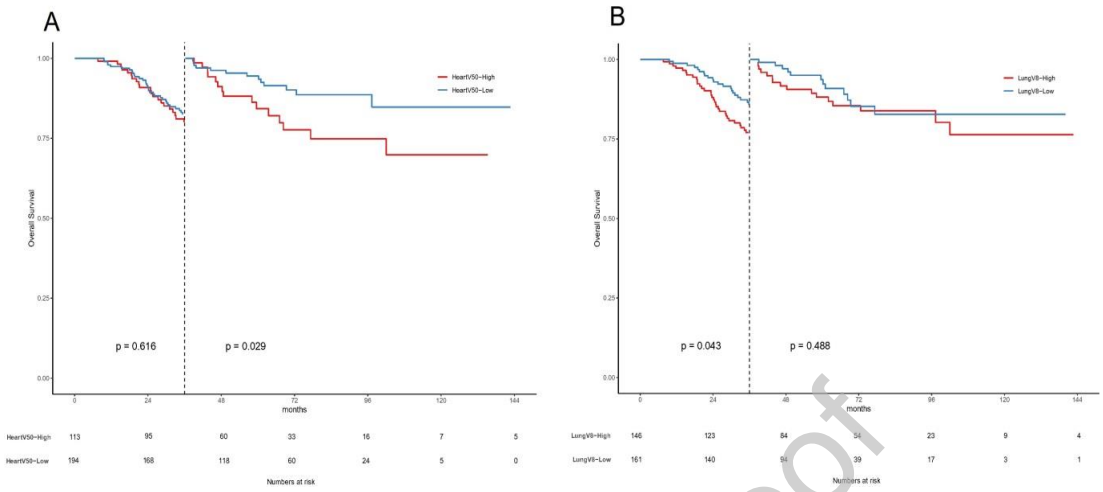

Table 1. Patient characteristics

| Characteristics | | 307 |
|---|---|---|
| Sex (%) | Male | 183 (59.6) |
| | Female | 124 (40.4) |
| Age (median [IQR]) | | 56.00 [49.00, 62.00] |
| SmokingStatus (%) | Former or never | 206 (67.1) |
| | Current | 101 (32.9) |
| ECOGPS (%) | 0 | 23 (7.5) |
| | 1 | 284 (92.5) |
| TumorLocation (%) | 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 node (median [IQR]) | | 22.00 [16.00, 28.00] |
| Positive lymph node (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 performances status; SCC, squamous cell carcinoma; MHD, mean heart dose; MLD, mean lung dose; PTV: planning target volume; IQR, interquartile range. 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.

Table 2. Univariate analysis of heart and lung dose parameters

| | Whole survival | | Long-term survival | | Early survival | |
|---|---|---|---|---|---|---|
| Characteristics | HR (95%CI) | P | HR (95%CI) | P | HR (95%CI) | P |
| MHD | 1.03 (1-1.06) | 0.093 | 1.07 (1.01-1.13) | 0.017 | 1.01 (0.97-1.05) | 0.657 |
| HeartDmax | 1.02 (1-1.04) | 0.093 | 1.07 (1.01-1.12) | 0.016 | 1 (0.98-1.02) | 0.781 |
| | | | | | | |
| HeartEUD | 1.02 (1-1.05) | 0.081 | 1.08 (1.01-1.15) | 0.015 | 1 (0.98-1.03) | 0.751 |
| HeartV5 | 1 (1-1.01) | 0.327 | 1.01 (1-1.03) | 0.107 | 1 (0.99-1.01) | 0.945 |
| HeartV10 | 1.01 (1-1.02) | 0.142 | 1.02 (1-1.04) | 0.045 | 1 (0.99-1.02) | 0.676 |
| HeartV20 | 1.01 (1-1.03) | 0.103 | 1.03 (1.01-1.06) | 0.017 | 1 (0.99-1.02) | 0.687 |
| HeartV30 | 1.01 (1-1.03) | 0.134 | 1.05 (1.01-1.08) | 0.005 | 1 (0.98-1.02) | 0.998 |
| HeartV40 | 1.03 (1-1.06) | 0.048 | 1.08 (1.03-1.13) | 0.001 | 1.01 (0.97-1.04) | 0.763 |
| HeartV50 | 1.07 (1.02-1.12) | 0.008 | 1.13 (1.04-1.23) | 0.003 | 1.04 (0.98-1.11) | 0.198 |
| HeartV60 | 1.17 (1.07-1.27) | 0.001 | 1.13 (0.92-1.39) | 0.259 | 1.18 (1.07-1.3) | 0.001 |
| MLD | 1.1 (1-1.21) | 0.056 | 1.08 (0.93-1.25) | 0.336 | 1.11 (0.98-1.25) | 0.094 |
| LungDmax | 1.06 (1.02-1.1) | 0.002 | 1.05 (1-1.12) | 0.067 | 1.06 (1.01-1.11) | 0.009 |
| LungEUD | 1.06 (1.01-1.11) | 0.025 | 1.06 (0.98-1.15) | 0.119 | 1.05 (0.99-1.12) | 0.107 |
| LungV5 | 1.02 (1-1.03) | 0.086 | 1.01 (0.98-1.04) | 0.713 | 1.02 (1-1.04) | 0.06 |
| LungV8 | 1.03 (1.01-1.06) | 0.005 | 1.02 (0.98-1.06) | 0.261 | 1.04 (1.01-1.07) | 0.007 |
| LungV10 | 1.04 (1.01-1.07) | 0.008 | 1.03 (0.98-1.08) | 0.232 | 1.04 (1.01-1.08) | 0.016 |
| LungV20 | 1.05 (0.99-1.11) | 0.085 | 1.06 (0.97-1.16) | 0.213 | 1.04 (0.97-1.12) | 0.226 |
| LungV30 | 1.05 (0.98-1.12) | 0.159 | 1.05 (0.95-1.17) | 0.349 | 1.05 (0.96-1.13) | 0.291 |
| LungV40 | 1.02 (0.95-1.1) | 0.562 | 1.03 (0.92-1.16) | 0.606 | 1.02 (0.92-1.12) | 0.742 |
| LungV50 | 1.05 (0.95-1.16) | 0.354 | 1.04 (0.89-1.21) | 0.653 | 1.06 (0.93-1.2) | 0.403 |
| LungV60 | 1.14 (0.99-1.31) | 0.062 | 1.03 (0.8-1.34) | 0.805 | 1.21 (1.03-1.42) | 0.023 |

Abbreviations: MHD, mean heart dose; Dmax: max dose; EUD: equivalent uniform dose; Vx: volume receiving more than x Gy; MLD, mean lung dose.

Table 3. Multivariate COX regression analysis

| | Whole survival | | Long-term survival | | Early survival | |
|---|---|---|---|---|---|---|
| | HR | P | HR | P | HR | P |
| HeartV50 | 1.02 [0.96, 1.08] | 0.557 | 1.14 [1.03, 1.27] | 0.015 | 0.97 [0.90, 1.05] | 0.411 |
| LungV8 | 1.02 [1.00, 1.05] | 0.115 | 1.00 [0.96, 1.05] | 0.851 | 1.03 [1.00, 1.06] | 0.069 |
| Sex | | | | | | |
| Male | 1.00 (Referent) | | 1.00 (Referent) | | 1.00 (Referent) | |
| Female | 0.48 [0.26, 0.88] | 0.017 | 0.57 [0.23, 1.45] | 0.239 | 0.47 [0.21, 1.01] | 0.054 |
| Smoking Status | | | | | | |
| Former or never | 1.00 (Referent) | | 1.00 (Referent) | | 1.00 (Referent) | |
| Current | 1.06 [0.61, 1.84] | 0.832 | 0.78 [0.29, 2.11] | 0.626 | 1.23 [0.62, 2.43] | 0.553 |
| ECOG PS | | | | | | |
| 0 | 1.00 (Referent) | | 1.00 (Referent) | | 1.00 (Referent) | |
| 1 | 1.87 [0.58, 6.01] | 0.293 | 0.92 [0.21, 4.02] | 0.912 | 3.47 [0.47, 25.48] | 0.221 |
| Histology | | | | | | |
| Non-SCC | 1.00 (Referent) | | 1.00 (Referent) | | 1.00 (Referent) | |
| SCC | 0.77 [0.42, 1.41] | 0.392 | 0.72 [0.23, 2.25] | 0.567 | 0.81 [0.39, 1.66] | 0.562 |
| Tumor Size | 1.17 [1.06, 1.30] | 0.003 | 0.99 [0.80, 1.24] | 0.951 | 1.25 [1.11, 1.41] | <0.001 |
| Positive Lymph Node Ratio | 3.04 [1.11, 8.34] | 0.031 | 7.47 [1.53, 36.42] | 0.013 | 1.64 [0.44, 6.17] | 0.461 |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performances status; SCC, squamous cell carcinoma.

**Declaration of interests**

☒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.