

Clinical Investigation

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



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Purpose: Mean heart dose (MHD) over 10 Gy and left anterior descending (LAD) coronary artery volume (V) receiving 15 Gy (V15Gy) greater than 10% can significantly increase the risk of major adverse cardiac events (MACE) in patients with non-small cell lung cancer (NSCLC). We sought to characterize the discordance between MHD and LAD dose and the association of this classification on the risk of MACE after radiation therapy.

Methods and Materials: The coefficient of determination for MHD and LAD V15Gy was calculated in this retrospective analysis of 701 patients with locally advanced NSCLC treated with radiation therapy. Four groups were defined on the basis of high or low MHD (≥ 10 Gy vs < 10 Gy) and LAD V15Gy ($\geq 10\%$ vs $< 10\%$). MACE (unstable angina, heart failure, myocardial infarction, coronary revascularization, and cardiac death) cumulative incidence was estimated, and Fine and Gray regressions were performed.

Results: The proportion of variance in LAD V15Gy predictable from MHD was only 54.5% ($R^2 = 0.545$). There was discordance (where MHD was high [≥ 10 Gy] and LAD low [V15Gy $< 10\%$], or vice versa) in 23.1% of patients ($n = 162$). Two-year MACE estimates were 4.2% (MHD^{high}/LAD^{low}), 7.6% (MHD^{high}/LAD^{high}), 1.8% (MHD^{low}/LAD^{low}), and 13.0%

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(MHD^{low}/LAD^{high}). Adjusting for pre-existing coronary heart disease and other prognostic factors, MHD^{high}/LAD^{low} (subdistribution hazard ratio [SHR], 0.34; 95% CI, 0.13-0.93; $P = .036$) and MHD^{low}/LAD^{low} (SHR, 0.24; 95% CI, 0.10-0.53; $P < .001$) were associated with a significantly reduced risk of MACE.

Conclusions: MHD is insufficient to predict LAD V15Gy with confidence. When MHD and LAD V15Gy dose exposure is discordant, isolated low LAD V15Gy significantly reduces the risk of MACE in patients with locally advanced NSCLC after radiation therapy, suggesting that the validity of whole heart metrics for optimally predicting cardiac events should be reassessed. © 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Introduction

Radiation therapy (RT) in patients with locally advanced non-small cell lung cancer (LA-NSCLC) is associated with increased risk of major adverse cardiac events (MACE).¹⁻³ However, the majority of NSCLC cardiac toxicity studies analyzed radiation exposure to the whole heart, using dosimetric variables such as mean heart dose (MHD). Despite the significant association between MHD and increased risk of MACE in patients with LA-NSCLC,³ MHD is a poor surrogate for coronary artery dose,^{4,5} thereby limiting precise correlation of cardiac substructure injury with pathophysiologically relevant toxicity (eg, coronary injury with ischemic events).

In a recent report using comprehensive sensitivity and cut-point analyses and accounting for baseline cardiac risk, we observed that left anterior descending (LAD) coronary artery volume receiving 15 Gy (V15Gy) is most predictive of MACE compared with whole heart and other cardiac substructure dose variables and is an independent predictor of MACE in patients with LA-NSCLC.⁶ Given that MHD remains the most commonly used dose metric in national RT guidelines, yet is a poor surrogate for LAD dose, we sought to characterize the discordance between MHD and LAD dose and the association of this classification with the risk of MACE after RT.

Methods and Materials

This retrospective analysis includes 701 consecutive patients with LA-NSCLC treated with thoracic RT at Brigham and Women's Hospital/Dana-Farber Cancer Institute between December 2003 and January 2014.^{3,6} Eligible patients included those with 2010 American Joint Commission on Cancer clinical stage II (medically inoperable or unresectable) or stage III disease treated with thoracic RT using 3-dimensional or intensity modulated RT techniques. The analysis excluded patients with metastatic disease at presentation and those who underwent stereotactic body RT. Patients received definitive concurrent chemoradiation therapy, neoadjuvant RT or chemoradiation therapy, or adjuvant RT or chemoradiation therapy. This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board.

Cardiac substructures were segmented manually⁷ (8-mm brush size for coronary arteries) in MIM (MIM Software Inc, Cleveland, OH), as described previously.⁶ Four groups

were defined on the basis of recent work, specifically high and low MHD (≥ 10 Gy vs < 10 Gy)³ and LAD V15Gy ($\geq 10\%$ vs $< 10\%$).⁶ Discordance was defined as occurring when MHD was high and LAD V15Gy was low (or vice versa). MACE data (cardiac death, unstable angina, myocardial infarction, heart failure hospitalization or urgent visit, coronary revascularization, cardiac death)⁸ were collected via in-depth manual medical record review.^{3,6}

The correlation between MHD and LAD V15Gy was assessed using the Pearson correlation coefficient, whereas the coefficient of determination (R^2) was calculated to assess the proportion of variance in LAD V15Gy predictable from MHD ($R^2 \geq 0.70$ was considered sufficient for prediction). The cumulative incidence of MACE was estimated, and Fine and Gray regressions were performed,⁹ adjusting for noncardiac death as a competing risk.¹⁰ A 2-sided $P \leq 0.05$ was considered statistically significant. Stata (version 15.1; StataCorp LLC, College Station, TX) statistical software was used for all analyses.

Results

Characteristics of the 701-patient cohort have been reported previously.⁶ By dosimetric group, patients with MHD^{high}/LAD^{high} and MHD^{low}/LAD^{high} were more likely to be male (57.6% and 58.7%, respectively) and have pre-existing coronary artery disease (32.4% and 36.5%, respectively) versus those with MHD^{high}/LAD^{low} and MHD^{low}/LAD^{low} (41.4% and 43.5% male, respectively, $P = .001$; 29.3% and 21.7% coronary artery disease, respectively, $P = .03$; Table 1). Patients with MHD^{high}/LAD^{high} had the highest frequency of stage IIIB disease (39.2%; $P = .02$). Patients with low LAD dose (MHD^{high}/LAD^{low} or MHD^{low}/LAD^{low}) had significantly higher rates of right-sided tumors (86.9% and 67.4%, respectively) than those with high LAD dose (MHD^{high}/LAD^{high} or MHD^{low}/LAD^{high}; 43.7% and 25.4%, respectively; $P < .001$).

There was a positive correlation between MHD and LAD V15Gy ($r = 0.74$; $P < .0001$); however, the proportion of variance in LAD V15Gy explained by MHD was only 54.5%, which is insufficient for prediction ($R^2 = 0.545$; Fig. 1). There was discordance between MHD and LAD (where MHD was high and LAD low, or vice versa) in 23.1% of patients ($n = 162$), including 14.1% ($n = 99$) with MHD^{high}/LAD^{low} and 9.0% ($n = 63$) with MHD^{low}/LAD^{high}.

The overall median follow-up was 20.4 months (interquartile range [IQR], 8.2-44.6 months) and 47.8 months in

Table 1 Patient and treatment characteristics by dosimetric group

	MHD/LAD Concordant		MHD/LAD Discordant		P value
	MHD ^{high} /LAD ^{high} (n = 309)	MHD ^{low} /LAD ^{low} (n = 230)	MHD ^{high} /LAD ^{low} (n = 99)	MHD ^{low} /LAD ^{high} (n = 63)	
Median age (IQR), y	64.0 (57.0–72.0)	67.0 (57.0–74.0)	64.0 (57.0–71.0)	62.0 (53.0–72.0)	.18
Sex, n (%)					
Female	131 (42.4)	130 (56.5)	58 (58.6)	26 (41.3)	
Male	178 (57.6)	100 (43.5)	41 (41.4)	37 (58.7)	.001
ECOG performance, n (%)					
0-1	278 (90.0)	193 (83.9)	92 (92.3)	53 (84.1)	
2	23 (7.4)	31 (13.5)	5 (5.1)	8 (12.7)	
3-4	8 (2.6)	6 (2.6)	2 (2.0)	2 (3.2)	.17
Weight loss, (%)	106 (34.3)	76 (33.0)	25 (25.3)	17 (26.9)	.30
Tobacco use, n (%)					
Never	22 (7.1)	19 (8.3)	10 (10.1)	5 (7.9)	
Current	121 (39.2)	98 (42.6)	37 (37.4)	23 (36.5)	
Former	166 (53.7)	113 (49.1)	52 (52.5)	35 (55.6)	.88
Median pack-years (IQR)	45.0 (30.0–60.0)	40.0 (29.3–60.0)	40.0 (30.0–55.0)	50.0 (30.0–88.0)	.06
Medical history, n (%)					
Hypertension	164 (53.1)	116 (50.4)	49 (49.5)	33 (52.4)	.90
Hyperlipidemia	156 (50.5)	98 (42.6)	57 (57.9)	30 (47.6)	.07
Diabetes mellitus	52 (16.8)	25 (10.9)	10 (10.1)	10 (15.9)	.15
DVT/PE	13 (4.2)	12 (5.2)	2 (2.0)	3 (4.8)	.62
Arrhythmia	43 (13.9)	33 (14.4)	15 (15.2)	8 (12.7)	.98
Valvulopathy	17 (5.5)	13 (5.7)	8 (8.1)	3 (4.8)	.77
PVD	24 (7.8)	21 (9.1)	6 (6.1)	4 (6.4)	.76
Stroke	1 (0.3)	6 (2.6)	3 (3.0)	3 (4.8)	.04
CAD	100 (32.4)	50 (21.7)	29 (29.3)	23 (36.5)	.03
Myocardial infarction	40 (12.9)	21 (9.1)	11 (11.1)	10 (15.9)	.39
CHF	21 (6.8)	21 (9.1)	7 (7.1)	9 (14.3)	.23
Framingham risk, N*	191	127	66	29	
Median (IQR), %	16.6 (9.9–30.5)	13.5 (7.9–25.5)	14.5 (9.1–27.8)	12.7 (6.8–22.6)	.17
Low (<10%), n (%)	44 (23.0)	46 (29.3)	19 (28.8)	12 (34.3)	
Moderate (10%-20%), n (%)	51 (26.7)	37 (23.6)	16 (24.2)	7 (20.0)	
High-risk (>20%), n (%)	96 (50.3)	74 (47.1)	31 (47.0)	16 (45.7)	.79
NSCLC clinical stage, n (%)					
II	26 (8.4)	34 (14.8)	8 (8.1)	10 (15.9)	
IIIA	162 (52.4)	130 (56.5)	60 (60.6)	38 (60.3)	
IIIB	121 (39.2)	66 (28.7)	31 (31.3)	15 (23.8)	.02
NSCLC clinical nodal stage, n (%)					
0-1	69 (22.3)	69 (30.0)	25 (25.3)	16 (25.4)	
2	152 (49.2)	114 (49.6)	56 (56.7)	37 (58.7)	
3	87 (28.2)	47 (20.4)	18 (18.2)	10 (15.9)	.002
Tumor laterality, n (%)					
Right	135 (43.7)	155 (67.4)	86 (86.9)	16 (25.4)	
Left	155 (50.2)	56 (24.4)	7 (7.1)	45 (71.4)	<.001
Chemotherapy type, n (%)					
Induction	55 (17.8)	41 (17.8)	21 (21.2)	16 (25.4)	.48
Concurrent	265 (85.8)	189 (82.2)	88 (88.9)	52 (82.5)	.40
Adjuvant	120 (38.8)	62 (27.0)	34 (34.3)	22 (34.9)	.04
Treatment sequence, n (%)					
Definitive chemoRT	193 (62.5)	120 (52.2)	61 (61.6)	31 (49.2)	
Neoadjuvant chemoRT	53 (17.2)	62 (27.0)	24 (24.2)	15 (23.8)	
Adjuvant RT/chemoRT	42 (13.6)	23 (10.0)	8 (8.1)	13 (20.6)	
RT alone	21 (6.8)	25 (10.9)	6 (6.1)	4 (6.4)	.02
RT technique, n (%)					
3D-CRT	232 (75.1)	178 (77.4)	74 (74.8)	55 (87.3)	
IMRT	77 (24.9)	52 (22.6)	25 (25.3)	8 (12.7)	.20

(Continued)

Table 1 (Continued)

	MHD/LAD Concordant		MHD/LAD Discordant		P value
	MHD ^{high} /LAD ^{high} (n = 309)	MHD ^{low} /LAD ^{low} (n = 230)	MHD ^{high} /LAD ^{low} (n = 99)	MHD ^{low} /LAD ^{high} (n = 63)	
Median prescribed RT dose (IQR), Gy	66.0 (60.0–66.0)	66.0 (54.0–66.0)	60.0 (54.0–66.0)	61.2 (54.0–66.0)	.09
Median dose					
Heart mean (IQR), Gy	19.1 (15.4–26.4)	4.6 (2.2–6.5)	13.4 (11.8–18.3)	7.8 (5.9–9.1)	<.001
LAD V15 Gy, % (IQR)	43.7 (27.2–60.1)	0.0 (0.0–0.0)	2.2 (0.0–5.6)	28.0 (19.0–37.1)	<.001

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; CAD = coronary artery disease; CHD = coronary heart disease; chemoRT = chemoradiation therapy; CHF = congestive heart failure; DVT = deep venous thrombosis; ECOG = Eastern Cooperative Oncology Group; IMRT = intensity modulated radiation therapy; IQR = interquartile range; NSCLC = non-small cell lung cancer; PE = pulmonary embolism; PVD = peripheral vascular disease; RT = radiation therapy.

* Total reflects patients without CHD. The distributions of categorical covariates were compared using the χ^2 test, whereas continuous variables were compared using Kruskal–Wallis test.

patients alive (IQR, 31.6–75.4 months). The 2-year cumulative incidence of MACE was 5.7% (95% confidence interval [CI], 4.1%–7.5%) overall and by MHD/LAD subgroup: 4.2% for MHD^{high}/LAD^{low} (95% CI, 1.4%–9.5%), 7.6% for MHD^{high}/LAD^{high} (95% CI, 4.9%–10.9%), 1.8% for MHD^{low}/LAD^{low} (95% CI, 0.6%–4.2%), and 13.0% for MHD^{low}/LAD^{high} (95% CI, 6.1%–22.6%; Fig. 2).

Adjusting for age, history of hypertension, diabetes, pre-existing coronary heart disease, and intensity modulated RT use, only the dosimetric groups with low LAD dose were associated with significantly reduced risk of major adverse cardiac events, specifically MHD^{high}/LAD^{low} (subdistribution hazard ratio, 0.34; 95% CI, 0.13–0.93; $P = .036$) and MHD^{low}/LAD^{low} (subdistribution hazard ratio, 0.24; 95% CI, 0.10–0.53; $P < .001$; Table 2).

Discussion

We observed that MHD is insufficient to predict LAD V15Gy with confidence and that isolated low LAD V15Gy

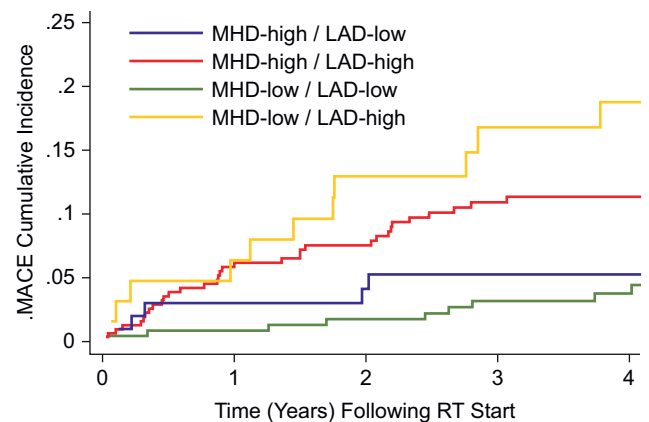


Fig. 2. Cumulative incidence of MACE by dosimetric group: MHD^{high}/LAD^{low} ($P = .009$), MHD^{high}/LAD^{high} ($P = .14$), MHD^{low}/LAD^{low} ($P < .001$), and MHD^{low}/LAD^{high} ($P = \text{NA}$, reference). *Abbreviations:* LAD = left anterior descending coronary artery; MACE = major adverse cardiac event; MHD = mean heart dose.

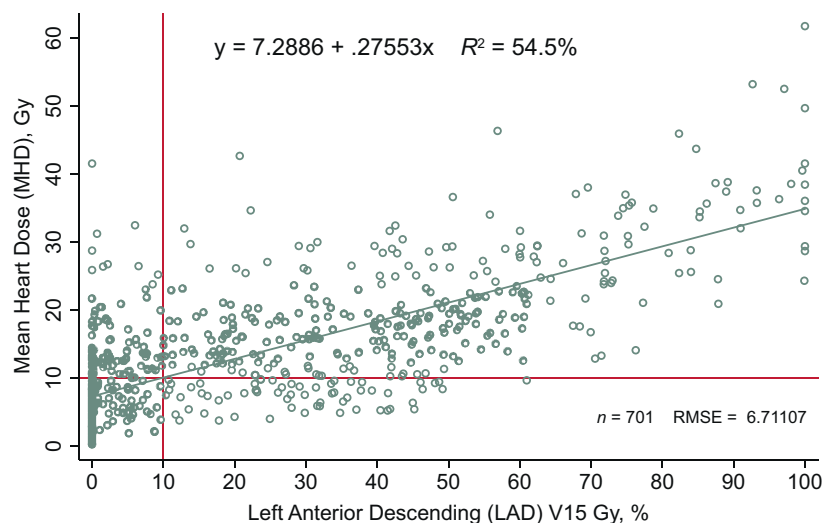


Fig. 1. Relationship between mean heart dose and left anterior descending coronary artery dose (V15Gy). *Abbreviation:* RMSE = root mean square error.

Table 2 Competing risks regression analysis for major adverse cardiac events

Covariable	No. of patients	No. of MACE	Univariable		Multivariable	
			HR (95% CI)	P value	SHR (95% CI)	P value
Age	701	70	1.03 (1.01–1.05)	.014	1.01 (0.98–1.03)	.56
Sex						
Female	345	33	1.0 (Reference)		—	—
Male	356	37	1.11 (0.70–1.77)	.67		
ECOG PS						
0-1	616	62	1.0 (Reference)			
2-4	85	8	0.93 (0.44–1.94)	.84		
Smoking						
Never	56	4	1.0 (Reference)			
Current	279	22	1.11 (0.38–3.23)	.85		
Former	366	44	1.73 (0.62–4.85)	.30		
Overall stage						
II	78	11	1.0 (Reference)			
III	623	59	0.67 (0.36–1.27)	.22		
Nodal stage						
0-1	179	20	1.0 (Reference)			
≥2	521	50	0.83 (0.50–1.39)	.48		
Tumor laterality						
Right	179	35	1.0 (Reference)			
Left	521	30	1.35 (0.83–2.19)	.23		
Hypertension	362	55	3.61 (2.05–6.36)	<.001	2.65 (1.49–4.74)	.001
Hyperlipidemia	341	37	1.19 (0.75–1.90)	.46	—	—
Diabetes	97	17	2.09 (1.21–3.59)	.008	1.12 (0.62–2.02)	.72
CHD	252	46	3.68 (2.26–6.02)	<.001	2.46 (1.43–4.23)	.001
RT/chemoRT						
Definitive	461	47	1.0 (Reference)			
Neoadj./adj.	240	23	0.95 (0.58–1.55)	.83		
Chemotherapy	659	66	1.01 (0.37–2.78)	.98		
RT technique						
3D-CRT	539	63	1.0 (Reference)		1.0 (Reference)	
IMRT	162	7	0.38 (0.17–0.83)	.015	0.40 (0.18–0.88)	.023
MHD/LAD dose group						
MHD ^{low} /LAD ^{high}	63	13	1.0 (Reference)		1.0 (Reference)	
MHD ^{high} /LAD ^{low}	99	6	0.28 (0.10–0.73)	.009	0.34 (0.13–0.93)	.036
MHD ^{high} /LAD ^{high}	309	40	0.62 (0.33–1.16)	.14	0.66 (0.35–1.24)	.20
MHD ^{low} /LAD ^{low}	230	11	0.21 (0.10–0.47)	<.001	0.24 (0.10–0.53)	<.001

Abbreviations: adj. = adjuvant; 3D-CRT = 3-dimensional conformal radiation therapy; CHD = coronary heart disease; chemoRT = chemoradiation therapy; HR = hazard ratio; IMRT = intensity modulated radiation therapy; LAD = left anterior descending coronary artery; MACE = major adverse cardiac event; neoadj. = neoadjuvant; RT = radiation therapy; SHR = subdistribution hazard ratio.

is associated with a significantly reduced risk of MACE in patients with locally advanced NSCLC after RT. The cut-points used for MHD and LAD are based on prior work demonstrating that MHD ≥ 10 Gy and LAD V15Gy $\geq 10\%$ are independent predictors of MACE. Specifically, MHD < 10 Gy correlates with 2-year MACE estimates of 1% and 10% in patients without or with pre-existing coronary heart disease,³ whereas LAD V15Gy $< 10\%$ correlates with 1-year MACE estimates of 0% and 5%, respectively.⁶

Cardiac event outcomes and individual cardiac substructure segmentation are laborious to collect and have precluded consistent and large-scale reporting. Before the previous report,⁶ there was limited data describing cardiac event endpoints. These studies have been hampered by small sample sizes (<250 patients), limited numbers of

cardiac events, and inconsistent assessment of baseline cardiac risk.^{2,11-13} Other studies have evaluated cardiac substructure dosimetry associated with survival. A recent secondary analysis of RTOG 0617 identified atrium, pericardium, and ventricle doses associated with survival¹⁴; however, coronary arteries were not analyzed, and there was no assessment of baseline cardiac risk or cardiac events. McWilliam et al used a noncontouring method matching 1161 patients to 5 template anatomies, identifying right atrium and right coronary artery doses associated with survival, although this study also lacked assessment of cardiac events or baseline cardiac risk.¹⁵ These studies illustrate the importance of the toxicity endpoints used, the specificity of the cardiac structures contoured, and whether baseline cardiac risk was assessed. The latter is essential for

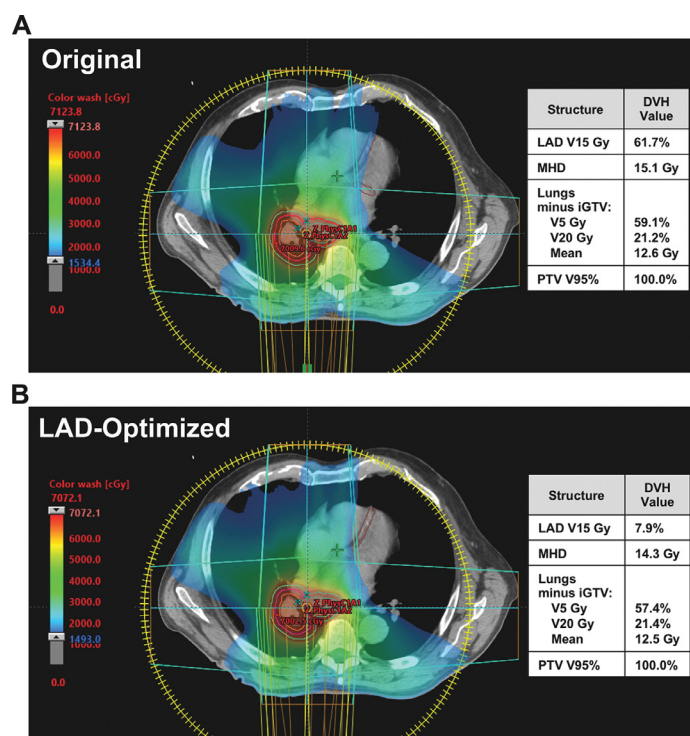


Fig. 3. Example of treatment plan optimization with dose color wash lower threshold of 15 Gy in (A) an original plan (LAD V15Gy, 61.7%) and (B) an LAD-optimized plan with LAD V15Gy of 7.9%. *Abbreviations:* iGTV = internal gross tumor volume; LAD = left anterior descending coronary artery; MHD = mean heart dose; PTV = planning target volume.

estimating cardiac toxicity risk, given the high prevalence of baseline cardiovascular disease¹⁶ and its known interaction with heart dose.³

Potential limitations include the retrospective nature of this study; therefore, captured cardiac events might underrepresent true MACE rates. We limited our analysis to LAD V15Gy based on recent work⁶; however, it is likely that additional dosimetric predictors are also significant. Furthermore, the extent of concordance or discordance may be inherent to the treatment techniques used in this cohort, and intentionally limiting LAD dose could result in a larger proportion of patients with favorable coronary metrics. For instance, an example patient with an initial RT plan demonstrating LAD V15Gy of 61.7% was replanned with LAD V15Gy optimization (reduced to 7.9%) with remaining dose-volume metrics grossly unchanged (Fig. 3).

Conclusion

We observed that MHD is not sufficient to predict LAD V15Gy with confidence and that isolated low LAD V15Gy significantly reduces the risk of MACE. These findings further question the validity of continued use of whole heart metrics to predict cardiac toxicity and similarly question the reliance on MHD constraints in guidelines and clinical trials.

References

- 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.
- 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* 2017;35:1387–1394.
- 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.
- Jacob S, Camilleri J, Derreux S, et al. Is mean heart dose a relevant surrogate parameter of left ventricle and coronary arteries exposure during breast cancer radiotherapy: A dosimetric evaluation based on individually-determined radiation dose (BACCARAT study). *Radiat Oncol* 2019;14:29.
- Hoppe BS, Bates JE, Mendenhall NP, et al. The meaningless meaning of mean heart dose in mediastinal lymphoma in the modern radiation therapy era. *Pract Radiat Oncol* 2020;10:e147–e154.
- 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.
- 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.
- Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and stroke endpoint definitions for clinical trials. *J Am Coll Cardiol* 2018;71:1021–1034.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.

10. Gaynor JJ, Feuer EJ, Tan CC, et al. On the use of cause-specific failure and conditional failure probabilities: Examples from clinical oncology data. *J Am Stat Assoc* 1993;88:400–409.
11. 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* 2017;125:293–300.
12. Schytte T, Hansen O, Stolberg-Rohr T, Brink C. Cardiac toxicity and radiation dose to the heart in definitive treated non-small cell lung cancer. *Acta Oncol* 2010;49:1058–1060.
13. 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;99:70–79.
14. Thor M, Deasy JO, Hu C, et al. Modeling the impact of cardiopulmonary irradiation on overall survival in NRG Oncology Trial RTOG 0617. *Clin Cancer Res* 2020;26:4643–4650.
15. McWilliam A, Khalifa J, Vasquez Osorio E, et al. Novel methodology to investigate the impact of radiation dose to heart sub-structures on overall survival. *Int J Radiat Oncol Biol Phys* 2020;108:1073–1081.
16. Al-Kindi SG, Oliveira GH. Prevalence of preexisting cardiovascular disease in patients with different types of cancer: The unmet need for onco-cardiology. *Mayo Clin Proc* 2016;91:81–83.