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Death without progression as an endpoint to describe cardiac radiation effects in locally advanced non-small cell lung cancer

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ABSTRACT

Background and purpose: Prior studies have examined associations of cardiovascular substructure dose with overall survival (OS) or cardiac events after chemoradiotherapy (CRT) for non-small cell lung cancer (NSCLC). Herein, we investigate an alternative endpoint, death without cancer progression (DWP), which is potentially more specific than OS and more sensitive than cardiac events for understanding CRT toxicity.
Materials and methods: We retrospectively reviewed records of 187 patients with locally advanced or oligometastatic NSCLC treated with definitive CRT from 2008 to 2016 at a single institution. Dosimetric parameters to the heart, lung, and ten cardiovascular substructures were extracted. Charlson Comorbidity Index (CCI), excluding NSCLC diagnosis, was used to stratify patients into CCI low (0–2; n = 66), CCI intermediate (3–4; n = 78), and CCI high (≥5; n = 43) groups. Primary endpoint was DWP, modeled with competing risk regression. Secondary endpoints included OS. An external cohort consisted of 140 patients from another institution.
Results: Median follow-up was 7.3 years for survivors. Death occurred in 143 patients (76.5 %), including death after progression in 118 (63.1 %) and DWP in 25 (13.4 %). On multivariable analysis, increasing CCI stratum and mean heart dose were associated with DWP. For mean heart dose ≥ 10 Gy vs < 10 Gy, DWP was higher (5-year rate, 16.9 % vs 6.7 %, p = 0.04) and OS worse (median, 22.9 vs 34.1 months, p < 0.001). Ventricle (left, right, and bilateral) and pericardial but not atrial substructure dose were associated with DWP, whereas all three were inversely associated with OS. Cutpoint analysis identified right ventricle mean dose ≥ 5.5 Gy as a predictor of DWP. In the external cohort, we confirmed an association of ventricle, but not atrial, dose with DWP.
Conclusion: Cardiovascular substructure dose showed distinct associations with DWP. Future cardiotoxicity studies in NSCLC could consider DWP as an endpoint.

Introduction:

Patients with locally advanced non-small cell lung cancer (LA-NSCLC) treated with chemoradiotherapy (CRT) receive considerable radiotherapy (RT) dose to cardiopulmonary structures frequently in the setting of multiple baseline co-morbid conditions. RTOG 0617 demonstrated inferior overall survival (OS) with higher dose RT, believed to be at least partially attributable to a higher heart dose [1,2]. Subsequent

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work has described independent associations of heart dose with OS, cardiac events, and immunosuppression [3–8].

There is considerable interest in understanding which cardiovascular substructures are most important to protect during RT planning. Prior studies have examined associations of cardiovascular substructure dose with OS or cardiac events [9–13]. However, challenges arise with both endpoints. First, because most patients die from NSCLC progression, OS is dominated by disease progression events that may mask RT effects on cardiovascular substructures despite best efforts to control for confounders. Second, cardiac events after RT often may not be fatal and thus cannot fully explain the association between heart dose and worse OS. Cardiac events are also difficult to record retrospectively. Selection of a suitable endpoint is critical to accurately determine which regions of the heart to prioritize for dose sparing during RT planning.

Death without progression (DWP), defined as death in the absence of NSCLC progression, is another endpoint to consider [14]. DWP is potentially more specific than OS (ie, selects out death from NSCLC progression), and potentially more sensitive than cardiac-specific death (ie, includes a variety of non-cancer causes of death) for understanding CRT toxicity. DWP may be a better endpoint to show the impact of CRT on survival isolated from anti-cancer effects. With controlled cancer, the relative impact of baseline comorbidity or CRT toxicity on longevity is expected to increase.

Accordingly, we hypothesized that both baseline comorbidity and dose to cardiovascular substructures would correlate with DWP. Additionally, we hypothesized that cardiovascular substructure dose would show distinct associations with DWP from those seen with OS.

Materials and methods

Patients

We retrospectively reviewed an institutional database of patients with locally advanced or oligometastatic (1 metastatic lesion) NSCLC treated with definitive concurrent or sequential CRT between December 2008 and November 2016 at the University of Pennsylvania. All patients in this cohort underwent baseline positron emission tomography and magnetic resonance imaging of the brain, and 4-dimensional computed tomography (CT) simulation. No patient received consolidation immunotherapy as the period predated the results of the PACIFIC trial [15]. We excluded those who received prior thoracic RT or thoracic RT doses < 50 Gy, and those who died during RT. The final cohort included 187 patients.

Treatment

RT was delivered with 3-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), or proton therapy (either pencil beam scanning [PBS] or passive scattering) to a prescription dose of 60–74 Gy in 1.8–2 Gy per fraction. Daily image guidance consisted of either kilovoltage imaging (proton therapy) or cone beam CT (photon therapy). RT dose constraints were as follows: spinal cord maximum dose ≤ 50 Gy, mean lung dose < 20 Gy, lung V20 < 37 %, and mean heart dose ≤ 26 Gy.

Follow-up

Follow-up CT chest and clinical visits were performed every 2–3 months for the first year after RT, every 4–6 months for the following two years, and every 6–12 months thereafter.

Study endpoints

The primary endpoint was DWP, defined as death in the absence of NSCLC progression on last CT chest and clinical visit. All clinical records (eg, hospitalization, clinic and telephone notes, imaging, death certificates) were reviewed to determine cause of DWP. For patients who died with a recent (defined according to the follow-up section above) stable CT chest but no notes describing a cause of death, cause of DWP was "unknown". Secondary endpoints were OS and death after cancer progression. All endpoints were measured from the start of RT to the event of interest.

Baseline comorbidity

Baseline cardiovascular comorbidity (any cardiac condition, cerebrovascular accident [CVA] or peripheral arterial disease [PAD]), pulmonary comorbidity (chronic obstructive pulmonary disease [COPD], asthma, interstitial lung disease, obstructive sleep apnea, or pulmonary embolism), and Charlson Comorbidity Index (CCI), excluding NSCLC diagnosis, were manually extracted from medical records [16]. CCI assigns points for the following: age, myocardial infarction, congestive heart failure, PAD, CVA or transient ischemic attack, dementia, COPD, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, chronic kidney disease, leukemia, lymphoma, solid tumor (NSCLC excluded for this analysis), and acquired immunodeficiency syndrome. CCI was grouped into CCI low (0–2), CCI intermediate (3–4), and CCI high ($\geq$5) based on approximate terciles and previously used cutpoints [17,18]. Prior work suggests these cutpoints predict the risk of mortality in patients without cancer [17,18]; because we were interested in the impact of baseline comorbidity on non-cancer deaths, these cutpoints were deemed appropriate for use in our study.

Dosimetric parameters

Heart and lung minus gross tumor volume contours were reviewed and manually re-contoured, as necessary. Mean heart dose (MHD), heart volume receiving $\geq$ 5 Gy (V5), heart V30, heart V50, and mean lung dose (MLD) were then extracted from the Eclipse treatment planning software (Varian Medical Systems, Palo Alto, CA).

RT plans were exported to MIM (version 7.1.4, MIM Software, Cleveland, OH). Ten cardiovascular substructures – atria (bilateral), right atrium, left atrium, ventricles (bilateral), right ventricle, left ventricle, pericardium, aorta, superior vena cava, and pulmonary artery – were auto-segmented using a previously validated deep learning model [19,20]. Cardiovascular substructures were then manually reviewed and edited based on a validated cardiac contouring atlas [21]. Dosimetric parameters (mean dose, V5, V30, V50) to each substructure were extracted, chosen based on prior work assessing the significance of cardiovascular substructure dose for NSCLC [7,10].

Statistical analysis

The cumulative incidence method was used to model DWP and death after progression. For the former, disease progression was considered a competing event, and for the latter, DWP was considered a competing event. For DWP, patients with incomplete follow-up prior to death were censored on the date of the last CT chest or clinical encounter.

Gray's test was used to compare the cumulative incidence of DWP among CCI strata and mean heart dose cutpoint of 10 Gy. The latter cutpoint was chosen based on Atkins et al [8]. Fine-Gray regression was used to assess associations of patient-, tumor- and treatment-related factors with DWP. Significant factors on univariable analysis ($p < 0.05$) were considered for inclusion in multivariable models. Because of a limited number of DWP events (25), multivariable models included 2 variables. CCI strata was preferentially included in multivariable models as CCI is a combined measure of age and a variety of comorbidities. Given collinearity between different normal tissue dosimetric parameters, only one such parameter (treated as a continuous covariate) was included in each model.

Exploratory associations between cardiovascular substructure dose and DWP were assessed separately from the above process. For each

cardiovascular substructure (heart and 10 substructures), associations between dosimetric parameters (mean, V5, V30, V50) and DWP were assessed, and the candidate parameter with the lowest significant p value was promoted to multivariable analysis. MLD was also included. Benjamini-Hochberg procedure was used to correct for multiple (45) comparisons, accepting a false discovery rate of 5 %. Multivariable models with 2 variables (CCI and different dosimetric parameters) were generated and ranked by Akaike information criterion (AIC) to determine the "best fit" models (lowest AIC). In a sensitivity analysis, we included 3 variables per model (age, internal target volume [ITV], and different dosimetric parameters) to see if the ordering of models changed. Cutpoint analysis was done with Contal and O'Quigley method [22].

For OS, the Kaplan-Meier method and Cox regression were used. Given the greater number of OS (versus DWP) events, multivariable models for OS preferentially included individual measures of comorbidity rather than CCI, along with one normal tissue dosimetric parameter. The exploratory associations described above were repeated in a similar fashion for cardiovascular substructure dose and OS.

All hypothesis tests were two-sided and $p < 0.05$ was considered statistically significant. Analyses were performed using SAS OnDemand for Academics.

External cohort

In an independent cohort of 140 patients from Rutgers Cancer Institute of New Jersey, associations between cardiac substructure dosimetric parameters and both DWP and OS were assessed in a similar fashion to the analysis described above. Details of this cohort have been previously published [7]. Mean, V5, and V30 to the heart, atria, right atrium, left atrium, ventricles, right ventricle, and left ventricle were included. Pericardium, aorta, superior vena cava, and pulmonary artery substructures, as well as CCI, were not available.

Results

Baseline characteristics

Baseline characteristics are shown in Table 1. Median age was 67 years. Cardiovascular, pulmonary, and either cardiovascular or pulmonary comorbidities were present in 94 (50.3 %), 78 (41.7 %), and 127 patients (67.9 %), respectively. CCI was low (0–2), intermediate (3–4), and high (5–9) in 66 (35.3 %), 78 (41.7 %), and 43 patients (23 %), respectively. Median RT prescription dose was 66.6 Gy. Proton therapy was used in 98 (52.4 %; n = 9 PBS) and photon therapy in 89 patients (47.6 %, n = 68 IMRT). Median mean heart dose was 8.1 Gy.

Table 1
Baseline characteristics (N = 187).

Characteristic	N (%)
Age (median, IQR)	67 (59–73)
Sex	
Female	99 (52.9)
Male	88 (47.1)
ECOG PS	
0	70 (37.4)
1	102 (54.5)
2	15 (8.0)
Smoking, pack-years (median, IQR)	35 (15–50)
Cardiovascular comorbidity	94 (50.3)
Coronary artery disease	34 (18.2)
Pulmonary comorbidity	78 (41.7)
Cardiovascular or pulmonary comorbidities	127 (67.9)
CCI (median, IQR)	3 (2–4)
0–2 (low)	66 (35.3)
3–4 (intermediate)	78 (41.7)
5–9 (high)	43 (23.0)
Histology	
Adenocarcinoma	147 (78.6)
Squamous cell carcinoma	29 (15.5)
Other	11 (5.9)
AJCC Stage (7th edition)	
IIA-B	4 (2.1)
IIIA	119 (63.6)
IIIB	62 (33.2)
IV (oligometastatic)	2 (1.1)
T stage	
x, 1–2	108 (57.8)
3–4	79 (42.2)
N stage	
0–2	144 (77.0)
3	43 (23.0)
Left-sided primary	74 (39.6)
RT dose, Gy (median, IQR)	66.6 (66.6–66.6)
RT technique	
Proton therapy	98 (52.4)
PBS-PT	9 (4.8)
PS-PT	89 (47.6)
Photon therapy	89 (47.6)
IMRT	68 (36.4)
3D-CRT	21 (11.2)
Internal target volume (cc; median, IQR)	242.9 (165.3–427.2)
Mean heart dose (Gy; median, IQR)	8.1 (4.8–17.8)
Mean lung dose (Gy; median, IQR)	16.8 (13.5–19.3)
Chemotherapy regimen	
Carboplatin/paclitaxel	106 (56.7)
Cisplatin/etoposide	57 (30.5)
Other	24 (12.8)
Chemotherapy sequence	
Concurrent	184 (98.4)
Sequential	3 (1.6)

IQR, interquartile range; PS, performance status; CCI, Charlson Comorbidity Index; RT, radiotherapy; PT, proton therapy; PBS, pencil beam scanning; PS, passive scattering; IMRT, intensity-modulated radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy.

Death without progression

Median follow-up was 29.9 months (interquartile range [IQR], 16.4–71.8) for all patients and 7.3 years (IQR, 5.7–8.7) for survivors. Death occurred in 143 (76.5 %), including death after progression in 118 (63.1 %), and DWP in 25 patients (13.4 %) (Fig. 1A). 1-, 2-, and 5-year cumulative incidence of DWP was 3.7 %, 8.6 %, and 11.2 %, respectively. DWP was attributed to underlying comorbidity (n = 6, 24 %), infection (n = 6, 24 %), out-of-hospital cardiopulmonary arrest (n = 4, 16 %), chemoradiation toxicity (n = 2, 8 %), and unknown (n = 7, 28 %) (Table 2). Of the 25 patients with DWP, baseline cardiovascular, pulmonary, and either cardiovascular or pulmonary comorbidities were present in 15 (60 %), 14 (56 %), and 20 patients (80 %), respectively (Supplementary Table 1).

DWP (Fig. 1B-C), but not death after progression (Supplementary Fig. 1A-B), increased with higher CCI strata and MHD ≥ 10 Gy (5-year DWP rate, 16.9 % vs 6.7 %, p = 0.04). On univariable analysis, age, ECOG performance status, CCI strata, and MHD were associated with an increased risk of DWP (Table 3). On multivariable analysis, MHD (sHR 1.06/Gy, 95 % CI 1.02–1.10, p = 0.002) retained significance when paired with CCI strata (sHR 2.60/stratum, 95 % CI 1.50–4.49, p < 0.001). There was no significant interaction between CCI strata and MHD (interaction p = 0.73). There was a significant interaction between proton therapy and MHD (interaction p = 0.024): MHD was associated with DWP among those receiving photon therapy (sHR 1.06/Gy, 95 % CI 1.03–1.10, p < 0.001) but not proton therapy (sHR 0.87/Gy, 95 % CI 0.73–1.03, p = 0.1).

Overall survival

Median OS was 28.9 months (95 % CI, 23.5–31.6) and lower for those with MHD ≥ 10 Gy (median, 22.9 vs 34.1 months, p < 0.001) (Fig. 2). On multivariable analysis, MHD (HR 1.03/Gy, 95 % CI 1.01–1.05, p = 0.010) was associated with inferior OS after accounting

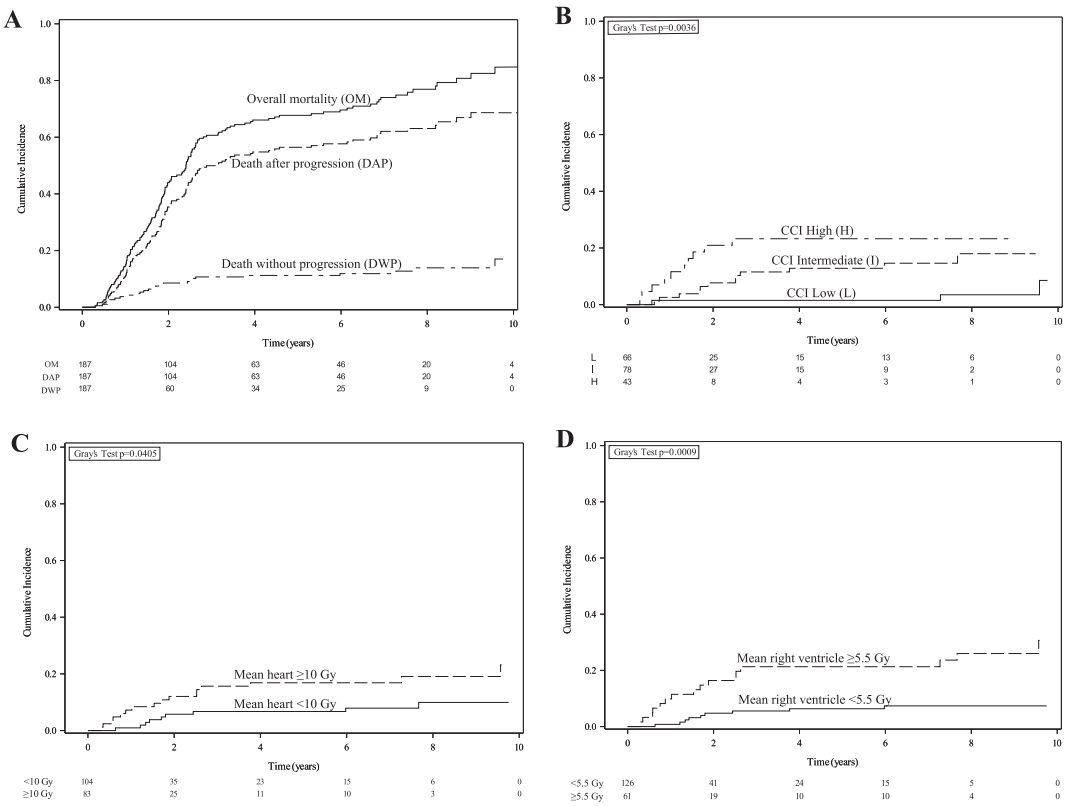

Fig. 1. (A) Cumulative incidence of overall mortality, death after progression, and death without progression. (B-D) Death without progression stratified by (B) Charlson Comorbidity Index (CCI) (low = 0–2; intermediate = 3–4; high = 5–9), (C) mean heart dose ≥ 10 Gy, and (D) mean right ventricle dose ≥ 5.5 Gy.

Table 2
Presumed causes of death without progression (N = 25).

Cause of death	N
Pre-existing comorbidity	
COPD (pre-existing)	1
COPD (pre-existing) + pulmonary embolism (new)	1
Heart failure (pre-existing)	1
COPD (pre-existing) + heart failure (new)	1
Heart failure (pre-existing) + renal failure (pre-existing CKD) +/- pneumonitis	1
IPF (pre-existing) + pneumonia	1
Infection	
Pneumonia	4
Undifferentiated sepsis	2
Out-of-hospital cardiopulmonary arrest	4
Chemoradiation toxicity	
Pneumonitis +/- pneumonia	1
Esophagopleural fistula	1
Unknown	7

COPD, chronic obstructive pulmonary disease; IPF, interstitial pulmonary fibrosis.

for age, ECOG performance status, pulmonary comorbidity, and ITV. MLD was also associated with inferior OS in a separate multivariable model (Table 3).

Associations between cardiovascular substructure dose and either DWP or OS

On univariable analysis, dose to the right ventricle, left ventricle, ventricles, pericardium, and heart were associated with DWP (Supplementary Table 2). Mean right ventricle dose (AIC 229; lowest), ventricles V5 (AIC 235; second lowest), heart V5, mean pericardium dose, and left ventricle V5 were associated with an increased risk of DWP in separate multivariable models that included CCI (Table 4). Model rankings were similar using an alternative set of multivariable models that incorporated age and ITV instead of CCI (Supplementary Table 3). Mean right ventricle cutpoint of 5.5 Gy was identified; this threshold predicted for DWP (Fig. 1D) but not death after progression (Supplementary Fig. 1C).

On univariable analysis, dose to the left atrium, right atrium, atria, pericardium, heart, right ventricle, left ventricle, and ventricles were associated with OS (Supplementary Table 2). Left atrium V5 (AIC 1277; lowest), atria V5 (AIC 1278; second lowest), pericardium V5, right atrium V5, mean heart dose, right ventricle V5, left ventricle V50, and ventricles V5 were associated with inferior OS in separate multivariable models (Table 4).

External cohort

In the external cohort, median follow-up was 18.7 months (IQR, 8.2–36.6) for all patients and 36.6 months (IQR, 26.6–51.9) for survivors. DWP occurred in 19 of 140 patients (13.6 %). Right ventricle V30, ventricles V30, heart V30, and left ventricle V30 were associated with DWP after adjusting for age (Supplementary Table 4), whereas doses to atria, right atrium, and left atrium were not. Mean right ventricle dose ≥ 5.5 Gy was associated with numerically but not significantly higher cumulative incidence of DWP (2-year rate, 13.4 % vs 6.3 %, p = 0.35). No cardiac substructure dosimetric parameters were associated with OS.

Discussion

Among patients with NSCLC treated with CRT, we describe three main findings: 1) DWP occurred in 13 % of patients; 2) After controlling for baseline comorbidity burden, MHD and dose to specific cardiovascular substructures (right ventricle, ventricles, left ventricle, pericardium) were associated with DWP; and 3) Cardiovascular substructure dose showed associations with DWP distinct from those seen with OS.

Table 3
Fine-Gray regression for death without progression and Cox regression for overall survival.

Variable	Univariable		Multivariable	
Death without progression	sHR (95 % CI)	P	sHR (95 % CI)	P
Age (y)	1.07 (1.03–1.11)	<0.001		
Female sex	0.97 (0.45–2.11)	0.94		
ECOG PS (stratum)	2.16 (1.21–3.85)	0.009		
Cardiovascular comorbidity	1.90 (0.85–4.25)	0.12		
Pulmonary comorbidity	1.93 (0.88–4.22)	0.099		
CCI (stratum)	2.23 (1.35–3.69)	0.002	2.60 (1.50–4.49)	<0.001
Adenocarcinoma (vs all else)	1.06 (0.40–2.82)	0.90		
N3 (vs all else)	1.68 (0.72–3.92)	0.23		
Left-sided primary	1.00 (0.45–2.21)	1		
RT dose (Gy)	1.14 (0.97–1.33)	0.11		
Proton therapy (vs all else)	0.50 (0.22–1.12)	0.092		
Proton therapy (vs IMRT)	0.50 (0.21–1.17)	0.11		
Internal target volume (per 100 cc)	0.97 (0.84–1.12)	0.67		
Mean heart dose (Gy)	1.05 (1.01–1.08)	0.007	1.06 (1.02–1.10)	0.002
Mean lung dose (Gy)	0.97 (0.89–1.06)	0.45		
Carbo/taxol (vs all else)	2.03 (0.85–4.82)	0.11		
Overall survival	**HR (95 % CI)**	**P**	**HR (95 % CI)**	**P**
Age (y)	1.03 (1.02–1.05)	<0.001	1.04 (1.02–1.06)[2]	<0.001
Female sex	0.82 (0.59–1.14)	0.24		
ECOG PS (stratum)	1.67 (1.25–2.30)	<0.001	1.59 (1.18–2.16)[2]	0.003
Cardiovascular comorbidity	1.28 (0.92–1.78)	0.15		
Pulmonary comorbidity	1.42 (1.02–1.98)	0.040	1.48 (1.05–2.09)[2]	0.027
CCI (stratum)	1.67 (1.33–2.09)	<0.001		
Adenocarcinoma (vs all else)	0.89 (0.60–1.33)	0.89		
N3 (vs all else)	1.21 (0.82–1.78)	0.34		
Left-sided primary	1.07 (0.77–1.50)	0.68		
RT dose (Gy)	0.97 (0.91–1.03)	0.36		
Proton therapy (vs all else)	1.09 (0.78–1.53)	0.61		
Proton therapy (vs IMRT)	1.12 (0.78–1.61)	0.54		
Internal target volume (per 100 cc)	1.08 (1.03–1.14)	0.002	1.10 (1.03–1.16)[2]	0.002
Mean heart dose (Gy)	1.02 (1.01–1.04)	0.002	1.03 (1.01–1.05)[1]	0.010
Mean lung dose (Gy)	1.04 (1.00–1.09)	0.041	1.05 (1.01–1.10)[2]	0.027
Carbo/taxol (vs all else)	1.11 (0.80–1.55)	0.52		

sHR, subdistribution hazard ratio; y, years; PS, performance status; CCI, Charlson Comorbidity Index; RT, radiotherapy; IMRT, intensity-modulated radiotherapy; carbo/taxol, carboplatin/paclitaxel; HR, hazard ratio.

[1] Model with mean heart dose, age, ECOG PS, pulmonary comorbidity, internal target volume.
[2] Model with mean lung dose, age, ECOG PS, pulmonary comorbidity, internal target volume.

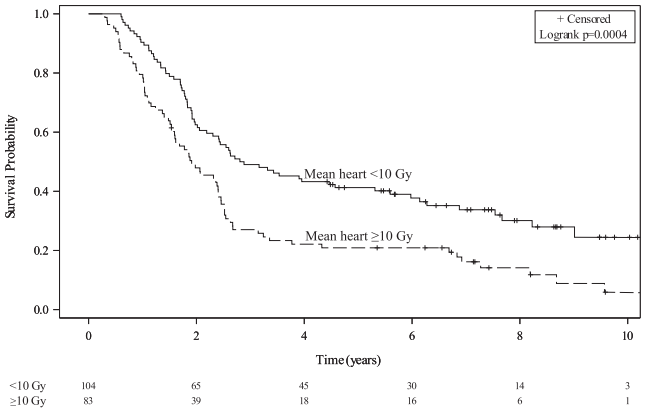

Fig. 2. Overall survival stratified by mean heart dose ≥ 10 Gy.

Table 4
Exploratory associations between cardiovascular substructure dose and either death without progression or overall survival[1].

Dosimetric parameter	Multivariable analysis[2]		
Death without progression	sHR (95 % CI)	P	AIC
Mean right ventricle dose (Gy)	1.08 (1.04–1.11)	<0.001	229
Ventricles V5 (%)	1.02 (1.01–1.03)	<0.001	235
Heart V5 (%)	1.02 (1.01–1.04)	0.002	236
Mean pericardium dose (Gy)	1.07 (1.03–1.11)	<0.001	236
Left ventricle V5 (%)	1.02 (1.01–1.03)	0.002	239
Overall survival	**HR (95 % CI)**	**P**	**AIC**
Left atrium V5 (%)	1.01 (1.00–1.02)	0.003	1277
Atria V5 (%)	1.01 (1.00–1.02)	0.004	1278
Pericardium V5 (%)	1.01 (1.00–1.02)	0.008	1279
Right atrium V5 (%)	1.01 (1.00–1.01)	0.010	1280
Mean heart dose (Gy)	1.03 (1.01–1.05)	0.010	1280
Right ventricle V5 (%)	1.01 (1.00–1.01)	0.016	1281
Left ventricle V50 (%)	1.02 (1.00–1.03)	0.014	1281
Ventricles V5 (%)	1.01 (1.00–1.01)	0.053	1283

sHR, subdistribution hazard ratio; AIC, Akaike information criterion; Vx, volume receiving ≥ x Gy; HR, hazard ratio.
[1] Shown are only those dosimetric parameters that were significant on univariable analysis. In addition to 44 total cardiovascular dosimetric parameters (11 cardiovascular structures, 4 parameters per structure), mean lung dose was tested.
[2] For death without progression, each dosimetric parameter was tested in a separate multivariable model with Charlson Comorbidity Index. For overall survival, each dosimetric parameter was tested in a separate multivariable model with age, ECOG performance status, pulmonary comorbidity, and internal target volume.

For DWP, the critical structures identified in the primary cohort were confirmed in the external cohort, but additional work is needed to determine the optimal dose-volume constraints for these structures. Our results support DWP as an endpoint to consider in studies assessing the significance of cardiovascular substructure dose for NSCLC.

Patients with NSCLC frequently present with baseline cardiopulmonary comorbidities (67.9 % in this cohort), and comorbidity burden is a known negative prognostic factor [23,24]. In our cohort, both CCI and MHD ≥ 10 Gy were associated with an increased risk of DWP, but not death after progression, supporting the utility of DWP in assessing the effects of comorbidity and CRT toxicity on longevity. Although pre-existing comorbidity was listed as a cause of DWP in only 6/25

patients, it likely contributed, at least partially, to DWP among many of the remaining cases (based on Supplementary Table 1). No significant interaction was observed between CCI strata and MHD (ie, the association between MHD and DWP did not differ based on CCI stratum); however, power was limited.

Prior studies attempting to identify the most dose-sensitive cardiovascular substructures in LA-NSCLC have focused on OS and cardiac events [9,11–13] (Supplementary Table 5). In our cohort, we found that right ventricle, ventricles, heart, pericardium, and left ventricle dose were associated with both DWP and OS, whereas left atrium, atria, and right atrium dose were associated with OS but not DWP. Thus, DWP may be a more specific endpoint and can provide additional dose-toxicity information beyond OS. Though mean right ventricle dose had the lowest AIC for prediction of DWP, this finding is hypothesis-generating given the limited number of events and lack of more robust model-selection methods.

RT likely has a multi-faceted effect on the cardiovascular system that could explain an association with DWP. RT potentially leads to early microvascular changes and perfusion defects [25,26], impaired ventricle ejection fraction [27], and may affect circulating immune cells in the blood to increase the risk of immunosuppression [6,28]. Additionally, the association with right ventricle dose raises the question of underdiagnosed pulmonary hypertension in this patient population [29]. Conceivably, any of these factors could weaken a patient's cardiopulmonary and immune system and increase their susceptibility to succumb to infection, comorbidity exacerbation, or another event unrelated to cancer progression.

Efforts to reduce RT dose to the heart appear warranted. Based on our findings and those from Atkins et al. [8], we advocate for a mean heart dose < 10 Gy, below the currently recommended threshold of 20 Gy [30]. Efforts toward plan optimization and standardization of cardiac dose constraints may reduce cardiac dose without comprising tumor coverage or other normal tissue constraints [31,32]. Specific recommendations for cardiovascular substructure dose thresholds appear less obvious. For select tumors abutting the heart, proton therapy may significantly reduce heart dose [33]. Notably, in our cohort proton therapy was associated with a marginally lower risk of DWP, lower MHD (median, 6.7 Gy vs 15 Gy, Wilcoxon rank-sum $p < 0.001$), and lower dose to multiple cardiovascular substructures (eg, right ventricle mean dose 0.03 Gy vs 7.7 Gy, $p < 0.001$, Supplementary Table 6). Given the possibility of selection bias and non-significant difference in DWP, these observations should be interpreted with caution. A secondary analysis of the ongoing RTOG 1308 trial could assess differences in DWP between the proton and photon groups.

Patients in this cohort were treated prior to approval of consolidation with durvalumab. With improved disease control and OS seen with durvalumab [15], the risk of NSCLC progression and death from NSCLC is expected to decrease and the relative importance of baseline comorbidity and heart dose on longevity may increase.

There are limitations to this work. First, the study was retrospective with a limited number of DWP events, restricting the ability to control for potential confounders beyond CCI (eg, chemotherapy regimen) and introducing the possibility of unmeasured confounders. Given the limited number of events, we restricted our analysis to four dosimetric parameters per cardiovascular structure (mean, V5, V30, V50), realizing that other parameters (e.g., maximum dose, minimum dose to the hottest x% volume [Dx%]) may be more predictive. Second, DWP does not account for toxicity or death from intercurrent disease that may occur after disease progression (limiting sensitivity), and includes death from causes such as second cancers or accidents unrelated to comorbidity or CRT (limiting specificity). However, we did not observe any causes of DWP that were clearly unrelated to comorbidity or CRT. Furthermore, DWP removes the often-subjective nature of attributing causes of death (i.e., any patient without disease progression at the time of death experiences DWP). Third, this work assumes that heart dose should not increase the risk of disease progression, but emerging evidence suggests that effective dose to immune cells, which factors in heart dose, may be associated with worse disease control [34,35]. Fourth, left anterior descending coronary artery (LAD) dose statistics were not available as LAD was not included in our autocontouring model. LAD V15 has been associated with major adverse cardiac events and worse OS after CRT [11,36], and should be included in future cardiotoxicity studies. Fifth, the external cohort should not be interpreted as a validation cohort since certain variables were unavailable (e.g., CCI) and different dose metrics emerged as predictive (e.g., RV V30 instead of mean). Nevertheless, it suggests a degree of external validity to our findings.

Conclusion

In conclusion, baseline comorbidity, MHD, and dose to several cardiovascular substructures were associated with DWP after CRT for NSCLC. Future studies should consider using DWP as an endpoint when assessing the significance of cardiovascular substructure dose.

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Declaration of Competing Interest

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100581.

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