



## Original Article

# Associations between cardiac irradiation and survival in patients with non-small cell lung cancer: Validation and new discoveries in an independent dataset



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## ABSTRACT

**Introduction:** In 'IDEAL-6' patients (N = 78) treated for locally-advanced non-small-cell lung cancer using isotoxically dose-escalated radiotherapy, overall survival (OS) was associated more strongly with  $V_{LAwall-64-73-EQD2}$ , the left atrial (LA) wall volume receiving 64–73 Gy equivalent dose in 2 Gy fractions (EQD2), than with whole-heart irradiation measures. Here we test this in an independent cohort 'OX-RT' (N = 64) treated routinely.

**Methods:** Using Cox regression analysis we assessed how strongly OS was associated with  $V_{LAwall-64-73-EQD2}$ , with whole-heart volumes receiving 64–73 Gy EQD2 or doses above 10-to-70 Gy thresholds, and with principal components of whole-heart dose-distributions. Additionally, we tested associations between OS and volumes of cardiac substructures receiving dose-ranges described by whole-heart principal components significantly associated with OS.

**Results:** In univariable analyses of OX-RT, OS was associated more strongly with  $V_{LAwall-64-73-EQD2}$  than with whole-heart irradiation measures, but more strongly still with  $V_{AortV-29-38-EQD2}$ , the volume of the aortic valve region receiving 29–38 Gy EQD2. The best multivariable OS model included LA wall and aortic valve region mean doses, and the aortic valve volume receiving  $\geq 38$  Gy EQD2,  $V_{AortV-38-EQD2}$ . In a subsidiary analysis of IDEAL-6, the best multivariable model included  $V_{LAwall-64-73-EQD2}$ ,  $V_{AortV-29-38-EQD2}$ ,  $V_{AortV-38-EQD2}$  and mean aortic valve dose.

**Conclusion:** We propose reducing heart mean doses to the lowest levels possible while meeting protocol dose-limits for lung, oesophagus, proximal bronchial tree, cord and brachial plexus. This in turn achieves large reductions in  $V_{AortV-29-38-EQD2}$  and  $V_{LAwall-64-73-EQD2}$ , and we plan to closely monitor patients with values of these measures still >0% (their median value in OX-RT) following reduction.

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Investigators have recently reported significant negative associations between heart irradiation and overall survival (OS) following radical radiotherapy (RT) for non-small cell lung cancer (NSCLC) [1–8]. We analysed OS in a cohort of patients, 'IDEAL-6', treated in the IDEAL-CRT phase 1/2 trial of isotoxically dose-escalated RT for locally-advanced NSCLC given in 30 fractions over 6 weeks concurrent with chemotherapy [8,9]. OS was significantly associated with one principal component (PC) of patients' heart dose-distributions, which described fractional heart volumes receiving equivalent doses in 2 Gy fractions (EQD2) of 64–73 Gy

( $\alpha/\beta = 3$  Gy [10]), delivered largely to the left atrial (LA) wall. The best multivariable (MV) model of survival identified for IDEAL-6 included the fractional LA wall volume receiving 64–73 Gy EQD2 ( $V_{LAwall-64-73-EQD2}$ ) in preference to the corresponding whole-heart volume ( $V_{Heart-64-73-EQD2}$ ) [8].

Here, we report a post-hoc analysis of survival in an independent cohort of locally-advanced NSCLC patients, 'OX-RT', treated with curative intent using RT alone or chemo-RT given in 2 Gy fractions. We assess the association between OS and  $V_{LAwall-64-73-EQD2}$ , and compare it with associations between OS and other cardiac irradiation measures. MV models of OS in OX-RT are built from dose-volume measures and clinical factors, and judged according to the Akaike Information Criterion (AIC) and Harrell's C-statistic.

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**Materials and methods**

*Patient data*

The independent cohort, OX-RT, was drawn from Oxford Cancer Centre. Following institutional approval, medical records were retrieved for 80 patients with locally-advanced NSCLC treated consecutively during 2010–2014. Of these, 64 had evaluable datasets with accessible electronic treatment plans including dose-distribution data and no re-planning during RT. Patient and treatment characteristics were collated for this cohort, along with time to last follow-up or death.

RT was delivered using 3D conformal or volumetric modulated arc therapy (VMAT) techniques, as monotherapy or with sequential or concurrent chemotherapy comprising 3–4 or 2 cycles of platinum doublet respectively. For most OX-RT patients the prescribed dose was 66 Gy in 33 daily fractions over 6.5 weeks, but eight received doses ≤12% lower due to toxicity. Treatment characteristics are summarized in Table 1 for OX-RT and the IDEAL-6 cohort originally studied.

*Statistics*

Differences in patient and treatment factors between the cohorts were assessed using the Mann-Whitney test for continuous data, Fisher’s exact test for binary data, and the chi-square test for data with >2 categories. Reported confidence intervals (CIs) and significance-levels are 2-sided.

OS was measured from treatment commencement, censored at last follow-up, and estimated using the Kaplan-Meier method. Significances of differences between survival curves were assessed using the log-rank test. MV models of OS were constructed from patient and treatment factors with  $p < 0.30$  on univariable (UV) analysis, using bi-directional variable elimination to find the best models with the lowest AIC scores. MV model performance was measured using Harrell’s C-statistic [11,12] which describes the fraction of all pairs of evaluable patients in which observed and modelled survivals are both shorter for the same patient. Where necessary, the false discovery rate after multiple hypothesis testing was limited to 10% via the Benjamini-Hochberg step-up procedure.

For some OX-RT patients data was incomplete. These patients were omitted from UV analyses of the factors concerned, which were not carried forward to MV analysis since their associations with OS were insufficiently significant in the UV analyses.

*Validation in OX-RT of association between OS and  $V_{LAwall-64-73-EQD2}$*

Heart and left atrium were segmented on CT scans using a validated atlas [13]. LA wall was defined as the region lying ≤5 mm within the LA contour [8]. RT plans were imported into the Computational Environment for Radiotherapy Research (CERR) software, and dose-volume histograms (DVHs) were generated and exported to SPSS version 25 (IBM Corp, Armonk, NY) and R 4 (R Foundation, Vienna, Austria) for analysis.

In the OX-RT validation cohort we determined how strongly OS was associated with  $V_{LAwall-64-73-EQD2}$  according to UV Cox proportional hazards regression. To further describe the association, OX-RT was dichotomized into groups with  $V_{LAwall-64-73-EQD2}$  values ≤ or > the median, plotting Kaplan-Meier OS curves for both groups.

Additional UV analyses of OX-RT were carried out to determine strengths of associations of OS with  $V_{Heart-64-73-EQD2}$  and  $V_{Heart-10, 20, \dots, 70}$ , the whole-heart fractional volumes receiving 64–73 Gy EQD2 or physical doses exceeding thresholds of 10 to 70 Gy rising in 10 Gy increments, and with heart and LA wall mean physical doses. We hypothesized that OS would not be associated as strongly with

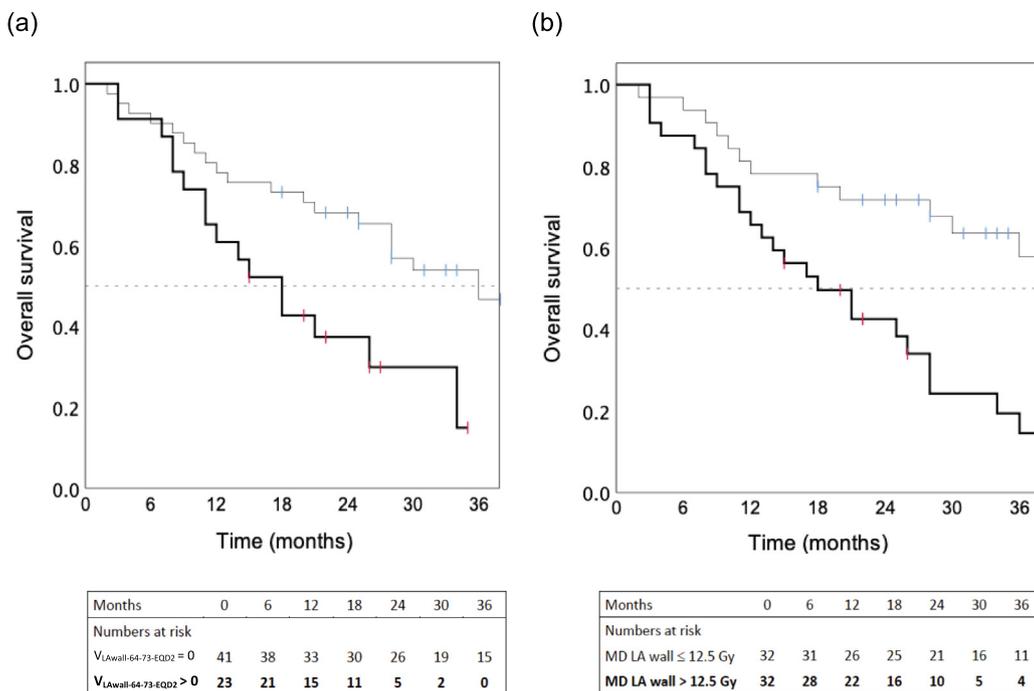
**Table 1**  
Characteristics of OX-RT and IDEAL-6 patients and their treatments.

Characteristic	OX-RT (No. = 64)	IDEAL-6 (No. = 78)	p-value
Age (years)			
median (range)	71 (44–89)	66 (43–84)	0.002
Gender (No.)			0.10
Female	25 (39.1%)	20 (25.6%)	
Male	39 (60.9%)	58 (74.4%)	
WHO PS (No.)			0.03
0	17 (26.6%)	32 (41.0%)	
1	34 (53.1%)	46 (59.0%)	
2	5 (7.8%)	0	
3	1 (1.6%)	0	
Missing	7 (10.9%)	–	
Tumour stage (No.)			<0.001
T1	3 (4.7%)	10 (12.8%)	
T2	17 (26.6%)	20 (25.6%)	
T3	40 (62.5%)	26 (33.3%)	
T4	0 (0%)	22 (28.2%)	
Missing	4 (6.3%)	0	
Nodal status (No.)			<0.001
N0 or 1	29 (45.3%)	13 (16.7%)	
N2 or 3	32 (50.0%)	65 (83.3%)	
Missing	3 (4.7%)	–	
Histology (No.)			0.44
Squamous	36 (56.3%)	42 (53.8%)	
Non-squamous	24 (37.5%)	36 (46.2%)	
Missing	4 (6.3%)	–	
PTV (cm <sup>3</sup> )			0.004
median (range)	319 (82–1120)	401 (139–1262)	
4D-CT used for planning (No.)	56 (87.5%)	34 (43.6%)	<0.001
RT technique (No.)			<0.001
3D conformal	48 (75.0%)	75 (96.2%)	
VMAT	16 (25.0%)	3 (3.8%)	
OX-RT or IDEAL-6 prescribed dose (No.)			
66 Gy in 33# or 71.1–73 Gy in 30#	56 (87.5%)	20 (25.6%)	
64 Gy in 32# or 69.1–71 Gy in 30#	3 (4.7%)	11 (14.1%)	
62 Gy in 31# or 67.1–69 Gy in 30#	2 (3.1%)	10 (12.8%)	
60 Gy in 30# or 65.1–67 Gy in 30#	2 (3.1%)	15 (19.2%)	
58 Gy in 29# or 63–65 Gy in 30#	1 (1.6%)	22 (28.2%)	
Prescribed tumour EQD2* (Gy)			<0.001
median (range)	66 (58–66)	69.0 (63.5–75.6)	
Heart mean dose (Gy)			0.19
median (range)	7.6 (0.5–32.2)	10.3 (1.1–32.2)	
LA wall mean dose (Gy)			0.004
median (range)	12.5 (0.5–56.2)	20.4 (1.3–63.0)	
$V_{LAwall-64-73-EQD2}$ (%)			0.003
median (range)	0.0 (0–25.5)	1.9 (0–76.1)	
Chemotherapy (No.)			<0.001
Concurrent	17 (26.5%)	78 (100%)	
Sequential	16 (25.0%)	0	
No chemotherapy	29 (45.3%)	0	
Missing	2 (3.1%)	0	

\*EQD2s calculated using  $\alpha/\beta = 10$  Gy, no time-factor. Abbreviations: CT = computed tomography; EQD2 = equivalent dose in 2 Gy fractions; LA = left atrium; PTV = planning target volume;  $V_{LAwall-64-73-EQD2}$  = fraction of LA wall receiving 64–73 Gy EQD; VMAT = volumetric modulated arc therapy; WHO PS = World Health Organization performance status.

the whole-heart irradiation measures as with  $V_{LAwall-64-73-EQD2}$ , following the pattern observed in IDEAL-6 [8].

MV Cox regression analysis was performed to further characterize associations in OX-RT between OS and these dosimetric measures and patient and treatment factors potentially related to survival.



**Fig. 1.** Kaplan-Meier survival curves for OX-RT patients dichotomized by: (a) fraction of left atrial wall receiving 64–73 Gy EQD2 ( $V_{LAwall-64-73-EQD2}$ ) equal to (light) or > (bold) the 0% median OX-RT value (log-rank  $p = 0.009$ ); (b) mean dose to the wall of the left atrium (MD LA wall)  $\leq$  (light) or > (bold) the 12.5 Gy median OX-RT value (log-rank  $p = 0.007$ ).

**Table 2**

Associations between overall survival in the OX-RT cohort and LA wall and whole-heart dose-volume measures, and patient and treatment factors potentially related to survival. Unadjusted (univariable) results are shown together with the best multivariable model built from these factors.

Covariate	Unadjusted analysis		Best multivariable model <sup>†</sup> C = 0.71, AIC = 265.2*	
	p-value	HR (95% CI)	p-value	HR (95% CI)
$V_{LAwall-64-73-EQD2}$ (%)	0.006	1.077 (1.022–1.134)	–	–
Mean LA wall dose (Gy)	$2 \times 10^{-4}$	1.049 (1.023–1.075)	$2 \times 10^{-4}$	1.094 (1.043–1.148)
$V_{Heart-64-73-EQD2}$ (%)	0.27	1.048 (0.965–1.139)	–	–
$V_{Heart-10}$ (%)	0.04	1.012 (1.001–1.024)	–	–
$V_{Heart-20}$ (%)	0.02	1.022 (1.003–1.040)	0.06	0.958 (0.916, 1.002)
$V_{Heart-30}$ (%)	0.02	1.028 (1.004–1.052)	–	–
$V_{Heart-40}$ (%)	0.03	1.034 (1.003–1.066)	–	–
$V_{Heart-50}$ (%)	0.19	1.027 (0.987–1.068)	–	–
$V_{Heart-60}$ (%)	0.26	1.030 (0.978–1.085)	–	–
$V_{Heart-70}$ (%)	0.10	8.326 (0.665–104.2)	–	–
Mean heart dose (Gy)	0.02	1.046 (1.007–1.087)	–	–
Prescribed tumour EQD2 (Gy)	0.18	0.905 (0.781–1.048)	0.02	0.834 (0.718, 0.974)
PTV (cm <sup>3</sup> )	0.17	1.001 (1.000–1.002)	0.03	1.002 (1.000, 1.003)
Technique (3D conf vs VMAT)	0.14	1.627 (0.818–4.081)	–	–
RT alone vs chemo-RT	0.76	0.905 (0.475–1.726)	–	–
Age (years)	0.03	0.965 (0.935–0.996)	–	–
Gender (male vs female)	0.26	1.457 (0.754–2.818)	–	–
WHO PS 0 or 1 vs 2 or 3	0.95	0.971 (0.342–2.756)	–	–
Nodal status (N0 or 1 vs 2 or 3)	0.91	1.037 (0.543–1.983)	–	–
Histology (non-squam vs squam)	0.60	1.193 (0.616–2.309)	–	–
Baseline cardiac comorbidity (1 present, 0 absent)	0.57	0.805 (0.380–1.704)	–	–
Smoker (1 at any time, 0 never)	0.48	2.056 (0.279–15.17)	–	–
Pack-year history	0.84	1.001 (0.990, 1.013)	–	–

<sup>†</sup>Constructed from factors with  $p < 0.30$  in univariable analyses, using bi-directional variable elimination to find the best multivariable model with the lowest AIC score.

\*AICs for univariable models based on mean LA wall dose,  $V_{Heart-20}$ , mean heart dose or PTV alone were 267.4, 275.6, 278.8 and 278.8 respectively.

For binary factors, an HR > 1 implies the risk of death is greater for the value listed first.

Abbreviations: AIC = Akaike information criterion, C = Harrell’s C-statistic, HR = hazard ratio, LA = left atrium, PS = performance status, PTV = planning target volume,  $V_{Structure-X-Y-EQD2}$  = fraction of structure receiving X-Y Gy EQD2,  $V_{Structure-Z}$  = fraction of structure receiving > Z Gy physical dose.

**Additional discovery work in OX-RT**

**Whole-heart PC analysis and dose-localization**

PCs of whole-heart dose-volume histograms (DVHs) were obtained using varimax rotation to simplify their structure [8].

DVHs were approximated using linear combinations of ten PCs which accounted for >95% of the DVH variance. UV Cox regression was performed to determine associations between OS and patient-specific coefficients of PCs in the combinations approximating whole-heart DVHs.

**Table 3**

Associations between overall survival in the OX-RT cohort and cardiac substructure dose-volume measures. Unadjusted (univariable) results are shown together with the best multivariable model built from these factors and those included in the best MV model from Table 2. Best fits to bootstrap resampled data are also summarised.

Covariate	Unadjusted analysis		Best multivariable model <sup>†</sup> (C = 0.74, AIC = 262.5*)		Bootstrap models Inclusion** (%)
	p-value	HR (95% CI)	p-value	HR (95% CI)	
<i>Substructure measures</i>					
V <sub>AortV-29-38-EQD2</sub> (%)	7 × 10 <sup>-5</sup>	1.069 (1.035–1.105)	–	–	30.9
V <sub>AortV-38-EQD2</sub> (%)	0.16	1.013 (0.995–1.030)	0.02	0.956 (0.921–0.991)	29.2
Mean aortic valve dose (Gy)	0.007	1.036 (1.015–1.057)	0.01	1.100 (1.019–1.186)	33.8
V <sub>LMCA-29-38-EQD2</sub> (%)	0.11	1.019 (0.996–1.042)	–	–	28.6
V <sub>LMCA-38-EQD2</sub> (%)	0.02	1.012 (1.002–1.024)	–	–	34.4
Mean LMCA dose (Gy)	0.004	1.027 (1.009–1.046)	–	–	35.4
V <sub>LAWall-64-73-EQD2</sub> (%)	0.006	1.077 (1.022–1.134)	–	–	29.9
V <sub>LAWall-73-EQD2</sub> (%)	0.32	1.633 (0.628–4.248)	–	–	32.0
Mean LA wall dose (Gy)	2 × 10 <sup>-4</sup>	1.049 (1.023–1.075)	0.04	1.059 (1.002–1.120)	31.1
<i>Other factors</i>					
V <sub>Heart-20</sub> (%)	0.02	1.022 (1.003–1.040)	0.02	0.936 (0.887–0.989)	29.8
PTV (cm <sup>3</sup> )	0.17	1.001 (1.000–1.002)	0.005	1.002 (1.001–1.004)	25.8
Prescribed tumour EQD2 (Gy)	0.18	0.905 (0.781–1.048)	0.006	0.794 (0.674–0.935)	23.0

<sup>†</sup>Constructed from factors with p < 0.30 in univariable analyses, using bi-directional variable elimination to find the best multivariable model with the lowest AIC score. \*AICs for univariable models based on V<sub>AortV-29-38-EQD2</sub>, mean aortic valve dose, mean LA wall dose, V<sub>Heart-20</sub>, PTV or prescribed tumour dose alone were 268.4, 271.0, 267.4, 275.6, 278.8 and 278.8 respectively.

\*\*Percentage of the best models of survival in each of 1000 bootstraps of the OX-RT dataset in which a covariate is included.

Abbreviations: AIC = Akaike information criterion, AortV = aortic valve region, C = Harrell’s C-statistic, HR = hazard ratio, LA = left atrium, LMCA = left main coronary artery, PTV = planning target volume, V<sub>Structure-X-Y-EQD2</sub> = fraction of structure receiving X-Y Gy EQD2, V<sub>Structure-Y-EQD2</sub> = fraction of structure receiving > Y Gy EQD2, V<sub>Structure-Z</sub> = fraction of structure receiving > Z Gy physical dose.

Dose-ranges described by PCs significantly associated with OS were identified from peaks in PC variable-loading plots, and heart substructures irradiated to these dose-levels were found using an approach described previously [8]. A single heart with typical volume and shape was selected as a reference geometry, and heart dose-distributions of all OX-RT patients were mapped to it via affine transformations derived from heart and left atrium outlines. Then 2D axial, coronal and sagittal projections through the heart were constructed, in which each pixel described the percentage of patients for whom the associated projection line ran through heart voxels irradiated to doses within the range identified. Having localized dose-ranges to specific heart regions, substructures within the regions were delineated on each patient’s CT scan using a validated atlas [13] and DVHs were calculated for them.

*Associations between OS and additional cardiac substructure dose-volume measures*

For substructures most commonly irradiated to the dose-ranges described by whole-heart PCs significantly associated with OS, we performed UV Cox regression of OS versus substructure volumes receiving these doses. Associations of OS with substructure mean doses and volumes receiving higher doses were also assessed. MV analysis was performed to determine the best model of OS in OX-RT, according to the AIC, that could be built from these measures and factors in the earlier MV model.

*Back-validating new discoveries in IDEAL-6*

For new substructures found to have dose-volume measures significantly associated with OS in MV analysis of OX-RT, we carried out additional subsidiary analyses of the original IDEAL-6 dataset to determine whether substructure irradiation was associated with OS in that cohort too.

**Results**

Characteristics of OX-RT and IDEAL-6 patients and treatments are compared in Table 1. At the cut-off point for our databases, median follow-up after commencing RT was 38 months for OX-RT patients and 25 months for IDEAL-6. Median OS was 28 months

(95% CI, 21.9–34.1 months) for OX-RT and 39 months (95% CI not yet determinable) for IDEAL-6. Of 53 OX-RT patients for whom the relevant data was available, 17 (32%) had baseline cardiac comorbidity and 51 (96%) were ex/current smokers. For IDEAL-6 patients this data was not collected.

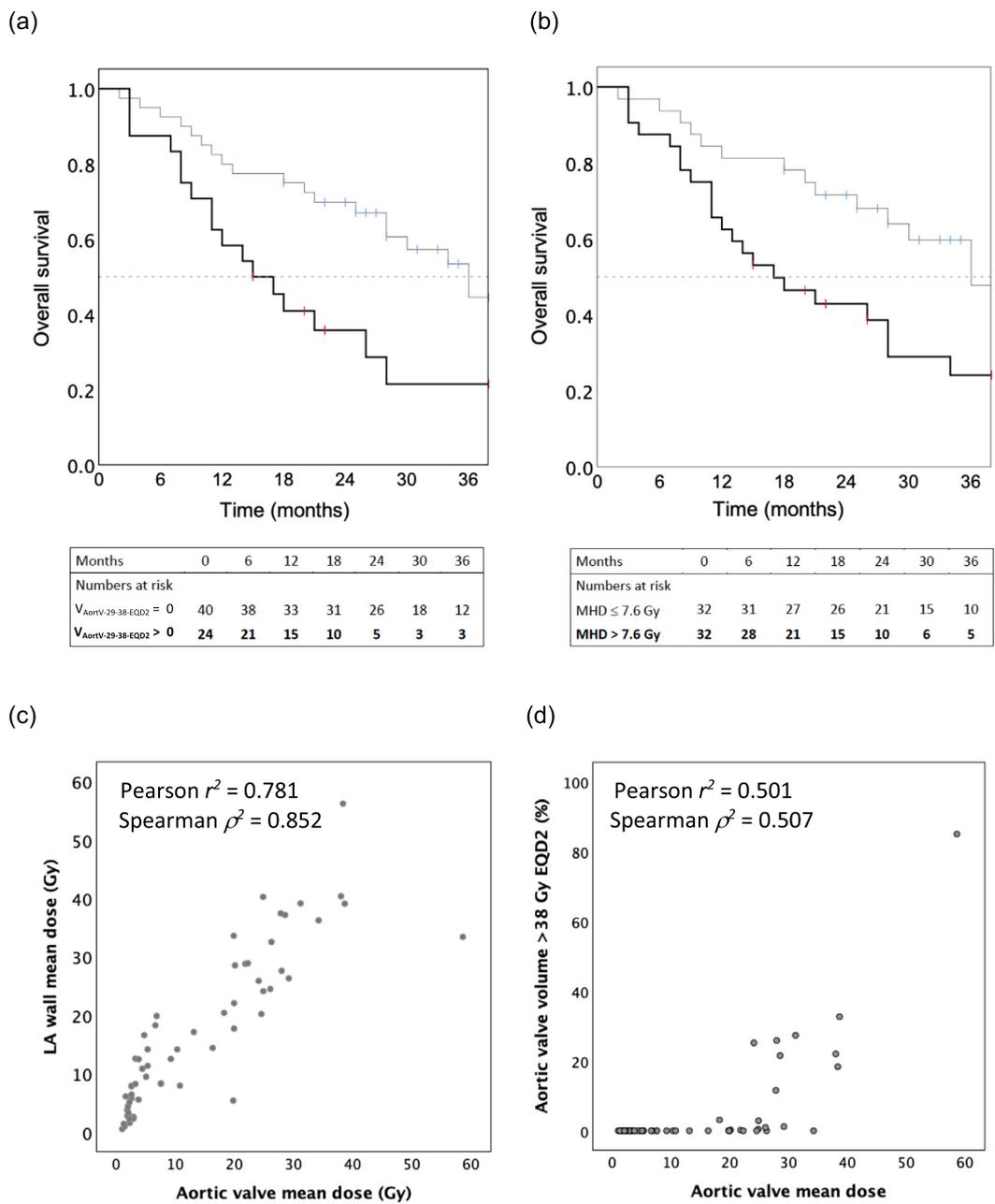
In UV analyses of OX-RT, OS was significantly associated with V<sub>LAWall-64-73-EQD2</sub> (HR, 1.08; 95% CI, 1.02–1.13; p = 0.006). Fig. 1(a) shows OS curves for OX-RT patients dichotomized by V<sub>LAWall-64-73-EQD2</sub> equal to or >0%, the median value. The curves differed significantly with an HR of 2.46 (95% CI, 1.22–4.94; p = 0.009).

OS was associated more strongly with V<sub>LAWall-64-73-EQD2</sub> than with V<sub>Heart-64-73-EQD2</sub>, V<sub>Heart-10, 20, ..., 70</sub>, mean heart dose, patient characteristics or treatment factors (Table 2). However, OS was associated more strongly still with LA wall mean physical dose (HR, 1.05; 95% CI, 1.02–1.08, p = 2 × 10<sup>-4</sup>), and this association and that with V<sub>LAWall-64-73-EQD2</sub> remained positive discoveries after allowing for multiple hypothesis testing. Fig. 1(b) shows OS curves for OX-RT patients dichotomized by LA wall mean physical dose ≤ or > the median of 12.5 Gy. Again, the two curves differed substantially (HR, 2.39; 95% CI, 1.25–4.58; p = 0.007).

The best MV survival model built for OX-RT patients from all these factors comprised LA wall mean physical dose, V<sub>Heart-20</sub>, prescribed dose and PTV size (Table 2). This model performed better than UV models based on LA wall mean physical dose or V<sub>LAWall-65-71-EQD2</sub> alone, with a lower AIC score and a higher C-statistic.

In OX-RT only whole-heart PC5 was significantly associated with OS (HR, 1.46; 95% CI, 1.11–1.92; p = 0.0074) (Supplementary Table 1), an association that remained a positive discovery after allowing for multiple hypothesis testing. PC5 had a prominent peak at 29–38 Gy EQD2 (Supplementary Fig. 1), most commonly delivered to a region around the aortic valve and left main coronary artery (Supplementary Fig. 2).

Table 3 lists associations in OX-RT between OS and irradiation of the aortic valve and left main coronary artery volumes expanded by 5 mm to allow for cardiac motion [14], and with LA wall irradiation. In UV analyses OS was significantly associated with the aortic valve volume receiving 29–38 Gy EQD2 (V<sub>AortV-29-38-EQD2</sub>), the left main coronary artery volume receiving ≥38 Gy EQD2 (V<sub>LMCA-38-EQD2</sub>), and the mean doses in both regions. The association between OS and V<sub>AortV-29-38-EQD2</sub> (HR, 1.07; 95% CI, 1.04–1.11;



**Fig. 2.** Kaplan-Meier survival curves for OX-RT patients dichotomized by: (a) fraction of the aortic valve region receiving 29–38 Gy EQD2 ( $V_{AortV-29-38-EQD2}$ ) equal to (light) or > (bold) the 0% median OX-RT value (log-rank  $p = 0.006$ ); (b) mean heart dose (MHD)  $\leq$  (light) or > (bold) the 7.6 Gy median OX-RT value (log-rank  $p = 0.045$ ). Also shown are plots of correlations between: (c) LA wall mean dose and the aortic valve region mean dose; and (d) aortic volume receiving >38 Gy and aortic valve region mean dose.

$p = 7 \times 10^{-5}$ ) was stronger than associations between OS and  $V_{LAwall-64-73-EQD2}$  or mean LA wall physical dose, and remained a positive discovery allowing for multiple hypothesis testing. For OX-RT patients dichotomized by whether  $V_{AortV-29-38-EQD2}$  was greater than the median value of 0%, OS curves differed significantly (HR, 2.39; 95% CI, 1.25–4.58;  $p = 0.006$ ; Fig. 2).

The best MV model built from all the substructure dosimetric indices together with factors included in the MV model of Table 2 comprised the volume of the aortic valve region receiving  $\geq 38$  Gy EQD2 ( $V_{AortV-38-EQD2}$ ),  $V_{Heart-20}$ , mean physical doses in the aortic valve region and LA wall, PTV size and prescribed dose (Table 3). This model had a lower AIC score than the earlier MV model, and at 0.74 its Harrell’s C-statistic was good.

Given these results we re-investigated survival in the original IDEAL-6 cohort, finding that  $V_{AortV-29-38-EQD2}$  was significantly associated with OS in UV analyses (Table 4). We also found the best MV model of OS in IDEAL-6 that could be built from several LA wall and aortic valve dose-volume measures and the factors considered in our original analysis of this cohort [8], excluding ‘any ECG change’ for which corresponding OX-RT data were unavailable. This model comprised  $V_{LAwall-64-73-EQD2}$ ,  $V_{AortV-29-38-EQD2}$ ,  $V_{AortV-38-EQD2}$ , mean aortic valve dose and PTV size (Table 4), and had better AIC and C-index values than a model comprising only  $V_{LAwall-63-73-EQD2}$  and PTV size, the two factors included alongside ‘any ECG change’ in the best model in our original analysis of IDEAL-6 [8].

**Table 4**

Associations between OS in the IDEAL-6 cohort and cardiac substructure dose-volume measures. Unadjusted (univariable) results are shown together with the best multivariable model built from these factors and those considered in our original study of IDEAL-6 excluding 'any ECG change'.

Covariate	Unadjusted analysis		Best multivariable model <sup>†</sup> C = 0.70, AIC = 193.0*	
	p-value	HR (95% CI)	p-value	HR (95% CI)
<i>Substructure measures</i>				
V <sub>AortV-29-38-EQD2</sub> (%)	0.04	1.043 (1.002–1.086)	0.002	1.112 (1.040–1.188)
V <sub>AortV-38-EQD2</sub> (%)	0.05	1.017 (1.000–1.034)	0.04	1.045 (1.002–1.091)
Mean aortic valve dose (Gy)	0.27	1.017 (0.987–1.047)	0.009	0.895 (0.824–0.973)
V <sub>LAwall-64-73-EQD2</sub> (%)	0.01	1.035 (1.008–1.063)	0.05	1.040 (1.001–1.081)
V <sub>LAwall-73-EQD2</sub> (%)	0.78	0.980 (0.852–1.127)	–	–
Mean LA wall dose (Gy)	0.26	1.016 (0.989–1.045)	–	–
<i>Other factors in best MV model</i>				
PTV (cm <sup>3</sup> )	0.04	1.002 (1.000–1.003)	0.02	1.002 (1.001–1.004)

<sup>†</sup>Constructed from factors with  $p < 0.30$  in univariable analyses, using bi-directional variable elimination to find the best multivariable model with the lowest AIC score.  
<sup>\*</sup>AICs for univariable models based on V<sub>AortV-29-38-EQD2</sub>, V<sub>AortV-38-EQD2</sub>, mean aortic valve dose, V<sub>LAwall-64-73-EQD2</sub> or PTV were 198.5, 199.0, 200.8, 197.4 and 198.2 respectively. Abbreviations: AIC = Akaike information criterion, AortV = aortic valve, C = Harrell's C-statistic, HR = hazard ratio, LA = left atrium, PTV = planning target volume, V<sub>Structure-X-Y-EQD2</sub> = fraction of structure receiving X-Y Gy EQD2, V<sub>Structure-Y-EQD2</sub> = fraction of structure receiving > Y Gy.

## Discussion

In the OX-RT validation cohort, OS was associated more strongly with V<sub>LAwall-64-73-EQD2</sub> than with any whole-heart irradiation measure investigated including V<sub>Heart-64-73-EQD2</sub>, as we had previously found in the original IDEAL-6 patient group [8]. The validation is encouraging, since patient- and treatment-related factors differed significantly between the routinely-treated single-centre OX-RT and dose-escalated multi-centre IDEAL-6 cohorts (Table 2).

In IDEAL-6, OS was associated with one PC of patients' whole-heart dose-distributions, which described 64–73 Gy EQD2s most often delivered to the LA wall [8]. In OX-RT, OS was also significantly associated with one whole-heart PC, which had a small peak at 67–72 Gy EQD2 (Supplementary Fig. 1) but a larger peak describing 29–38 Gy EQD2s typically delivered to the region around the aortic valve and left main coronary artery. Correspondingly, OS was associated with V<sub>AortV-29-38-EQD2</sub> more significantly than with V<sub>LAwall-64-73-EQD2</sub> in UV analyses of OX-RT, but less significantly in UV analyses of IDEAL-6. This may reflect dosimetric differences between the two cohorts, since in OX-RT V<sub>AortV-29-38-EQD2</sub> took a wider range of values than V<sub>LAwall-64-73-EQD2</sub>, 0–76% versus 0–45%, but in IDEAL-6 it took a narrower range, 0–26% versus 0–46%.

The best MV model of OS in OX-RT included V<sub>AortV-38-EQD2</sub>, V<sub>Heart-20</sub> and mean doses delivered to the aortic valve region and LA wall. These measures were inter-correlated (Pearson  $r^2$  values of 0.250–0.781, Fig. 2) but their variance-inflation factors were <10 (3.21–9.41) and each retained significance in the best model [15] which was selected using the AIC to avoid over-fitting. HRs were >1 for the mean dose factors but <1 for V<sub>AortV-38-EQD2</sub> and V<sub>Heart-20</sub>, suggesting the mean dose terms alone may over-penalize volumes receiving high doses. Notably, the model included terms describing irradiation of the LA wall and aortic valve, as did the best model of OS in IDEAL-6. In 1000 bootstrap resamples [16] of OX-RT, the best MV survival models included measures of irradiation of the LA wall, aortic valve and left main coronary artery with roughly equal frequencies and with an average of 2.9 measures per model, similar to the 3 in the fit to the original data (Table 3).

Our results parallel studies that found OS was associated with irradiation of the base-of-heart [2] and left atrium and superior vena cava [17], although in those studies the measures identified as most strongly associated with OS were physical dose >8.5 Gy to the base-of-heart in regularly fractionated patients [2], and the

maximum left atrium physical dose in SABR patients (6.5 and 77.6 Gy median and maximum values in SABR patients) [17]. In other studies, however, MV models have been built from combinations of atrial, pericardial, right-sided cardiac substructure, ventricular and lung irradiation measures [3,7].

The prominence of base-of-heart structures in several analyses concurs with a pre-clinical study in which heart failure followed more rapidly after whole-heart than heart-minus-atria irradiation [18], suggesting that survival might be reduced more by base-of-heart toxicity. Clinically, in LA-NSCLC patients base-of-heart doses might also be more damaging because they are relatively high [19]: in IDEAL-6, mean EQD2s in the left and right atrial walls were 19.7 and 9.0 Gy compared to 5.3 and 3.6 Gy for the ventricles. Fibrosis can be visualized via late gadolinium enhancement (LGE) on MRI [20] and is found in LA walls of patients with atrial fibrillation [21]. In oesophageal cancer patients LGE was more evident in areas of the heart receiving higher radiation doses [22].

Given the variety of cardiac irradiation measures reported to be associated with OS, and the possibility that measures most closely associated with survival might be specific to particular RT techniques or cohorts, we have investigated the usefulness of reducing a broad measure, mean heart dose. In OX-RT this measure was significantly associated with OS (HR, 1.046; 95% CI, 1.007–1.087;  $p = 0.02$ ), survival at 2 years post-treatment being 29% higher in patients with mean heart doses <7.6 Gy, the median value (Fig. 2 (b)). Similarly, in a large retrospective study the all-cause death-rate at 2 years was respectively 40% and 52% in patients with mean heart doses less or greater than 10 Gy [23].

In a planning study carried out for LA-NSCLC patients treated using VMAT we found that by introducing a mean heart dose penalty into plan optimization, in addition to the penalty used routinely to control cardiac hot-spots, mean heart doses could be reduced by an average 4.8 Gy while respecting tumour coverage protocol limits and without markedly increasing irradiation of the lungs, oesophagus, proximal bronchial tree, cord or brachial plexus [19]. This reduction amounted to 36% of the average baseline mean heart dose, and on the basis of the OX-RT data corresponds to a predicted hazard ratio for death of 0.81. Furthermore, mean heart dose reductions led to knock-on reductions in many cardiac substructure dose-volume measures. In particular, V<sub>LAwall-64-73-EQD2</sub>, V<sub>AortV-29-38-EQD2</sub> and mean left and right ventricle doses fell by 68%, 100%, 41% and 51% relative to baseline values, insuring against survival being related more specifically to

these measures than to whole-heart irradiation. Presently we are preparing a cardiac-sparing RT trial in which mean heart doses are reduced in this way.

## Conclusion

In UV analyses of two independent cohorts of LA-NSCLC patients, *OX-RT* and *IDEAL-6*, OS was associated more strongly with  $V_{\text{LAWall-64-73-EQD2}}$  than with any measure of whole-heart irradiation investigated. OS was also significantly associated with  $V_{\text{AortV-29-38-EQD2}}$  in both cohorts, and in *OX-RT* was additionally significantly associated with mean heart dose. In a separate planning study we found that by penalizing cardiac irradiation and re-optimizing plans, mean heart doses could be reduced by an average 36% relative to baseline while respecting protocol limits on irradiation of other normal tissues, in the process achieving large reductions in  $V_{\text{LAWall-64-73-EQD2}}$  and  $V_{\text{AortV-29-38-EQD2}}$ . We therefore intend to trial a treatment in which mean heart doses are reduced like this, closely monitoring patients in whom  $V_{\text{LAWall-64-73-EQD2}}$  and  $V_{\text{AortV-29-38-EQD2}}$  are not consequentially reduced to 0%, the median value of both measures in the *OX-RT* cohort.

## 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.radonc.2021.10.016>.

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