

Radiotherapy and Oncology

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:	<p>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 VLAwall-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 VLAwall-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 VLAwall-64-73-EQD2 than with whole-heart irradiation measures, but more strongly still with VAortV-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 ≥ 38 Gy EQD2, VAortV-38-EQD2. In a subsidiary analysis of IDEAL-6, the best multivariable model included VLAwall-64-73-EQD2, VAortV-29-38-EQD2, VAortV-38-EQD2 and mean aortic valve dose.</p> <p>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 VAortV-29-38-EQD2 and VLAwall-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.</p>

Highlights

Associations between heart doses and survival following RT for LA-NSCLC were analyzed

High left atrial wall volumes receiving 64-73Gy were associated with poorer survival

This result confirms earlier findings in an independent dataset

Aortic valve volumes receiving 29-38Gy were also negatively associated with survival

Additionally, mean heart dose was negatively associated with survival

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Key words: Lung cancer, radiotherapy, cardiac irradiation, survival

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8 Shortened running title: Cardiac irradiation and survival after NSCLC RT
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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 ≥ 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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Introduction

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 ($V_{\text{LAwall-64-73-EQD2}}$) in preference to the corresponding whole-heart volume ($V_{\text{Heart-64-73-EQD2}}$) [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 $V_{\text{LAwall-64-73-EQD2}}$, 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.

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-

1 advanced NSCLC treated consecutively during 2010-2014. Of these, 64 had evaluable
2 datasets with accessible electronic treatment plans including dose-distribution data
3 and no re-planning during RT. Patient and treatment characteristics were collated for
4 this cohort, along with time to last follow-up or death.
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10 RT was delivered using 3D conformal or volumetric modulated arc therapy (VMAT)
11 techniques, as monotherapy or with sequential or concurrent chemotherapy
12 comprising 3-4 or 2 cycles of platinum doublet respectively. For most *OX-RT* patients
13 the prescribed dose was 66 Gy in 33 daily fractions over 6.5 weeks, but eight received
14 doses $\leq 12\%$ lower due to toxicity. Treatment characteristics are summarized in Table
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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

1 false discovery rate after multiple hypothesis testing was limited to 10% via the
2 Benjamini-Hochberg step-up procedure.
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5 For some *OX-RT* patients data was incomplete. These patients were omitted from UV
6 analyses of the factors concerned, which were not carried forward to MV analysis
7 since their associations with OS were insufficiently significant in the UV analyses.
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10 *Validation in OX-RT of association between OS and $V_{LAwall-64-73-EQD2}$*

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12 Heart and left atrium were segmented on CT scans using a validated atlas [13]. LA
13 wall was defined as the region lying ≤ 5 mm within the LA contour [8]. RT plans were
14 imported into the Computational Environment for Radiotherapy Research (CERR)
15 software, and dose-volume histograms (DVHs) were generated and exported to SPSS
16 version 25 (IBM Corp, Armonk, NY) and R 4 (R Foundation, Vienna, Austria) for
17 analysis.
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21 In the *OX-RT* validation cohort we determined how strongly OS was associated with
22 $V_{LAwall-64-73-EQD2}$ according to UV Cox proportional hazards regression. To further
23 describe the association, *OX-RT* was dichotomized into groups with $V_{LAwall-64-73-EQD2}$
24 values \leq or $>$ the median, plotting Kaplan-Meier OS curves for both groups.
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28 Additional UV analyses of *OX-RT* were carried out to determine strengths of
29 associations of OS with $V_{Heart-64-73-EQD2}$ and $V_{Heart-10, 20, \dots, 70}$, the whole-heart fractional
30 volumes receiving 64-73 Gy EQD2 or physical doses exceeding thresholds of 10 to
31 70 Gy rising in 10 Gy increments, and with heart and LA wall mean physical doses.
32 We hypothesized that OS would not be associated as strongly with the whole-heart
33 irradiation measures as with $V_{LAwall-64-73-EQD2}$, following the pattern observed in *IDEAL-*
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1 MV Cox regression analysis was performed to further characterize associations in OX-
2 RT between OS and these dosimetric measures and patient and treatment factors
3 potentially related to survival.
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6 7 8 *Additional discovery work in OX-RT* 9

10 11 Whole-heart PC analysis and dose-localization 12

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14 PCs of whole-heart dose-volume histograms (DVHs) were obtained using varimax
15 rotation to simplify their structure [8]. DVHs were approximated using linear
16 combinations of ten PCs which accounted for >95% of the DVH variance. UV Cox
17 regression was performed to determine associations between OS and patient-specific
18 coefficients of PCs in the combinations approximating whole-heart DVHs.
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27 Dose-ranges described by PCs significantly associated with OS were identified from
28 peaks in PC variable-loading plots, and heart substructures irradiated to these dose-
29 levels were found using an approach described previously [8]. A single heart with
30 typical volume and shape was selected as a reference geometry, and heart dose-
31 distributions of all OX-RT patients were mapped to it via affine transformations derived
32 from heart and left atrium outlines. Then 2D axial, coronal and sagittal projections
33 through the heart were constructed, in which each pixel described the percentage of
34 patients for whom the associated projection line ran through heart voxels irradiated to
35 doses within the range identified. Having localized dose-ranges to specific heart
36 regions, substructures within the regions were delineated on each patient's CT scan
37 using a validated atlas [13] and DVHs were calculated for them.
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54 55 Associations between OS and additional cardiac substructure dose-volume measures 56

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58 For substructures most commonly irradiated to the dose-ranges described by whole-
59 heart PCs significantly associated with OS, we performed UV Cox regression of OS
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1 versus substructure volumes receiving these doses. Associations of OS with
2 substructure mean doses and volumes receiving higher doses were also assessed.
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4 MV analysis was performed to determine the best model of OS in *OX-RT*, according
5 to the AIC, that could be built from these measures and factors in the earlier MV model.
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8 9 10 *Back-validating new discoveries in IDEAL-6*

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

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24 Characteristics of *OX-RT* and *IDEAL-6* patients and treatments are compared in Table
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28 1. At the cut-off point for our databases, median follow-up after commencing RT was
29 38 months for *OX-RT* patients and 25 months for *IDEAL-6*. Median OS was 28 months
30 (95% CI, 21.9-34.1 months) for *OX-RT* and 39 months (95% CI not yet determinable)
31 for *IDEAL-6*. Of 53 *OX-RT* patients for whom the relevant data was available, 17 (32%)
32 had baseline cardiac comorbidity and 51 (96%) were ex/current smokers. For *IDEAL-6*
33 patients this data was not collected.
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45 In UV analyses of *OX-RT*, OS was significantly associated with $V_{\text{LAWall-64-73-EQD2}}$
46 (HR,1.08; 95% CI, 1.02-1.13; p=0.006). Figure 1(a) shows OS curves for *OX-RT*
47 patients dichotomized by $V_{\text{LAWall-64-73-EQD2}}$ equal to or >0%, the median value. The
48 curves differed significantly with an HR of 2.46 (95% CI, 1.22-4.94; p=0.009).
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53 OS was associated more strongly with $V_{\text{LAWall-64-73-EQD2}}$ than with $V_{\text{Heart-64-73-EQD2}}$, $V_{\text{Heart-}}$
54 10, 20, ..., 70, mean heart dose, patient characteristics or treatment factors (Table 2).
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However, OS was associated more strongly still with LA wall mean physical dose (HR, 1.05; 95% CI, 1.02-1.08, $p = 2 \times 10^{-4}$), and this association and that with $V_{LAwall-64-73-EQD2}$ remained positive discoveries after allowing for multiple hypothesis testing. Figure 1(b) shows OS curves for *OX-RT* patients dichotomized by LA wall mean physical dose \leq 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, $V_{Heart-20}$, prescribed dose and PTV size (Table 2). This model performed better than UV models based on LA wall mean physical dose or $V_{LAwall-65-71-EQD2}$ 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 Figure 1), most commonly delivered to a region around the aortic valve and left main coronary artery (Supplementary Figure 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 ($V_{AortV-29-38-EQD2}$), the left main coronary artery volume receiving ≥ 38 Gy EQD2 ($V_{LMCA-38-EQD2}$), and the mean doses in both regions. The association between OS and $V_{AortV-29-38-EQD2}$ (HR, 1.07; 95% CI, 1.04-1.11; $p=7 \times 10^{-5}$) 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

1 greater than the median value of 0%, OS curves differed significantly (HR, 2.39; 95%
2 CI, 1.25-4.58; p=0.006; Figure 2).
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5 The best MV model built from all the substructure dosimetric indices together with
6 factors included in the MV model of Table 2 comprised the volume of the aortic valve
7 region receiving ≥ 38 Gy EQD2 ($V_{\text{AortV-38-EQD2}}$), $V_{\text{Heart-20}}$, mean physical doses in the
8 aortic valve region and LA wall, PTV size and prescribed dose (Table 3). This model
9 had a lower AIC score than the earlier MV model, and at 0.74 its Harrell's C-statistic
10 was good.
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13 Given these results we re-investigated survival in the original *IDEAL-6* cohort, finding
14 that $V_{\text{AortV-29-38-EQD2}}$ was significantly associated with OS in UV analyses (Table 4). We
15 also found the best MV model of OS in *IDEAL-6* that could be built from several LA
16 wall and aortic valve dose-volume measures and the factors considered in our original
17 analysis of this cohort [8], excluding 'any ECG change' for which corresponding *OX-*
18 *RT* data were unavailable. This model comprised $V_{\text{LAwall-64-73-EQD2}}$, $V_{\text{AortV-29-38-EQD2}}$,
19 $V_{\text{AortV-38-EQD2}}$, mean aortic valve dose and PTV size (Table 4), and had better AIC and
20 C-index values than a model comprising only $V_{\text{LAwall-63-73-EQD2}}$ and PTV size, the two
21 factors included alongside 'any ECG change' in the best model in our original analysis
22 of *IDEAL-6* [8].
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46 Discussion

47 In the *OX-RT* validation cohort, OS was associated more strongly with $V_{\text{LAwall-64-73-EQD2}}$
48 than with any whole-heart irradiation measure investigated including $V_{\text{Heart-64-73-EQD2}}$,
49 as we had previously found in the original *IDEAL-6* patient group [8]. The validation is
50 encouraging, since patient- and treatment-related factors differed significantly
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1 between the routinely-treated single-centre *OX-RT* and dose-escalated multi-centre
2 *IDEAL-6* cohorts (Table 2).
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5 In *IDEAL-6*, OS was associated with one PC of patients' whole-heart dose-
6 distributions, which described 64-73 Gy EQD2s most often delivered to the LA wall [8].
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9 In *OX-RT*, OS was also significantly associated with one whole-heart PC, which had
10 a small peak at 67-72 Gy EQD2 (Supplementary Figure 1) but a larger peak describing
11 29-38 Gy EQD2s typically delivered to the region around the aortic valve and left main
12 coronary artery. Correspondingly, OS was associated with $V_{AortV-29-38-EQD2}$ more
13 significantly than with $V_{LAwall-64-73-EQD2}$ in UV analyses of *OX-RT*, but less significantly
14 in UV analyses of *IDEAL-6*. This may reflect dosimetric differences between the two
15 cohorts, since in *OX-RT* $V_{AortV-29-38-EQD2}$ took a wider range of values than $V_{LAwall-64-73-}$
16 $EQD2$, 0-76% versus 0-45%, but in *IDEAL-6* it took a narrower range, 0-26% versus 0-
17 46%.
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32 The best MV model of OS in *OX-RT* included $V_{AortV-38-EQD2}$, $V_{Heart-20}$ and mean doses
33 delivered to the aortic valve region and LA wall. These measures were inter-correlated
34 (Pearson r^2 values of 0.250-0.781, Figure 2) but their variance-inflation factors were
35 <10 (3.21-9.41) and each retained significance in the best model [15] which was
36 selected using the AIC to avoid over-fitting. HRs were >1 for the mean dose factors
37 but <1 for $V_{AortV-38-EQD2}$ and $V_{Heart-20}$, suggesting the mean dose terms alone may over-
38 penalize volumes receiving high doses. Notably, the model included terms describing
39 irradiation of the LA wall and aortic valve, as did the best model of OS in *IDEAL-6*. In
40 1000 bootstrap resamples [16] of *OX-RT*, the best MV survival models included
41 measures of irradiation of the LA wall, aortic valve and left main coronary artery with
42 roughly equal frequencies and with an average of 2.9 measures per model, similar to
43 the 3 in the fit to the original data (Table 3).
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1 Our results parallel studies that found OS was associated with irradiation of the base-
2 of-heart [2] and left atrium and superior vena cava [17], although in those studies the
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4 measures identified as most strongly associated with OS were physical dose >8.5 Gy
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6 to the base-of-heart in regularly fractionated patients [2], and the maximum left atrium
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8 physical dose in SABR patients (6.5 and 77.6 Gy median and maximum values in
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10 SABR patients) [17]. In other studies, however, MV models have been built from
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12 combinations of atrial, pericardial, right-sided cardiac substructure, ventricular and
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14 lung irradiation measures [3,7].
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20 The prominence of base-of-heart structures in several analyses concurs with a pre-
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22 clinical study in which heart failure followed more rapidly after whole-heart than heart-
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24 minus-atria irradiation [18], suggesting that survival might be reduced more by base-
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26 of-heart toxicity. Clinically, in LA-NSCLC patients base-of-heart doses might also be
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28 more damaging because they are relatively high [19]: in *IDEAL-6*, mean EQD2s in the
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30 left and right atrial walls were 19.7 and 9.0 Gy compared to 5.3 and 3.6 Gy for the
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32 ventricles. Fibrosis can be visualized via late gadolinium enhancement (LGE) on MRI
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34 [20] and is found in LA walls of patients with atrial fibrillation [21]. In oesophageal
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36 cancer patients LGE was more evident in areas of the heart receiving higher radiation
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38 doses [22].
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45 Given the variety of cardiac irradiation measures reported to be associated with OS,
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47 and the possibility that measures most closely associated with survival might be
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49 specific to particular RT techniques or cohorts, we have investigated the usefulness
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51 of reducing a broad measure, mean heart dose. In *OX-RT* this measure was
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53 significantly associated with OS (HR, 1.046; 95% CI, 1.007-1.087; p=0.02), survival at
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55 2 years post-treatment being 29% higher in patients with mean heart doses <7.6 Gy,
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57 the median value (Figure 2(b)). Similarly, in a large retrospective study the all-cause
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1 death-rate at 2 years was respectively 40% and 52% in patents with mean heart doses
2 less or greater than 10 Gy [23].
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5 In a planning study carried out for LA-NSCLC patients treated using VMAT we found
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7 that by introducing a mean heart dose penalty into plan optimization, in addition to the
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9 penalty used routinely to control cardiac hot-spots, mean heart doses could be
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11 reduced by an average 4.8 Gy while respecting tumour coverage protocol limits and
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13 without markedly increasing irradiation of the lungs, oesophagus, proximal bronchial
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15 tree, cord or brachial plexus [19]. This reduction amounted to 36% of the average
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17 baseline mean heart dose, and on the basis of the *OX-RT* data corresponds to a
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19 predicted hazard ratio for death of 0.81. Furthermore, mean heart dose reductions led
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21 to knock-on reductions in many cardiac substructure dose-volume measures. In
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23 particular, $V_{LAwall-64-73-EQD2}$, $V_{AortV-29-38-EQD2}$ and mean left and right ventricle doses fell
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25 by 68%, 100%, 41% and 51% relative to baseline values, insuring against survival
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27 being related more specifically to these measures than to whole-heart irradiation.
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29 Presently we are preparing a cardiac-sparing RT trial in which mean heart doses are
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31 reduced in this way.
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41 **Conclusion**

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43 In UV analyses of two independent cohorts of LA-NSCLC patients, *OX-RT* and *IDEAL-*
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45 *6*, OS was associated more strongly with $V_{LAwall-64-73-EQD2}$ than with any measure of
46
47 whole-heart irradiation investigated. OS was also significantly associated with V_{AortV-}
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49 $29-38-EQD2$ in both cohorts, and in *OX-RT* was additionally significantly associated with
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51 mean heart dose. In a separate planning study we found that by penalizing cardiac
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53 irradiation and re-optimizing plans, mean heart doses could be reduced by an average
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55 36% relative to baseline while respecting protocol limits on irradiation of other normal
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1 tissues, in the process achieving large reductions in $V_{LAwall-64-73-EQD2}$ and $V_{AortV-29-38-}$
2 $EQD2$. We therefore intend to trial a treatment in which mean heart doses are reduced
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4 like this, closely monitoring patients in whom $V_{LAwall-64-73-EQD2}$ and $V_{AortV-29-38-EQD2}$ are
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6 not consequentially reduced to 0%, the median value of both measures in the *OX-RT*
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9 cohort.
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65
- [1] Zhang TW, Snir J, Boldt RG, Rodrigues GB, Louie AV, Gaede S et al. Is the importance of heart dose overstated in the treatment of non-small cell lung cancer? A systematic review of the literature. *Int J Radiat Oncol Biol Phys.* 2019; 104:582-589. doi: 10.1016/j.ijrobp.2018.12.044.
- [2] McWilliam A, Kennedy J, Hodgson C, Vasquez Osorio E, Faivre-Finn C, and van Herk M, Radiation dose to heart base linked with poorer survival in lung cancer patients. *Eur J Cancer* 2017; 85:106–113. doi: 10.1016/j.ejca.2017.07.053.
- [3] Thor M, Deasy JO, Hu C, Gore E, Bar-Ad V, Robinson C et al. Modeling the impact of cardio-pulmonary irradiation on overall survival in NRG Oncology trial RTOG 0617. *Clin Cancer Res* 2020; 26: 4643-4650. doi: 10.1158/1078-0432.CCR-19-2627.
- [4] Guberina M, Eberhardt W, Stuschke M, Gauler T, Heinzlmann F, Cheufou D et al. Heart dose exposure as prognostic marker after radiotherapy for resectable stage IIIA/B non-small-cell lung cancer: secondary analysis of a randomized trial. *Ann Oncol* 2017; 28: 1084–1089. doi: 10.1093/annonc/mdx069.
- [5] Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015; 16: 187–199. doi: 10.1016/S1470-2045(14)71207-0.

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- [6] Tucker SL, Liu A, Gomez D, Tang LL, Allen P, Yang J et al. Impact of heart and lung dose on early survival in patients with non-small cell lung cancer treated with chemoradiation. *Radiother Oncol* 2016; 119: 495–500. doi:10.1016/j.radonc.2016.04.025.
- [7] McWilliam A, Khalifa J, Vasquez Osorio E, Banfill K, Abravan A, Faivre-Finn C 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: 1073-81. doi: 10.1016/j.ijrobp.2020.06.031.
- [8] Vivekanandan S, Landau DB, Counsell N, Warren DR, Khwanda A, Rosen SD, et al. The impact of cardiac radiation dosimetry on survival after radiation therapy for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.*2017; 99: 51–60. doi: 10.1016/j.ijrobp.2017.04.026.
- [9] Landau DB, Hughes L, Baker A, Bates AT, Bayne MC, Counsell N et al. IDEAL-CRT: A Phase 1/2 Trial of Isotoxic Dose-Escalated Radiation Therapy and Concurrent Chemotherapy in Patients With Stage II/III Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys.* 2016; 95: 1367–1377. doi: 10.1016/j.ijrobp.2016.03.031.
- [10] Schultz-Hector S, Sund M, and Thames HD. Fractionation response and repair kinetics of radiation-induced heart failure in the rat. *Radiother Oncol* 1992; 23: 33–40. doi: 10.1016/0167-8140(92)90303-c.
- [11] Harrell FE, Lee KL and Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, an measuring and reducing errors. *Stat Med* 1996; 15: 361–387. doi: 10.1002/(SICI)1097-

0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4.

- 1
2
3
4 [12] Pencina MJ and D'Agostino RB. Overall C as a measure of discrimination in
5 survival analysis: model specific population value and confidence interval
6 estimation. *Stat Med* 2004; 23: 2109–2123. doi: 10.1002/sim.1802.
7
8
9
10
11 [13] Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L et al.
12 Development and validation of a heart atlas to study cardiac exposure to
13 radiation following treatment for breast cancer. *Int J Radiat Oncol Biol Phys*
14 2011; 79: 10–8. doi: 10.1016/j.ijrobp.2009.10.058.
15
16
17
18
19
20
21
22 [14] Ganem GCA, Coelho RC and de Godoy CMG. (2020) Animation of atrial and
23 ventricular external walls of a virtual 3D heart based on echocardiogram
24 images. In: González Díaz C et al. (eds) VIII Latin American Conference on
25 Biomedical Engineering and XLII National Conference on Biomedical
26 Engineering. CLAIB 2019. IFMBE Proceedings, vol 75. Springer, Cham.
27 https://doi-org.liverpool.idm.oclc.org/10.1007/978-3-030-30648-9_90
28
29
30
31
32
33
34
35
36
37
38 [15] O'Brien RM. A caution regarding rules of thumb for variance inflation factors.
39 *Qual Quant* 2007; 41: 673-690. doi: 10.1007/s11135-006-9018-6.
40
41
42
43
44 [16] Abram SV, Helwig NE, Moodie CA, DeYoung CG, MacDonald AW and Waller
45 HG. Bootstrap enhanced penalized regression for variable selection with
46 neuroimaging data. *Front Neurosci* 2016; 10: 344. doi:
47 10.3389/fnins.2016.00344
48
49
50
51
52
53
54
55 [17] Stam B, Peulen H, Guckenberger M, Mantel F, Hope A, Werner-Wasik M et al.
56 Dose to heart substructures is associated with non-cancer death after SBRT in
57 stage I–II NSCLC patients. *Radiother Oncol* 2017; 123: 370–375. doi:
58
59
60
61
62
63
64
65

10.1016/j.radonc.2017.04.017.

- 1
2
3 [18] Kitahara T, Liu K, Solanki K and Trott KR. Functional and morphological
4 damage after local heart irradiation and/or adriamycin in Wistar rats. Radiat
5 Oncol Investig 1993; 1: 198–205.
6
7
8
9
10
11 [19] Turtle L, Bhalla N, Willett A, Biggar R, Leadbetter J, Georgiou G et al. Cardiac-
12 sparing radiotherapy for locally advanced non-small cell lung cancer. Radiat
13 Oncol 2021; 16: 95. [https://doi:10.1186/s13014-021-01824-3](https://doi.org/10.1186/s13014-021-01824-3)
14
15
16
17
18
19 [20] Fukumoto K, Habibi M, Ipek EG, Zahid S, Khurram IM, Zimmerman SL et al.
20 Association of left atrial local conduction velocity with late gadolinium
21 enhancement on cardiac magnetic resonance in patients with atrial fibrillation.
22 Circ Arrhythm Electrophysiol 2016; 9: e002897. doi: 10.1161/CIRCEP.115.
23 002897
24
25
26
27
28
29
30
31
32 [21] Burstein B and Nattel S. “Atrial fibrosis: Mechanisms and clinical relevance in
33 atrial fibrillation. J Am Coll Cardiol 2008; 51: 802-809. doi:10.1016/j.jacc.
34 2007.09.064
35
36
37
38
39
40 [22] Umezawa R, Ota H, Takanami K, Ichinose A, Matsushita H, Saito H et al. MRI
41 findings of radiation-induced myocardial damage in patients with oesophageal
42 cancer. Clin Radiol 2014; 69: 1273-1279. [http://dx.doi.org/10.1016/j.crad.](http://dx.doi.org/10.1016/j.crad.2014.08.010)
43 2014.08.010
44
45
46
47
48
49
50
51 [23] Atkins KM, Rawal B, Chaunzwa TL, Lamba N, Bitterman DS, Williams CL et al.
52 Cardiac radiation dose, cardiac disease, and mortality in patients with lung
53 cancer. J Am Coll Cardiol 2019; 73: 2976–2987. doi: 10.1016/j.jacc.2019.03.
54 500.
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Table and figure headings

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

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.

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 listed in Table 2. Best fits to bootstrap resampled data are also summarised.

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'.

Figure 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 $p = 0.007$).

Figure 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.

Supplementary table and figure headings

Supplementary Table 1. Associations between OS in the *OX-RT* cohort and PCs of whole-heart dose-volume histograms (DVHs) in unadjusted (univariable) analyses.

Supplementary Figure 1. Principal component PC5 of *OX-RT* whole-heart dose-distributions has a peak that represents heart volumes receiving physical doses of 36-44 Gy and a smaller peak representing volumes receiving 67-70 Gy. Given the *OX-RT* schedule, these doses translate into EQD2s of 29-38 Gy and 67-72 Gy for an α/β ratio of 3 Gy.

Supplementary Figure 2. Projection plots through the heart for the 20 patients with the highest scores for whole-heart PC5 and for the 44 other patients. The LA contour is shown in white. Projection lines coloured red pass through cardiac volumes with high probabilities of receiving 29-38 Gy EQD2 and localize to the region of aortic valve/left main coronary artery.

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

Characteristic	<i>OX-RT</i> (No.=64)	<i>IDEAL-6</i> (No.=78)	p-value
<i>Age</i> (years)			
median (range)	71 (44-89)	66 (43-84)	.002
<i>Gender</i> (No.)			.10
Female	25 (39.1%)	20 (25.6%)	
Male	39 (60.9%)	58 (74.4%)	
<i>WHO PS</i> (No.)			.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%)	-	
<i>Tumour stage</i> (No.)			<.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	
<i>Nodal status</i> (No.)			<.001
N0 or 1	29 (45.3%)	13 (16.7%)	
N2 or 3	32 (50.0%)	65 (83.3%)	
Missing	3 (4.7%)	-	
<i>Histology</i> (No.)			.44
Squamous	36 (56.3%)	42 (53.8%)	
Non-squamous	24 (37.5%)	36 (46.2%)	
Missing	4 (6.3%)	-	
<i>PTV</i> (cm ³)			
median (range)	319 (82-1120)	401 (139-1262)	.004
<i>4D-CT used for planning</i> (No.)	56 (87.5%)	34 (43.6%)	<.001
<i>RT technique</i> (No.)			<.001
3D conformal	48 (75.0%)	75 (96.2%)	
VMAT	16 (25.0%)	3 (3.8%)	
<i>OX-RT or IDEAL-6 prescribed dose</i> (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%)	
<i>Prescribed tumour EQD2*</i> (Gy)			
median (range)	66 (58-66)	69.0 (63.5-75.6)	<.001
<i>Heart mean dose</i> (Gy)			
median (range)	7.6 (0.5-32.2)	10.3 (1.1-32.2)	.19
<i>LA wall mean dose</i> (Gy)			
median (range)	12.5 (0.5-56.2)	20.4 (1.3-63.0)	.004
<i>V_{LAwall-64-73-EQD2}</i> (%),			
median (range)	0.0 (0-25.5)	1.9 (0-76.1)	.003
<i>Chemotherapy</i> (No.)			<.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.

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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 [†] 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)	2×10 ⁻⁴	1.049 (1.023-1.075)	2×10 ⁻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 (.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 ³)	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)	-	-

[†]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, $V_{\text{Structure-X-Y-EQD2}}$ = fraction of structure receiving X-Y Gy EQD2, $V_{\text{Structure-Z}}$ = fraction of structure receiving > Z Gy physical dose.

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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 [†] (C = 0.74, AIC = 262.5*)		Bootstrap models
	p-value	HR (95% CI)	p-value	HR (95% CI)	Inclusion** (%)
<i>Substructure measures</i>					
V _{AortV-29-38-EQD2} (%)	7×10 ⁻⁵	1.069 (1.035-1.105)	-	-	30.9
V _{AortV-38-EQD2} (%)	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 _{LMCA-29-38-EQD2} (%)	0.11	1.019 (0.996-1.042)	-	-	28.6
V _{LMCA-38-EQD2} (%)	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 _{LAwall-64-73-EQD2} (%)	0.006	1.077 (1.022-1.134)	-	-	29.9
V _{LAwall-73-EQD2} (%)	0.32	1.633 (0.628-4.248)	-	-	32.0
Mean LA wall dose (Gy)	2×10 ⁻⁴	1.049 (1.023-1.075)	0.04	1.059 (1.002-1.120)	31.1
<i>Other factors</i>					
V _{Heart-20} (%)	0.02	1.022 (1.003-1.040)	0.02	0.936 (0.887-0.989)	29.8
PTV (cm ³)	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

[†]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_{AortV-29-38-EQD2}, mean aortic valve dose, mean LA wall dose, V_{Heart-20}, 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_{Structure-X-Y-EQD2} = fraction of structure receiving X-Y Gy EQD2, V_{Structure-Y-EQD2} = fraction of structure receiving > Y Gy EQD2, V_{Structure-Z} = fraction of structure receiving > Z Gy physical dose.

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 [†] C = 0.70, AIC=193.0*	
	p-value	HR (95% CI)	p-value	HR (95% CI)
<i>Substructure measures</i>				
V _{AortV-29-38-EQD2} (%)	0.04	1.043 (1.002-1.086)	0.002	1.112 (1.040-1.188)
V _{AortV-38-EQD2} (%)	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 _{LAwall-64-73-EQD2} (%)	0.01	1.035 (1.008-1.063)	0.05	1.040 (1.001-1.081)
V _{LAwall-73-EQD2} (%)	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 ³)	0.04	1.002 (1.000-1.003)	0.02	1.002 (1.001-1.004)

[†]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_{AortV-29-38-EQD2}, V_{AortV-38-EQD2}, mean aortic valve dose, V_{LAwall-64-73-EQD2} 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_{Structure-X-Y-EQD2} = fraction of structure receiving X-Y Gy EQD2, V_{Structure-Y-EQD2} = fraction of structure receiving > Y Gy.

Figure 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 $p = 0.007$).

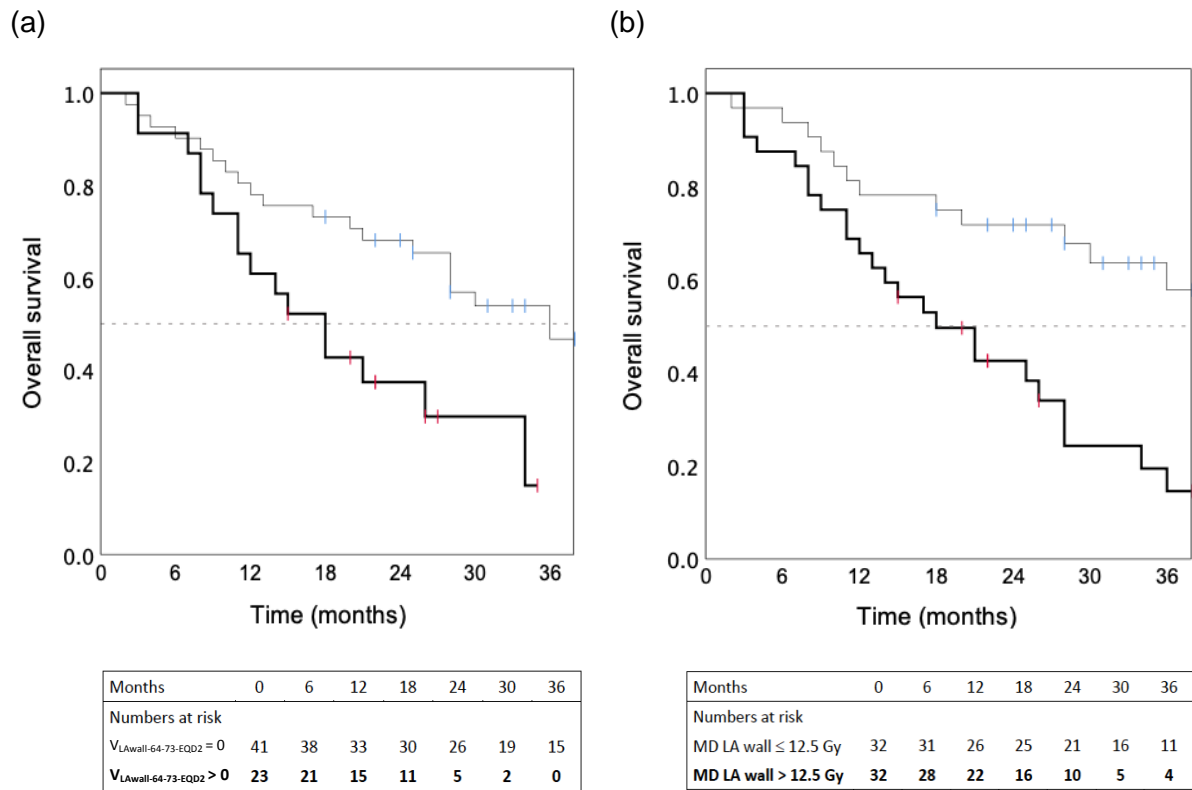
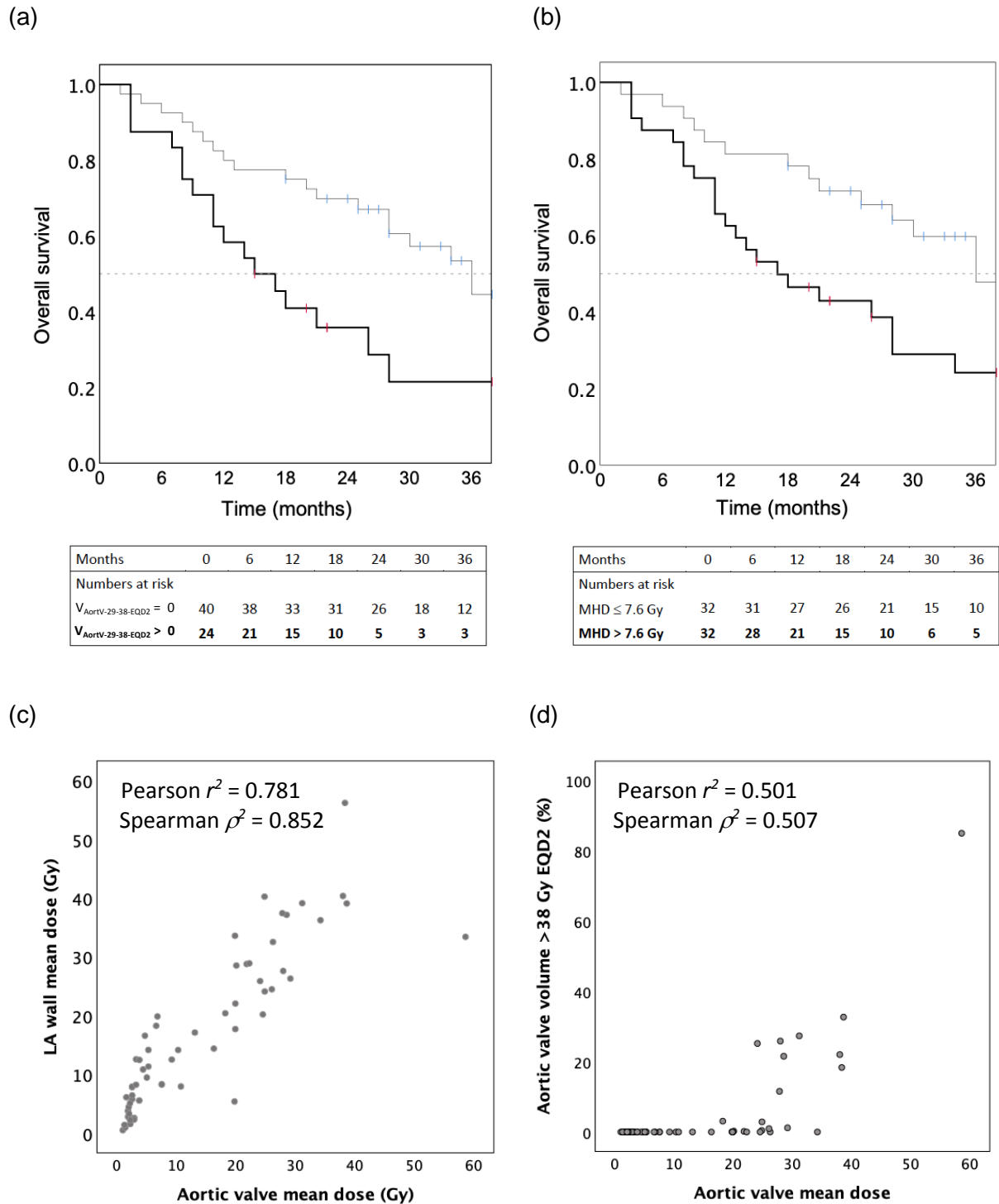


Figure 2. Kaplan-Meier survival curves for *OX-RT* patients dichotomized by: (a) fraction of the aortic valve region receiving 29-38 Gy EQD2 ($V_{\text{AortV-29-38-EQD2}}$) equal to (light) or > (bold) the 0% median *OX-RT* value (log-rank $p = 0.006$); (b) mean heart dose (MHD) \leq (light) or > (bold) 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.

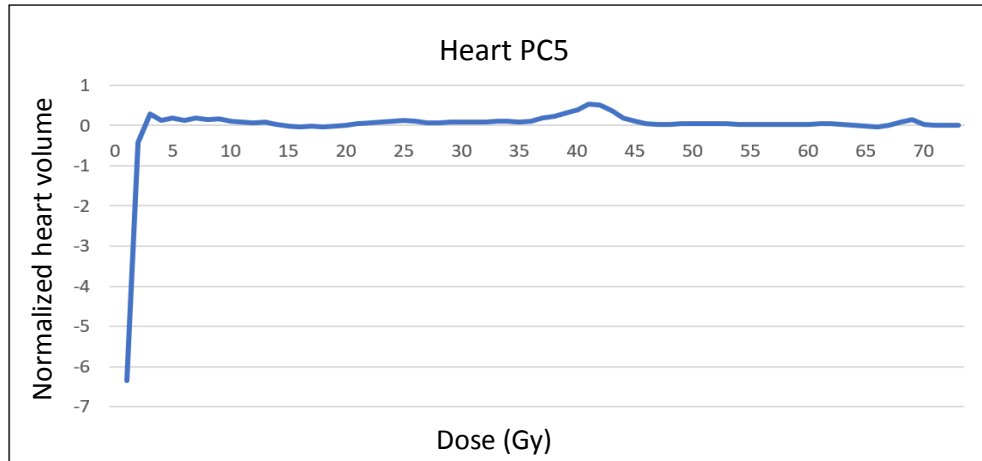


Supplementary Table 1. Associations between OS in the *OX-RT* cohort and principal components (PCs) of whole-heart dose-volume histograms (DVHs) in unadjusted (univariable) analyses.

Whole-heart PC scores	p-value	HR (95% CI)
PC1	0.31	1.164 (0.869-1.560)
PC2	0.99	1.001 (0.753-1.332)
PC3	0.57	1.078 (0.833-1.396)
PC4	0.31	1.139 (0.908-1.429)
PC5	0.007	1.457 (1.106-1.919)
PC6	0.15	1.201 (0.935-1.542)
PC7	0.34	1.184 (0.837-1.675)
PC8	0.23	1.202 (0.892-1.620)
PC9	0.63	0.923 (0.782-1.502)
PC10	0.79	0.960 (0.711-1.296)

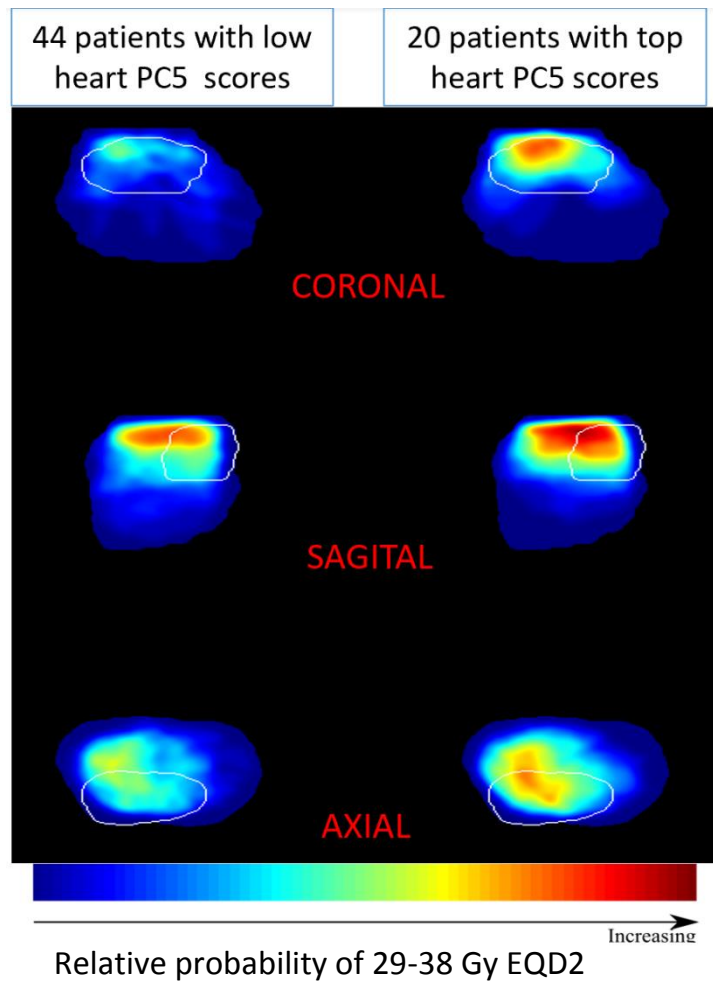
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Supplementary Figure 1. Principal component PC5 of *OX-RT* whole-heart dose-distributions has a peak that represents heart volumes receiving physical doses of 36-44 Gy and a smaller peak representing volumes receiving 67-70 Gy. Given the *OX-RT* schedule, these doses translate into EQD2s of 29-38 Gy and 67-72 Gy for an α/β ratio of 3 Gy.



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Supplementary Figure 2. Projection plots through the heart for the 20 patients with the highest scores for whole-heart PC5 and for the 44 other patients. The LA contour is shown in white. Projection lines coloured red pass through cardiac volumes with high probabilities of receiving 29-38 Gy EQD2 and localize to the region of aortic valve/left main coronary artery.



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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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Key words: Lung cancer, radiotherapy, cardiac irradiation, survival

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2 ASSOCIATIONS BETWEEN CARDIAC IRRADIATION AND
3 SURVIVAL IN PATIENTS WITH NON-SMALL CELL LUNG CANCER:
4 VALIDATION AND NEW DISCOVERIES IN AN INDEPENDENT DATASET
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8 Shortened running title: Cardiac irradiation and survival after NSCLC RT
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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 $V_{\text{LAwall-64-73-EQD2}}$, 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 $V_{\text{LAwall-64-73-EQD2}}$, 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 $V_{\text{LAwall-64-73-EQD2}}$ than with whole-heart irradiation measures, but more strongly still with $V_{\text{AortV-29-38-EQD2}}$, 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 ≥ 38 Gy EQD2, $V_{\text{AortV-38-EQD2}}$. In a subsidiary analysis of IDEAL-6, the best multivariable model included $V_{\text{LAwall-64-73-EQD2}}$, $V_{\text{AortV-29-38-EQD2}}$, $V_{\text{AortV-38-EQD2}}$ 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 $V_{\text{AortV-29-38-EQD2}}$ 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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Introduction

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 ($V_{\text{LAwall-64-73-EQD2}}$) in preference to the corresponding whole-heart volume ($V_{\text{Heart-64-73-EQD2}}$) [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 $V_{\text{LAwall-64-73-EQD2}}$, 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.

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-

1 advanced NSCLC treated consecutively during 2010-2014. Of these, 64 had evaluable
2 datasets with accessible electronic treatment plans including dose-distribution data
3 and no re-planning during RT. Patient and treatment characteristics were collated for
4 this cohort, along with time to last follow-up or death.
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10 RT was delivered using 3D conformal or volumetric modulated arc therapy (VMAT)
11 techniques, as monotherapy or with sequential or concurrent chemotherapy
12 comprising 3-4 or 2 cycles of platinum doublet respectively. For most *OX-RT* patients
13 the prescribed dose was 66 Gy in 33 daily fractions over 6.5 weeks, but eight received
14 doses $\leq 12\%$ lower due to toxicity. Treatment characteristics are summarized in Table
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22 1 for *OX-RT* and the *IDEAL-6* cohort originally studied.
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25 *Statistics*

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28 Differences in patient and treatment factors between the cohorts were assessed using
29 the Mann-Whitney test for continuous data, Fisher's exact test for binary data, and the
30 chi-square test for data with >2 categories. Reported confidence intervals (CIs) and
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66 OS was measured from treatment commencement, censored at last follow-up, and
67 estimated using the Kaplan-Meier method. Significances of differences between
68 survival curves were assessed using the log-rank test. MV models of OS were
69 constructed from patient and treatment factors with $p < 0.30$ on univariable (UV)
70 analysis, using bi-directional variable elimination to find the best models with the
71 lowest AIC scores. MV model performance was measured using Harrell's C-statistic
72 [11,12] which describes the fraction of all pairs of evaluable patients in which observed
73 and modelled survivals are both shorter for the same patient. Where necessary, the

1 false discovery rate after multiple hypothesis testing was limited to 10% via the
2 Benjamini-Hochberg step-up procedure.
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5 For some *OX-RT* patients data was incomplete. These patients were omitted from UV
6 analyses of the factors concerned, which were not carried forward to MV analysis
7 since their associations with OS were insufficiently significant in the UV analyses.
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10 *Validation in OX-RT of association between OS and $V_{LAwall-64-73-EQD2}$*

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12 Heart and left atrium were segmented on CT scans using a validated atlas [13]. LA
13 wall was defined as the region lying ≤ 5 mm within the LA contour [8]. RT plans were
14 imported into the Computational Environment for Radiotherapy Research (CERR)
15 software, and dose-volume histograms (DVHs) were generated and exported to SPSS
16 version 25 (IBM Corp, Armonk, NY) and R 4 (R Foundation, Vienna, Austria) for
17 analysis.
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21 In the *OX-RT* validation cohort we determined how strongly OS was associated with
22 $V_{LAwall-64-73-EQD2}$ according to UV Cox proportional hazards regression. To further
23 describe the association, *OX-RT* was dichotomized into groups with $V_{LAwall-64-73-EQD2}$
24 values \leq or $>$ the median, plotting Kaplan-Meier OS curves for both groups.
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28 Additional UV analyses of *OX-RT* were carried out to determine strengths of
29 associations of OS with $V_{Heart-64-73-EQD2}$ and $V_{Heart-10, 20, \dots, 70}$, the whole-heart fractional
30 volumes receiving 64-73 Gy EQD2 or physical doses exceeding thresholds of 10 to
31 70 Gy rising in 10 Gy increments, and with heart and LA wall mean physical doses.
32 We hypothesized that OS would not be associated as strongly with the whole-heart
33 irradiation measures as with $V_{LAwall-64-73-EQD2}$, following the pattern observed in *IDEAL-*
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1 MV Cox regression analysis was performed to further characterize associations in OX-
2 RT between OS and these dosimetric measures and patient and treatment factors
3 potentially related to survival.
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6 7 8 *Additional discovery work in OX-RT* 9

10 11 Whole-heart PC analysis and dose-localization 12

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14 PCs of whole-heart dose-volume histograms (DVHs) were obtained using varimax
15 rotation to simplify their structure [8]. DVHs were approximated using linear
16 combinations of ten PCs which accounted for >95% of the DVH variance. UV Cox
17 regression was performed to determine associations between OS and patient-specific
18 coefficients of PCs in the combinations approximating whole-heart DVHs.
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26 Dose-ranges described by PCs significantly associated with OS were identified from
27 peaks in PC variable-loading plots, and heart substructures irradiated to these dose-
28 levels were found using an approach described previously [8]. A single heart with
29 typical volume and shape was selected as a reference geometry, and heart dose-
30 distributions of all OX-RT patients were mapped to it via affine transformations derived
31 from heart and left atrium outlines. Then 2D axial, coronal and sagittal projections
32 through the heart were constructed, in which each pixel described the percentage of
33 patients for whom the associated projection line ran through heart voxels irradiated to
34 doses within the range identified. Having localized dose-ranges to specific heart
35 regions, substructures within the regions were delineated on each patient's CT scan
36 using a validated atlas [13] and DVHs were calculated for them.
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54 55 Associations between OS and additional cardiac substructure dose-volume measures 56

57 For substructures most commonly irradiated to the dose-ranges described by whole-
58 heart PCs significantly associated with OS, we performed UV Cox regression of OS
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1 versus substructure volumes receiving these doses. Associations of OS with
2 substructure mean doses and volumes receiving higher doses were also assessed.
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4 MV analysis was performed to determine the best model of OS in *OX-RT*, according
5 to the AIC, that could be built from these measures and factors in the earlier MV model.
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8 9 10 *Back-validating new discoveries in IDEAL-6*

11
12 For new substructures found to have dose-volume measures significantly associated
13 with OS in MV analysis of *OX-RT*, we carried out additional subsidiary analyses of the
14 original *IDEAL-6* dataset to determine whether substructure irradiation was associated
15 with OS in that cohort too.
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22 **Results**

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24 Characteristics of *OX-RT* and *IDEAL-6* patients and treatments are compared in Table
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28 1. At the cut-off point for our databases, median follow-up after commencing RT was
29 38 months for *OX-RT* patients and 25 months for *IDEAL-6*. Median OS was 28 months
30 (95% CI, 21.9-34.1 months) for *OX-RT* and 39 months (95% CI not yet determinable)
31 for *IDEAL-6*. Of 53 *OX-RT* patients for whom the relevant data was available, 17 (32%)
32 had baseline cardiac comorbidity and 51 (96%) were ex/current smokers. For *IDEAL-6*
33 patients this data was not collected.
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45 In UV analyses of *OX-RT*, OS was significantly associated with $V_{\text{LAWall-64-73-EQD2}}$
46 (HR,1.08; 95% CI, 1.02-1.13; p=0.006). Figure 1(a) shows OS curves for *OX-RT*
47 patients dichotomized by $V_{\text{LAWall-64-73-EQD2}}$ equal to or >0%, the median value. The
48 curves differed significantly with an HR of 2.46 (95% CI, 1.22-4.94; p=0.009).
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53 OS was associated more strongly with $V_{\text{LAWall-64-73-EQD2}}$ than with $V_{\text{Heart-64-73-EQD2}}$, $V_{\text{Heart-}}$
54 10, 20, ..., 70, mean heart dose, patient characteristics or treatment factors (Table 2).
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However, OS was associated more strongly still with LA wall mean physical dose (HR, 1.05; 95% CI, 1.02-1.08, $p = 2 \times 10^{-4}$), and this association and that with $V_{LAwall-64-73-EQD2}$ remained positive discoveries after allowing for multiple hypothesis testing. Figure 1(b) shows OS curves for *OX-RT* patients dichotomized by LA wall mean physical dose \leq 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, $V_{Heart-20}$, prescribed dose and PTV size (Table 2). This model performed better than UV models based on LA wall mean physical dose or $V_{LAwall-65-71-EQD2}$ 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 Figure 1), most commonly delivered to a region around the aortic valve and left main coronary artery (Supplementary Figure 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 ($V_{AortV-29-38-EQD2}$), the left main coronary artery volume receiving ≥ 38 Gy EQD2 ($V_{LMCA-38-EQD2}$), and the mean doses in both regions. The association between OS and $V_{AortV-29-38-EQD2}$ (HR, 1.07; 95% CI, 1.04-1.11; $p=7 \times 10^{-5}$) 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

1 greater than the median value of 0%, OS curves differed significantly (HR, 2.39; 95%
2 CI, 1.25-4.58; p=0.006; Figure 2).
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5 The best MV model built from all the substructure dosimetric indices together with
6 factors included in the MV model of Table 2 comprised the volume of the aortic valve
7 region receiving ≥ 38 Gy EQD2 ($V_{\text{AortV-38-EQD2}}$), $V_{\text{Heart-20}}$, mean physical doses in the
8 aortic valve region and LA wall, PTV size and prescribed dose (Table 3). This model
9 had a lower AIC score than the earlier MV model, and at 0.74 its Harrell's C-statistic
10 was good.
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13 Given these results we re-investigated survival in the original *IDEAL-6* cohort, finding
14 that $V_{\text{AortV-29-38-EQD2}}$ was significantly associated with OS in UV analyses (Table 4). We
15 also found the best MV model of OS in *IDEAL-6* that could be built from several LA
16 wall and aortic valve dose-volume measures and the factors considered in our original
17 analysis of this cohort [8], excluding 'any ECG change' for which corresponding *OX-*
18 *RT* data were unavailable. This model comprised $V_{\text{LAwall-64-73-EQD2}}$, $V_{\text{AortV-29-38-EQD2}}$,
19 $V_{\text{AortV-38-EQD2}}$, mean aortic valve dose and PTV size (Table 4), and had better AIC and
20 C-index values than a model comprising only $V_{\text{LAwall-63-73-EQD2}}$ and PTV size, the two
21 factors included alongside 'any ECG change' in the best model in our original analysis
22 of *IDEAL-6* [8].
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46 Discussion

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48 In the *OX-RT* validation cohort, OS was associated more strongly with $V_{\text{LAwall-64-73-EQD2}}$
49 than with any whole-heart irradiation measure investigated including $V_{\text{Heart-64-73-EQD2}}$,
50 as we had previously found in the original *IDEAL-6* patient group [8]. The validation is
51 encouraging, since patient- and treatment-related factors differed significantly
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1 between the routinely-treated single-centre *OX-RT* and dose-escalated multi-centre
2 *IDEAL-6* cohorts (Table 2).
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5 In *IDEAL-6*, OS was associated with one PC of patients' whole-heart dose-
6 distributions, which described 64-73 Gy EQD2s most often delivered to the LA wall [8].
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9 In *OX-RT*, OS was also significantly associated with one whole-heart PC, which had
10 a small peak at 67-72 Gy EQD2 (Supplementary Figure 1) but a larger peak describing
11 29-38 Gy EQD2s typically delivered to the region around the aortic valve and left main
12 coronary artery. Correspondingly, OS was associated with $V_{AortV-29-38-EQD2}$ more
13 significantly than with $V_{LAwall-64-73-EQD2}$ in UV analyses of *OX-RT*, but less significantly
14 in UV analyses of *IDEAL-6*. This may reflect dosimetric differences between the two
15 cohorts, since in *OX-RT* $V_{AortV-29-38-EQD2}$ took a wider range of values than $V_{LAwall-64-73-}$
16 $EQD2$, 0-76% versus 0-45%, but in *IDEAL-6* it took a narrower range, 0-26% versus 0-
17 46%.
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32 The best MV model of OS in *OX-RT* included $V_{AortV-38-EQD2}$, $V_{Heart-20}$ and mean doses
33 delivered to the aortic valve region and LA wall. These measures were inter-correlated
34 (Pearson r^2 values of 0.250-0.781, Figure 2) but their variance-inflation factors were
35 <10 (3.21-9.41) and each retained significance in the best model [15] which was
36 selected using the AIC to avoid over-fitting. HRs were >1 for the mean dose factors
37 but <1 for $V_{AortV-38-EQD2}$ and $V_{Heart-20}$, suggesting the mean dose terms alone may over-
38 penalize volumes receiving high doses. Notably, the model included terms describing
39 irradiation of the LA wall and aortic valve, as did the best model of OS in *IDEAL-6*. In
40 1000 bootstrap resamples [16] of *OX-RT*, the best MV survival models included
41 measures of irradiation of the LA wall, aortic valve and left main coronary artery with
42 roughly equal frequencies and with an average of 2.9 measures per model, similar to
43 the 3 in the fit to the original data (Table 3).
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1 Our results parallel studies that found OS was associated with irradiation of the base-
2 of-heart [2] and left atrium and superior vena cava [17], although in those studies the
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4 measures identified as most strongly associated with OS were physical dose >8.5 Gy
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6 to the base-of-heart in regularly fractionated patients [2], and the maximum left atrium
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8 physical dose in SABR patients (6.5 and 77.6 Gy median and maximum values in
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10 SABR patients) [17]. In other studies, however, MV models have been built from
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12 combinations of atrial, pericardial, right-sided cardiac substructure, ventricular and
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14 lung irradiation measures [3,7].
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20 The prominence of base-of-heart structures in several analyses concurs with a pre-
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22 clinical study in which heart failure followed more rapidly after whole-heart than heart-
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24 minus-atria irradiation [18], suggesting that survival might be reduced more by base-
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26 of-heart toxicity. Clinically, in LA-NSCLC patients base-of-heart doses might also be
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28 more damaging because they are relatively high [19]: in *IDEAL-6*, mean EQD2s in the
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30 left and right atrial walls were 19.7 and 9.0 Gy compared to 5.3 and 3.6 Gy for the
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32 ventricles. Fibrosis can be visualized via late gadolinium enhancement (LGE) on MRI
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34 [20] and is found in LA walls of patients with atrial fibrillation [21]. In oesophageal
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36 cancer patients LGE was more evident in areas of the heart receiving higher radiation
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38 doses [22].
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45 Given the variety of cardiac irradiation measures reported to be associated with OS,
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47 and the possibility that measures most closely associated with survival might be
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49 specific to particular RT techniques or cohorts, we have investigated the usefulness
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51 of reducing a broad measure, mean heart dose. In *OX-RT* this measure was
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53 significantly associated with OS (HR, 1.046; 95% CI, 1.007-1.087; p=0.02), survival at
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55 2 years post-treatment being 29% higher in patients with mean heart doses <7.6 Gy,
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57 the median value (Figure 2(b)). Similarly, in a large retrospective study the all-cause
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1 death-rate at 2 years was respectively 40% and 52% in patents with mean heart doses
2 less or greater than 10 Gy [23].
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5 In a planning study carried out for LA-NSCLC patients treated using VMAT we found
6 that by introducing a mean heart dose penalty into plan optimization, in addition to the
7 penalty used routinely to control cardiac hot-spots, mean heart doses could be
8 reduced by an average 4.8 Gy while respecting tumour coverage protocol limits and
9 without markedly increasing irradiation of the lungs, oesophagus, proximal bronchial
10 tree, cord or brachial plexus [19]. This reduction amounted to 36% of the average
11 baseline mean heart dose, and on the basis of the *OX-RT* data corresponds to a
12 predicted hazard ratio for death of 0.81. Furthermore, mean heart dose reductions led
13 to knock-on reductions in many cardiac substructure dose-volume measures. In
14 particular, $V_{LAwall-64-73-EQD2}$, $V_{AortV-29-38-EQD2}$ and mean left and right ventricle doses fell
15 by 68%, 100%, 41% and 51% relative to baseline values, insuring against survival
16 being related more specifically to these measures than to whole-heart irradiation.
17 Presently we are preparing a cardiac-sparing RT trial in which mean heart doses are
18 reduced in this way.
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41 **Conclusion**

42 In UV analyses of two independent cohorts of LA-NSCLC patients, *OX-RT* and *IDEAL-*
43 *6*, OS was associated more strongly with $V_{LAwall-64-73-EQD2}$ than with any measure of
44 whole-heart irradiation investigated. OS was also significantly associated with V_{AortV-}
45 $29-38-EQD2$ in both cohorts, and in *OX-RT* was additionally significantly associated with
46 mean heart dose. In a separate planning study we found that by penalizing cardiac
47 irradiation and re-optimizing plans, mean heart doses could be reduced by an average
48 36% relative to baseline while respecting protocol limits on irradiation of other normal
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1 tissues, in the process achieving large reductions in $V_{LAWall-64-73-EQD2}$ and $V_{AortV-29-38-}$
2 $EQD2$. We therefore intend to trial a treatment in which mean heart doses are reduced
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4 like this, closely monitoring patients in whom $V_{LAWall-64-73-EQD2}$ and $V_{AortV-29-38-EQD2}$ are
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6 not consequentially reduced to 0%, the median value of both measures in the *OX-RT*
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8 cohort.
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- [1] Zhang TW, Snir J, Boldt RG, Rodrigues GB, Louie AV, Gaede S et al. Is the importance of heart dose overstated in the treatment of non-small cell lung cancer? A systematic review of the literature. *Int J Radiat Oncol Biol Phys.* 2019; 104:582-589. doi: 10.1016/j.ijrobp.2018.12.044.
- [2] McWilliam A, Kennedy J, Hodgson C, Vasquez Osorio E, Faivre-Finn C, and van Herk M, Radiation dose to heart base linked with poorer survival in lung cancer patients. *Eur J Cancer* 2017; 85:106–113. doi: 10.1016/j.ejca.2017.07.053.
- [3] Thor M, Deasy JO, Hu C, Gore E, Bar-Ad V, Robinson C et al. Modeling the impact of cardio-pulmonary irradiation on overall survival in NRG Oncology trial RTOG 0617. *Clin Cancer Res* 2020; 26: 4643-4650. doi: 10.1158/1078-0432.CCR-19-2627.
- [4] Guberina M, Eberhardt W, Stuschke M, Gauler T, Heinzlmann F, Cheufou D et al. Heart dose exposure as prognostic marker after radiotherapy for resectable stage IIIA/B non-small-cell lung cancer: secondary analysis of a randomized trial. *Ann Oncol* 2017; 28: 1084–1089. doi: 10.1093/annonc/mdx069.
- [5] Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015; 16: 187–199. doi: 10.1016/S1470-2045(14)71207-0.

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- [6] Tucker SL, Liu A, Gomez D, Tang LL, Allen P, Yang J et al. Impact of heart and lung dose on early survival in patients with non-small cell lung cancer treated with chemoradiation. *Radiother Oncol* 2016; 119: 495–500. doi:10.1016/j.radonc.2016.04.025.
- [7] McWilliam A, Khalifa J, Vasquez Osorio E, Banfill K, Abravan A, Faivre-Finn C 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: 1073-81. doi: 10.1016/j.ijrobp.2020.06.031.
- [8] Vivekanandan S, Landau DB, Counsell N, Warren DR, Khwanda A, Rosen SD, et al. The impact of cardiac radiation dosimetry on survival after radiation therapy for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.*2017; 99: 51–60. doi: 10.1016/j.ijrobp.2017.04.026.
- [9] Landau DB, Hughes L, Baker A, Bates AT, Bayne MC, Counsell N et al. IDEAL-CRT: A Phase 1/2 Trial of Isotoxic Dose-Escalated Radiation Therapy and Concurrent Chemotherapy in Patients With Stage II/III Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys.* 2016; 95: 1367–1377. doi: 10.1016/j.ijrobp.2016.03.031.
- [10] Schultz-Hector S, Sund M, and Thames HD. Fractionation response and repair kinetics of radiation-induced heart failure in the rat. *Radiother Oncol* 1992; 23: 33–40. doi: 10.1016/0167-8140(92)90303-c.
- [11] Harrell FE, Lee KL and Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, an measuring and reducing errors. *Stat Med* 1996; 15: 361–387. doi: 10.1002/(SICI)1097-

0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4.

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- [12] Pencina MJ and D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med* 2004; 23: 2109–2123. doi: 10.1002/sim.1802.
- [13] Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L 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: 10–8. doi: 10.1016/j.ijrobp.2009.10.058.
- [14] Ganem GCA, Coelho RC and de Godoy CMG. (2020) Animation of atrial and ventricular external walls of a virtual 3D heart based on echocardiogram images. In: González Díaz C et al. (eds) VIII Latin American Conference on Biomedical Engineering and XLII National Conference on Biomedical Engineering. CLAIB 2019. IFMBE Proceedings, vol 75. Springer, Cham. https://doi-org.liverpool.idm.oclc.org/10.1007/978-3-030-30648-9_90
- [15] O'Brien RM. A caution regarding rules of thumb for variance inflation factors. *Qual Quant* 2007; 41: 673-690. doi: 10.1007/s11135-006-9018-6.
- [16] Abram SV, Helwig NE, Moodie CA, DeYoung CG, MacDonald AW and Waller HG. Bootstrap enhanced penalized regression for variable selection with neuroimaging data. *Front Neurosci* 2016; 10: 344. doi: 10.3389/fnins.2016.00344
- [17] Stam B, Peulen H, Guckenberger M, Mantel F, Hope A, Werner-Wasik M et al. Dose to heart substructures is associated with non-cancer death after SBRT in stage I–II NSCLC patients. *Radiother Oncol* 2017; 123: 370–375. doi:

10.1016/j.radonc.2017.04.017.

- 1
2
3
4 [18] Kitahara T, Liu K, Solanki K and Trott KR. Functional and morphological
5 damage after local heart irradiation and/or adriamycin in Wistar rats. *Radiat*
6 *Oncol Investig* 1993; 1: 198–205.
7
8
9
10
11 [19] Turtle L, Bhalla N, Willett A, Biggar R, Leadbetter J, Georgiou G et al. Cardiac-
12 sparing radiotherapy for locally advanced non-small cell lung cancer. *Radiat*
13 *Oncol* 2021; 16: 95. [https://doi:10.1186/s13014-021-01824-3](https://doi.org/10.1186/s13014-021-01824-3)
14
15
16
17
18
19 [20] Fukumoto K, Habibi M, Ipek EG, Zahid S, Khurram IM, Zimmerman SL et al.
20 Association of left atrial local conduction velocity with late gadolinium
21 enhancement on cardiac magnetic resonance in patients with atrial fibrillation.
22 *Circ Arrhythm Electrophysiol* 2016; 9: e002897. doi: 10.1161/CIRCEP.115.
23 002897
24
25
26
27
28
29
30
31
32 [21] Burstein B and Nattel S. “Atrial fibrosis: Mechanisms and clinical relevance in
33 atrial fibrillation. *J Am Coll Cardiol* 2008; 51: 802-809. doi:10.1016/j.jacc.
34 2007.09.064
35
36
37
38
39
40 [22] Umezawa R, Ota H, Takanami K, Ichinose A, Matsushita H, Saito H et al. MRI
41 findings of radiation-induced myocardial damage in patients with oesophageal
42 cancer. *Clin Radiol* 2014; 69: 1273-1279. [http://dx.doi.org/10.1016/j.crad.](http://dx.doi.org/10.1016/j.crad.2014.08.010)
43 2014.08.010
44
45
46
47
48
49
50
51 [23] Atkins KM, Rawal B, Chaunzwa TL, Lamba N, Bitterman DS, Williams CL et al.
52 Cardiac radiation dose, cardiac disease, and mortality in patients with lung
53 cancer. *J Am Coll Cardiol* 2019; 73: 2976–2987. doi: 10.1016/j.jacc.2019.03.
54 500.
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Table and figure headings

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

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.

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 listed in Table 2. Best fits to bootstrap resampled data are also summarised.

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'.

Figure 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 $p = 0.007$).

Figure 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.

Supplementary table and figure headings

Supplementary Table 1. Associations between OS in the *OX-RT* cohort and PCs of whole-heart dose-volume histograms (DVHs) in unadjusted (univariable) analyses.

Supplementary Figure 1. Principal component PC5 of *OX-RT* whole-heart dose-distributions has a peak that represents heart volumes receiving physical doses of 36-44 Gy and a smaller peak representing volumes receiving 67-70 Gy. Given the *OX-RT* schedule, these doses translate into EQD2s of 29-38 Gy and 67-72 Gy for an α/β ratio of 3 Gy.

Supplementary Figure 2. Projection plots through the heart for the 20 patients with the highest scores for whole-heart PC5 and for the 44 other patients. The LA contour is shown in white. Projection lines coloured red pass through cardiac volumes with high probabilities of receiving 29-38 Gy EQD2 and localize to the region of aortic valve/left main coronary artery.

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

Characteristic	<i>OX-RT</i> (No.=64)	<i>IDEAL-6</i> (No.=78)	p-value
<i>Age</i> (years)			
median (range)	71 (44-89)	66 (43-84)	.002
<i>Gender</i> (No.)			.10
Female	25 (39.1%)	20 (25.6%)	
Male	39 (60.9%)	58 (74.4%)	
<i>WHO PS</i> (No.)			.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%)	-	
<i>Tumour stage</i> (No.)			<.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	
<i>Nodal status</i> (No.)			<.001
N0 or 1	29 (45.3%)	13 (16.7%)	
N2 or 3	32 (50.0%)	65 (83.3%)	
Missing	3 (4.7%)	-	
<i>Histology</i> (No.)			.44
Squamous	36 (56.3%)	42 (53.8%)	
Non-squamous	24 (37.5%)	36 (46.2%)	
Missing	4 (6.3%)	-	
<i>PTV</i> (cm ³)			
median (range)	319 (82-1120)	401 (139-1262)	.004
<i>4D-CT used for planning</i> (No.)	56 (87.5%)	34 (43.6%)	<.001
<i>RT technique</i> (No.)			<.001
3D conformal	48 (75.0%)	75 (96.2%)	
VMAT	16 (25.0%)	3 (3.8%)	
<i>OX-RT or IDEAL-6 prescribed dose</i> (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%)	
<i>Prescribed tumour EQD2*</i> (Gy)			
median (range)	66 (58-66)	69.0 (63.5-75.6)	<.001
<i>Heart mean dose</i> (Gy)			
median (range)	7.6 (0.5-32.2)	10.3 (1.1-32.2)	.19
<i>LA wall mean dose</i> (Gy)			
median (range)	12.5 (0.5-56.2)	20.4 (1.3-63.0)	.004
<i>V_{LAwall-64-73-EQD2}</i> (%),			
median (range)	0.0 (0-25.5)	1.9 (0-76.1)	.003
<i>Chemotherapy</i> (No.)			<.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.

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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† 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)	2×10 ⁻⁴	1.049 (1.023-1.075)	2×10 ⁻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 (.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 ³)	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)	-	-

†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, $V_{\text{Structure-X-Y-EQD2}}$ = fraction of structure receiving X-Y Gy EQD2, $V_{\text{Structure-Z}}$ = fraction of structure receiving > Z Gy physical dose.

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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 [†] (C = 0.74, AIC = 262.5*)		Bootstrap models
	p-value	HR (95% CI)	p-value	HR (95% CI)	Inclusion** (%)
<i>Substructure measures</i>					
V _{AortV-29-38-EQD2} (%)	7×10 ⁻⁵	1.069 (1.035-1.105)	-	-	30.9
V _{AortV-38-EQD2} (%)	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 _{LMCA-29-38-EQD2} (%)	0.11	1.019 (0.996-1.042)	-	-	28.6
V _{LMCA-38-EQD2} (%)	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 _{LAwall-64-73-EQD2} (%)	0.006	1.077 (1.022-1.134)	-	-	29.9
V _{LAwall-73-EQD2} (%)	0.32	1.633 (0.628-4.248)	-	-	32.0
Mean LA wall dose (Gy)	2×10 ⁻⁴	1.049 (1.023-1.075)	0.04	1.059 (1.002-1.120)	31.1
<i>Other factors</i>					
V _{Heart-20} (%)	0.02	1.022 (1.003-1.040)	0.02	0.936 (0.887-0.989)	29.8
PTV (cm ³)	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

[†]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_{AortV-29-38-EQD2}, mean aortic valve dose, mean LA wall dose, V_{Heart-20}, 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_{Structure-X-Y-EQD2} = fraction of structure receiving X-Y Gy EQD2, V_{Structure-Y-EQD2} = fraction of structure receiving > Y Gy EQD2, V_{Structure-Z} = fraction of structure receiving > Z Gy physical dose.

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 [†] C = 0.70, AIC=193.0*	
	p-value	HR (95% CI)	p-value	HR (95% CI)
<i>Substructure measures</i>				
V _{AortV-29-38-EQD2} (%)	0.04	1.043 (1.002-1.086)	0.002	1.112 (1.040-1.188)
V _{AortV-38-EQD2} (%)	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 _{LAwall-64-73-EQD2} (%)	0.01	1.035 (1.008-1.063)	0.05	1.040 (1.001-1.081)
V _{LAwall-73-EQD2} (%)	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 ³)	0.04	1.002 (1.000-1.003)	0.02	1.002 (1.001-1.004)

[†]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_{AortV-29-38-EQD2}, V_{AortV-38-EQD2}, mean aortic valve dose, V_{LAwall-64-73-EQD2} 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_{Structure-X-Y-EQD2} = fraction of structure receiving X-Y Gy EQD2, V_{Structure-Y-EQD2} = fraction of structure receiving > Y Gy.

Figure 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 $p = 0.007$).

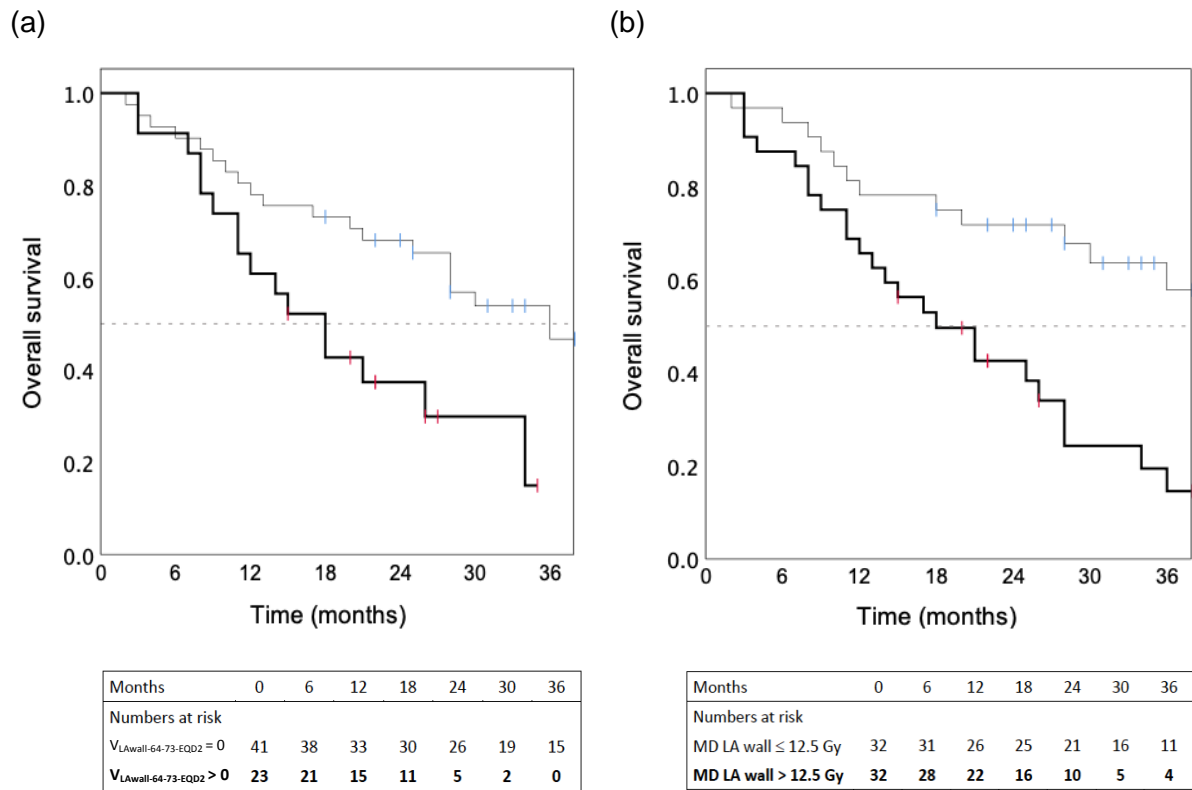
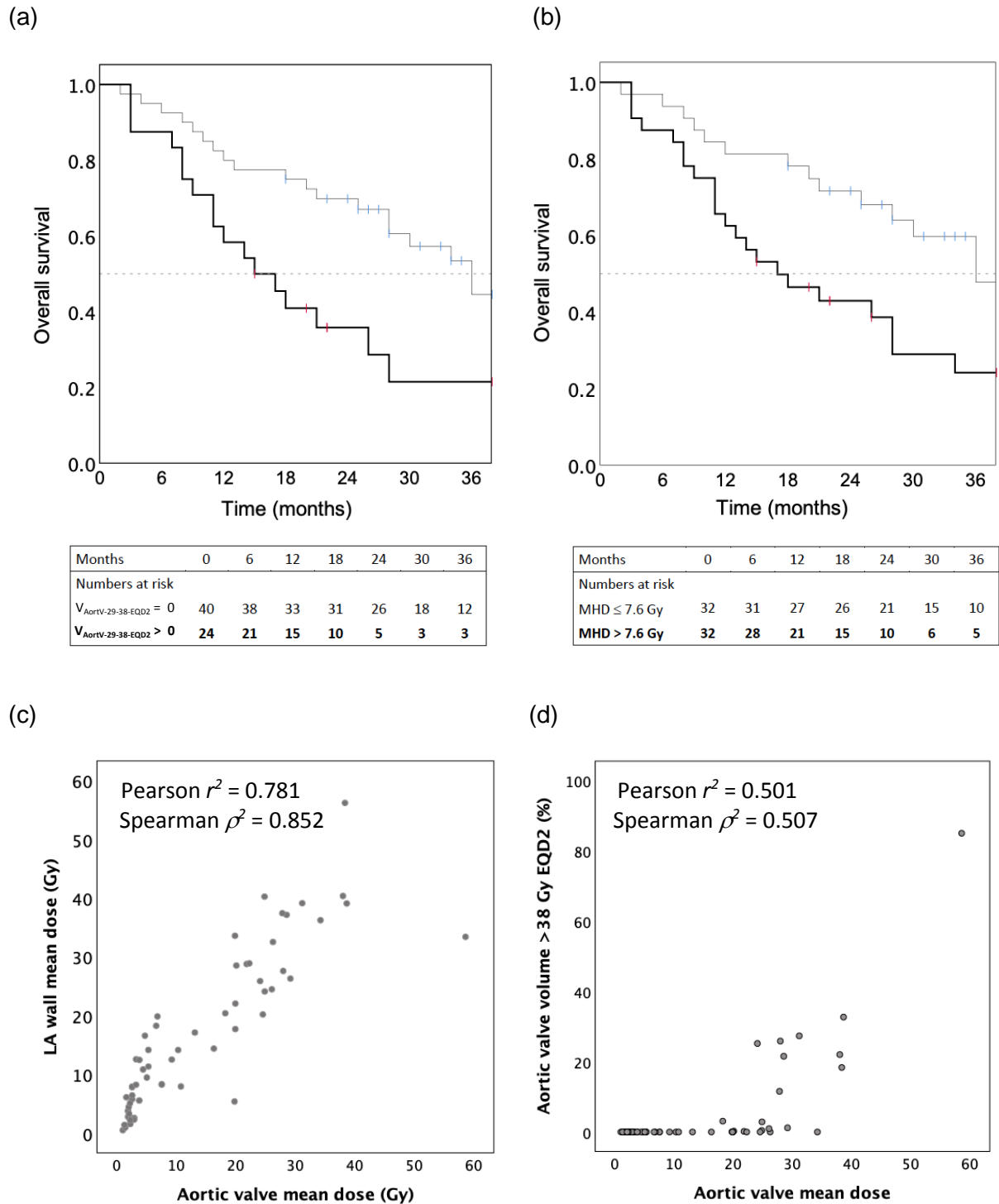


Figure 2. Kaplan-Meier survival curves for *OX-RT* patients dichotomized by: (a) fraction of the aortic valve region receiving 29-38 Gy EQD2 ($V_{\text{AortV-29-38-EQD2}}$) equal to (light) or > (bold) the 0% median *OX-RT* value (log-rank $p = 0.006$); (b) mean heart dose (MHD) \leq (light) or > (bold) 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.

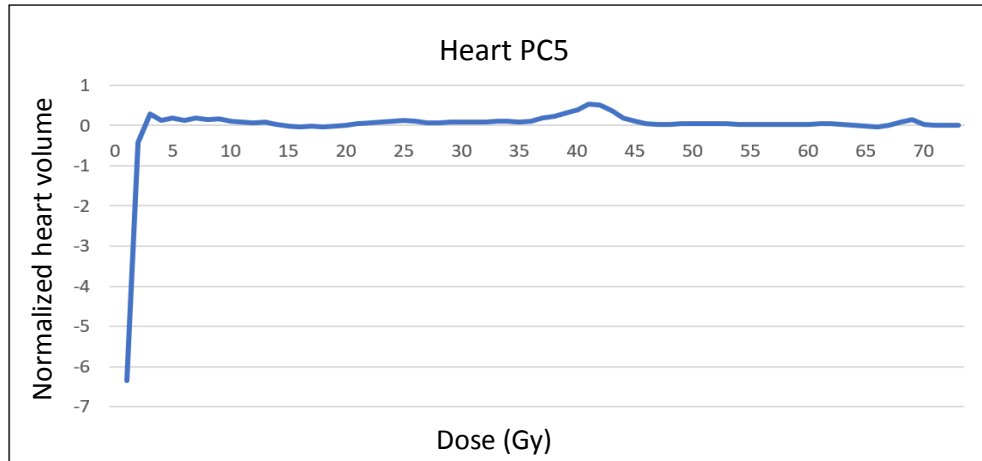


Supplementary Table 1. Associations between OS in the *OX-RT* cohort and principal components (PCs) of whole-heart dose-volume histograms (DVHs) in unadjusted (univariable) analyses.

Whole-heart PC scores	p-value	HR (95% CI)
PC1	0.31	1.164 (0.869-1.560)
PC2	0.99	1.001 (0.753-1.332)
PC3	0.57	1.078 (0.833-1.396)
PC4	0.31	1.139 (0.908-1.429)
PC5	0.007	1.457 (1.106-1.919)
PC6	0.15	1.201 (0.935-1.542)
PC7	0.34	1.184 (0.837-1.675)
PC8	0.23	1.202 (0.892-1.620)
PC9	0.63	0.923 (0.782-1.502)
PC10	0.79	0.960 (0.711-1.296)

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Supplementary Figure 1. Principal component PC5 of *OX-RT* whole-heart dose-distributions has a peak that represents heart volumes receiving physical doses of 36-44 Gy and a smaller peak representing volumes receiving 67-70 Gy. Given the *OX-RT* schedule, these doses translate into EQD2s of 29-38 Gy and 67-72 Gy for an α/β ratio of 3 Gy.



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Supplementary Figure 2. Projection plots through the heart for the 20 patients with the highest scores for whole-heart PC5 and for the 44 other patients. The LA contour is shown in white. Projection lines coloured red pass through cardiac volumes with high probabilities of receiving 29-38 Gy EQD2 and localize to the region of aortic valve/left main coronary artery.

