

**Widening the therapeutic window of thoracic radiotherapy:
cardiopulmonary toxicity modelling**

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ABSTRACT

Introduction: Prognosis for locally advanced non-small cell lung cancer (LA-NSCLC) remain poor despite attempts with radiation dose escalation to improve overall survival (OS). A major limitation of radiation dose escalation is normal tissue toxicity. Here, I investigate the hypothesis that cardiac and its substructure irradiation impact OS in LA-NSCLC patients with a dose-volume-time effect. As cardiac avoidance can potentially increase lung toxicity (radiation pneumonitis (RP) acutely) the hypothesis that novel predictive models for RP combining clinical and dosimetric factors accounting for potential heart and lung irradiation synergistic effect are better than mean lung dose alone as a predictor was also tested.

Methods: Complementary methodologies were utilised to provide additional knowledge and derive novel Cox regression OS models and logistic regression RP models. The highly correlated dose volume data were best analysed through principal component analysis. 1) A post hoc analysis of a prospective phase 1/2 isotoxic dose escalation study of 78 patients was conducted to derive an OS model incorporating clinical and cardiac substructure dosimetric factors, and electrocardiographic (ECG) changes. 2) OS model identified in part 1 was validated and refined in an independent retrospective 64 patient cohort where direct impact of cardiac dosimetry on cardiac-morbidity and cardiac-related-death was also assessed. 3) The further refined OS model from part 2 was validated in another independent cohort and the model refined using a large combined cohort and a dose-volume-time effect was tested. 4) A modelling study to predict $\geq$ grade 2 RP

(G2RP) risk combining clinical and dosimetric factors including heart and lung irradiation interaction was conducted.

Results: High volume of left atrial wall receiving high doses (64-73 Gy in equivalent 2 Gy per fraction (EQD2)), coronary ostia region receiving intermediate doses (29-38 Gy EQD2), large planning target volume size, younger age and any ECG changes or recorded cardiac events after RT were associated with poorer OS. A prognostic index was derived from these factors with good performance. High whole heart volume receiving low doses (3-12 Gy EQD2) was associated with poorer OS with the low dose effect seen later than high or intermediate dose effects. Poorer performance status, higher baseline forced vital capacity, higher contralateral tumour free lung volumes, especially lower and middle sections, receiving 2-5 Gy EQD2 and high heart volume receiving 37-55 Gy EQD2 were associated with higher G2RP risk. A model combining these factors performed better at predicting G2RP than the standard mean lung dose model in isotoxically dose escalated patients.

Conclusions: This work adds to the knowledge about the nature, magnitude and timing of cardiac and its substructure irradiation on OS and derived novel survival and lung toxicity models combining clinical and dosimetric factors. This can be used to help future management of LA-NSCLC and personalisation of radiation dose escalation. The planned in-silico study and the prospective cardiopulmonary functional imaging study will contribute further knowledge regarding the practical implications and underlying mechanism of damage.

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Work from thesis: Published papers and list of abstracts presented at conferences

Published Paper – Results from chapter 3

- **Vivekanandan S et al.** The impact of cardiac radiation dosimetry on survival after radiation therapy for non-small cell lung cancer. *Int J Rad Onc Biol Phys* 2017;99(1); 51-60. Doi: 10.1016/j.ijrobp.2017.04.026

Published Abstracts

- **Vivekanandan S et al.** Validation of the survival model including cardiac substructure dosimetry in NSCLC. *Radiother Oncol* 2018 – **Results from chapter 4**
- **Vivekanandan S et al.** Clinical and dosimetric factors impacting radiation pneumonitis in isotoxically dose-escalated NSCLC. *Int J Rad Onc Biol Phys* 2017; 99(suppl 2):S153 – **Results from chapter 6**
- **Vivekanandan S et al.** Cardiotoxicity and cardiac substructure dosimetry in dose escalated lung radiotherapy. *Radiother Oncol* 2016; 117 (suppl 1): S24-25 - **Results from chapter 3**
- **Vivekanandan S et al.** Dose escalated radiotherapy for NSCLC: heart doses versus survival in IDEAL-CRT. *J Thor Onc* 10 2015; (suppl 2):S384 - **Results from chapter 3**

Presentations at conferences

- Validation of the survival model including cardiac substructure dosimetry in NSCLC. *ESTRO 2018, Barcelona, Spain – Poster Presentation*
- Clinical and dosimetric factors impacting radiation pneumonitis in isotoxically dose-escalated NSCLC. *ASTRO 2017, San Diego, USA – Oral Presentation*
- Clinical and dosimetric factors impacting radiation pneumonitis in isotoxically dose-escalated NSCLC. *NCRI Conference 2017, Liverpool – Poster presentation*
- Data on cardiac toxicity from IDEAL. *BTOG 2017, Dublin, Ireland – Oral presentation*
- Cardiotoxicity and cardiac substructure dosimetry in dose escalated lung radiotherapy. *ESTRO 2016, Turin, Italy - Oral presentation*
- Dose escalated radiotherapy for NSCLC: heart doses versus survival in IDEAL-CRT. *WCLC 2016, Denver, USA - Oral presentation*
- Clinical and dosimetric factors impacting radiation pneumonitis in isotoxically dose-escalated NSCLC. *OIRO/CRUK Symposium 2017, Oxford – Poster presentation*
- Dose escalated radiotherapy for non small cell lung cancer: association between heart dosimetry and survival in IDEAL-CRT. *NCRI Conference 2015, Liverpool – Poster presentation*

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ABBREVIATIONS

3DCRT	three dimensional conformal radiotherapy
4DCT	four dimensional computer tomography
4DGTV	four dimensional gross tumour volume
#	fraction
α/β	alpha:beta ratio
ADL	activities of daily living
AF	atrial fibrillation
AIC	Akaike Information Criteria
AUC	area under the curve
AV	aortic valve
AVN	atrioventricular node
B-H	Benjamini-Hochberg
BMIPP	beta-methyl iodophenyl pentadecanoic acid
CERR	computational environment for radiotherapy research
c	Harrell's-c-statistic
CI	confidence interval
CL	contralateral lung
CLL	contralateral lower lung
CML	contralateral middle lung
CRT	chemoradiotherapy
CT	computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	clinical target volume
CTVexh	clinical target volume defined on maximum exhale 4 dimensional computer tomography dataset
CTVinh	clinical target volume defined on maximum inhale 4 dimensional computer tomography dataset
CUL	contralateral upper lung
dDVH	differential DVH
DLCO	diffusing capacity for carbon monoxide
Dmax	maximum dose
Dmean	mean dose
DR	all cause death rate
DVH	dose-volume histogram
Dx%	minimum dose to the hottest x% of the organ
ECG	electrocardiography
EORTC	European Organization for Research and Treatment of Cancer
EQD2	equivalent dose in 2 Gray per fraction
FEV1	forced expiratory volume at 1 second
FVC	forced vital capacity
FVC0	baseline forced vital capacity
G2RP	grade 2 or higher radiation pneumonitis
GTV	gross tumour volume
GTVexh	gross tumour volume defined on maximum exhale 4 dimensional computer tomography dataset
GTVinh	gross tumour volume defined on maximum inhale 4 dimensional computer tomography dataset

GTVn	gross tumour volume of involved nodes
GTVp	gross tumour volume of primary tumour
Gy	gray
heart-PC _{max}	whole-heart principal component most strongly associated with death rate
HR	hazards ratio
IASLC	International Association for the Study of Lung Cancer
IDEAL-5	phase I/II trial of concurrent chemoradiation with dose-escalated radiotherapy in patients with stage II or stage III non-small cell lung cancer delivered in 5 weeks
IDEAL-6	phase I/II trial of concurrent chemoradiation with dose-escalated radiotherapy in patients with stage II or stage III non-small cell lung cancer delivered in 6 weeks
IDEAL-CRT	isotoxic dose-escalated radiation therapy and concurrent chemotherapy trial
IL	ipsilateral lung
ILL	ipsilateral lower lung
IML	ipsilateral middle lung
IMRT	intensity modulated radiotherapy
ITV	internal target volume
IUL	ipsilateral upper lung
iv	intravenous
KM	kaplan meier
LA	left atrium
LA-NSCLC	locally advanced non small cell lung cancer
LA-Wall	left atrial wall
LGE	late gadolinium enhancement
LMCA	left main coronary artery
Lung-GTV	volume of lung excluding gross tumour volume
LV	left ventricle
LV-wall	left ventricular wall
LVEF	left ventricular ejection fraction
MH-EQD2	Mean heart dose in equivalent dose in 2 Gy fractions
MIBI	99mTc-methoxyisobutylisonitrile
MLD	mean lung dose
ML-EQD2	Mean lung dose in equivalent dose in 2 Gy fractions
MRI	magnetic resonance imaging
MV	multivariable
MVA	multivariable analysis
NCCN	national comprehensive cancer network
nCRT	neoadjuvant-chemoradiotherapy
NICE	national institute for health and care excellence
NSCLC	non small cell lung cancer
NTCP	normal tissue complication probability
OAR	organ at risk
OR	odds ratio
OS	overall survival
OUH	Oxford University Hospitals
p	p-value
PCA	principal component analysis
PC	principal component

PET-CT	positron emission computer tomography
PI	prognostic index
PORT	post-operative radiotherapy
PRV	planning risk volume
PS	performance status
PTV	planning target volume
r	correlation coefficient
RA	right atrium
RA-wall	right atrial wall
RCA	right coronary artery
RF	radiation fibrosis
RIHD	radiation induced heart disease
RILD	radiation induced lung disease
ROC	Receiver Operating Characteristic
RP	radiation pneumonitis
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
RV	right ventricle
RV-wall	right ventricular wall
SABR	stereotactic ablative radiotherapy
SAN	sinoatrial node
SCLC	small cell lung cancer
SPECT	single photon emission computed tomography
ssPC	cardiac substructure principal component
SWOG	Southwest Oncology Group
TI	therapeutic index
UK	United Kingdom
UVA	univariable analysis
V _{eff}	effective volume
VIF	variance inflation factor
V _x	volume receiving greater than x Gy
WHO	World Health Organisation

1. Introduction

1.1 Locally advanced NSCLC: an area in need of research

1.1.1 Epidemiology

Lung cancer is the most common cancer associated with mortality in the UK.[1] In 2014, around 24,800 men and 21,600 women were diagnosed with lung cancer and smoking can be linked to approximately 86% of these cases. Other risk factors include exposure to radon gas, chemicals in the workplace, treatment for other types of cancer and a lowered immune system.

Primary lung cancer can be divided into 2 main types: small cell lung cancer (SCLC) and non small cell lung cancer (NSCLC). About 87% of lung cancer patients diagnosed in the UK have NSCLC. The three subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma and large cell carcinoma with adenocarcinoma being the most common subtype.[2]

1.1.2 Staging

Seventh edition of TNM (Appendix 1 Table 1) and anatomic tumour staging of 2009 (Appendix 1 Table 2) were used to assist treatment planning and estimate prognosis in patients in the work described in the following chapters. Around a third of patients with NSCLC present with locally advanced NSCLC (LA-NSCLC). There is no universally agreed definition of unresectable LA-NSCLC though patients with primary tumours involving major blood vessels and/or vertebral body or those with

multi-station mediastinal lymph node involvement where a complete resection would not be possible based on evaluation within a multidisciplinary team are deemed to have unresectable LA-NSCLC.[3][4] This usually includes patients with stage IIb or higher stage disease.

1.1.3 Treatment

The standard of care for patients with unresectable or inoperable LA-NSCLC and good WHO performance status (PS) (Appendix 2) is radical chemoradiotherapy (CRT) or CHART (continuous hyperfractionated accelerated radiotherapy) as per NICE guidelines.[5] CRT can be delivered using chemotherapy concomitantly with radiotherapy (RT) or sequentially before RT. CRT results in better overall survival (OS) than RT alone with patients receiving concurrent CRT having even better OS than patients receiving sequential CRT.[6] As an example of radical RT and CRT delivery for NSCLC, below (*in italics*) are some salient points extracted from the Oxford University Hospital (OUH) guidelines. (Refer to Appendix 3 for OUH RT guidelines and Appendix 4 for IDEAL-CRT (isotoxic dose-escalated radiation therapy and concurrent chemotherapy trial) RT guidelines).

CRT: Sequential CRT involves 3-4 cycles of a platinum doublet (induction chemotherapy). Concurrent CRT is offered to patients who are WHO PS 0-1 with no significant comorbidities and have localised disease encompassable within a radical RT field.

RT: For Stage I-II NSCLC, radical RT alone can be used. For patients with small and central disease not suitable for stereotactic ablative RT (SABR) and for LA-NSCLC CRT, 60-66 Gy in 30-33 fractions over 6-6 ½ weeks, 5 days per week, can be prescribed.

Volume delineation: A free-breathing helical computer tomography (CT) with intravenous (iv) contrast and a 4-dimensional CT (4DCT) scan to assess respiratory motion are acquired. Gross tumour volume (GTV) is delineated on the helical CT scan. Following induction chemotherapy, GTV is the post-chemotherapy extent of primary disease (GTVp) and pre-chemotherapy involved nodes (GTVn). The composite of GTV defined on the maximum exhale 4DCT dataset (GTVexh) and maximum inhale 4DCT dataset (GTVinh) is the 4DGTV. Clinical target volume (CTV) is created by adding a margin to the GTV to account for any subclinical or microscopic disease. This is normally a minimum of .6 cm for squamous cell carcinomas and .8 cm for adenocarcinomas. CTV is edited to exclude anatomical boundaries that limit microscopic spread. CTVinh and CTVexh are created from the GTVinh and GTVexh respectively by adding the above margins. CTVinh and CTVexh are merged to produce the final CTV. If induction chemotherapy is used to reduce primary tumour size to make the disease encompassable within a radical RT field, treating the post-chemotherapy extent of disease in the GTVp with a margin for CTV is acceptable. If pre-chemotherapy primary tumour size is acceptable, the pre-chemotherapy extent of primary disease respecting anatomical boundaries is treated.

A set-up margin is added to the CTV to create a planning target volume (PTV) to account for variations in set-up with the immobilisation technique employed and corrected for by using daily image guided cone-beam CT. With daily cone-beam CT, a .5 cm margin is considered sufficient to account for setup variability. If 4DCT is not available but fluoroscopy is available, the conventional margins below can be modified at the discretion of the clinician. Conventional CTV to PTV margins where 4DCT or fluoroscopy is unavailable:

Tumour position	Anterior/posterior	Lateral	Superior/inferior
Upper Lobe	0.8 cm	0.8 cm	1.0 cm
Lower Lobe	1.0 cm	1.0 cm	1.5 cm

The following organs at risk (OAR) are delineated: pericardium, oesophagus, brachial plexus (for upper lobe tumours), right lung, left lung, lung-GTV (volume of lung excluding GTV), spinal canal, and stomach and liver for lower lobe tumours.

Treatment planning: *A minimum of 95% of the prescribed dose should be delivered to at least 98% of the PTV, provided all OAR dose constraints are met (Table in Appendix 3). If the planning objectives and OAR constraints cannot be met with 3D conformal RT (3DCRT) then intensity modulated RT (IMRT) or Rapid arc is used. Hybrid Rapid arc may be considered for difficult cases where combined 3DCRT and Rapid arc plans are delivered each fraction. Contralateral lung should be spared traversing radiation wherever possible. Lung volume receiving greater than 5 Gy (V5) should be less than 42% but 65% may be acceptable if the patient's lung function is adequate.*

The GTV to CTV expansions vary depending on protocol. The expansions for IDEAL-6[7] and studies such as CHART[8] are isotropic and consistent for both squamous and adenocarcinoma.

1.1.4 Outcome

Unlike majority of other cancers, 5-year OS for lung cancer has not improved a great deal since the 1970s and prognosis for stage II and III LA-NSCLC remains poor (Figures 1 and 2).

Figure 1. Age-standardised five-year net (overall) survival for lung cancer, adults (aged 15-99), England and Wales, 1971-2011. *Adapted from [1]*

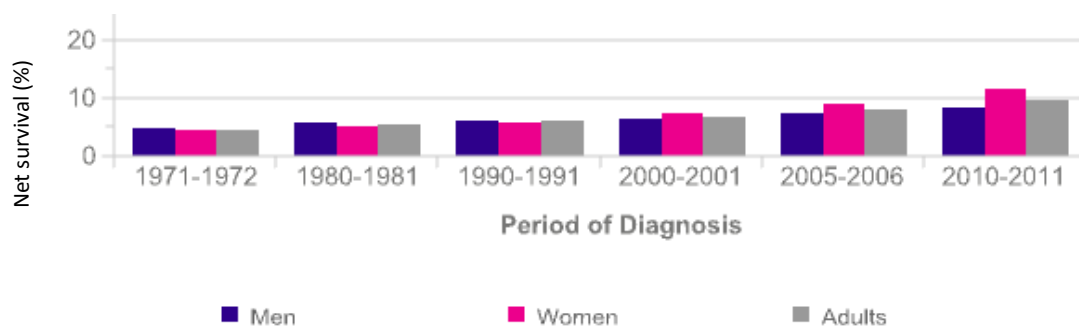
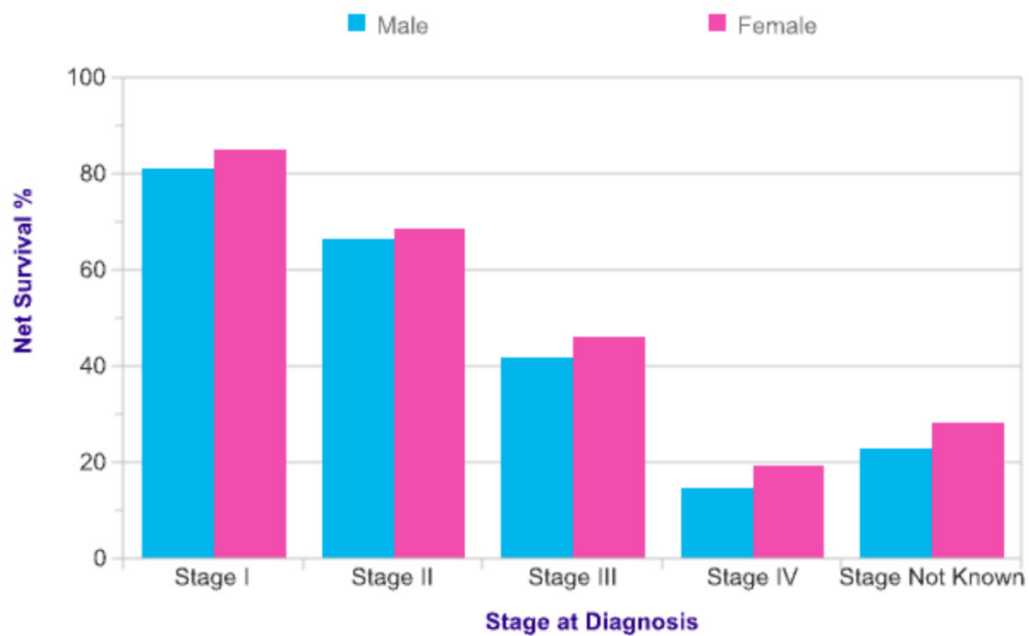


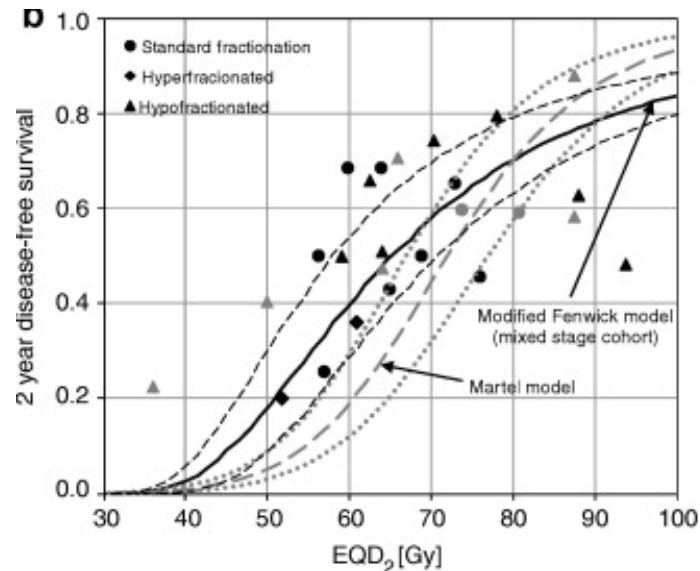
Figure 2. One-year relative survival rates by stage of lung cancer, adults aged 15-99 years, England, 2014. *Adapted from [1]*



1.2 Radiation dose escalation attempts to improve survival in LA-NSCLC

For more than 30 years, the accepted standard RT dose for LA-NSCLC was 60–63 Gy in 1.8–2.0 Gy fraction sizes established by the Radiation Therapy Oncology Group (RTOG) 7301 trial.[9][10] However, local failure rates at these doses remain high with poor OS. Progress has been slow over the past 30 years with 3-year OS increasing from less than 10% to 25% in some trials. Therefore, there has been much interest in strategies to increase therapeutic gain using RT dose escalation. Though biological modelling suggests a tumour dose–response (Figure 3)[11], the clinical benefit of high dose radiation remains controversial in LA-NSCLC. Prospective phase I/II studies showed that concurrent CRT up to 74 Gy was safe and RT dose escalation may improve local control and OS.[12][13][14][15][16][17][18][19][20][21][22][23] This has been challenged by the results of a phase III randomised CRT trial, RTOG-0617,[24] which showed patients receiving 74 Gy had inferior OS compared to 60 Gy. In this study RT dose escalation was not carried out isotoxically (i.e. prescription dose was not individualised to the patient to achieve maximum prescribed tumour dose limited by the maximum toxicity risk) and RT planning constraints were not adhered to stringently. In contrast, the phase I/II isotoxic dose-escalated RT and concurrent chemotherapy UK trial (IDEAL-CRT) in patients with stage II/III NSCLC, delivering mean and maximum tumour doses equivalent to 69 and 75.6 Gy in 2 Gy fractions respectively reported better OS.[7] This suggests normal tissue toxicity may impact OS.

Figure 3. Modelled radiotherapy dose-response relationship for NSCLC based on clinical data [11]



Stage-corrected disease-free survival at 24 months versus EQD₂ for standard fractionation (●), hyperfractionated (■) and hypofractionated (▲) schedules. This shows the stage-corrected data together with the Martel and Fenwick models; symbols representing cohorts with less than 20 patients are shown in grey

1.3 Radiation dose escalation limitation: normal tissue toxicity

A major limitation of high dose irradiation of the tumour is radiation induced normal tissue toxicity. The therapeutic index (TI) is a comparison of the radiation dose that causes the therapeutic effect to the dose that causes toxicity (Figure 4). Therapeutic window refers to a range of doses which optimise between efficacy and toxicity, achieving the greatest therapeutic benefit without resulting in unacceptable toxicity. The therapeutic window exists due to the higher sensitivity of cancer cells to radiation induced damage than normal cells. One approach to achieve better TI is to improve dose distributions using better radiation delivery techniques such as IMRT to reduce dose to normal tissue.

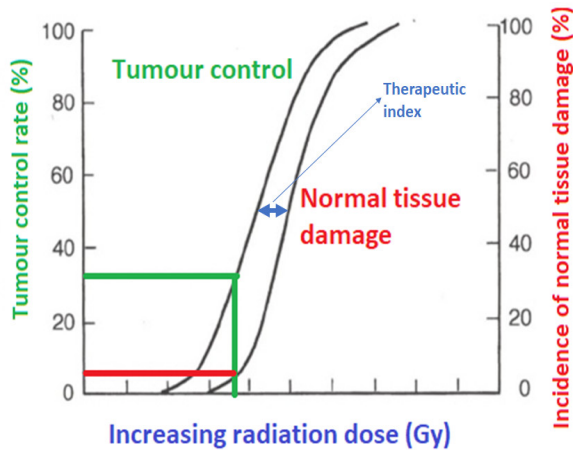


Figure 4. Normal tissue damage and tumour control rates in response to increasing radiation dose with therapeutic index (TI) comparing radiation doses that cause the therapeutic effect to the doses that cause toxicity.

Two major thoracic organs which are in close proximity to lung tumours are the heart and lungs. Better understanding of the relationship between normal tissue toxicity and radiation dose distributions could potentially aid safer increase in radiation doses delivered to the tumour.

1.3.1 Radiation induced cardiac damage

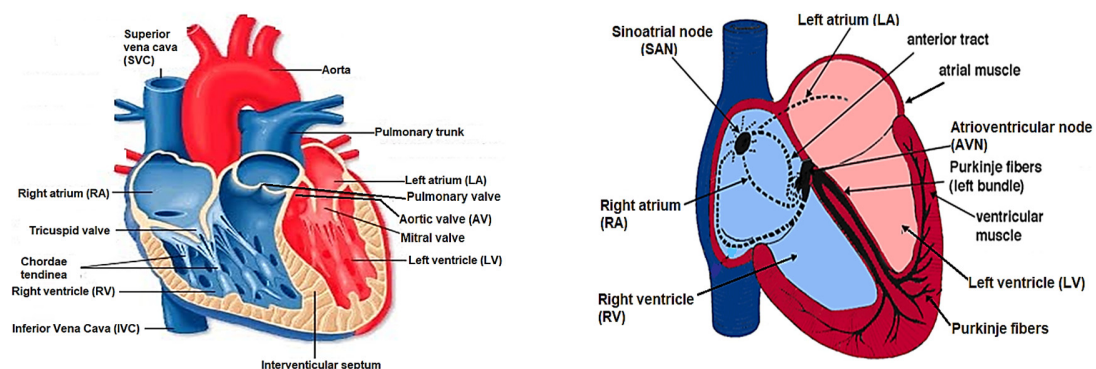
1.3.1.1 Cardiac anatomy [25][26]

The heart is a complex organ consisting of multiple substructures working in harmony to circulate blood around the body (Figure 5). The 4 chambers of the heart, the right and left atria and ventricles, are involved in its contractile function. The pace-making signal for coordinated contraction of the heart is generated in the sinoatrial node (SAN). This signal travels through the right atrium (RA) to the atrioventricular node (AVN), along the Bundle of His and bundle branches to cause heart muscle contraction, first of the RA and left atrium (LA), and then the right (RV) and left (LV) ventricles pumping blood throughout the body. Blood passes through one-way valves before leaving each heart chamber which prevents backward flow.

There are 4 valves of which the aortic valve (AV) is located between the LV and aorta. The pericardium is a fluid filled sac surrounding the heart and proximal ends of the aorta, vena cava, and the pulmonary artery. It keeps the heart contained in the chest cavity, prevents the heart from over-expanding and limits heart motion.

Coronary arteries supply blood to the heart muscle. They originate as the right and left main coronary arteries, which exit the ascending aorta just above the AV. Coronary ostia are two openings in the aortic sinuses that mark the origins of the left and right coronary arteries. AV has three cusps: the non-coronary cusp which contains no ostia, the right coronary cusp which contains the ostia of the right coronary artery (RCA), and the left coronary cusp which contains the ostia of the left main coronary artery (LMCA). LMCA supplies the LV and LA. LMCA divides into the left-anterior-descending artery supplying the anterior part of the left side of the heart and the circumflex artery supplying the outer side and posterior part of the heart. RCA supplies blood to RV, RA, SAN and AVN. Together with the left-anterior-descending artery, the RCA supplies the middle (septum) of the heart.

Figure 5. Cardiac substructures and vessels. *Adapted from [27][28]*

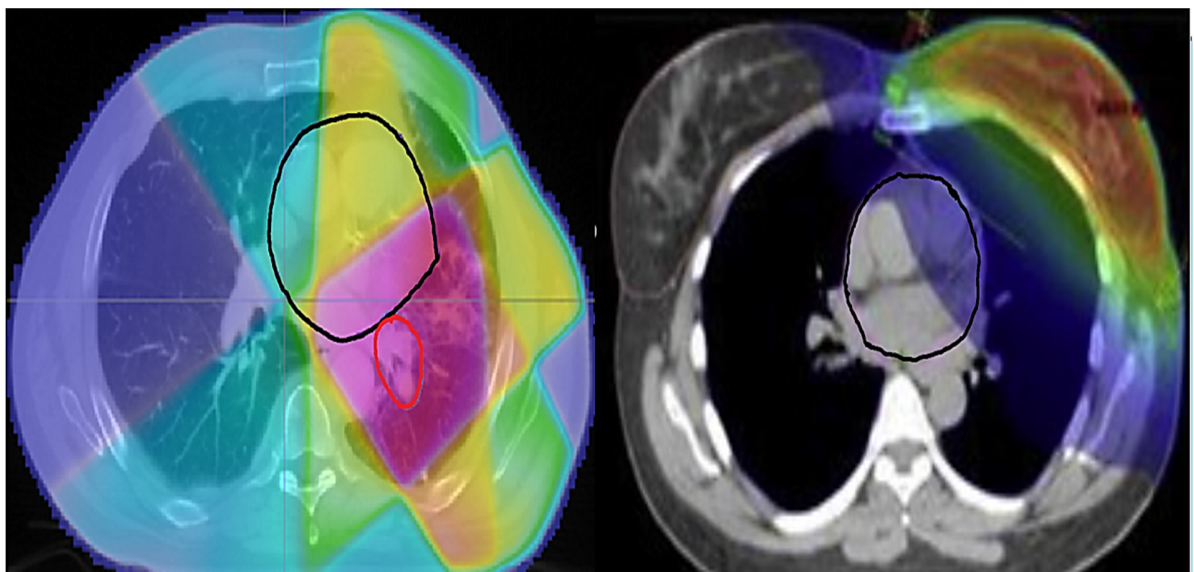


Radiation induced heart diseases (RIHD) such as pericarditis, cardiomyopathy, coronary artery disease, pericardial effusions, valvular diseases and arrhythmias could occur due to damage to any of the above substructures.

1.3.1.2 Radiation induced heart disease impact on survival: knowledge till 2016

Increased mortality associated with cardiac irradiation has been described in detail in breast cancer and lymphoma survivors.[29][30][31] Darby et al. analysed survival of more than 300,000 women with early breast cancer between 1973 and 2001.[32] They found patients with left sided tumours had higher mortality than right sided tumours likely due to increased cardiac irradiation. They also found a decrease in this mortality over time, paralleling possible advances in RT planning and delivery. Radiation doses delivered in breast cancer (50 Gy in 25 fractions or 45 Gy in 15 fractions) are lower than those delivered in lung cancer (60-66 Gy in 30-33 fractions). The RT beam arrangement used in breast cancer, shown in Figure 6, usually results in small volumes of heart receiving high radiation doses (mostly LV and left-anterior-descending artery which are closest to left chest wall). In contrast, lung cancer RT beam arrangements result in higher heart volume receiving high doses as well as the whole heart being bathed in low dose due to the proximity of tumour to heart (Figure 6).

Figure 6. Radiotherapy plans for patients with lung cancer and breast cancer. *Left: axial section through a CT showing radiotherapy dose-distribution for a patient with lung cancer (outlined in red) with high heart volume (outlined in black) receiving high/intermediate doses. Right: axial section through a CT showing a radiotherapy dose distribution for a patient with breast cancer with heart (outlined in black) receiving low doses. High radiation doses in red/pink; intermediate doses in yellow; low doses in blue.*



Mean heart doses seen in breast cancer patients are lower (around 6 Gy for left sided tumours [31]) than in lung cancer patients (9-25 Gy [33][34][35]) and oesophageal cancer patients (17-29 Gy [36][37][38][39]). Darby et al found in breast cancer patients, for every 1 Gy of mean heart dose delivered major coronary events increased relatively by 7.4%.[31] In patients with lung and oesophageal cancer, the combination of the potential increased cardiac event risk associated with the higher mean heart doses, higher heart volumes receiving high and intermediate doses,

higher baseline cardiac event risk associated with their older age and smoking history, could result in a much higher overall RIHD risk than the relatively small risk seen in breast cancer patients. However, the impact of RIHD on survival of lung and oesophageal cancer patients has not been well characterised due to their poor prognosis and RIHD being thought to have a late onset. With increasing potential for longer survival due to the advent of new therapies and RT dose escalation, and emerging evidence suggesting that RIHD can impact OS earlier than previously thought, there has been increased interest in RIHD in patients with lung and oesophageal cancer.[40] The evidence available till 2016 when this work was conducted is summarised below to understand RIHD in oesophageal and lung cancer patients and identify gaps in the evidence.

1.3.1.2.1 Impact of high radiation doses on RIHD and overall survival

1.3.1.2.1.1 Oesophageal Cancer

Definitive-chemoradiotherapy[41][42] and neoadjuvant-chemoradiotherapy[43] can improve survival rates in patients with locally advanced oesophageal cancer with a median survival of 48·6 months in the neoadjuvant-chemoradiotherapy group. CRT can however result in appreciable morbidity, including cardiac toxicity which in the setting of neoadjuvant-chemoradiotherapy is especially important as it could have direct implications on anaesthetic and postoperative management. In fact, RT modalities with potentially different normal tissue doses have been shown to be independent predictors of post-operative cardiopulmonary complication.[44]

Large studies have shown cardiac mortality rates are lower in patients treated with RT techniques such as IMRT which spare normal tissue better than 3DCRT, and cardiac mortality can occur as early as 1 year after RT.[40][45] A recent review showed that 10.8% (range: 5–44%) of oesophageal cancer patients treated with RT experience $\geq$ grade 3 cardiopulmonary toxicity and that most events occur within 26–57 months.[46] But the actual rates are likely higher as cardiac morbidity is possibly under-reported in older trials due to the relationship with radiation damage not being considered. The most frequently observed cardiac toxicities are ischaemia, pericardial effusion and heart failure.[46] It is difficult however to determine relevant dosimetric parameters associated with these toxicities as the toxicities assessed in the studies are diverse.

Pericardial effusion/pericarditis: Various dosimetric parameters have been related to the incidence of pericardial disease. A retrospective review of 57 oesophageal cancer patients reported 5 patients had non-malignant pericardial effusion after CRT and found mean and maximum heart doses of 27.1 Gy and 47.0 Gy, respectively, were predictive of pericarditis.[47] In a larger study of 101 oesophageal cancer patients who received definitive-chemoradiotherapy, the mean time to onset of pericardial effusion was 5.3 months, with an incidence rate of 27.7% and a mean pericardial dose of 26.1 Gy and V30 (the percentage volume of pericardium receiving 30Gy or more) of >46% was associated with pericardial effusion.[48] A follow up study confirmed V30 as well as V45 were predictive factors for pericardial effusion in oesophageal cancer patients after CRT.[49] Koniski et al studied 102 locally advanced oesophageal cancer patients treated with CRT.[50]

Significant associations between heart V20, V30 and V40 and symptomatic cardiac toxicity were seen with thresholds of 70%, 65% and 60% respectively. However, the number of events were small with treatment related cardiac toxicity seen in only 12 patients, 6 of which were symptomatic, and 4 of the 6 had pericardial effusion. A more recent study of 60 oesophageal cancer patients treated with definitive-chemoradiotherapy at 60 Gy in 30 fractions, a pericardial effusion rate of 52.2% was seen and pericardial V30 >41.6% was significantly associated with pericardial effusion.[51] Shirai et al [52] found 35% of the 43 oesophageal cancer patients in their study developed pericardial effusion and a higher heart dosimetric parameter of V50 was a significant predictor for it. In contrast, another study of 143 oesophageal cancer patients treated with CRT using >50Gy found 38.5% developed pericardial effusion at a median of 3.5 months (range 0.2-9.9) and a lower dosimetric parameter of V10 >72.8% was identified as the most important factor.[53]

Ischaemia/rhythm abnormalities: These have been associated with higher radiation doses with shorter onset time from RT than seen in breast cancer patients. Ogino et al studied the hospital charts of 343 patients treated with CRT or RT alone for evidence of cardiac symptoms after RT, history of cardiac disease, and risk factors for the development of cardiac disease, such as diabetes mellitus, total cholesterol, hypertension, and smoking habits.[54] Symptomatic cardiac disease was defined as abnormalities noted on electrocardiogram and echocardiogram in symptomatic patients by a cardiologist comparing data before and after RT. 13.8% patients had symptomatic cardiac disease at 5 years and the most frequent events were pericardial effusion and rhythm changes (paroxysmal atrial tachycardia, AF,

sinus tachycardia).[54] The risk depended on heart V45, V50, and V55 with the lowest significant cutoff values of 15, 10, and 5%, respectively indicating high radiation dose to small heart volume and intermediate dose to larger heart volume could increase symptomatic cardiac disease.

Heart failure/left ventricular impairment: Tripp et al observed a statistically significant but not clinically significant reduction in median left ventricular ejection fraction (LVEF) (59% to 54%) 6 weeks after CRT using multiple-gated acquisition cardiac scans in oesophageal cancer patients, but did not observe any significant association between radiation doses to the heart, LV, or left-anterior-descending artery and LVEF impairment.[55] This is in line with the results of another small retrospective study of 15 patients treated with neoadjuvant-chemoradiotherapy at 45-50 Gy in 25 fractions which also showed a decrease in LVEF in 12 patients.[37] The median LVEF fell from 63% to 58% at a median of 32 days post treatment. A decline in LVEF from 64% to 40% precluded surgery in one patient, but otherwise no clinically significant morbidity was observed. Further support for RT inducing acute impairment of LVEF is provided by another study which demonstrated changes following neoadjuvant-chemoradiotherapy but not neoadjuvant chemotherapy alone.[56] None of these studies found a significant association between heart dosimetry and heart toxicity, likely due to the small number of patients and events. Hatakenaka et al studied 31 patients treated with CRT and found LV function impairment from an early treatment stage.[57] LVEF decreased irrespective of LV dose as early as 1 to 3 days after completing CRT. Also, heart rate increased significantly during CRT in patients receiving high LV dose which was consistent with

the findings by Zhang et al also and suggest this may be a compensation response to LVEF decrease.[58] Impaired LV function could impact the incidence of postoperative cardiovascular and pulmonary morbidity after oesophagectomy in patients receiving neoadjuvant-chemoradiotherapy and therefore is an important factor to consider in these patients.

Subclinical short-term imaging changes may be seen early without changes in LV function or symptomatic cardiac toxicity after RT. This could identify patients for early intervention to reduce further damage. Gayed et al found more perfusion abnormalities and inferior LV ischaemia in irradiated patients than non-irradiated patients especially in areas receiving >45 Gy using gated myocardial perfusion, but functional parameters did not differ significantly.[59] A further study of 40 patients supports these findings as perfusion defects were seen in a third of the patients who were not symptomatic at a median follow up of 11 months.[60] Zhang et al conducted 99mTc-methoxyisobutylisonitrile (MIBI) single photon emission computed tomography (SPECT) gated myocardial perfusion imaging in 18 patients at 40 Gy and found new myocardial perfusion defects in 8 patients.[58] V37–V40 were significantly higher in the patients with the new perfusion defects. When radiation dose reached 40 Gy, chamber wall motion, wall thickening, end-diastolic perfusion and end-systolic perfusion decreased significantly. Takanami et al [61] investigated changes in myocardial fatty acid metabolism caused by CRT in 12 oesophageal cancer patients who underwent SPECT using Iodine-123 beta-methyl iodophenyl pentadecanoic acid (BMIPP). At 3-month post-CRT, myocardial BMIPP uptake significantly correlated with LV V40, and heart V40 and V60. However, there were

no statistically significant correlations at 1-year post CRT, suggesting that in the long term, myocardial metabolism may be affected by factors other than heart irradiation. This highlights the need for careful planning of timing of investigations in future dosimetric studies aimed at detecting radiation induced heart changes.

1.3.1.2.1.2 Lung cancer

In an attempt to improve prognosis, CRT has been delivered in the post-operative and definitive setting in patients with lung cancer. High radiation doses are delivered to the heart in these patients who have a higher baseline cardiac morbidity risk due to their high smoking rate.[62][63] Therefore, there is a potential increased risk of RIHD in lung cancer patients. As symptoms of cardiac dysfunction such as dyspnoea and chest pain overlap with symptoms of lung cancer, cardiac morbidity and mortality may be under reported. So, care must be taken to minimise possible adverse cardiac effects of RT that might negate the anticipated survival benefits.

Although there is no direct evidence of cardiac irradiation and RIHD impacting survival in patient with lung cancer, there is some indirect evidence. Incidental intake of beta-blockers or aspirin, which are cardioprotective drugs, have been seen to have a protective effect on survival in patients with lung cancer post RT, which supports RIHD potentially impacting their survival.[64] ECG changes and increase in cardiac biomarkers such as B-type natriuretic peptide can be detected early after high dose radiation without onset of any clinical symptoms.[65] The early detection of cardiac damage may allow early intervention with cardioprotective drugs to reduce risk of further damage.

Post-operative radiotherapy (PORT)

PORT studies in lung cancer have alluded to the lower OS associated with PORT being partly due to increased RIHD. A systemic review and meta-analysis of over 2000 patients treated in nine randomised controlled lung cancer trials showed an absolute detriment of 7% in OS at 2 years with PORT compared to surgery alone (55% vs 48%).[66] The death rate due to non-cancer causes among the patients who received PORT was 19% compared to 11% in the surgery only group, suggesting that treatment related toxicity may account for this difference. One of the trials which randomised 728 patients with NSCLC to either PORT at 60 Gy or observation had 27.5% non-cancer deaths in the PORT group versus 11% in the control group.[67] Five-year OS was 43% for the control group and 30% for the PORT group.[67] The excess mortality rate in the PORT group was due to an excess of intercurrent deaths (8% Vs 31%). PORT however had no significant effect on local recurrence or metastasis. The OS detriment in the group with higher nodal stage was less, likely due to the greater survival benefit of PORT in this group, with the higher risk of recurrence offsetting the increase in non-cardiac death risk due to RIHD.

In a study of 98 patients with lung cancer treated between 1994 and 2004 mostly using cobalt-60 rather than modern conformal RT, the median OS was significantly lower for patients with left-sided than right-sided tumours (25 months versus 100 months) suggesting higher RIHD due to the left chest being closer to the heart.[68] Further support arises from an analysis of the Surveillance, Epidemiology and End Results (SEER) database which included 6148 lung cancer patients who underwent

surgery, 3589 of whom received PORT.[69] The median follow-up for all patients was 2.1 years. They found PORT was associated with an increased risk of heart disease mortality (Hazard Ratio (HR) 1.30) likely due to RIHD. However, this excess heart disease mortality after PORT was only seen in patients treated between 1983 and 1988 but not in patients treated later ((HR 1.49, p .009] and (HR 1.08, p .639) respectively) possibly due to modern RT techniques allowing better normal tissue sparing. They also observed PORT was not associated with higher heart disease mortality rate in patients with right upper lobe tumours (i.e. those furthest away from heart) regardless of treatment period. This provides further indirect evidence to support higher cardiac dose resulting in RIHD increasing heart disease mortality.

Definitive radiotherapy

A study by Hardy et al analysed 34209 patients with NSCLC.[70] Of these, 31.2% received no chemotherapy or RT, 9.4% received chemotherapy only, 34.4% received RT only, and 25.1% received chemoradiation. The median time to the development of cardiac toxicity ranged from 78 to 510.5 days. An increased risk of cardiac dysfunction (ischaemic heart disease, conduction disorders, and heart failure) (HR 1.54) was seen in patients treated with RT or CRT. Also, the risk of cardiac dysfunction and ischemic heart disease was higher when radiation was administered to the left than right lung providing further support for RIHD. This also suggests that RIHD in lung cancer occurs earlier than in breast cancer patients.

Direct evidence for cardiac irradiation impacting OS in lung cancer is starting to emerge. A phase III randomised CRT trial, RTOG-0617, showed lower 2 year OS in

patients treated with 74 Gy than 60 Gy in 2 Gy per fraction (44.6% Vs 57.6%), despite no significant difference in local failure rate, distant metastases rate or progression free survival.[24] The authors noted high heart volumes receiving 5 Gy (V5) and 30 Gy (V30) were significantly associated with poorer OS, though specific heart toxicity outcomes were not tracked. In this trial, the radiation dose escalation was not carried out isotoxically respecting normal tissue dose constraints and there was poor compliance to heart dose constraints set out in the protocol.

Belliere et al undertook a retrospective analysis of 50 NSCLC patients treated with 74 Gy using 3DCRT.[71] Three patients had RIHD and 2 of these died of cardiac failure. Gayed et al evaluated 24 patients who received concurrent or adjuvant CRT, or RT alone.[60] Myocardial perfusion imaging studies before and after RT showed that 29% developed cardiac complications but none died from cardiac events. In a retrospective study of 250 inoperable NSCLC patients with no previous cardiac disease who received definitive CRT, 84% died without cardiac events whilst 15% developed cardiac disease after RT, mostly supraventricular tachycardia and myocardial infarctions.[72] Although there was a trend for poorer OS in patients receiving >14.5 Gy to the LV, they did not find a significant correlation between RIHD and high mean-dose to LV, both ventricles or whole heart.

Further exploration of direct impact of cardiac and cardiac substructure dosimetry on OS and cardiac related deaths is required to identify the most relevant substructures impacting OS. However, some issues associated with cardiac endpoints also need to be acknowledged. Due to the limited number of patients and low survival rates, the endpoint in most studies so far has been cardiac event. However, due to the

overlap of symptoms of cardiac events and tumour progression, there may be misclassification and underreporting of cardiac events in these studies. A further complicating factor is the possible interplay between cardiac complications and lung toxicity, resulting in increasing dyspnoea which may be misclassified as lung toxicity leading to further underestimation of cardiac toxicity. Prospective studies incorporating electrocardiograms and other investigations specifically exploring cardiac damage could reduce some of this underreporting.

1.3.1.3 Mechanism of radiation induced cardiac substructure damage

Due to the proximity of heart to most lung tumours, it may not be feasible to spare whole heart from irradiation without compromising tumour coverage. So, it is vital to localise the cardiac substructures that are most affected by RT and impact OS so that cardiac substructure sparing RT can be attempted. In fact, animal studies have shown us that whole heart avoidance may not be necessary to avoid the detrimental effect of RIHD. In rats, better survival was seen when only ventricles were irradiated (i.e. atria excluded) compared to the entire heart (0–30 Gy) highlighting the need for better understanding of cardiac substructure radiation damage.[73]

In breast cancer patients coronary artery disease occur decades after RT and in lymphoma patients valvular dysfunction can have a latent period of 8 years or decades.[74][75] In lung cancer patients with shorter prognosis, more acute effects may be seen than in breast cancer and lymphoma patients possibly due to higher radiation doses causing damage to the conduction system resulting in arrhythmia, pericardium resulting in pericardial effusion and myocardium resulting in dysfunction.

As there is a more acute onset of RIHD in lung cancer patients, this is unlikely to be associated with vascular or valvular damage which tend to manifest over a much longer period as seen in breast cancer and lymphoma patients. Animal studies have suggested that the general underlying mechanism of acute radiation damage and cardiac dysfunction involves endothelial cell damage, changes in the microvasculature, inflammation, focal ischaemia and fibrosis resulting in dysfunction of both pericardium and myocardium.[76] The mechanism of radiation induced damage to potentially relevant cardiac substructures in lung cancer RT are described below.

Pericardium: 70–90% of patients with significant mediastinal radiation exposure may have pericardial disease.[77][74] This includes acute pericarditis, pericardial effusion, delayed thickening and constrictive pericarditis. Acute pericarditis is a short-term complication due to radiation induced pericardial inflammation. Presentation may be with chest pain, fever and/or ECG changes and elevations in cardiac markers within days to weeks of RT. Treatment of acute pericarditis is usually with non-steroidal anti-inflammatory drugs, colchicine and steroids. pericardial effusion may present months to years after RT and patients may be asymptomatic or develop progressive shortness of breath. Pericardial effusion resulting in tamponade require urgent drainage. Constrictive pericarditis is the most severe form of pericarditis and commonly presents 10 years post RT as congestive heart failure. Symptomatic treatment is with diuretics and definitive therapy is pericardiectomy or pericardial stripping.

In an autopsy study, after >35 Gy to the heart 15 of 16 patients had thickened pericardium, of which 5 patients had pericardial tamponade.[77] In another autopsy study of 20 patients post-RT, 70% had pericardial disease, mostly effusions or constrictive disease.[74] Initial pericardial injury is thought to be due to microvascular damage leading to episodic ischaemia. Tortuous and permeable neovascularisation in irradiated pericardium leads to additional ischaemia and fibrosis, especially of venous and lymphatic vessels, decreasing extracellular fluid drainage leading to the development of pericardial effusion.

Myocardium: In the early stages there may be inflammation in the myocardium, endothelial cell damage and decreased myocardial capillary density with no functional impairment.[78][79] Seemann et al found microvascular density in the LV was significantly decreased at 40 weeks after 16 Gy in mouse hearts.[80] At 40 weeks, half of the hearts irradiated to 2 Gy and almost all of the hearts irradiated to 8 or 16 Gy showed vascular leakage. In rats, 1 month after a single fraction of 15 Gy and 20 Gy, accumulation of fibrosis in the ventricles and atria and dose-dependent decrease in end-diastolic diameter have been seen, and after 22.5 Gy death due to cardiac failure was seen.[81][82] In patients with oesophageal cancer, high radiation doses have been implicated in decreasing LV end-diastolic volume index, LV stroke volume index, and LVEF within 2 weeks of treatment.[57] Main coronary artery damage has also been implicated in reduced myocardial perfusion in areas receiving ≥ 45 Gy at a median of 3 months from RT.[59]

Conduction system: The incidence of radiation induced conduction system disease remains unclear, but atrioventricular block with complete heart block is the most serious complication.[83] Myocardial fibrosis and ischaemia due to RT can cause conduction system abnormality.[84] Studies in larger animals have suggested that cardiac irradiation may induce conduction defects acutely. In pigs, transmural cardiac muscle scarring and fibrosis can be seen after a single fraction of >32.5 Gy with full thickness fibrosis causing AVN inflammation, resulting in un-coordinated myocardial contraction.[85] 40 Gy can lead to bidirectional block in the cavotricuspid isthmus (fibrous tissue targeted for ablation in atrial flutter) and AVN block, and 38 Gy has been seen to cause a lack of electrical activity in left atrial appendage.[86][87] High dose to the Bundle of His has been suggested to be a cause for left bundle branch block as early as 48 hours after 2 fractions of 7 Gy brachytherapy.[88]

At present, it is unclear which cardiac substructure is the most radiosensitive causing acute issues in lung cancer. Further work is needed to explore relationships between dose-distributions to heart substructures and RIHD and survival.

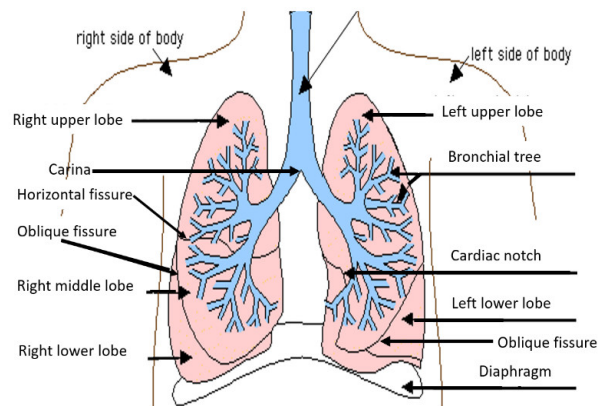
1.3.2 Radiation induced lung disease (RILD)

Cardiac substructure sparing RT and radiation dose escalation to the tumour could result in higher radiation doses being delivered to the lungs. Radiation induced lung disease (RILD), acutely radiation pneumonitis (RP) and chronically radiation fibrosis (RF), are dose-limiting toxicity factors in the treatment of patients with NSCLC. Hence, identification of relationships between lung radiation dosimetry and RILD remain vital when considering dose escalation and cardiac substructure sparing RT.

1.3.2.1 Lung anatomy

Figure 7 demonstrates the different lung substructures. Right lung is divided into three lobes (upper, middle, lower) by two fissures (one oblique and one horizontal). Left lung is divided into two lobes (upper and lower) by the oblique fissure.

Figure 7. Anatomy of the lungs



1.3.2.2 Radiation Pneumonitis (RP)

RP occurs due to sensitivity of normal lung parenchyma to RT and manifests in the first 6 months after RT. The rate of fatal RP is around 2%.[89] Symptoms include nonproductive cough, dyspnoea, low grade fever, malaise, weight loss and pleuritic chest pain. Differential diagnoses include concomitant pneumonia, chronic obstructive pulmonary disease exacerbation, reactivation of latent tuberculosis, tumor progression or mass effect of tumour on lung parenchyma and airways. The mildest cases of RP may be detected radiographically, without any symptoms. Chest radiograph shows early signs in about half the cases and consists of opacities representing confluent alveolar and interstitial infiltrates in the irradiated area. On CT scan there may be frosted glass like changes.

1.3.2.2.1 Pathophysiology of RP

The most radiosensitive part of the lung is the alveolar-capillary complex. The alveolar epithelium consists of type 1 and type 2 pneumocytes with type 1 covering 90% of alveolar surface. Type 1 pneumocyte destruction increases growth factors, proteases and cytokine secretion within days of RT which degrades extracellular matrix and cause inflammatory cell accumulation.[90] Vascular alterations appear with congestive perivascular oedema, and decreased perfusion followed by interstitial oedema, inflammatory infiltrates and moderate anarchic pneumocyte proliferation. Exudative alveolitis and acute inflammation lead to pathological sloughing of pneumocytes and endothelial cells. A second wave of cytokine is released around 8 weeks post RT increasing oxidative damage to DNA, decreasing lung perfusion and increasing transforming growth factor beta 1 expression causing influx of fibroblasts which convert to myofibroblasts resulting in lung fibrosis.

1.3.2.2.2 Scoring of RP grade

Multiple scoring systems to grade RP exist. Different studies use different RP scoring systems introducing difficulty in quantitatively comparing RP between studies. Furthermore, poor pre-RT pulmonary function and pre-existing respiratory symptoms increases the uncertainty in RP scoring.[91] The most commonly used scoring systems in RP studies are Southwest Oncology Group (SWOG), Common Terminology Criteria for Adverse Events (CTCAE) and Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG/EORTC) (Table 1).

Table 1. Criteria for scoring radiation pneumonitis

Grade	RTOG/EORTC[92]	SWOG[93]	CTCAE4.0[94]
1	Mild symptoms of dry cough or dyspnoea on exertion	Radiographic changes; symptoms do not require steroids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Persistent cough requiring narcotic, antitussive agents/ dyspnoea with minimal effort but not at rest	Steroids required or tap of effusion	Symptomatic; medical intervention indicated; limiting instrumental ADL
3	Severe cough unresponsive to narcotic antitussive agent or dyspnoea at rest/clinical or radiological evidence of acute pneumonitis/intermittent oxygen or steroids may be required	Oxygen required	Severe symptoms; limiting self-care ADL; oxygen indicated
4	Severe respiratory insufficiency/ continuous oxygen or assisted ventilation	Requires assisted ventilation	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
5	Death	Death	Death

Southwest Oncology Group (SWOG), Common Terminology Criteria for Adverse Events (CTCAE), Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG/EORTC), Activities of daily living (ADL)

1.3.2.2.3 Factors associated with RP

Identification of factors influencing RP risk has been of great interest. Published dose-response relationships for RP are estimates of the risk in an average patient with NSCLC but there is much heterogeneity among NSCLC patients, therefore generalisability of RP models can be challenging.

Patient and tumour factors

Patient factors found to be associated with increased RP risk include older age[89][95][96][97][98][99][100][101], poor PS[102][96] and female gender[103][101]. The impact of low baseline lung function on RP incidence is

controversial as some studies have reported lower RP risk whilst others a higher risk associated with this.[102][104][105][106][107][108] Also, some studies have shown that RP can be milder in patients with more severe chronic obstructive pulmonary disease than in patients with normal lung function.[109][108][110] Smoking may be a protective factor for RP.[111][95][98][112] Larger tumours and PTV sizes have been associated with increased risk of RP.[113][114][96][115][116][117][118][103] Irradiation of tumours in the lower lungs has also been associated with increased risk of RP.[89][119][120][121][95][102][122][123][113] [124].

Treatment Factors

Use of chemotherapy with RT has been associated with higher RP incidence especially sequential chemotherapy, Carboplatin and Paclitaxel in patients over the age of 65, and Gemcitabine.[89][95][98][99][125]

Several studies have demonstrated that exposure of various amounts of lung volume to different radiation doses may be associated with increased RP risk in patients receiving RT for lung cancer (Table 2) and there appears to be no consensus on a definite threshold. This is likely due to different patient groups being explored with variations in treatment methods and clinical characteristics, differences in measured outcomes and correlations between dose-volumes. The two most commonly and consistently described lung dosimetric parameters associated with RP are mean lung dose (MLD) and normal lung volume receiving at least 20 Gy (V20).[126] V20 $\leq$ 30–37% and/or MLD $\leq$ 20 Gy has been suggested to result in RP rates of $\leq$ 20%. The advent of modern RT techniques, such as IMRT, with increased number of radiation beams increase conformality and may reduce high radiation dose spillage

to surrounding normal lung. However, the use of multiple beams may result in larger lung volumes receiving lower radiation doses. Therefore, there has been increasing interest in studying the effects of normal lung volumes receiving low doses as well as high doses on RP risk.

Table 2. Lung dosimetric factors associated with increased risk of RP

Lung dosimetric parameter	Reference
MLD	[127][128][129][126][130][131][132][133][111]
Lung V5	[113][96][107][134][135][136][137][138][139][140][141][142][143][97][144][145][116][146][147]
Lung V10	[96][123][113][107][142][143][144][148][149][116][146][150][151][152][153]
Lung V20	[89][102][123][113][124][133][136][138][143] [97][144][154][155][114][156][157][158][159][145][116][160][161][162][151][163][164][100]
Lung V30	[123][113][131][111][144][148][155][114][158][145][116][161][165][166]
Lung V40	[167]
LungV50	[164]

1.3.2.2.4 RP models combining patient, tumour and treatment parameters

A few studies have explored RP models combining patient, tumour and treatment factors and have found these models outperform the predictive ability of single dosimetric parameters or mechanistic normal tissue complication probability (NTCP) models. These studies are described below.

Hope et al found a model combining inferior tumour position with lung D_{35} (minimum dose to the 35% volume receiving the highest dose) and maximum dose more strongly correlated with RP than any individual parameter.[119] In another multi-institutional dataset, the combination of inferior lung irradiation and MLD generated a more robust model.[120] A combined model consisting of pre-existing pulmonary comorbidity, mid/inferior tumour location, smoking status, age, receiving no

sequential chemotherapy and MLD has also been seen to be better than models with dosimetric parameters only for RP risk prediction.[168] In another study of 160 patients who received RT for NSCLC using the same dose and technique, a newly derived parameter termed Transfer Factor Spared from receiving >5 Gy created by combining the absolute volume of lung spared from receiving >5 Gy with the transfer coefficient for carbon monoxide was found to be useful for dichotomising patients into high and low RP risk groups.[169] Palma et al conducted a large systematic review consisting of 836 patients who underwent CRT and found the best validated predictive model for RP contained lung V20, Carboplatin/Taxol chemotherapy, age > 65, daily dose >2 Gy and lower lobe tumour.[89] Another study based on a data set of 219 lung cancer patients showed RP predictive model containing generalised equivalent uniform doses close to MLD and chemotherapy prior to RT performed better than models containing dosimetric parameters alone.[170]

Dosimetric and non-dosimetric combined predictive models for RP perform well and are important for personalisation of toxicity prediction and isotoxic dose escalation. But there appears to be no consensus on the best model, likely due to the differences in the datasets such as differences in dosimetric constraints used for planning, RT techniques, other differences in treatment, as well as the use of retrospective data with potential missing information. Another possible cause for this lack of consistency in studies regarding lung dosimetric parameters impacting RP could be the correlations between the lung dosimetric parameters rendering it difficult to clearly determine the effect of volume of lung receiving > x Gy (lung Vx) on RP.[134]

Prospective data from isotoxic dose escalation trials, with some of these variables controlled, may therefore be a better setting for RP modelling.

1.3.2.2.5 RP modelling in isotoxic dose escalation studies

In isotoxic dose escalation studies, radiation doses prescribed to tumour are controlled by pre-set lung dosimetric parameters such as MLD which in turn predicts a pre-defined rate of RP. These cohorts provide good opportunities to explore differences between predicted and observed RP rates to assess the impact of other potentially important dosimetric factors on RP when MLD is controlled.

Four isotoxic dose escalation studies exploring RP modelling in NSCLC were identified. In one phase I dose escalation study 47 patients with NSCLC were treated with 57 to 80.5 Gy in 25 fractions equating to 60 to 100 Gy EQD2.[171] For each bin, the starting dose was determined by the relative normalised tissue mean dose modelled to result in <20% grade 2 RP. The observed incidence of grade 2 RP was 13%. 24% of patients received induction chemotherapy and 33% adjuvant chemotherapy. Multivariable analysis (MVA) identified lung mean normalised tissue dose and adjuvant chemotherapy as significant independent risk factors for grade 2 RP. However, a DVH wide analysis of lung dosimetry in relation to RP was not conducted.

In another study, 109 patients with NSCLC were treated with radiation-dose escalation, on predicted lung toxicity basis, with daily RT in 2.1 Gy fractions of RT alone or with neoadjuvant chemotherapy.[133] Dose was escalated in 5 lung-

effective volume (V_{eff}) bins independently, starting at 63 to 84 Gy. V_{eff} represents the volume of an organ that, if uniformly irradiated to the prescription dose, would produce the same risk of radiation toxicity as the nonuniform dose-distribution that is actually administered. Lung V_{eff} , lung V_{20} , V_{13} , MLD and NTCP were computed. NTCP was computed using a model with the following parameters: volume-effect parameter of 0.99, dose–response steepness factor of 0.37, and the dose causing a 50% of complication rate of 30.8. MVA showed RP was significantly associated with MLD, V_{20} and NTCP of the lung with cut-offs of 20Gy, 30% and 10% respectively. In this study only 19% had chemotherapy and a DVH wide analysis of lung dosimetry in relation to RP was not conducted.

Yorke et al studied 49 patients with NSCLC treated in a dose escalation setting receiving 57.6–81 Gy.[122] RTOG RP was evaluated up to 6 months after the end of RT. 9 patients had $\geq$ grade 3 RP. Lungs were split into superior and inferior halves, and ipsilateral and contralateral lungs. Correlations with dosimetric and physical variables, as well as Lyman[172] and parallel[173] NTCP models, were assessed. $\geq$ grade 3 RP significantly correlated with mean dose and Lyman and parallel model indices (d_{eff} and f_{dam}), V_{20} of ipsilateral lung and mean dose and d_{eff} for the inferior half of the lungs. However, only 1 patient had chemotherapy in this cohort and lung DVH wide analysis was not conducted.

Yorke et al studied 78 NSCLC patients treated in a Phase I dose escalation study.[174] The prescription dose was 70.2 Gy to 81 Gy in 1.8 Gy fractions. Dose-escalation was carried out for patients who had calculated NTCP $\leq$ 20%. There were

12% RTOG $\geq$ Grade 3 RP within 6 months of RT. The most significant variables for RP were ipsilateral lung V5–V13. However, here only 10 patients received chemotherapy and the MLD varied from patient to patient.

The limitations of these studies were that chemotherapy and MLD, factors associated with RP, were not consistent in all patients and 3 of the 4 studies did not conduct DVH wide lung dosimetric analysis. RP modelling using a prospective cohort of isotoxically dose escalated patients where MLD and chemotherapy are controlled factors, such as IDEAL-CRT[7], could be a better setting to conduct DVH wide analysis to explore lung dosimetric parameters impacting RP.

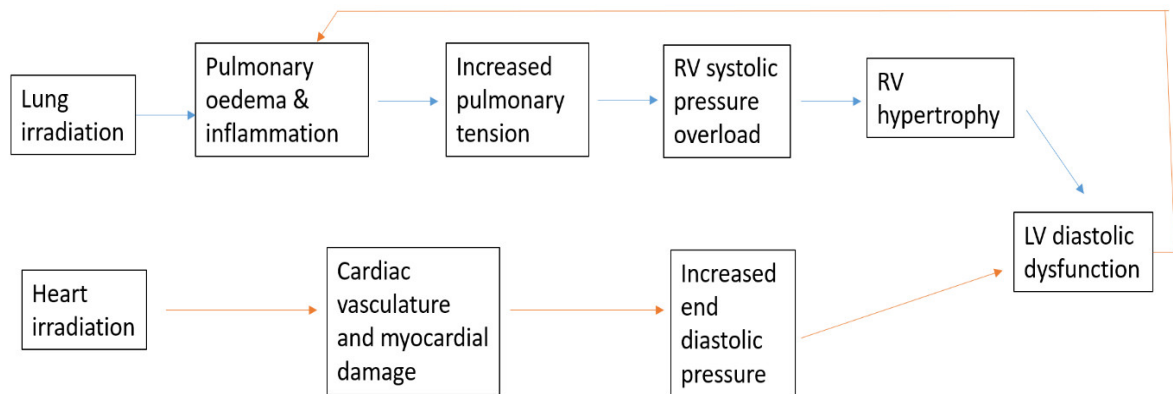
1.3.2.3 Synergistic effect of heart and lung damage on lung cardiopulmonary toxicity

Some studies suggest heart and lung radiation induced damage may act synergistically on cardiopulmonary function i.e. lung irradiation may increase cardiac toxicity and heart irradiation may increase lung toxicity, and irradiation of both may increase both toxicities[175][176][177][178][179][180][181][182]. The mechanism (Figure 8) is thought to be as follows: heart irradiation damages cardiac vasculature and myocardium and increases end-diastolic pressure, which may lead to LV diastolic dysfunction promoting pulmonary interstitial oedema which may increase the risk of RP and RF. Lung irradiation induces pulmonary oedema, inflammation and increased pulmonary tension leading to RV systolic pressure overload, which may lead to RV hypertrophy causing LV dysfunction. So, irradiation of both lung and heart may enhance cardiac diastolic dysfunction and this may be more evident in

patients with lung cancer as they tend to be smokers with potentially higher risk of underlying cardiac and lung problems which may worsen with radiation damage.

Animal experiments have suggested a connection between heart irradiation and lung toxicity.[176][177][178] In patients, this synergistic effect and correlations between heart doses and RP remains controversial. Huang et al conducted a retrospective study of 209 NSCLC patients treated with 50-84 Gy and found the best performing logistic regression model for RP included heart $D_{10\%}$ (minimum dose to the hottest 10% of the heart), lung $D_{35\%}$, and maximum lung dose.[175] However another study by Tucker et al found no evidence of incidental heart irradiation impacting moderate or severe RP in a study of 629 patients with NSCLC, possibly due to strong correlations between heart and lung factors.[183] In another dose escalation study of 78 patients heart dosimetry was not found to be significantly associated with RP, however only a selected few heart variables were tested here.[174] In contrast, in a study where principal component analysis (PCA) (*details in Chapter 2 section 2.4.2*) was conducted to explore the whole heart DVH, some heart variables including mean heart dose was associated with RP on univariable analysis (UVA), with only MLD remaining significant on MVA likely due to the correlations between MLD and mean heart dose.[184] Further studies in a setting where MLD is controlled would be useful to determine the effect of cardiac irradiation on RP.

Figure 8. Hypothesised mechanism for lung and heart synergistic effect on radiation induced cardiopulmonary toxicity



RV=right ventricle; LV=left ventricle

1.4 Gaps in evidence and hypotheses to be tested

The aim of this work is to try and close some of the identified gaps in evidence in cardiopulmonary toxicity modelling and improve understanding of radiation induced cardiopulmonary toxicity to aid strategies to widen the therapeutic index of LA-NSCLC RT and individualise tumour dose prescription.

1.4.1 Gaps in evidence at start of my DPhil work in November 2014

- Lack of direct evidence of radiation induced cardiotoxicity impacting OS in patients with lung cancer.
- No consensus on heart or heart substructure dosimetric parameters to be used in NSCLC RT to reduce radiation induced cardiotoxicity.

- The underlying mechanism of radiation induced cardiac damage impacting survival in lung cancer patients remains unclear.
- Impact of cardiac irradiation on cardiac events and cardiac deaths is unclear.
- Possible synergistic effect of heart and lung irradiation induced cardiopulmonary dysfunction remains controversial.
- Impact of other lung dosimetric factors on RP once MLD and chemotherapy factors are controlled in an isotoxic dose escalation setting is not well studied.
- No consensus on best RP predictive model combining patient and treatment factors derived from an isotoxic dose escalation setting.
- No clear evidence of lung substructure radiation dosimetry impacting RP.

1.4.2 Hypotheses to test in part 1 of work

- Cardiac irradiation is associated with higher all cause death rate (DR) in patients with LA-NSCLC treated with radical CRT in an isotoxically dose escalated trial.
- Irradiation of cardiac substructures and ECG changes indicating radiation induced heart disease is associated with higher DR.
- Post progression survival is worse in patients who receive higher radiation dose to the heart.
- A prognostic index to dichotomise patients into low and high risk of death can be derived combining cardiac dosimetric and clinical factors.

1.4.3 Hypotheses to test in part 2 of work

- Prognostic index developed in part 1 including cardiac factors can be validated in an independent non-dose escalated standard radiation dose cohort.

- Heart irradiation impacts cardiac event rate and cardiac related death rate.
- Smoking and baseline cardiac comorbidity increases DR.
- Heart dose-volume response exists with high dose to small volume and small dose to high volume of heart impacting OS
- Prognostic index from part 1 can be refined with additional factors from the standard radiation dose cohort

1.4.4 Hypotheses to test in part 3 of work

- Refined prognostic index from part 2 can be validated in an independent cohort.
- A heart dose-volume-time effect exists for OS with a longer time frame for low dose effect on OS and a shorter time frame for high dose effect on OS.
- Combining datasets to increase sample size can strengthen the statistical power of models and identify factors that were of borderline significance in smaller individual cohorts.

1.4.5 Hypotheses to test in part 4 of work

- Mean lung dose alone has limited predictive ability for RP in isotoxically dose escalated patients.
- Additional clinical and lung dosimetric factors impact RP risk in isotoxically dose escalated patients.
- Irradiation of lower lung subsections is important in RP models.
- RP models combining dosimetric and non-dosimetric parameters are more robust than dosimetric models alone.
- A synergistic effect exists between heart and lung irradiation and RP risk.

2. METHODS

In this chapter, the population and common methodologies used to test the hypotheses formulated in chapter 1 are described.

2.1 Population

Three sources of data were analysed to test the hypotheses outlined in chapter 1: two prospective isotoxic dose-escalated RT trials (IDEAL-CRT) and one standard RT dose retrospective cohort (Oxford).

2.1.1 IDEAL-6: Phase I/II trial of concurrent chemoradiation with dose-escalated radiotherapy in patients with stage II or stage III non-small cell lung cancer delivered in 6 weeks (ISRCTN12155469) [185]

Following trials unit approval, data were analysed for 78 of all 82 stage IIB/III LA-NSCLC patients recruited and treated in IDEAL-6,[7] a phase I/II prospective trial of isotoxically-escalated CRT, between September 2010 and March 2013 in 8 centres. Treatment involved 63-73 Gy in 30 fractions over 6 weeks once daily fractionation with concurrent chemotherapy. Tumour dose was prescribed isotoxically (details in Appendix 4). Heart constraints were D33% <60 Gy; D67% <53 Gy; D100% <45 Gy (details of OAR constraints in Appendix 4). CT scan or 4DCT with free breathing CT scan were obtained. GTV, internal target volume (ITV), CTV, PTV and OARs were outlined as described in the trial protocol (Appendix 4). Patients were treated using static non-coplanar beams or IMRT. The mean prescribed dose was 67.8 Gy (range 63-73 Gy). 2 cycles of Vinorelbine (15mg/m² IV or 40mg/m² PO) and Cisplatin

(75mg/m² iv) chemotherapy were delivered concurrently on days 1 and 29 or on days 2 and 30 and Vinorelbine alone on days 8 and 36 or days 9 and 37 of RT. Four patients were excluded: one due to corrupted RT planning archival records, two due to re-planning during treatment, and one due to treatment termination following toxicity after five fractions resulting in very low OAR doses. Standard follow up including history and physical examination was carried out weekly during RT and for a month post RT, monthly until 6 months post RT, and 3 monthly until 2 years post RT. The median follow up was 25 months. The survival outcomes and details of IDEAL-6 have now been published.[7]

2.1.2 IDEAL-5: Phase I/II trial of concurrent chemoradiation with dose-escalated radiotherapy in patients with stage II or stage III non-small cell lung cancer delivered in 5 weeks (ISRCTN12155469) [185]

All 36 patients treated in IDEAL-5, a phase I/II prospective trial of concurrent CRT with isotoxic RT dose escalation in patients with stage II and III LA-NSCLC, were analysed. 63–71 Gy in 30 fractions were delivered to the PTV over five weeks (once daily except one day per week twice daily). CT or 4DCT with free breathing CT scan were obtained and GTV, ITV, CTV, PTV and OARs outlined as described in Appendix 4. Patients were treated using static non-coplanar beams or IMRT. The mean and range of prescribed doses were 65.7 Gy (63-71 Gy). 2 cycles of Cisplatin (75mg/m² iv) and Vinorelbine (15mg/m² iv) were delivered concurrently on days 1 and 22 or days 2 and 23 of RT, and Vinorelbine alone on days 8 and 29 or days 9 and 30 of RT. The chemotherapy was intensified by completing in 29-30 days instead of the 36-37 days in IDEAL-6. Standard follow up including history and

physical examination was carried out at similar time points to IDEAL-6. The median follow up was 15 months.

2.1.3 Oxford Cohort

Following institutional approval, the medical records of all consecutive patients treated with radical RT for LA-NSCLC between March 2010 and March 2014 at Oxford University Hospitals (OUH) were retrieved and reviewed. 80 patients were identified, of which 64 were eligible as they had retrievable electronic treatment plans with radiation dose volume data, a minimum follow-up of 3 months or until death and were not re-planned due to lung collapse or expansion. CT or 4DCT with free breathing CT scan were obtained and GTV, CTV, PTV and OARs outlined as described in Appendix 3 and Section 1.1.3. Patients were treated using static non-coplanar beams or IMRT to a prescribed dose of 66 Gy in 33 fractions in once daily fractions 5 days a week over 6.5 weeks however 12% did not complete 66 Gy in 33 fractions due to toxicity. Patients received RT only, or sequential or concurrent chemotherapy (details in Appendix 3 and Section 1.1.3). Chemotherapy involved 3-4 cycles of platinum doublet for sequential CRT and 2 cycles for concurrent CRT. Standard follow up included history and physical examination weekly during RT, then at 6 and 12 weeks post RT, and then 3 monthly until 1-year post RT. The median follow up was 38 months. Patient and treatment characteristics and toxicity data was collated from hospital medical records and cause of death data from death certificates from the registry office.

The population characteristics of the 3 cohorts are detailed in Table 1.

Table 1. Population characteristics of the three cohorts

Characteristic	IDEAL-5 (n=36)	IDEAL-6 (n=78)	OXFORD (n=64)
Data type	Prospective	Prospective	Retrospective
Age in years (median (range))	67 (46-76)	66 (43-84)	71 (44-89)
WHO® performance status No. (%)			
0	20 (55.6)	32 (41.0)	17 (26.6)
1	16 (44.4)	46 (59.0)	34 (53.1)
2	0	0	5 (7.8)
3	0	0	1 (1.6)
Missing	0	0	7 (10.9)
Gender No. (%)			
Female	13 (36.1)	20 (25.6)	25 (39.1)
Male	23 (63.9)	58 (74.4)	39 (60.9)
Nodal status No. (%)			
N 2 or 3	29 (80.6)	65 (83.3)	32 (50.0)
N 0 or 1	7 (19.4)	13 (16.7)	29 (45.3)
Missing	0	0	3 (4.7)
Histology No. (%)			
Squamous	23 (63.9)	42 (53.8)	36 (56.3)
Non-squamous	13 (36.1)	36 (46.2)	24 (37.5)
Missing	0	0	4 (6.3)
Planning target volume (cm³; median (range))	353 (181-720)	400.6 (138.7-1262.1)	319 (82 – 1120)
4-Dimensional CT for planning No. (%)	unknown	34 (44)	56 (88)
Intensity modulated radiotherapy (IMRT) No. (%)	10 (28)	3 (4)	16 (25)
Prescribed dose in Gy (No.)	63-65 in 30# (20) 65.1-67 in 30# (6) 67.1-69 in 30# (2) 69.1-71 in 30# (8)	63-65 in 30# (22) 65.1-67 in 30# (15) 67.1-69 in 30# (10) 69.1-71 in 30# (11) 71.1-73 in 30# (20)	66Gy in 33# (56) 64Gy in 32# (3) 62Gy in 31# (2) 60Gy in 30# (2) 58Gy in 29# (1)
Prescribed tumour *EQD2 $\alpha/\beta \times 10$ (No.)			
≤ 66 Gy	20	22	64
> 66 Gy	16	56	0
Mean prescribed tumour dose (EQD2) (Gy)	66.8	69.3	65.5
Chemotherapy (No.)			
Concurrent	36	78	17
Sequential	0	0	16
No chemotherapy	0	0	29
Missing	0	0	2

*EQD2 – equivalent 2Gy per fraction dose (not time corrected); $\times \alpha/\beta$ – alpha:beta ratio; No. = number of patients; ®WHO – World Health Organisation; # - fraction

2.2 Assessment of organ function

2.2.1 Heart function

2.2.1.1 Electrocardiographic (ECG) changes

The spectrum of radiation-induced heart diseases (RIHD) include pericarditis, cardiomyopathy, coronary artery disease, pericardial effusions, valvular disease and arrhythmias. Some of these abnormalities may be detected by ECG. ECG records the electrical activity of the heart due to the heart's electrophysiologic pattern of depolarisation and repolarisation during a heart beat using 12 leads on the skin to detect electrical changes. Depolarisation starts in SAN and spreads through the atrium to the AVN, bundle of His and Purkinje fibres to reach the ventricles. ECG graphs voltage versus time and contains information regarding heart structure and electrical conduction system.

The interpretation of ECG involves assessing the morphology and rate of the waves, as well as intervals between the various peak and dips. A normal ECG wave representing 1 heart beat is shown in Figure 1. A normal 12 lead ECG is shown in Figure 2. The P wave represents atrial depolarisation. The PR interval represents the interval between onset of P wave and onset of QRS complex and represents conduction through AVN from atria to ventricle. The QRS complex represents ventricle depolarisation with a wide QRS complex indicating slow ventricle depolarisation due to conduction dysfunction. ST segment represents the plateau phase. ST depression (ST below the level of PR segment) and ST elevation (ST above PR segment) can occur due to myocardial ischaemia. T wave represents ventricular repolarisation.

Figure 1. ECG components of one heart beat

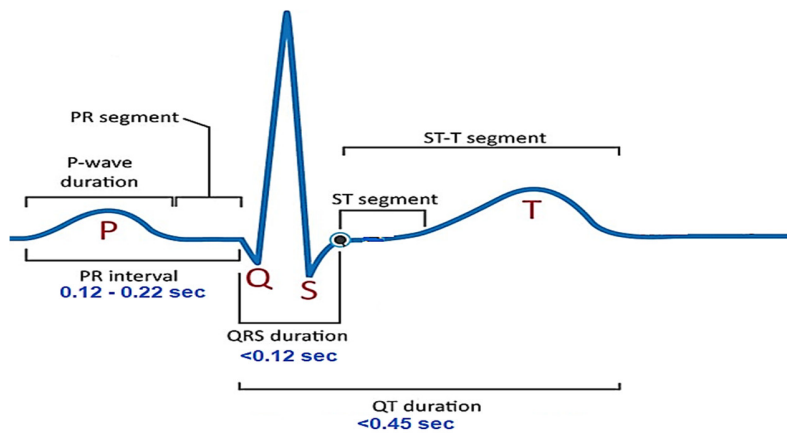
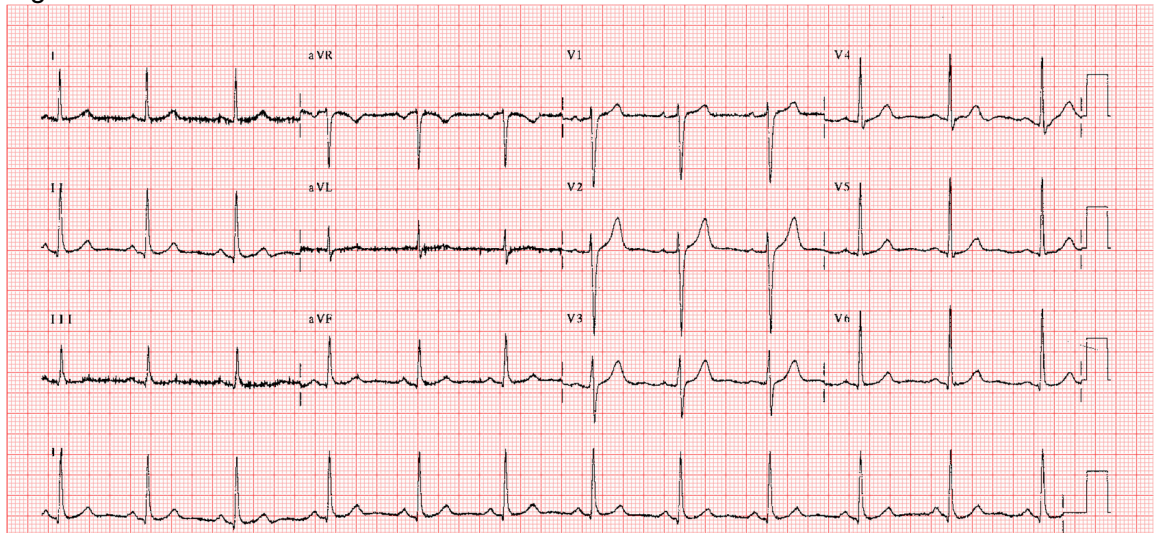


Figure 2. Normal 12 lead ECG



ECG changes indicative of myocardial ischaemia

Two main ECG patterns associated with non-ST-elevation acute coronary syndrome are ST segment depression and T wave flattening or inversion and include non-ST-elevation myocardial infarction and unstable angina. T wave inversion may be due to myocardial ischaemia if at least 1 mm deep, present in ≥ 2 continuous leads that have dominant R waves ($R/S \text{ ratio} > 1$), and are dynamic (new ECG change or changing over time). T wave inversion is normal in leads III, aVR and V1.

ECG changes indicative of pericarditis

Pericarditis may be associated with ECG changes that evolve through 4 stages:

- Stage 1 – widespread ST elevation (0.5-1mm) and PR depression with reciprocal changes in aVR (first 2 weeks)
- Stage 2 – generalised T wave flattening (1 to 3 weeks)
- Stage 3 – inverted T waves (3 to several weeks)
- Stage 4 – ECG returns to normal (several weeks onwards)

ECG changes indicative of atrial fibrillation (AF)

AF is the most common sustained arrhythmia with associated complications of haemodynamic instability, cardiomyopathy, cardiac failure and embolic events. AF is characterised by disorganised atrial electrical activity and contraction. ECG changes in AF include irregularly irregular rhythm with variable ventricular rate, no P waves, absence of an isoelectric baseline, and QRS complexes usually <120 milliseconds. AF originates from an area of focal activity which may be triggered due to increased automaticity or from micro re-entry. AF is maintained by re-entry circuits formed by some of the multiple wandering wavelets. This process is potentiated in dilated LA with the larger surface area facilitating continuous waveform propagation.

ECG changes indicative of sinus tachycardia

Sinus tachycardia involves normal rhythm but with a resting heart rate of > 100 beats per minute.

In IDEAL-6, ECGs obtained at baseline and 6 months after CRT were assessed by two cardiologists in a blinded manner for the following characteristics: normal ECG; new rhythm changes compared to baseline (sinus tachycardia/bradycardia, conduction abnormalities such as bundle branch block, atrial fibrillation); and ischaemic or pericarditis-like changes (new or worsening ST and T wave changes compared to baseline). ECG changes between the two time-points were then scored dichotomously as present or absent ('Any ECG change').

2.2.1.2 Cardiac-morbidity

In the Oxford cohort, recorded cardiac-morbidity following RT were identified from medical notes and follow up clinic letters in the first year post RT. Cardiac-morbidity was defined as new cardiac events (ischaemic heart disease as angina, acute myocardial infarction, coronary artery bypass grafting procedure, angioplasty or stent placement, diagnosis of coronary artery disease, cardiomyopathy, heart failure, pericardial disease, arrhythmias) or worsening of pre-existing cardiac events within 1 year of completion of RT both symptomatic and asymptomatic. As 'Any ECG change' data collected in IDEAL-6 was missing in Oxford cohort, cardiac-morbidity effectively substituted for 'Any ECG change' variable in the models in chapter 4. As asymptomatic ECG changes noted in IDEAL-6 on routine follow up investigation at 6 months post RT may not manifest as clinically significant events for a further few months, cardiac-morbidity within 12 months instead of 6 months was chosen to be the timepoint to reduce cardiac event data loss. Death certificates of all patients who died in the Oxford cohort were sought to determine whether cardiac cause was recorded in any part of the death certificate to assess cardiac-related-death rate.

2.2.2 Lung function

2.2.2.1 Spirometry

Spirometry is the most common of pulmonary function tests. It measures the volume of air expelled after maximal inspiration. The most common parameters measured are forced vital capacity (FVC), forced expiratory volume (FEV) at 1 second (FEV1), and diffusing capacity for carbon monoxide (DLCO). FVC is the volume of air forcibly expelled after full inspiration. FEV1 is the volume of air forcibly expelled in 1 second after full inspiration. FEV1/FVC ratio in healthy adults is 70–85%. DLCO is the carbon monoxide uptake from a single inspiration in 10 seconds. The exhaled gas is tested to determine how much of the tracer gas was absorbed during the breath. In restrictive disorders such as radiation fibrosis (RF), FEV1 and FVC may both be proportionally reduced with typically normal or increased FEV1/FVC ratio (>0.7) due to reduced lung compliance. Reduction in DLCO may detect diffusion impairments seen in RF and a change in DLCO from baseline to 6 months may predict RF risk later on.

2.2.2.2 Radiation pneumonitis (RP) scores

Acute lung radiation induced toxicity, radiation pneumonitis (RP), was scored at the following time intervals in IDEAL-5 and IDEAL-6: once a week during and for 4 weeks after RT, and then once a month until 6 months post RT. RP was scored according to the SWOG RP system (Table 2), and patients' maximum RP scores within 6 months of RT were collated.[93] For outcomes analysis, patients were dichotomised according to whether they experienced grade 2 or higher RP from start of RT to

within 6 months of completion of RT (G2RP). 6 months post RT was chosen as RP usually occurs within this time interval.

Table 2. Southwest Oncology Group (SWOG) Radiation Pneumonitis (RP) scoring system.[93]

Grade 0 – normal
Grade 1 – radiographic changes, symptoms do not require steroids
Grade 2 – steroids required or tap of effusion
Grade 3 – oxygen required
Grade 4 – requires assisted ventilation

2.3 Delineation of organs at risk (OAR)

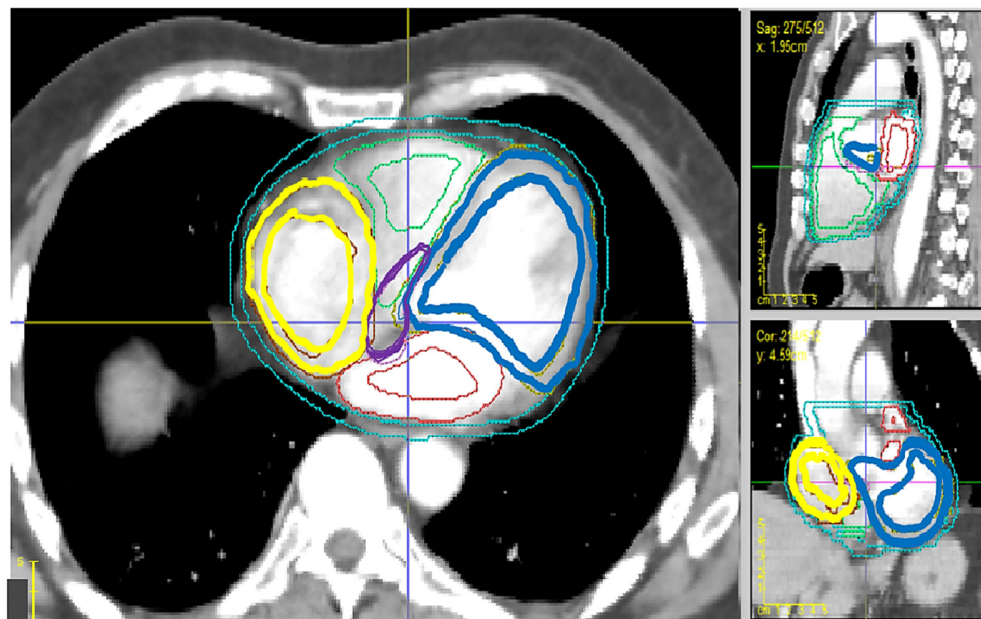
RT plans for all patients were imported into the treatment plan analysis system, the computational environment for radiotherapy research (CERR), which is an open source, freely available general treatment plan analysis package based on MATLAB, a high-level data analysis, programming, and visualisation package (The Mathworks, Inc., Natick, MA; <http://www.mathworks.com>). Contours corresponding to lung minus GTV (Lung-GTV), whole heart and oesophagus were outlined by the physicians at the treating centres and edited for IDEAL-5 and IDEAL-6 by the PI and myself, and for Oxford cohort by myself using a validated atlas.[186]

2.3.1 Heart substructure outlining

The heart is a complex organ consisting of numerous substructures with different functions which have been described in section 1.3.1.1. The cardiac substructures (left atria (LA), left ventricle (LV), right atria (RA), right ventricle (RV), atrioventricular

node (AVN), pericardium, aortic valve (AV), coronary ostia, left main coronary artery (LMCA)) were delineated as individual substructures by myself using a modified version of a validated cardiac atlas.[186] The pericardium was defined as a rim volume lying 5mm or less beyond the heart, and the outlined AVN was expanded by 3mm superiorly-inferiorly to account for delineation variability. RA-Wall, RV-Wall, LA-Wall and LV-Wall were defined as wall regions lying 5mm or less within the RA, RV, LA and LV contours (Figure 3). 5mm was used as this is considered an average thickness of heart chamber walls.[187] Based on the results of the localisation technique described in section 2.7 and Appendix 5, other substructures were subsequently defined using the atlas [186] if the dose bins localised consistently to a specific region.

Figure 3. Axial, coronal and sagittal sections of heart and heart substructures outlined using modified validated cardiac atlas.[186] *Pericardium in cyan, left atria wall in red, right atria wall in yellow, left ventricle wall in blue, right ventricle wall in green, AV node in purple.*



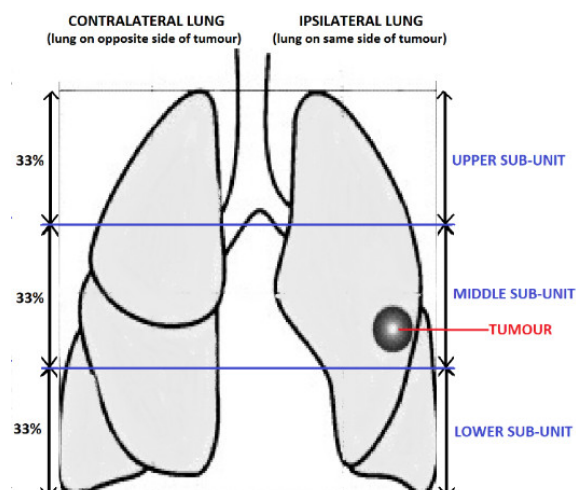
Delineation of the substructures can be tedious and subject to inter and intra observer bias. Also, the heart and its substructures vary in shape and size from patient to patient. Intravenous (iv) contrast provides valuable information regarding heart anatomy, especially in aiding the differentiation of the different heart chambers, the coronary vessels and AV. IV contrast was not used in all patients and in these patients substructures were outlined using the validated atlas non-contrast section and anatomical landmarks. Structures such as the AVN cannot be visualised on CT scans even with iv contrast. Therefore, its boundaries are defined using knowledge of the underlying anatomy. Also, despite the use of contrast, due to the thin walls of the atria, the boundaries between them may be difficult to define. Another issue is heart motion due to contraction of the chambers and the constant blood flow within the chambers and the vessels. This motion may cause artefacts in the imaging impacting the delineation of the substructures.

2.3.2 Lung subvolume segmentation

Lung-GTV outlines were edited using lung window setting (window level -600; window width 1500) to ensure collapse and consolidation were included and GTV excluded from Lung-GTV. Lung-GTV was divided into contralateral lung (CL) (lung on the opposite side to the tumour) and ipsilateral lung (IL) (lung on the same side as the tumour). CL and IL were then split into equal thirds by dividing the longitudinal extent of each lung into 3 sections to create upper, middle and lower sub-sections of IL and CL (IUL, IML, ILL, CUL, CML, CLL respectively) (Figure 4). A pragmatic approach was taken and the lungs were divided into geographic divisions instead of anatomical lobes based on fissures, since other studies have suggested inferior

tumour location may be associated with increased lung toxicity as explained in chapter 1, and the association between radiation dose to lower lung regions and lung toxicity is the hypotheses being tested.

Figure 4. Schematic overview of construction of different lung subunits. Lungs split into equal thirds by dividing the longitudinal extent of each lung into 3 sections: Upper sub-unit, middle sub-unit, lower subunit of contralateral lung (CUL, CML, CLL respectively); upper sub-unit, middle sub-unit, lower sub-unit of ipsilateral lung (IUL, IML, ILL respectively).

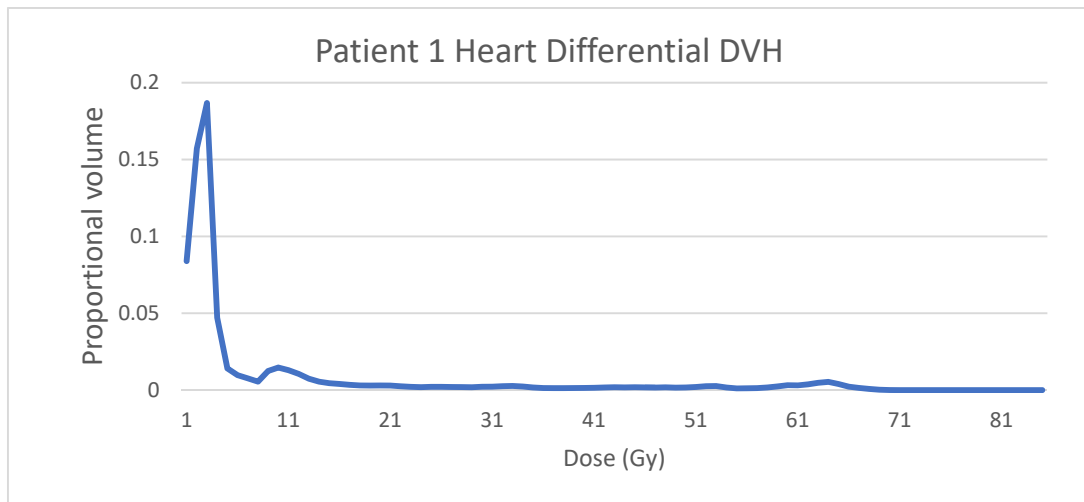


2.4 Extraction and processing of dose volume histogram (DVH) data

2.4.1 Dose Volume Histogram (DVH)

A DVH summarises a 3-dimensional dose distribution in a graphical 2-dimensional representation of the fractional volume of an organ receiving specific radiation doses and is used to quantitatively evaluate treatment plans. In a differential DVH (dDVH), bar or column height indicates the volume of structure receiving a dose given by the bin calculated by summing voxels in an organ receiving each dose level. A disadvantage of DVHs is that they do not offer spatial information. dDVH with 1 Gy dose-bins were constructed in CERR for all outlined organs and exported to SPSS.23 (IBM Corp., Armonk, NY) and R3.2.3 (R Foundation, Vienna, Austria) for further processing. An example of a heart dDVH of a patient treated in IDEAL-6 is shown in Figure 5.

Figure 5. Heart differential dose volume histogram of a patient treated in IDEAL-6



As doses were delivered in 30 fractions in all patients in IDEAL-5 and IDEAL-6, these doses were not converted to biologically equivalent doses when the patient dose-volume data were combined in chapter 6. In the Oxford cohort, total prescribed doses were delivered in 33 fractions. For ease of comparison between cohorts of patients, when all 3 cohorts were combined in chapter 5, doses were converted to a fraction-size equivalent dose of 2 Gy per fraction (EQD2) using linear-quadratic equation with an α/β ratio of 3 Gy for all OARs. The total number of dose bins were defined by the maximal dose in the data set evaluated, with volume defined as proportional volume irradiated.

2.4.2 Principal component analysis (PCA) in radiotherapy dosimetry

Three problems exist with traditional DVH analysis methods:

1) Unique dose-volume combinations that most strongly associate with outcomes are difficult to determine directly from statistical analysis of DVHs of patients since

there are many high correlations between normal tissue volumes irradiated to different dose-levels.

2) Single points on a DVH such as the volume receiving a specified dose or the dose to a specified volume, two or more points on a DVH, or a portion of a DVH (e.g., the volume receiving dose of a – b Gy), reductions of the DVH to mean dose, effective volume (V_{eff}), or equivalent uniform dose have been used to estimate the risk of complications. In reducing dose distribution to DVH, and subsequently DVH to a single metric, potentially critical dose-volume information which may help best discriminate between plans at high or low risk for complications might be lost.

3) If all dose bins in a DVH are considered then there are likely to be approximately 80 independent variables (e.g. using 1 Gy dose bins for dDVH data). As the number of patients in the cohorts are not very large, this could result in a high number of variables being studied in relation to the sample size, reducing the power of the study after allowing for multiple hypotheses testing. Therefore, efficiently reducing the number of independent variables without losing potentially pertinent information is important factor in this setting.

Principal components analysis (PCA) is one of the factor reduction methods which can be utilised to simplify the data for meaningful further analysis.[188] It reduces the dimensionality of a data set consisting of large numbers of inter-related variables, such as in the case of DVH data in RT, without losing much of the variation in the data set. It uses a linear transformation to convert potentially highly correlated variables into new uncorrelated variables, principal components (PCs). Only a small number of these PCs may be needed to describe most of the variance within the

data set, with the rest accounting for increasingly small variations in the data. PCs are orthogonal to each other and each PC describes a different dimension of the dataset, hence explains a unique portion of the data. The first PC describes the greatest amount of variance in the dataset, the second describes the greatest amount of remaining variance in the dataset, and so on. So, in a data set of DVHs, PCA describes the variability in the DVHs and segregates DVHs with similar morphology (i.e., comparable doses to similar relative volumes), thus summarising and extracting the salient patterns of the dose-distribution data. This allows groups of similar DVHs to be compared with respect to complication risk or survival.

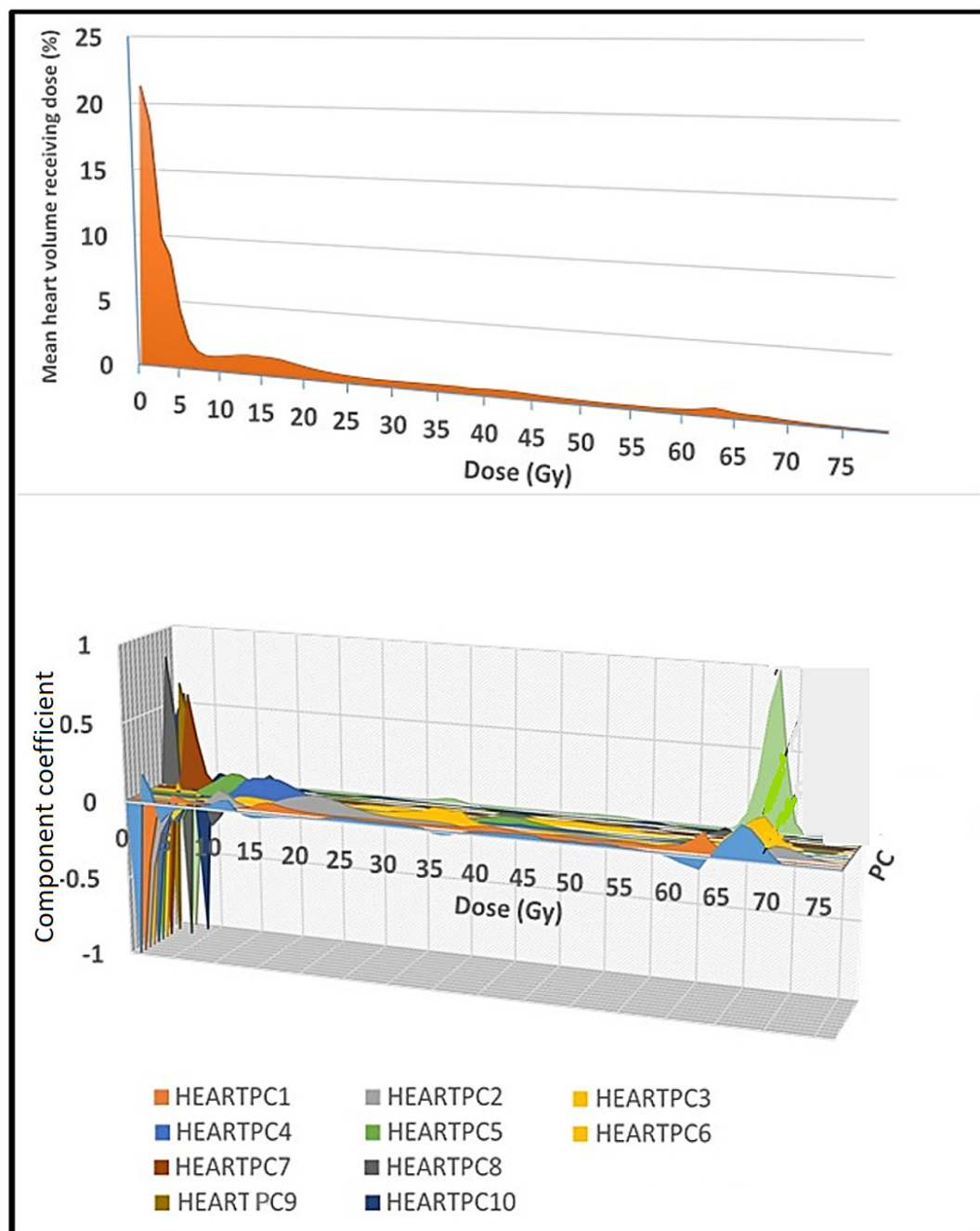
PCA has been used in DVH-based modelling of RT-induced toxicities of the liver, parotid, rectum and bladder; however it has not previously been used for DVH analysis of outcomes of RT in thoracic tumours.[189][190][191] In the work described in the subsequent chapters, PCA was used to approximately represent patients' organ DVHs as linear sums of the population-averaged DVH for a structure together with structure-specific ≥ 10 highest-ranked orthogonal PCs representing at least 95% variance amongst the DVHs of the structure (Figure 6). The method for approximating the dDVH using the mean dDVH and PCs is shown in Box 1.

Component coefficient of each PC, the correlation coefficient between the variable and the scores of the PCs, in these linear sums reflect the degrees to which each PC is present in a patient's dDVH. Scores of the initially-obtained PCs were uncorrelated across the patient group, as each PC describes a unique and independent portion of the dosimetric variability, not only are the dose structures of

the different PCs orthogonal, but so are the scores. However, these PCs can contain numerous peaks obscuring their physical interpretation. So, they were simplified using varimax rotation [192] (applying an orthogonal rotation to the truncated set of PCs) to obtain PCs with modes that are simpler to interpret as they mostly having non-negligible amplitudes across only narrow dose regions. However, the scores of varimax rotated PCs may no longer be orthogonal, therefore may re-introduce correlations between the contributions of different PCs to patients' dDVHs, though not between the dosimetric structures of the PCs. Correlations between PC scores were hence assessed using Spearman rank correlation test if not normally distributed and Pearson correlation test if normally distributed on Shapiro-Wilks test, Q-Q plot and histograms.

The dose bins represented by PCs which were found to be significantly associated with outcomes were those clearly differing from zero, which lie in identifiable peaks within the varimax-rotated PCs. If 2 PCs with overlapping peaks were found to be significantly associated with the outcome, the associated doses represented by both PCs were taken to be the whole range of doses lying in the overlap region of the peaks.

Figure 6. Mean heart differential DVH (dDVH) (top) and 10 varimax rotated principal components (PC) (bottom) describing >95% heart dosimetric variance in 78 patients in IDEAL-6



Box 1 - Approximating differential DVHs (dDVH) using the mean dDVH and principal components (PCs)

DVH data PCA proceeds by forming the mean-adjusted variance–covariance matrix which consists of correlations between mean-adjusted volumes exposed to a particular dose. The mean-adjusted volume for each dose bin are obtained by subtracting the dose-bin mean over all patients from each individual patient’s DVH.

Denoting the dDVH of a structure in patient i as $dDVH_i$, and representing the fractional volume of the structure lying in the j th dose-bin as $dDVH_i(d_j)$, then $dDVH_i$ can be represented exactly as

$$dDVH_i(d_j) \approx \text{mean } dDVH(d_j) + \sum_k PC_{\text{score-}ki} \times PC_k(d_j) \quad (A1)$$

where PC_k is the k th PC, $PC_{\text{score-}ki}$ is the score (contribution) of the k th PC for the dDVH of patient i , mean dDVH is the average of all patients’ dDVHs for the structure, and k is summed over all PCs. If k is only summed over a subset comprising the top-ranked PCs (which together account for a large fraction of the patient-patient dDVH variability), then (A1) will instead provide an efficient approximation to $dDVH_i$.

2.5 Outcomes measures

- All cause death rate (DR) was measured from start of RT.
- Cardiac-related-death was measured from start of RT.
- Any ECG change within 6 months of completion of RT compared to baseline.
- Cardiac-morbidity in the first year after completion of RT.
- The highest RP score within 6 months of completion of RT. Patients were dichotomised according to whether or not they experienced grade 2 or higher RP within 6 months of completion of RT (G2RP).

2.6 Outcomes modelling

2.6.1 Regression modelling

To predict outcomes based on a set of variables in a data set, regression modelling was used. Regression is a group of methods that summarise the degree of association between an independent variable (or set of independent variables (explanatory/predictor variables)) and another dependent variable (response variable/outcome). Regression modelling can be carried out using various methods including linear regression, logistic regression and proportional hazards (Cox) regression. The methods used in different analyses depend on the types of dependent variable being modelled, and are described in more detail below.

The general equation for a linear regression model is:

$$\text{Dependent variable} = \text{constant} + \sum (r_i \times b_i)$$

r_i = regression coefficient of independent variable *i*

b_i = independent variable *i*

Regression coefficient represents the mean change in the dependent variable for one unit of change in the independent variable while holding other dependent variables in the model constant. Odds ratio (OR) for logistic regression model and hazard ratio (HR) for Cox regression model are equal to the antilogarithm of the regression coefficient (e raised to the power of the coefficient's value). Confidence intervals (CI) explain the range of plausible values for regression co-efficients, ORs and HRs and measures the precision of these: a large CI suggests the sample size is too small to determine values of these quantities with useful precision. The constant (intercept) is the mean response value when all independent variables are set to zero and is the value at which the fitted regression line crosses the y-axis

in linear regression. In logistic regression the constant is the log odds when all independent variables are 0, so the curve crosses the y-axis at exponentiated constant. A zero setting for all independent variables in a model is clinically not plausible. Therefore, the constant is of no importance clinically. However, the constant makes sure the residuals (difference between predicted and observed dependent values) have a mean of zero.

The p value for each analysis tests the null hypothesis that the coefficient is equal to zero (i.e. there is no association between the independent and dependent variables). A low p value indicates that the null hypothesis can be rejected. Fisher suggested 5% ($\alpha=.05$) level could be used to conclude that strong evidence exists against the null hypothesis.[193] So, an independent variable having a p value $<.05$ is likely to be a meaningful addition to the model because changes in this variable may be related to changes in the dependent variable. However, statisticians warn of the perils of being 'slaves' to the cut-off of p value $<.05$ as this assumes a variable is insignificant if for example the p value is .056. So it has been suggested that p values should be used in conjunction with previous findings as well as the biological and clinical plausibility, sample size and quality of data.[194][195][196] In the following chapters, a p value of $<.05$ is not rigidly used to determine significance, and variables are sometimes kept in models if thought clinically significant.

Univariable analysis (UVA) tests the association of one independent variable at a time with the dependent variable without considering other variables. Multivariable analysis (MVA) takes into account the effect of multiple independent variables on

the dependent variable.[197] Multivariable (MV) models model the reality, in which clinical outcomes are likely to be influenced by more than one independent variable. However, UVA is essential to shortlist independent variables for MVA, especially when there are large numbers of independent variables, as in the case of DVH analysis. Here, clinically significant independent variables and variables with a p value of $<.2$ on UVA were considered for MVA. Excluding variables with p value $>.2$ on UVA from entering MVA avoids variables that do not show any significant association with the outcome on their own from being included, as they are unlikely to be related to the outcome after adjusting for other variables. Assumptions associated with the different MV models are shown in Table 3.[197]

Table 3: Assumptions associated with different types of regression models [197]

	logistic regression	cox regression
What is being modeled?	The logarithm of the odds of the outcome (referred to as <i>logit</i>).	The logarithm of the relative hazard.
Relationship of multiple independent variables to outcome	The logit of the outcome changes <i>linearly</i> with multiple independent variables.	The logarithm of the relative hazard changes <i>linearly</i> with multiple independent variables.
Relationship of an interval-independent variable to outcome	The logit of outcome changes <i>linearly</i> with each unit change in interval-independent variable.	The logarithm of the relative hazard changes <i>linearly</i> with each unit change in interval-independent variable.
Distribution of outcome variable	Binomial	None specified
Variance of outcome variable	Depends only on the mean	None specified
Censored observations	Not applicable	Censored cases have the same time to outcome as noncensored cases
Relative hazards over time	Not applicable	Proportional

Model diagnostics: Studying residuals (difference between observations and predicted values based on model) helps assess whether model assumptions are met. They also aid in assessing goodness of fit of a model (how close the fitted model's predicted values are to the observed values). Different residual measures are used to assess goodness of fit depending on the modelling method. To assess how well a model describes the data, the uncertainty on the data need to be assessed before comparing the residuals. Many of the statistical procedures used in regression analysis assume random departures from the proposed model. So, if the fitted model is correct, the residuals should exhibit a pattern of independence. If the data was collected in time there could be a strong possibility that the random departures from the model are autocorrelated i.e. the random departures for observations that were taken at neighbouring points in time are correlated. Runs test measures the structure of residuals (numbers of runs of consecutive positive or negative residuals) to assess whether they are random. In a runs test, the time sequence of the "sign" of the residuals and counts runs (i.e. the number of periods that the residuals keep the same sign) are monitored. Residuals oscillate about zero at a normal rate if the random departures are independent. However, this oscillation will be of lower frequency if the residuals are positively autocorrelated and higher frequency if negatively autocorrelated.

Model performance measures include calibration referring to the agreement of predicted and observed predictions and discrimination referring to the ability to distinguish low from high risk patients.

Model validation is important to assess a model's generalisability. It can be carried out in 2 ways: 1) internal validation assesses the model performance on the population underlying the sample from which the model was developed and delivers an estimate of performance for patients that are similar to those in the development sample 2) external validation assesses the performance of the model on a different population. Internal validation techniques include: 1) Split-sample: a random split is made, resulting in e.g. a 50% development and a 50% validation sample 2) cross-validation: uses the same principle, but alternates the development and validation samples (e.g. 50:50 split means 2 development and test rounds; a 90:10 split 10 rounds). 3) bootstrap: a random sample is drawn with replacement from the sample which includes the same number of patients as in the original sample, but some are excluded, others included once, twice, etc. The model is developed in the bootstrap sample, and validated in the original sample with the procedure repeated at least 100 times for stability and the difference indicates the optimism in model performance. In external validation, predictions are calculated from the previously developed model, and tested in a new dataset that is independent from the development population. External validation may show different results from internal validation, as factors such as patient selection, definition of variables, diagnostic or therapeutic procedures may be different.[198]

2.6.1.1 Logistic regression model

Logistic regression models assess the relationship between independent variables and a categorical dependent variable, categorical variables being ones where the outcome is dichotomised into 2 values which are mutually exclusive. Logistic

regression predicts the probability that an observation falls into 1 of the 2 categories based on the independent variables which can be continuous or categorical. The logit (inverse of the sigmoidal logistic function) of the outcome is modelled as the sum of unit change of the independent variable. With multiple logistic regression, the logit changes linearly with the weighted sum of the independent variables and is written as:

$$\text{logit}(p) = a + b_1x_1 + b_2x_2 + \dots + b_ix_i$$

p is the probability of the dependent variable and $x_1, x_2 \dots x_i$ are the independent variables. The regression coefficient b is the estimated increase in the log odds of the dependent variable per unit increase of the independent variable. When the function's variable represents a probability p , the logit function gives the logarithm of the odds $p/(1 - p)$. So, a linearly increasing quantity ($a + b_1x_1 + b_2x_2 \dots$) is converted to a sigmoidally rising quantity (e.g. risk of toxicity).

The exponential function of the regression coefficient (e^b) is the odds ratio (OR) and determines how the odds of the dependent variable changes with one unit change in the independent variable. OR of <1 indicate a decrease in risk of dependent variable with change in the independent variable; OR of > 1 indicate an increase in the risk. The 95% CI estimates the precision of the OR with a large CI indicating low precision.

Model diagnostics: Nagelkerke's R^2 test was conducted to assess model discrimination. This is based on the log likelihood for the logistic regression model compared to the log likelihood for a baseline model.[199][200] The R^2 statistic indicates how useful the explanatory variables are in predicting the dependent variable.[201] The Wald χ^2 test determined statistical significance for each of the independent variable coefficients in the model.[199][201] The runs test of residuals

was carried out to assess randomness as described above. Pearson χ^2 residuals [202] were used to assess agreement between observed and fitted values and identify non-linearity and a need for variable transformation. As visual inspection of plots is a rough estimation, a lack of fit test was performed by adding a squared variable to the model to see if the term statistically significantly showed a relationship between the variable and residuals i.e. $p < .05$ suggests that the variable is related to the residuals.

Outliers are observations with response values that are unusual, and which lie outside the covariate pattern and may significantly impact model fitting. Absence of studentized residuals with a Bonferroni p value $< .05$ was suggestive of absence of outliers.[202][203] Observations that are far from the average covariate pattern may also have high leverage, which is expressed as the hat value.[204] If high leverage or outlier observations were found, these cases were removed to assess impact on estimates of the coefficients in the model. An influential observation is one whose removal causes substantial change in the coefficient. Influence is the product of leverage and outlier and is measured by Cook's distance.[202][205] Influence can also be examined using influence plot which plots studentized residuals against hat-values, and the size of circle is proportional to Cook's distance. The cutoff values for these statistics are controversial so observations with the highest Cook's distance were omitted from models to assess impact on coefficients.

Model performance: Sensitivity and specificity measures are used to evaluate the accuracy of a model in predicting dichotomous outcomes. Sensitivity is the

proportion of true positives (the proportion of cases correctly predicted by the model to have the outcome). Specificity is the proportion of true negatives (the proportion of cases correctly predicted not to have the outcome). A Receiver Operating Characteristic (ROC) curve is a plot of the false positive rate (1-specificity) on the X axis and the true positive rate (sensitivity or 1 - false negative rate) on the Y axis for different cut-off points for the predicted risk. So, it demonstrates the predictive ability of the model as its discrimination threshold varies. Model discrimination was quantified using Area under the curve (AUC) of ROC curve. An AUC of .5 indicates a model performance no better than chance, whereas an AUC of 1 represents a perfect test. A model with high discrimination has both high sensitivity and specificity, resulting in an ROC curve which lies close to the top left corner of the plot.

Model performance were visually assessed using calibration plots created by splitting the cohort into 4 equally sized groups divided according to the MV model predicted risk (low, medium-low, medium-high, high) of outcome. The observed proportional incidence of the outcome in each group was plotted against the average calculated MV model predicted risk for each group to create calibration plots for the models. Model calibration was also assessed by the Hosmer-Lemeshow[204][206] goodness of fit test which is similar to a χ^2 goodness of fit test with $p > .05$ indicating a good fit with no statistical difference between predicted and observed rates of outcome in 10 cohorts of patients (partitioned into groups of approximately equal size) grouped according to predicted outcome.

Model validation: Where additional data set was not available, and therefore external validation not possible, a 6-fold internal cross validation was carried out by

splitting the original dataset into 6 subsets equally stratified for trial (i.e. the relative proportion of IDEAL-5 and 6 patients in each subset was the same as the whole data set) with each subset used once as the validation set and the remaining sets used as training. AUCs were calculated for each subset and the average AUC calculated.

2.6.1.2 Proportional hazards (Cox) regression model

The proportional hazards model proposed by Cox [207] has been widely used in modelling censored survival data. Patients are censored when the survival time information is incomplete i.e. if the patient does not die, withdraws from the study or is lost to follow up before the end of the study. In this case the survival time for the patient is considered to be at least as long as the study duration. Censoring represents a type of missing data and avoids bias in survival analysis. It allows all participants to contribute to the data until study end, rather than delete them and impact the study power. Cox regression tests differences in survival times between two or more groups while allowing adjustment of independent variables. Time to all cause death (DR) and cardiac-related-death were modelled from start of RT.

The hazard function ($\lambda(t,X)$) is the probability of the patient reaching the endpoint at time point t . The survivor function at time t is the probability of surviving to time t . For multivariable cox models, the hazard function is expressed as:

$$\lambda(t,X) = \lambda_0(t) \exp(\beta_1 X_1 + \beta_2 X_2 + \dots + \beta_k X_k)$$

$\lambda_0(t)$ = baseline hazard when all independent variables are set to 0
 $\beta_k X_k$ = coefficient of k^{th} independent variable
 $\beta_1 X_1$ = coefficient of the first independent variable

The logarithm of the hazard is modelled as a weighted sum of the unit changes of the independent variable which explains how much survival time changes with one-unit change in the independent variable. While a nonlinear relationship between the hazard function and the independent variables is assumed, the hazard ratio (HR) comparing two groups is constant over time as shown below (i.e. the effect of independent variables is constant over time and additive). This is called the proportional-hazards assumption.

HR for 2 subjects with covariate vectors X_i and X_j is independent of time.

$$\lambda_i(t)/\lambda_j(t) = (\lambda_0(t)\exp(\beta'X_i))/(\lambda_0(t)\exp(\beta'X_j)) = \exp\{\beta'(X_i - X_j)\},$$

HR = hazard in group A/hazard in group B

HR associated with an independent variable is the exponent of its regression coefficient. A positive coefficient for an independent variable means an increased hazard and therefore worse prognosis for patients with higher values of that variable. A negative regression coefficient implies better prognosis for patients with higher values of that variable.

In survival analysis the survival probabilities are usually reported at certain time points or the median survival time (the time at which 50% of the patients had died). Log-rank tests the null hypothesis that there is no difference in survival between the groups studied at all time points. The log rank test compares the observed and expected number of events for each group using the same test statistic as Chi² test with a p-value of <.05 suggesting the null hypothesis is false.

Model diagnostics: To test whether Cox model assumptions were met the following were carried out.

Testing proportional-hazards assumption: Schoenfeld [208] proposed a chi-squared goodness-of-fit test statistic for the proportional-hazards regression model which utilised Schoenfeld residuals. The proportional-hazards assumption was checked using graphical and statistical tests based on correlations between scaled Schoenfeld residuals for each covariate and transformed time (based on the Kaplan Meier (KM) estimate of the survival function) to test for independence between residuals and time.[209] Systematic drifts from the line which is a smoothing spline fit to the plot, were indicative of non-proportional hazards and therefore a violation of proportional-hazards assumption. Additionally, a non-significant relationship on χ^2 test between residuals and time for each covariate and the whole model supports proportional-hazards assumption. Violation of the proportional-hazards assumption can be solved by assessing covariate:time interaction or by stratification.

Testing for influential observations or outliers: *dfbeta* values for a predictor and a particular observation is the difference between the regression coefficient calculated for all of the data and the regression coefficient calculated with the observation deleted, scaled by the standard error. It measures how much impact each observation has on a particular predictor. *dfbeta* values were plotted in index plots. Very large *dfbeta* values compared to others suggest influential observations. Also, deviance residuals (normalised transform of martingale residual), were used to identify poorly predicted patients. These residuals should be roughly symmetrically distributed about zero on a plot with more negative values corresponding to

individual that “lived too long”. Cases with very large or small values may be outliers or influential observations, which are poorly predicted by the model so these were removed and modelling repeated to assess impact on coefficients.

Model performance: The discriminative abilities of MV Cox regression models was quantified by Harrell's-Concordance(C)-statistic.[210][211] The interpretation of the C-statistic is comparable to that of AUC of the ROC curve. The C-statistic measures the probability that a randomly selected patient who developed an event at a certain time point has a higher risk score than a randomly selected person who did not develop an event by the same time point.[212][210] The C-statistic of a model is 1.0 if for all possible pairs of patients, it correctly predicts which patient has the longer survival. A value of 0.5 indicates a model performance no better than chance. A Harrell C-statistic of >0.7 is considered acceptable or good, $0.80 \leq c < 0.90$ is considered excellent, and $c \geq 0.90$ is considered outstanding discriminatory power.[213] The Nam-D'Agostino χ^2 test, which is similar to the Hosmer-Lemeshow test for logistic regression, was also used to check Cox model calibration.[212] χ^2 values greater than 20 ($p < 0.01$) suggest lack of adequate calibration.[212] Goodness of fit was assessed using Cox-Snell residual plots.

Model validation: i) As the number of cases weren't very large in the individual cohorts after omitting cases with missing factors, instead of k-fold internal cross validation, bootstrapping internal validation was conducted. ii) Variables found to be significantly associated with survival in IDEAL-6 were tested for corroboration in the Oxford cohort by refitting the model and checking whether the HRs and p values

were similar in both cohorts iii) A prognostic index was derived from the best MV survival model from IDEAL-6 and tested in Oxford cohort. Linear-predictor values for Oxford patients were calculated using the formula below using regression coefficients from IDEAL-6 for each of the variables in best MV model. The patients were then dichotomised into low and high prognostic groups depending on whether their linear-predictor values were above or below the median calculated linear-predictor value for IDEAL-6. KM curves for low and high-risk patients were generated and the difference in survival between the groups tested using log rank test with a p-value of <.05 considered significant. A similar method was successfully used in another study.[214] The performance of the prognostic index was tested using the c-statistic.

$$\text{Linear-Predictor} = \sum(B_i * x_i)$$

B_i =regression coefficient of covariate x_i

2.6.2 Issues with regression modelling

2.6.2.1 Missing data

Multiple imputation [215][216] replaces missing data using a multiple regression or logistic model fitted for the variable with missing values using subjects with complete data on this variable and its important correlates. The fitted model provides an estimate of the mean and variance of each missing value. For each missing value, an observation is simulated from the estimated distribution using a random number generator, assuming normal distribution for continuous variables and binomial distribution for dichotomous variables. This procedure is repeated 100 times to allow standard error calculation and the results are combined. As it is impossible to ensure

the missing cases do not differ from non-missing cases, initially data set with these missing cases deleted was used for modelling and later this model was checked by analysing the data completed by the imputed missing values.

2.6.2.2 Confounders

Confounders are dependent variables that are related to both other dependent variables and the independent variable but do not lie on the causal pathway between them. Confounders can lead to an overestimate or underestimate of the true association between dependent and independent variables and may lead to wrong conclusions about the causality of an observed association between the independent and dependent variables.[217] Confounders are identified using prior knowledge of causality as there is no statistical algorithm to successfully identify them.[218][219] Potential confounders were dealt with using MV regression by adding the potential confounding variable to be controlled into the MV model and assessing the impact it has on the regression coefficients and p values of the other co-variables.[219] If the relationship between the independent and dependent variables are almost equal on comparison of models with and without potential confounding variables, it is thought there is no confounding.[220] It does not however clarify which variable is the confounder, but only confirms existence of a confounder in the model. Due to the small number of patients in the datasets used, fitting a stratified regression model by including a call to the strata function was carried out only if the potential confounding variable could be classified into 2 distinct groups.[209][220]

2.6.2.3 Multivariable (MV) model selection

Many model building strategies exist, such as purposeful selection of variables, stepwise selection and best subsets.[204][221] However, none have been proven to be optimal and the model building strategy is currently considered to be a combination of science, statistical methods, experience and common sense. Models are much more likely to be used in busy clinical setting if they have a small number of variables. Therefore, models with the least number of variables which capture the true relationship between variables whilst not losing generalisability by over-fitting data (parsimonious model) were sought. Akaike Information Criteria (AIC) model selection was used to choose the model that best balances these considerations.[222] AIC assesses the relative quality of the statistical models by calculating the relative estimate of information lost when a model is used to generate data. The preferred model is the one with the minimum AIC value. AIC rewards goodness of fit (assessed by the likelihood function), but includes a penalty as an increasing function of the number of variables, since increasing variables potentially increases both goodness of fit to the underlying data and fitting to noise. So, the penalty acts to reduce overfitting allowing a trade-off between complexity and goodness of fit.

Akaike showed that selection of the best model is determined by AIC score [223]:

$$\text{AIC}=2K-2\log(L)$$

where K is the number of estimable variables (degrees of freedom) and L is the log-likelihood at its maximum point of the model estimated.

Stepwise bi-directional variable elimination with a significance level for entrance of $\alpha=.1$ and exit of $\alpha=.05$ was performed to remove insignificant variables in the MV model and find the best MV model with the lowest AIC score.[224]

Independent variables to be included in the MV model were selected using the following rules to avoid large number of variables entering the MV model:

- 1) Independent variables on UVA with a p value of $\leq .2$ indicating some level of association with the outcome.[197]
- 2) Independent variables shown to be associated with the outcome in other studies or been hypothesised to be related to the outcome.
- 3) Some independent variables could be re-entered into the final model, even if they were not in the final AIC selected MV model, if they were thought to be clinically significantly associated with the outcome despite their statistical significance. This reflects the “part experience and common sense” nature of the model building strategy.

2.6.2.4 Multicollinearity

Collinearity occurs when independent variables in a regression model are so highly correlated to each other that it becomes difficult to distinguish their individual effects on the dependent variable. When 2 or more independent variables are highly correlated they contain same or similar information, and therefore explain almost the same variability in the outcome. Consequently, MVA cannot accurately assess the independent contribution of each variable on outcome leading to a less robust MV

model selection. This is multicollinearity.[197] Some of this collinearity in data is dealt with using PCA as described above. Further correlations between independent variables were explored and one of a pair of highly correlated variables excluded before conducting MVA. The correlation coefficient (Pearson/Spearman) is a bivariate statistic that measures how strongly two variables are related to one another. For quantitative variables, correlation is tested by Pearson correlation coefficient (if the variable is approximately normally distributed) and for ordinal variables by Spearman rank correlation coefficient. According to Evans' [225] classification, correlation co-efficient (r) of less than .20 is very weak, .20 to .39 is weak, .40 to .59 is moderate, .60 to .79 is strong and .80 or greater is a very strong correlation. Association between nominal variables can be tested by chi-square test and association between a categorical and a continuous variable can be assessed using the t-test. Another test for collinearity is that if 2 variables that are significant on UVA are entered into an MV model together, the significance of both may decrease (p value increases). To deal with multicollinearity, independent variables with at least moderate correlation ($r > .4$)[225] were entered into separate MV models. [226] When deciding which of two highly correlated variables to include in the MV model, the one a-priori considered more closely related to the outcome being studied, with less missing data, or with less measurement error was chosen. A third assessment for multicollinearity is the variance inflation factor (VIF).[227] Tolerance is derived by regressing an independent variable against every other independent variable in the model to calculate the coefficient of determination. Tolerance is 1 minus the coefficient of determination of a regression. VIF values, are the reciprocal of tolerance and measure the inflation in the variances of the parameter estimates

due to multicollinearity. Multicollinearity is indicated by small values for tolerance and large values of VIF. Though there is no clear consensus on a cut off for VIF,[227] some studies have shown VIF cut off of even 5 could impact results.[228] In the subsequent work a more stringent cut off of $VIF < 4$ was used.

2.6.2.5 Interaction terms

An interaction occurs when the association between an independent variable and dependent variable is changed by the value of a third independent variable. This can be dealt with by creating a variable whose value is the product of two independent variables (i.e. the two variables multiplied by each other). A product term between two independent variables is referred to as a two-way interaction. Because an interaction term describes the relationship between two risk factors and an outcome, it can only be interpreted as an interaction if the two variables constituting the interaction term are in the model. If only the interaction term is entered, without assessing the individual risk factors in the model and the interaction term is found to be significant, it would be unclear whether the interaction term is significant because there is an interaction or because the risk of outcome is significantly higher when both risk factors are present. If the two variables are not on their own statistically associated with the outcome in initial models, they could be removed from subsequent models. Interaction terms were used to assess the synergistic effect of heart and lung irradiation on outcomes in chapter 6.

2.6.2.6 Multiple hypotheses testing

When conducting a large number of UVA, some of the independent variables may be statistically significant at p value $< .05$ level by chance. Therefore, having a more stringent p value cut off before rejecting the null hypothesis may be beneficial. It is considered best practice to adjust for multiple hypotheses testing, however there is no clear agreement on what type of adjustment is best. One commonly used method is the Bonferroni correction. It penalises for the number of UVA by requiring a lower p value before concluding that a comparison is statistically significant. The Bonferroni corrected p value cut off is p value of $.05$ divided by the number of UVA tests performed. So, the null hypothesis is rejected only if $p \leq$ Bonferroni corrected p value. The risk with this method is that potentially causative variables may be discarded as chance as the basis of adjustment for multiple comparisons is the assumption that chance is the most common explanation for an association. Also, an individual comparison cannot be aware of how many other comparisons have been made. Therefore, an individual association cannot in principle be more or less likely to be caused by chance based on how many other associations are assessed. So strict adherence to multiple comparison correction has been questioned by many.[194][229] With MVA, multiple comparisons is not an issue when performing tests of the significance of the overall model as only a single test is needed to assess whether the independent variables as a group are associated with outcome.

A fairer method for multiple comparison correction is the Benjamini-Hochberg step up procedure (B-H).[230][231][232] The B-H procedure is a technique for controlling the false-discovery-rate following multiple hypotheses testing. It involves ranking the

p values of individual variables from smallest to largest, the smallest p value having a rank of $i=1$, the next smallest $i=2$, etc. Each individual p value is then compared to its B-H critical value, $(i/m)Q$, where i is the rank, m is the total number of tests, and Q is the level to which it is desired to limit the false-discovery-rate. Variables with $p < (i/m)Q$ and any variable ranked higher would be considered significant. The false-discovery-rate needs to be carefully chosen. The work on heart dosimetry on survival outlined in chapter 3 is a first exploratory step and requires further follow up studies to test the hypotheses generated. The cost of these additional studies is low (analysing heart dosimetry and OS data collected in the course of lung RT trials) and the cost of a false negative is high (missing a potentially important discovery impacting overall survival). So, for these situations a fairly high false-discovery-rate of 20% was set.

2.7 Localisation of dose bins in a structure to its substructures

Two approaches were used to localise the associations seen between the outcomes and whole heart dosimetry to corresponding cardiac substructures: a graphical interrogation of the shapes of heart dose-distributions in a sample of 20 patients with highest scores for heart PCs affecting OS mapped to a single reference geometry and a mathematical approach using dot products of principal components (PCs) of substructures. Details in Appendix 5. Both methods demonstrated similar results in the cardiac substructure localisation in chapter 3, so only the graphical approach was used for localisation in subsequent chapters.

Conclusion

Various methodologies exist for outcomes modelling. This chapter details the background information for the methodologies used in the subsequent results chapters and the rationale for the choices made. The aims of the studies that follow are to use the combination of complementary methodologies described here to identify robust models for survival and lung toxicity.

3. IMPACT OF WHOLE HEART AND CARDIAC SUBSTRUCTURE DOSIMETRY ON SURVIVAL FOLLOWING RADIOTHERAPY IN AN ISOTOXICALLY DOSE ESCALATED COHORT: IDEAL-6

3.1 Introduction

Definitive CRT is the standard of care for LA-NSCLC.[233] With standard radiation doses local-failure rates remain high with poor overall survival (OS).[9][10] Outcomes modelling and early phase studies indicate that RT dose-escalation is safe and might improve local control and OS.[11][13][15][16][17][19][20][22][234][235] But this has been challenged by RTOG-0617, a phase III randomised non-isotoxic dose escalation trial, which reported inferior OS for 74 Gy than 60 Gy in daily 2 Gy fractions.[24] Also, a recent meta-analysis of randomised NSCLC trials found that higher radiation doses with concurrent CRT result in poorer OS, possibly partly due to higher toxicity in the presence of concurrent chemotherapy.[236] In contrast, a relatively long OS has been reported for patients in IDEAL-6, a phase I/II trial of isotoxically-escalated CRT, which delivered minimum, mean and maximum prescribed doses of 63, 67.7 and 73 Gy respectively in 30 radiation fractions over 6 weeks, equivalent to 63.5, 69.1 and 75.6 Gy in 2 Gy fractions (linear-quadratic modelling, $\alpha/\beta=10$ Gy, uncorrected for schedule-duration).[7] These conflicting data suggest that the poorer OS seen in non-isotoxically dose escalated RTOG-0617 patients compared to isotoxically dose escalated IDEAL-6 patients may be due to differences in normal tissue toxicity.

For patients with LA-NSCLC radiation-induced heart disease (RIHD) latency was thought to be longer than OS, and consequently the impact of RIHD on their survival

had not been well-characterised. However, patients with lung cancer are generally older, have more underlying cardiopulmonary conditions and common risk factors for ischaemic heart disease, and receive higher radiation doses than lymphoma and breast cancer patients in whom RIHD has been associated with poorer long-term OS.[29][30] Evidence is now emerging that RIHD can impact OS earlier than previously thought in patients with oesophageal and lung tumours.[40][45] This, together with potential survival improvements offered by new therapies, has increased interest in RIHD in NSCLC.

In this chapter, a post-hoc analysis was conducted on the data collected prospectively in IDEAL-6 trial to test the following hypotheses:

- ***Cardiac irradiation is associated with higher all cause death rate (DR) in patients with LA-NSCLC treated with CRT.*** A DVH-wide analysis based on principal components analysis (PCA) is utilised here.
- ***Irradiation of cardiac substructures and ECG changes indicating RIHD is associated with higher DR.*** Localisation to relevant cardiac substructures is important since whole heart avoidance may not be feasible without tumour coverage compromise. This has not been explored in detail previously. An in-house program for graphical localisation was validated against a statistical technique. The impact of post RT ECG changes on DR was evaluated to understand the underlying pathophysiology of RIHD. The association between DR and baseline ECG changes was also assessed. Baseline and post RT ECG data in NSCLC patients is rarely collected and therefore this provided a novel opportunity.

- ***Post progression survival is worse in patients with higher radiation dose to the heart.*** RIHD may limit the patient's capacity for further treatment on disease progression and therefore result in poorer OS.

3.2 Summary of methods

3.2.1 Population (described in section 2.1.3)

78 stage IIB/III NSCLC patients treated in IDEAL-6, a phase I/II trial of isotoxically-escalated CRT were analysed. Treatment involved 63-73 Gy in 30 fractions over 6 weeks once daily fractionation with concurrent chemotherapy as described in section 2.1.3.

3.2.2 Data collection

Treatment and disease parameters, and time to last follow-up or death and disease progression were recorded. Paired ECGs collected at baseline and 6 months after RT were assessed by two cardiologists in a blinded manner for new or worsening changes as detailed in section 2.2.1.1. ECG changes between the two time-points were then scored dichotomously as present or absent ('Any ECG change').

3.2.3 Processing of radiotherapy dosimetric data (details in section 2.3 & 2.4)

GTV, PTV and OARs were outlined as described in section 1.1.3 and Appendix 3b and the heart and its substructures (pericardium, RA-Wall, RV-Wall, LA-Wall, LV-Wall and AVN) were delineated as described in Section 2.3.1.[186] Mean heart and Lung-GTV doses were extracted and separate PCA performed for heart and its substructures and oesophagus (Appendix 6) representing patients' dDVHs as linear

sums of ten or more highest-ranked varimax rotated PCs and the mean dDVH as described in section 2.4.2.

3.2.4 Regression modelling of all cause death rate (DR), post progression survival and Any ECG change

UVA and MVA of HRs for DR measured from start of RT were performed using Cox regression. Factors analysed for association with DR were: clinical (patient and treatment) characteristics, presence or absence of baseline ECG changes, presence or absence of Any ECG change, and scores of the 10 highest-ranked heart dosimetry PCs. Clinical factors and heart PCs having p-values $\leq .20$ on UVA and clinically significant factors (Age, dose, PTV, stage, PS) were initially included in MV models, and stepwise bi-directional variable elimination performed to find the model with the lowest AIC score. Multicollinearity was excluded using a VIF value of <4 and correlation coefficient of $<.4$. Model assumptions were checked using Schoenfeld and deviance residuals and dfbeta values as detailed in Section 2.6.1.2. Runs test was used to test for randomness of residuals. Goodness of fit of the model was assessed using Cox-Snell residual plots. Model performance was assessed for discrimination using Harrell's-Concordance(C)-statistic and calibration using Nam-D'Agostino χ^2 test. Multiple hypothesis testing was controlled using the Benjamini-Hochberg (B-H) step-up procedure to identify positive discoveries with false-discovery-rate set at 20% as detailed in Section 2.6.2.6. Variables found to be significantly associated with DR on MVA were tested for association with post progression survival evaluated from the progression time-point to death or lost to

follow up, using Cox regression. Associations between Any ECG change and clinically significant factors and variables identified in the best MV model for DR were tested using logistic regression.

3.2.5 Localisation of heart dose bin associated with DR to heart substructure

Two approaches were used to localise the associations seen between DR and heart dosimetry to specific heart substructures. The first approach was mathematical using normalised dot product and the second approach was an in-house graphical interrogation programme of the heart dose-distribution shapes (See Appendix 5) of 20 patients with highest scores for the heart PC most significantly associated with DR versus patients with any heart volume receiving doses described by the same heart PC. If there was moderate correlation ($r > .4$)[225] or multicollinearity with VIF > 4 between the heart and substructure dosimetric factors, they were entered into separate MV models. Model diagnostics, performance and multiple hypotheses testing correction were carried out as above. Missing data was accounted for by multiple imputation and the best MV model tested in the imputed dataset. Scale of survival variation was assessed by evaluating median volumes of significant dosimetric parameters by generating Kaplan Meier curves testing the differences in survival using log rank test.

3.2.6 Development of a prognostic index (PI) based on the best MV model

The linear-predictor values for all 78 patient were calculated using the formula below using regression co-efficients for each of the covariates in best MV model.[214]

$$\text{Linear-Predictor} = \sum(\text{Bi} * \text{xi})$$

Bi=regression coefficient of covariate xi

The patients were then dichotomised into low and high prognostic groups depending on whether their linear-predictor values were above or below the median linear-predictor value. KM curves for low and high-risk patients were generated and difference in survival between the groups tested using log rank test with a p value of <.05 considered significant.

3.2.7 Determining effect of oesophageal dosimetry on DR

UVA of HRs for DR were performed using Cox regression for oesophagus PCs. Variables with p-values $\leq .20$ on UVA were included in the MV model found to be significant in the heart analysis, and model selection carried out as described above. Oesophageal dosimetry is not expected to be associated with DR as there is no underlying pathophysiological cause. If no significant association is found for oesophagus, this lends weight to any significant correlations seen for heart, indicating that, at least in the case of the oesophagus, the data structure and analysis methodologies used do not generate non-causative associations.

3.3 Results

3.3.1 Patient, treatment and ECG characteristics

Patient characteristics are detailed in Table 1. Median follow up was 25 months. Median PTV size was 401cm³ (Range:139-1262). Median Age was 66 (Range 43-84). Treatment characteristics are detailed in Table 2. Median prescribed dose was

67.6 Gy (Range 63-73 Gy). One patient did not complete the 2 cycles of chemotherapy due to toxicity. ECG data are summarised in Table 3. Paired ECGs at both baseline and 6 months post RT were available for 53 patients and 20 of these patients (38%) had 'Any ECG change'.

Table 1. Patient characteristics

Characteristic	No. (%)
WHO performance status	
0	32 (41.0)
1	46 (59.0)
Gender	
Female	20 (25.6)
Male	58 (74.4)
Stage	
IIB	6 (7.7)
IIIA	54 (69.2)
IIIB	18 (23.1)
Nodal status	
N 2 or 3	65 (83.3)
N 0 or 1	13 (16.7)
Histology	
Squamous	42 (53.8)
Non-squamous	36 (46.2)
Tumour in contact with heart	42 (53.8)

Table 2. Treatment characteristics

Characteristic	No. (%)
Prescribed dose	
63-64.9Gy	21 (26.9)
65-66.9Gy	16 (20.5)
67-68.9Gy	9 (11.5)
69-70.9Gy	12 (15.4)
71-73Gy	20 (25.6)
Treatment delivery	
3DCRT	75 (96.2)
IMRT	3 (3.8)
4DCT for planning	33 (42.3)
Intravenous contrast with planning scan	50 (64.1)

IMRT = intensity modulated radiotherapy; 3DCRT = three dimensional conformal radiotherapy; 4DCT = 4 dimensional CT; No. = number of patients

Table 3. Summary of ECG data

Characteristic	No. (%)
Analysable ECGs	
Baseline	71 (91.0)
6 months	56 (71.8)
Baseline and 6 months	53 (67.9)
Normal ECG at baseline	38 (48.7)
Normal ECG at 6 months	18 (23.1)
ECG changes from baseline to 6 months	
Rhythm change	9 (11.5)
Ischemic or pericarditis-like change	11 (14.1)

3.3.2 Radiotherapy dosimetric data

Summary of mean doses to heart, substructures and lung is shown in Table 4. The mean heart dDVH is plotted in Figure 1, alongside the 10 varimax-rotated heart PCs which describe more than 98% of total variance. Table 5 details the variance explained by each heart PC.

Table 4. Summary of mean doses of organs at risk

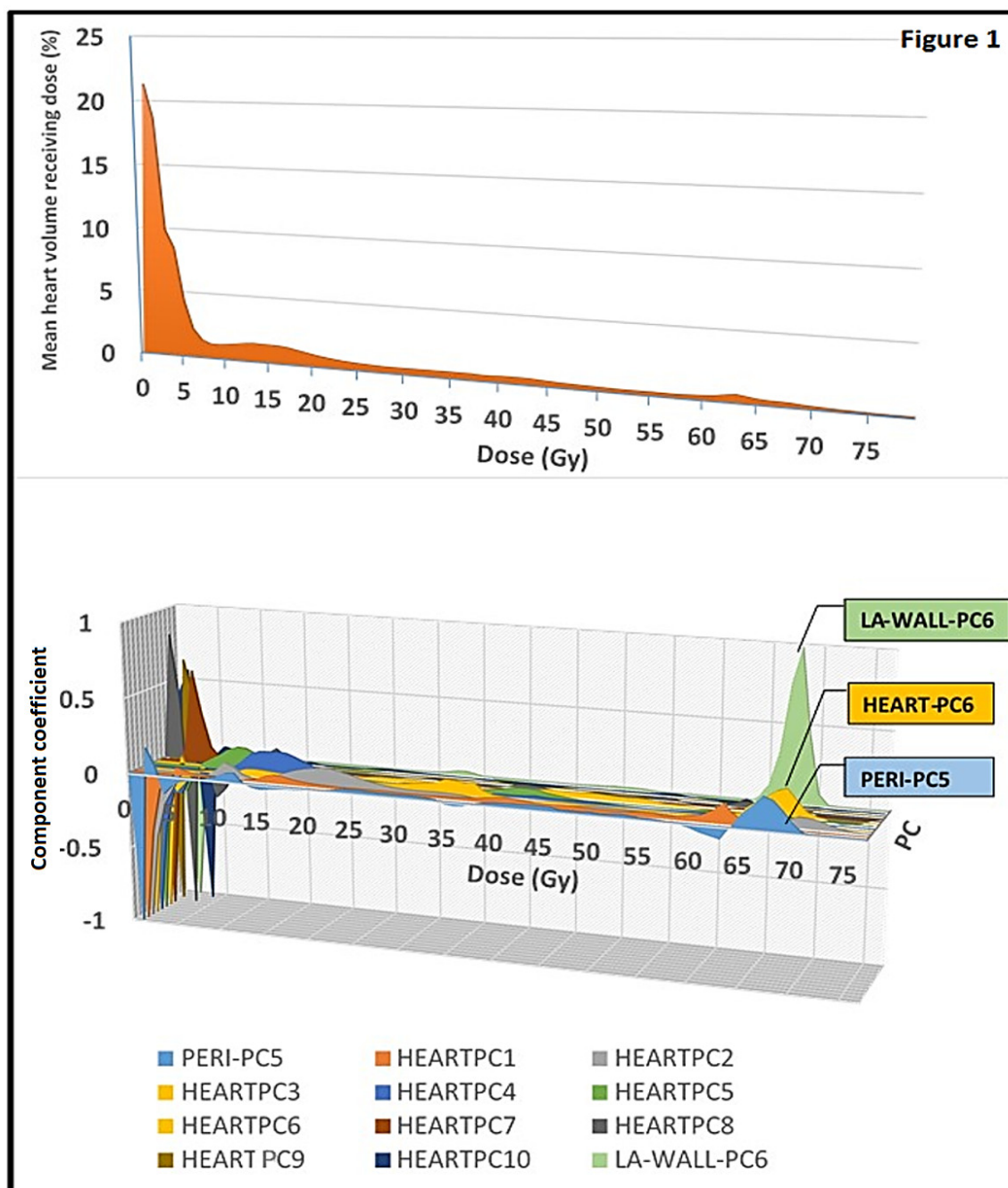
Mean EQD2*	Gy; median (range)
Lung-GTV	14.7 (7.9-21.2)
Heart	8.0 (0.4-29.2)
Left atrium wall	17.1 (0.5-64.2)
Left ventricle wall	2.8 (0.3-26.9)
Right atrium wall	4.3 (0.3-61.3)
Right ventricle wall	3.8 (0.3-29.0)
Atrioventricular node	2.2 (0.3-52.5)
Pericardium	10.8 (0.4-27.0)

*EQD2 = equivalent dose in 2 Gray per fraction

Table 5. Variance explained by 10 heart principal components (PC)

Heart PC	Variance explained (%)
1	12.3
2	5.3
3	7.3
4	9.3
5	8.5
6	2.8
7	31.5
8	1.0
9	17.9
10	3.7

Figure 1. The mean heart dDVH of 78 patients, plotted together with the 10 varimax-rotated principal components (PCs) describing >98% of the heart dosimetric variance. Also shown are LA-Wall-PC6 and Pericardium-PC5 (PERI-PC5) which have peaks at dose levels similar to HEARTPC6



3.3.3 Modelling of all cause death rate (DR) combining ECG changes, clinical and heart dosimetric factors

Results from UVA of clinical factors are shown in Table 6. Patients with larger PTVs had significantly higher DR. There was a trend for lower DR with increasing prescribed dose, but this did not reach statistical significance. Patients with Any ECG change had a statistically significantly higher DR on UVA. However, when analysed separately, ischaemic/pericarditis-like changes and conduction changes were not statistically significantly associated with DR on UVA likely due to the low event rates. The presence of an abnormal baseline ECG was not significantly associated with DR (Table 6), or with onset of Any ECG change (Table 14).

Table 6. Univariable Cox regression models of clinical factors for all cause death rate (DR).
HR = hazard ratio; CI = confidence interval; PTV = planning target volume; ECG = electrocardiogram

Co-variate	p-value	HR (95% CI)
Baseline abnormal ECG	.96	1.02 (0.47-2.24)
Any ECG change	.03	2.94 (1.12-7.76)
PTV size (cm ³)	.04	1.002 (1.00-1.003)
Prescribed dose (Gy)	.25	0.93 (0.83-1.05)
Performance status (0 vs 1)	.35	1.49 (0.64-3.47)
Nodal stage (0/1 vs 2/3)	.42	1.64 (0.49-5.49)
Age (years)	.60	1.01 (0.97-1.06)
Stage (IIba/IIIa vs IIIb)	.80	1.13 (0.45-2.83)
Gender (female vs male)	.82	1.11 (0.44-2.79)
Non-Squamous vs squamous	.94	1.03 (0.47-2.27)

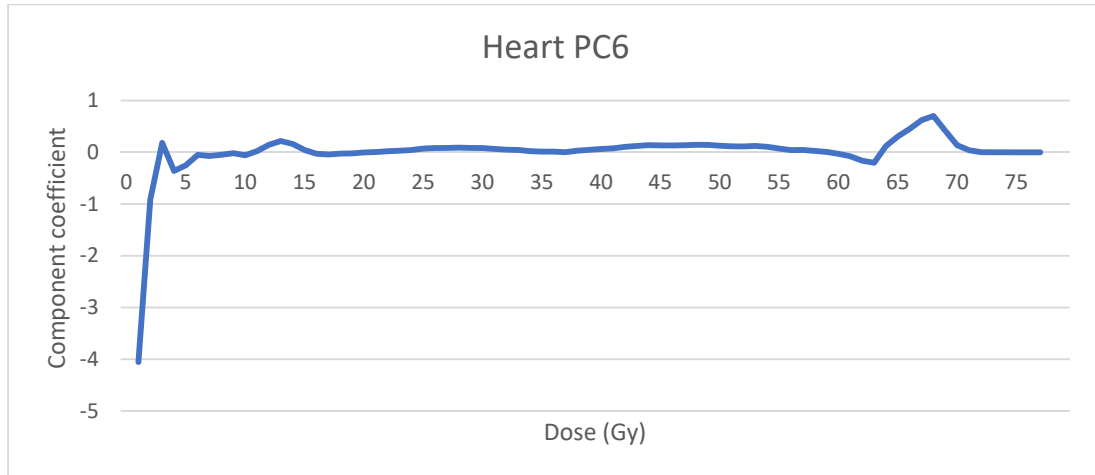
High Heart-PC6 scores were significantly associated with higher HR for DR on UVA (Table 7). Heart-PC6 has a high-dose peak at 63-69 Gy representing relative high

volume of heart receiving 63-69 Gy ($V_{\text{Heart-63-69}}$) and lowest dip at 0-4 Gy representing low volume receiving 0-4 Gy ($V_{\text{Heart-0-4}}$) (Figure 2). The direct interpretation of this is that patients with high heart V_{63-69} and low V_{0-4} have worse OS. However clinically this is not logical, and it is likely the lower heart volume receiving low doses is simply a consequence of a larger heart volume receiving high dose. Higher DR is more plausibly linked to larger volumes receiving high doses than to smaller volumes receiving low doses and this interpretation is supported by a significant association found between $V_{\text{Heart-63-69}}$ and DR but not between $V_{\text{Heart-0-4}}$ and DR (Table 7). Heart-PC6 was not significantly correlated with PTV size (Pearson $r=.21$; $p=.06$) or with prescribed dose ($r=.08$; $p=.51$).

Table 7. Univariable Cox regression models of whole heart dosimetry for all cause death rate (DR). *HR = hazard ratio; CI = confidence interval; PC = principal component; EQD2 = equivalent dose in 2 Gray per fraction*

Co-variate	p-value	HR (95% CI)
Heart-PC1	.29	1.17 (0.87-1.58)
Heart-PC2	.12	0.53 (0.23-1.19)
Heart-PC3	.56	0.83 (0.45-1.56)
Heart-PC4	.76	0.94 (0.62-1.43)
Heart-PC5	.49	1.15 (0.78-1.70)
Heart-PC6	<.01	1.54 (1.12-2.13)
Heart-PC7	.78	1.05 (0.73-1.52)
Heart-PC8	.64	1.10 (0.74-1.62)
Heart-PC9	.16	0.73 (0.47-1.13)
Heart-PC10	.64	0.92 (0.64-1.31)
Heart Mean EQD2	.41	1.02 (0.97-1.08)
$V_{\text{Heart-63-69}}$	.03	1.13 (1.01-1.27)
$V_{\text{Heart-0-4}}$	.76	1.00 (0.98-1.01)

Figure 2. Heart principal component 6 (Heart-PC6) with high-dose peak at 63-69 Gy representing relative high volume of heart receiving 63-69 Gy ($V_{\text{Heart-63-69}}$) and lowest dip at 0-4 Gy representing low heart volume receiving 0-4 Gy ($V_{\text{Heart-0-4}}$)



The MV model judged best according to AIC starting with all clinical factors and heart PCs with p-value <.2 on UVA (PTV, Any ECG change, Heart-PC2, Heart-PC6, Heart-PC9) plus clinically significant factors (prescribed dose, PS, age, nodal stage, gender) retained Heart-PC6, Any ECG change and PTV as factors associated with DR (Table 8 MV model 1a). This analysis was based on 53 patient data, as Any ECG change data was missing in 25 cases. There was no multicollinearity as VIF was <1.5 and all correlation coefficients were <.4 except for $r = -.46$ between PTV and dose. Significant correlations between DR and PTV size, Any ECG change, and Heart-PC6 remained classified as positive discoveries after correction for multiple hypothesis testing on B-H test. When Heart-PC6 is replaced by $V_{\text{Heart-63-69}}$ in MV model 2b in Table 8 without the outliers, it remained significant with a similar model performance (c-statistic of .76) as MV model 1a containing Heart-PC6.

Diagnostics of MV model 1a containing Heart-PC6, PTV and Any ECG change

Figure 3 shows index plots of dfbeta values for regression of time to death on covariates and the plot of deviance residuals which suggest that case 9 (furthest from 0 for Any ECG change) and case 42 (furthest away from 0 for Heart-PC6) furthest away from 0 on deviance residual plot may be outliers which are poorly predicted by the model. The remaining residuals are roughly symmetrically distributed about 0 with small PTV dfbeta values. Cases 9 and 42 were removed and MV modelling repeated which resulted in MV models with lower p values for the variables and higher Harrell's-C-statistic (Table 8 models 1b & 2b). Upon further exploration, patient 9 has high Heart PC-6 score (0.28) and high PTV (608cm³) and Any ECG change but had a very good survival. Patient 42 despite having low Heart PC-6 score (-.53) and low PTV (366 cm³) had a very poor survival.

Table 8. Multivariable (MV) Cox regression models of all cause death rate (DR) judged best according to the AIC measure. MV model 1 retains Heart-PC6 (MV model 1a modelled from all 53 cases and 1b modelled from 51 cases with cases 9 and 42 deleted). In MV model 2 Heart-PC6 is replaced by Heart Volume receiving 63-69 Gy ($V_{\text{Heart-63-69}}$) with MV model 2a modelled from 53 cases and 2b modelled from 51 cases with cases 9 and 42 deleted. *HR* = hazard ratio; *CI* = confidence interval; *c*=Harrell's-C-statistic

	MV model 1a including Heart-PC6 n=53 (c = .76)		MV model 1b including Heart-PC6 n=51 (c = .79)		MV model 2a including $V_{\text{Heart-63-69}}$ n=53 (c = .73)		MV model 2b including $V_{\text{Heart-63-69}}$ n=51 (c = .76)	
Covariate	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
Any ECG change	.04	2.79 (1.03-7.50)	.02	3.34 (1.18-9.44)	.06	2.56 (.96-6.82)	.05	2.74 (1.00-7.51)
PTV size (cm ³)	.08	1.00 (1.00-1.01)	.03	1.00 (1.00-1.01)	.08	1.00 (1.00-1.01)	.03	1.00 (1.00-1.01)
Heart-PC6	.02	1.58 (1.08-2.33)	<.01	1.90 (1.21-2.97)				
$V_{\text{Heart-63-69}}$					.09	1.13 (.98-1.29)	.04	1.16 (1.1-1.34)

Figure 3. Index plots to visualise $df\beta$ values for the Cox regression of time to death on covariates in MV model 1 Table 8 (top three) and deviance residuals (bottom) to test for influential observations. Case 9 (furthest from 0 for Any ECG change) and case 42 (furthest away from 0 for Heart-PC6) are circled in red.

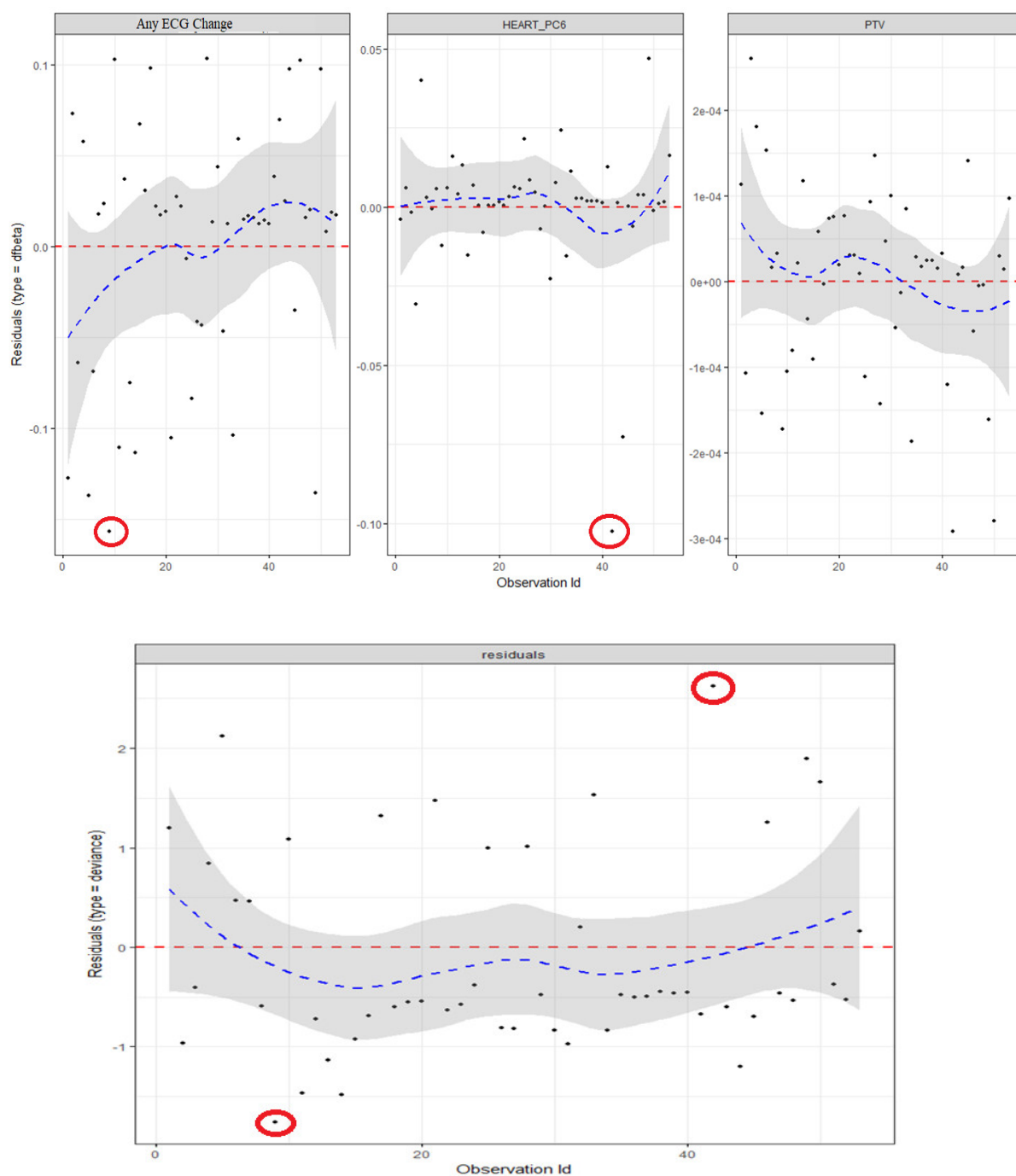
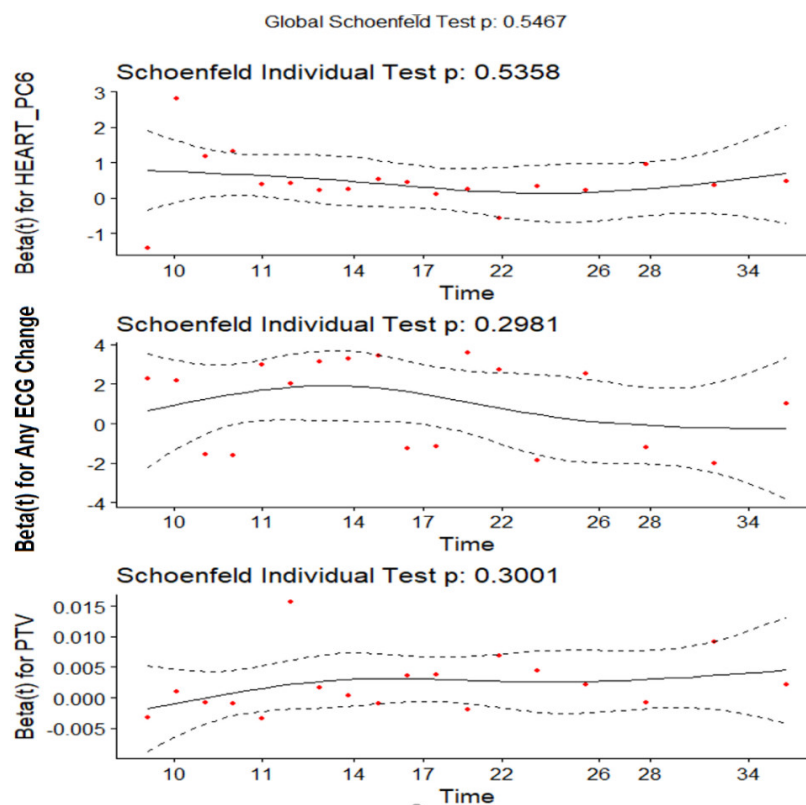


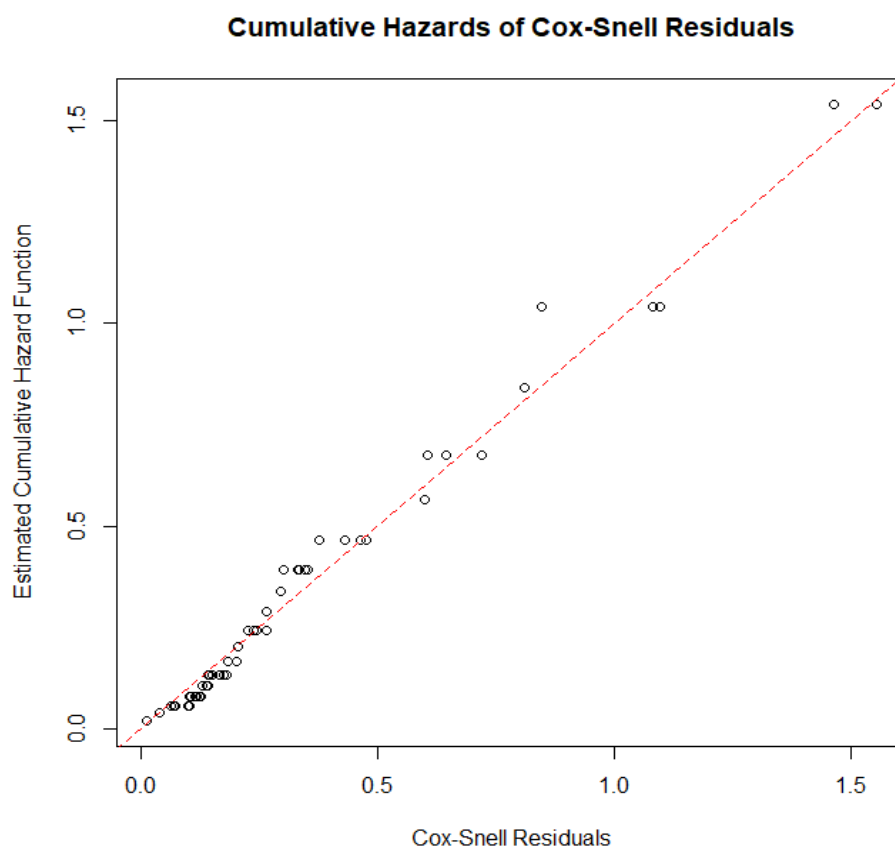
Figure 4 shows a random pattern of Schoenfeld residuals in the plot against time, with no systematic departures from the horizontal line indicating there was no violation of the proportional hazards assumption. Also, for each covariate and the whole model, there was no significant correlation on Chi² test ($p > .05$) between the Schoenfeld residuals and time suggesting independence between residuals and time and gives further support for proportional-hazards assumption being met. The runs test also showed all residuals displayed random structure with $p > .05$.

Figure 4. Plots of Schoenfeld residuals (Beta(t)) against time in months for each co-variate in MV model 1a in Table 8 showing random pattern around the horizontal line. The p-values for Chi square test for covariates and the whole model for proportional-hazards are also shown



There was good model fit as assessed by Cox-Snell residual plot (Figure 5) which showed no major deviation of residuals from the 45-degree line. Model performance was good based on a c-statistic of .73. Nam-D'Agostino χ^2 test when censored at 24 and 36 months, showed there was good model calibration with chi square values of .40 and 1.97 and p values of .53 and .16 respectively. The test was conducted, though, after splitting the data into halves not deciles, as 5 or more events are ideally required in each group and the groups had to be collapsed until this was met.

Figure 5. Plot of estimated cumulative hazard function against Cox-Snell residuals for MV 1a model containing Heart-PC6, Any ECG change and PTV



3.3.4 Localisation of heart volume receiving 63-69 Gy ($V_{\text{Heart-63-69}}$) represented by Heart-PC6 to cardiac substructure

Isodose of ≥ 63 Gy concentrated in left atrium (LA) and overlying pericardium consistently using the graphical approach (Figure 6). Hearts of 62 patients received ≥ 63 Gy (lower end of Heart-PC6 peak), and of these 51 patients received ≥ 63 Gy to $\geq 1\text{cm}^3$ of heart. Specifically, doses ≥ 63 Gy were delivered to the pericardium in all 62 patients, to LA-Wall in 48 (77%), RA-Wall in 22 (36%), LV-Wall in 18 (29%), RV-Wall in 16 (26%) and AVN in 2 (3%) patients. In the 20 patients with top quartile Heart-PC6 scores (high risk patients), the median heart and LA-wall fractional volumes receiving ≥ 63 Gy (V_{Heart63} , $V_{\text{LA-wall63}}$) were 4% (range 1-18%) and 16% (2-77%) respectively, compared to 0.3% (0-14%) and 0% (0-22%) in the other 58 patients (low risk patients). Table 9 describes the mean and range of heart and substructures percentage volumes receiving ≥ 63 Gy in high and low risk patients.

Table 9. Heart and substructure volume in percentage receiving ≥ 63 Gy

Volume receiving ≥ 63 Gy (%)		Heart	LA	LV	RA	RV	AVN	Peri
All 78 patients	Min	0	0	0	0	0	0	0
	Max	18.1	77.0	16.1	62.7	9.1	25.8	21.1
	Mean	2.3	7.9	0.9	2.5	0.3	0.5	4.7
20 patients with high Heart-PC6 scores	Min	1.4	1.8	0	0	0	0	3.8
	Max	18.1	77.0	9.4	33.8	9.1	25.8	21.1
	Mean	5.5	21.9	2.0	4.0	0.8	2.0	9.2
58 patients with low Heart-PC6 scores	Min	0	0	0	0	0	0	0
	Max	14.4	19.5	16.1	62.7	5.7	0	20.2
	Mean	1.1	3.1	0.5	2.0	0.2	0	3.1

LA=left atrium; RA=right atrium; LV=left ventricle; RV=right ventricle; AVN=atrioventricular node; Peri=pericardium

Figure 6. Three perspective views of the reference heart geometry, and the left/right atria (LA/RA) and ventricles (LV/RV) plotted separately. The colour-wash indicates percentage of patients whose heart dose-distributions, mapped to the reference geometry, have values ≥ 63 Gy somewhere along lines perpendicular to the image plane. Data are shown for the 51 patients with $V_{\text{Heart}63} > 1\text{cm}^3$ (left) and the 20 patients with the highest Heart-PC6 scores (right).

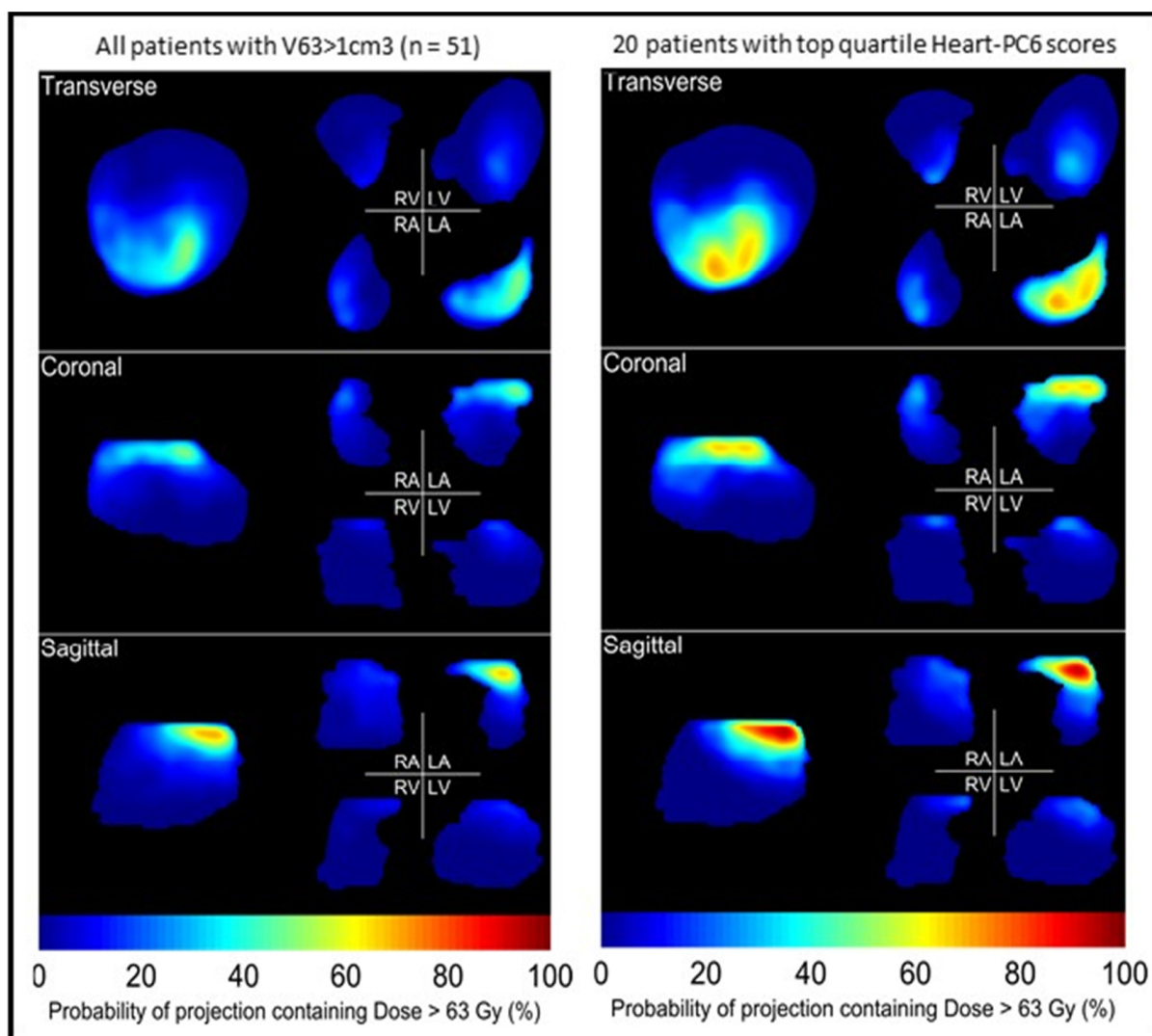


Table 10. Normalised dot products (NDP) for each cardiac substructure PC. NDP ≥ 1 indicate high-dose peak component of the substructure PC is at least as great as that of high dose peak of Heart-PC6 (Heart-PC_{max})

	Left atria	Left ventricle	Right atria	Right ventricle	AV node	Pericardium
PC1	0.306912162	0.099851359	0.205706513	0.028155981	0.382752649	0.149709752
PC2	-0.467627508	0.024479414	0.466217038	0.074305165	-0.029774186	0.039881623
PC3	-0.124375122	-0.004796849	-0.051173736	-0.002587203	0.003359913	0.193264718
PC4	-0.081010025	0.008979134	0.665452459	0.055443224	-0.012344046	0.013437174
PC5	-0.505477443	0.055721404	-0.084238845	0.005372654	0.002076228	1.19214625
PC6	2.702745151	-0.008113733	-0.0236041	-0.005795456	-0.001065049	-0.008349836
PC7	-0.56671751	-0.009068924	-0.012623973	-0.003294573	0.000143195	-0.083119054
PC8	-0.22824268	0.030478595	0.037079034	0.011040293	-0.000798996	-0.227436777
PC9	0.012507444	0.142853564	-0.006810306	0.008193253	0.000224774	0.056291724
PC10	0.037545323	-0.002099849	-0.172900165	0.02818046	0.000388441	0.011781409

LA-Wall-PC6 and Pericardium-PC5 most closely aligned with the Heart-PC6 peak at 63-69 Gy using the criterion of normalised dot product ≥ 1 (Table 10). Similar to Heart-PC6, both LA-Wall-PC6 and Pericardium-PC5 have prominent 63-69 Gy peaks representing high volume of these substructures receiving 63-69 Gy (Figure 7), and their PC scores were highly correlated with those of Heart-PC6 ($p < .01$, Spearman $r = .81$ and $.91$ respectively). High scores of LA-Wall-PC6 and Pericardium-PC5 were significantly associated with higher DR on UVA (Table 11). B-H test for multiple hypotheses correction showed Any ECG change, PTV, Heart-PC6, LA-Wall-PC6 and Pericardium-PC5 remained significant. Heart-PC6 and LA-Wall-PC6, and Heart-PC6 and Pericardium-PC5 were strongly correlated (Pearson correlation of $.81$ and $.91$ respectively) and the VIF were 9 for Heart-PC6, 7 for Pericardium-PC5 and 5 for LA-Wall-PC6 suggesting multicollinearity. So, these were

entered into MV models 3 and 4 separately to replace Heart-PC6 in MV model 1a shown in Table 8 and judged best by AIC. Both LAWall-PC6 and Pericardium-PC5 remained significant in MV models 3 and 4 respectively (Table 11). The performance of the model containing LAWall-PC6 was good with a c-statistic of .75. Higher LA-Wall volume receiving 63-69 Gy ($V_{\text{LAWall-63-69}}$) was significantly associated with higher DR in MV model 5 but higher volume of pericardium receiving 63-69 Gy ($V_{\text{Pericardium-63-69}}$) was not significantly associated with DR in MV model 6 (Table 11).

Figure 7. Heart-PC6, LAWall-PC6 and Pericardium-PC5

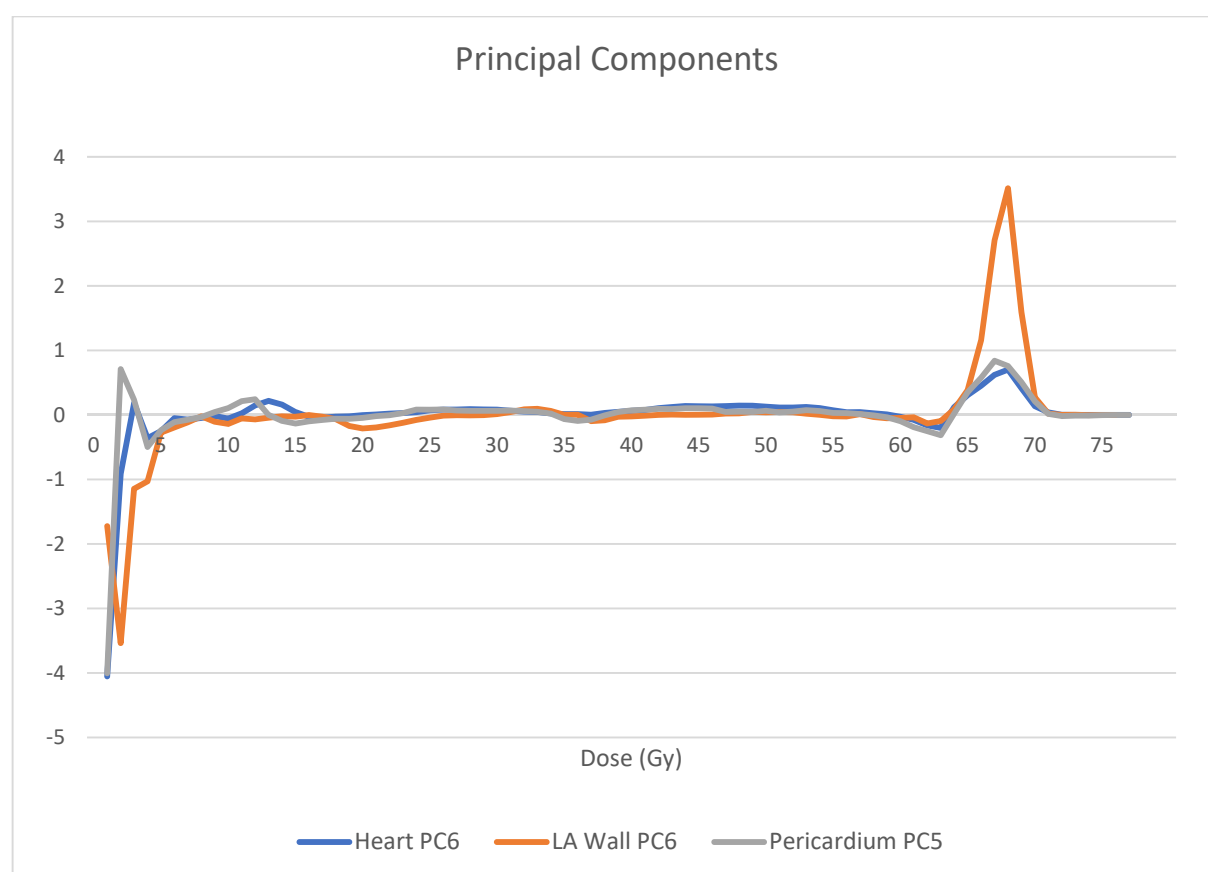


Table 11. Univariable (UV) and multivariable (MV) Cox regression models of all-cause death-rate (DR). Heart-PC6 in Table 8 MV model 1 is replaced by LAWall-PC6 in MV model 3, by Pericardium-PC5 in MV model 4, $V_{\text{LAWall-63-69}}$ in MV model 5 and $V_{\text{Pericardium-63-69}}$ in MV model 6. *HR* = hazard ratio; *CI* = confidence interval; *c* = Harrell's-C-statistic

	UV model		MV model 3 replacing Heart-PC6 with LAWall-PC6 (<i>c</i> = .75)		MV model 4 replacing Heart-PC6 with Pericardium-PC5 (<i>c</i> = .77)		MV model 5 replacing Heart-PC6 with $V_{\text{LAWall-63-69}}$ (<i>c</i> = .76)		MV model 6 replacing Heart-PC6 with $V_{\text{Pericardium-63-69}}$ (<i>c</i> = .72)	
Covariate	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
Any ECG change	.03	2.94 (1.12-7.76)	.07	2.51 (0.92-6.81)	.05	2.70 (.99-7.31)	.08	2.43 (.90-6.55)	.08	2.49 (.91-6.81)
PTV size	.04	1.00 (1.00-1.00)	.10	1.00 (1.00-1.01)	.14	1.00 (1.00-1.00)	.08	1.00 (1.00-1.01)	.08	1.00 (1.00-1.01)
LAWall-PC6	<.01	1.49 (1.14-1.94)	.02	1.51 (1.06-2.15)						
Pericardium-PC5	<.01	1.64 (1.16-2.33)			.03	1.64 (1.06-2.55)				
$V_{\text{LAWall-63-69}}$	.01	1.04 (1.01-1.06)					.02	1.04 (1.01-1.07)		
$V_{\text{Pericardium-63-69}}$	.04	1.09 (1.00-1.19)							.44	1.05 (.93-1.18)

Diagnostics of the best MV model containing heart substructure dosimetry:

MV model 5 containing PTV, Any ECG change and $V_{\text{LAWall-63-69}}$

Figure 8 and index plots in Figure 1 in Appendix 7 show that most residuals were roughly symmetrically distributed around 0 and had very small values with case 42 in the deviance residual plot being furthest from 0. MV modelling with case 42 removed did not majorly affect HR (Table in Appendix 7), suggesting this is not an influential observation. So, case 42 was not removed from remaining analyses.

Figure 8. Plot to visualise deviance residuals for the Cox regression of time to death on covariates in MV model 5 (Any ECG change, PTV and $V_{LAWall-63-69}$): case 42 circled in red is furthest away from 0

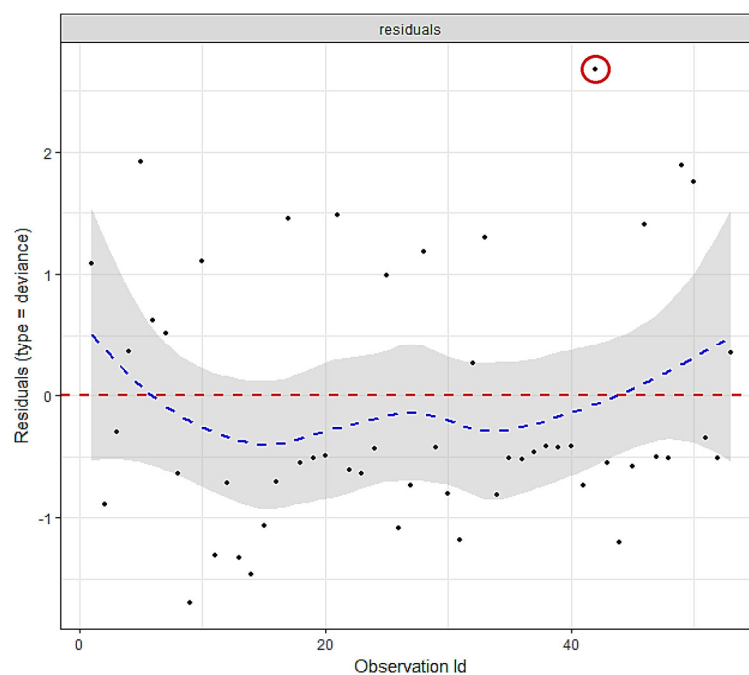
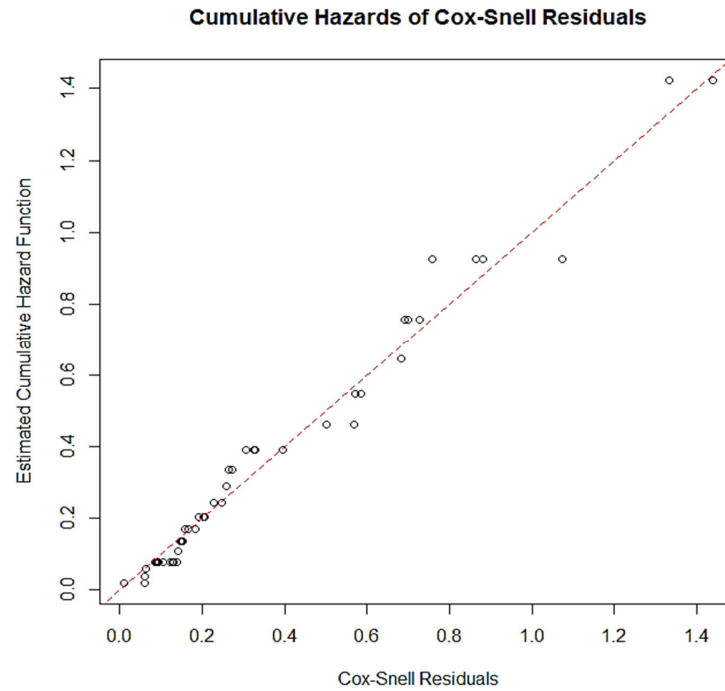


Figure 2 in Appendix 7 shows random pattern of Schoenfeld residuals and there was no significant correlation between Schoenfeld residuals and time (p values $>.05$) indicating there was no violation of the proportional hazards assumption. Runs test also showed all residuals displayed random structure with p values $>.05$. A good model fit was seen with no major deviation of residuals from the 45-degree line on Cox-Snell residual plot (Figure 9). Model performance was good with a c-statistic of .76. Nam-D'Agostino χ^2 test showed that when censored at 24 months and 36 months, there was good model calibration with chi square values of 1.01 and 2.19 and p values of .32 and .14 respectively, but the test was conducted after splitting the data into halves not deciles as 5 or more events are needed in each group.

Figure 9. Plot of estimated cumulative hazard function against Cox-Snell residuals for MV model 5 containing Any ECG change, PTV and $V_{\text{LAWall-63-69}}$



Assessing for confounding between Any ECG change and $V_{\text{LAWall-63-69}}$

$V_{\text{LAWall-63-69}}$ could impact DR directly, but may also impact onset of Any ECG change 6 months after RT which may also affect DR due to potentially a different mechanism to the direct effect. This potential confounding effect was checked by entering these variables separately in the MV model with PTV. The results in Table 12 show that though Any ECG change was no longer as statistically significant according to p-value when entered with $V_{\text{LAWall-63-69}}$, the HRs did not vary greatly for the covariates when entered together or separately or when stratified according to Any ECG change suggesting there was no confounding effect. Also, on logistic regression, $V_{\text{LAWall-63-69}}$ was not significantly associated with Any ECG change and no multicollinearity was seen.

Table 12. MV models assessing Any ECG change and $V_{LAWall-63-69}$ confounding effect

Covariate	MV model 5 containing PTV, Any ECG change, $V_{LAWall-63-69}$		MV model containing PTV, Any ECG change		MV model containing PTV, $V_{LAWall-63-69}$		MV model containing PTV, $V_{LAWall-63-69}$ stratified for Any ECG change	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
PTV size (cm ³)	.08	1.00 (1.00-1.01)	.04	1.00 (1.00-1.01)	.05	1.00 (1.00-1.01)	.08	1.00 (1.00-1.01)
Any ECG change	.08	2.43 (.90-6.55)	.04	2.73 (1.03-7.24)				
$V_{LAWall-63-69}$	.02	1.04 (1.01-1.07)			.01	1.04 (1.01-1.08)	.04	1.04 (1.00-1.07)

Accounting for missing data – MV model with multiple imputed data

As Any ECG change data was missing for 25 patients in the original 78 patient cohort, the above MV modelling was based on 53 patient data. Here, 100 fold multiple imputation is used to generate missing data for the 25 patients so that all 78 patient data are accounted for. The pooled MV model with data imputed is shown in Table 13. This confirms PTV, Any ECG change and $V_{LAWall-63-69}$ had similar HR values to MV model 5 generated from the 53 patient cohort.

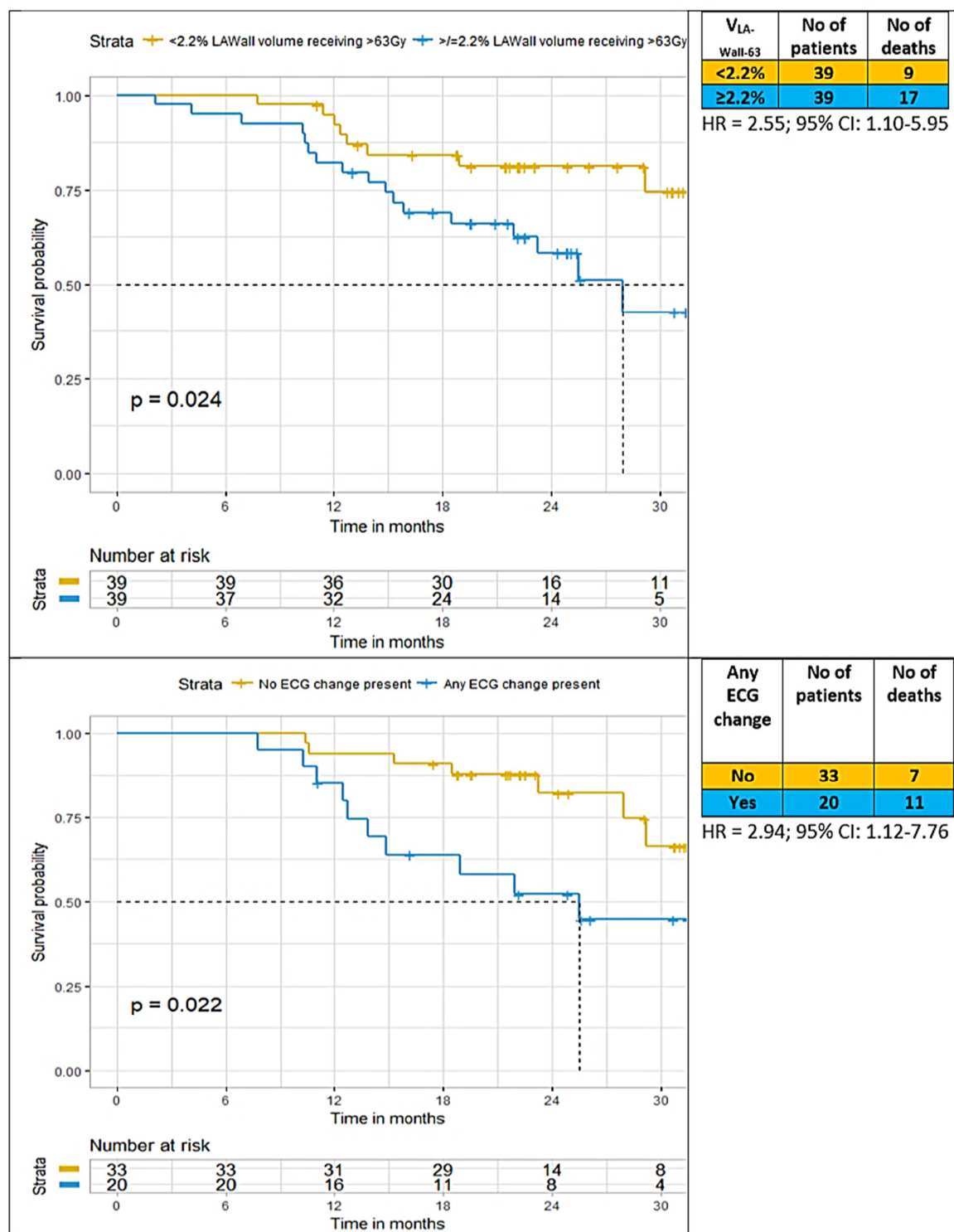
Table 13. Pooled MV model analysed using multiple imputed data

Variables	p-value	HR (95% CI)
PTV size (cm ³)	.15	1.00 (1.00-1.00)
Any ECG change	.09	2.52 (.88-7.18)
$V_{LAWall-63-69}$	.05	1.03 (1.00-1.06)

3.3.5 Scale of survival variation with LA wall dosimetry & Any ECG change

The scale of association between $V_{\text{LA-Wall-63}}$ and DR can be seen in survival curves plotted in Figure 10. For patients with $V_{\text{LA-Wall-63}}$ values below or above the median level of 2.2%, median OS was 39.2 and 27.9 months respectively. At 24 months post-treatment survival was 23% higher (81% vs 58%) for patients with <2.2% LA wall volumes irradiated to >63Gy. The scale of association between DR and ECG changes is shown in the survival curves split by the presence or absence of Any ECG change, also plotted in Figure 10. In patients with Any ECG change, the median OS was 25.5 months and median OS was not reached for those without.

Figure 10. Kaplan Meier curves dichotomised by (top) LA wall volume receiving >63Gy ($V_{LA-Wall-63}$) $\geq$ / $<$ 2.2% (its median value) (78 patients; 26 events); (bottom) presence or absence of Any ECG change (53 patients, 18 events). *p*-value of log rank test.



3.3.6 Prognostic index based on MV model 5

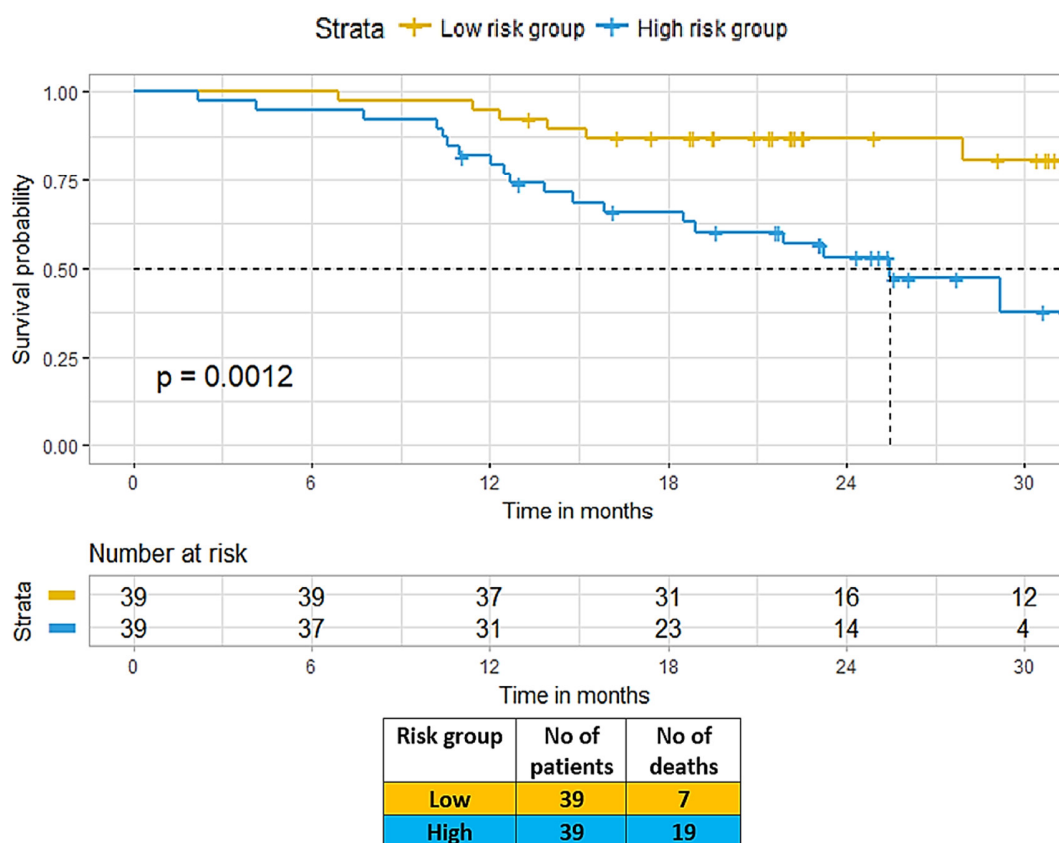
A prognostic index (PI) was developed using regression co-efficients of 53 patient data set with no missing data to classify patients into 2 risk groups based on the linear-predictor values for all 78 patients calculated using the formula below using the regression coefficients for each of the covariates in MV model 5 ($V_{LA-Wall-63}$, Any ECG change and PTV).

$$\text{Linear-predictor} = (.002 * \text{PTV}) + (.888 * \text{Any ECG change}) + (.039 * V_{LA-Wall-63})$$

PTV measured in cm³; Any ECG change present =1; Any ECG change absent = 0; Any ECG change data missing = .5; $V_{LA-Wall-63}$ measured in % of total LA Wall volume

Patients were classified as low or high risk based on their linear-predictor values being $<$ or ≥ 1.345 (median linear-predictor value) respectively. KM curves in Figure 11 show a significant difference in OS between the 2 risk groups. The median OS for high and low risk groups were 25 and 39 months respectively. Risk of death was 4 times higher in high than low risk group (HR 4.1; 95% CI:1.6-10.3; $p < .01$ on cox regression). Performance based on linear-predictor was good (Harrell-C-statistic .70).

Figure 11. Kaplan Meier curves for patients dichotomised to high and low risk based on linear predictors. *p*-value of log rank test.



3.3.7 Association between Any ECG change and dosimetry

There were no significant associations between scores for Heart-PC6, Pericardium-PC5 or LA-Wall-PC6, baseline ECG change and 'Any ECG change' (Table 14).

Table 14. Univariable logistic regression analysis of Any ECG change at 6 months

Co-variate	p-value	Odds ratio (95% CI)
Baseline ECG change	.21	2.11 (.67 - 6.66)
Heart-PC6	.90	1.03 (.62 - 1.73)
Pericardium-PC5	.77	1.09 (.63 - 1.86)
LA-Wall-PC6	.43	1.24 (.73 - 2.10)
V _{LAWall-63-69}	.43	1.02 (.98 - 1.06)

3.3.8 Impact of mean lung dose and oesophageal dosimetry on DR

No significant associations between DR and lung mean dose (HR 1.11; p .27) and 19 oesophageal PCs were seen on UVA (Appendix 6).

3.3.9 Post progression survival

All 26 patients who had died had progression of disease. Of the 26 patients, UVA of post progression survival defined as survival from date of progression of disease to death or last follow up was significantly worse in patients with larger PTV and higher $V_{LAWall-63-69}$ and Any ECG change approached significance. 26 of 53 patients with Any ECG change data had progression of disease, 18 of which had died. On MVA, $V_{LAWall-63-69}$ and Any ECG change remained significant but the number of cases were small (Table 15).

Table 15: Cox regression models of post progression survival

Variables	Univariable model		Multivariable model containing $V_{LAWall-63-69}$	
	p-value	HR (95% CI)	p-value	HR (95% CI)
Any ECG change	.08	2.55 (.91-7.16)	.02	5.44 (1.33-22.25)
PTV	<.01	1.003 (1.001-1.004)	.43	1.001 (.999-1.003)
$V_{LAWall-63-69}$	<.01	1.05 (1.02-1.09)	<.01	1.14 (1.04-1.25)

3.3.10 Summary of key findings

- In this isotoxically dose escalated cohort of LA-NSCLC patients, larger PTV size, Any ECG change at 6 months after RT and large heart volume receiving 63-69 Gy were associated with worse overall survival (OS).
- Specifically, high LA wall receiving 63-69 Gy ($V_{\text{LAWall-63-69}}$) was strongly associated with worse OS ($p = .01$). The findings of the graphical approach for localisation were validated using a statistical method.
- The prognostic index based on the best model containing PTV size, Any ECG change and $V_{\text{LAWall-63-69}}$ performed well at classifying patients into high and low DR risk groups.
- No direct significant associations between baseline ECG changes, heart, LA wall or pericardium dosimetric parameters and the presence of Any ECG change within 6 months of RT were seen likely due to the low event rates.
- Oesophageal dosimetry was not associated with DR as expected which gives strength to the methodology used to identify the associations between heart and its substructure dosimetry and DR.
- Higher $V_{\text{LAWall-63-69}}$ and Any ECG change were associated with poorer post progression survival though the sample size was small. This may reflect high radiation dose induced cardiac toxicity and comorbidity limiting tolerance of further treatment upon disease progression resulting in poorer survival.

3.4 Discussion of results

3.4.1 Clinical and heart dosimetric factors impacting survival

This is the first study to use a DVH-wide analysis based on PCA to explore associations between heart irradiation and DR in NSCLC patients, rather than using discrete dose-volume point metrics. It is also the first to analyse ECG changes and conduct detailed cardiac substructure dosimetric analysis in relation to DR in these patients. The results presented in this chapter provide some direct evidence that there is an association between OS and cardiac irradiation in NSCLC patients. This adds to the existing indirect evidence from the Post-Operative RT (PORT) studies described in Section 1.3.1.2.1.2 [237][69][69][70] and some emerging direct evidence such as from RTOG-0617 analysis showing heart V5 and V30 impacting OS in patients with NSCLC.[24] As non-RT-related cardiac morbidity in NSCLC patients is associated with worse OS, RIHD may have an additive effect to further worsen OS in these patients with high underlying cardiovascular disease risk due to smoking and age.[238][63]

The presence of Any ECG change 6 months after RT, large PTV size and higher $V_{\text{Heart-63-69}}$ represented by Heart-PC6 were associated with poorer survival. Cardiac doses of 63-69 Gy were concentrated in the LA wall and correspond to 64-73 Gy equivalent dose in 2 Gy fractions (EQD2) for α/β of 3 Gy. The scale of associations between DR and heart and substructure volumes receiving >63 Gy was substantial, despite median values of these volumes being low (2, 5 and 8% for whole-heart, pericardium and LA-Wall respectively). Since $V_{\text{Heart-63-69}}$ was not correlated to PTV

size or prescribed dose, the association between $V_{\text{Heart-63-69}}$ and DR is likely independent of these factors. These results are consistent with previous studies in finding tumour size to be an independent factor associated with local control and early OS in patients with unresected stage III NSCLC.[239][240][241][242]

Patients with T1-3 NSCLC without subcarinal (SC) lymph node metastatic involvement have been seen to have better survival after surgery than patients with SC involvement.[243] A recent study of NSCLC patients with N2 (mediastinal nodal involvement) disease found patients with single-level metastases had better survival rates than those with multilevel metastases and especially SC involvement.[244] It has been suggested that heart dosimetry may be a surrogate for the extent and location of mediastinal nodal involvement as another study found heart dosimetric parameters were significantly correlated with multilevel nodal metastases and SC nodal involvement.[245] The data analysed in this chapter showed no such correlation between SC nodal status or N0/1 Vs N2/3 disease status and $V_{\text{LAWall-63-69}}$. On UVA, neither N2/3 disease nor SC nodal status were significantly associated with DR ($p = .42$ and $.12$ respectively). After adding SC nodal status into the MV model containing PTV, Any ECG change and $V_{\text{LAWall-63-69}}$, and when stratified according to SC status, $V_{\text{LAWall-63-69}}$ remained significant with no change in HR (Appendix 8) suggesting in this dataset SC is not a confounding effect for the observed association between $V_{\text{LAWall-63-69}}$ and DR.

Little data exist regarding associations between cardiac substructure dosimetry and OS. Although LA wall irradiation was significantly associated with DR in this work, it

was not possible to determine whether this was due to LA wall damage being particularly critical, or whether the association simply reflects the strong correlation between heart and LA wall volumes receiving 63-69 Gy (Spearman correlation $r=.88$, $p<.01$). The finding that $V_{\text{LAWall-63-69}}$ was more significantly associated with DR than $V_{\text{Heart-63-69}}$ however strengthens the hypothesis that LA Wall is likely the substructure which has the highest impact on DR when irradiated to high doses.

All patients who had died had recorded progression of disease. Post progression survival was significantly worse in patients with high $V_{\text{LAWall-63-69}}$. High dose related heart toxicity may worsen cardiopulmonary function in these patients with higher baseline risk of cardiopulmonary problems, reducing their tolerance of further treatment lines upon progression of disease which could result in poorer survival.

3.4.2 Potential mechanism of substructure irradiation induced damage on DR

The mechanism of early heart radiation induced toxicity impacting survival remains unclear. There are multiple heart substructures with different functions, therefore the mechanism is likely multifactorial. In breast cancer studies, RT has been seen to accelerate late atherosclerosis of major vessels and cause early microvascular changes.[246] Recently in oesophageal cancer patients left ventricular perfusion defects due to ischemia associated with higher doses has been seen in the first year after RT.[59] In fact the rate of new perfusion defects can be as high as 27% within 6 months after RT.[247] Hatakenaka et al also reported early LV dysfunction on cardiac magnetic resonance imaging (MRI) scanning after chemoradiation for oesophageal cancer.[57] Another possible mechanism is pericardial effusion

development that can occur as early as 1-year after RT.[248] Effusions may be more symptomatic in NSCLC patients due to baseline cardiopulmonary comorbidities. Other potential mechanisms are valvular dysfunction or conduction pathway damage i.e. cardiac nervous system damage resulting in arrhythmia. The data analysed in this chapter showed the most frequent cardiac event was arrhythmia.

The underlying mechanism of radiation induced damage leading to arrhythmia may be fibrosis. In rats, fibrosis accumulation and dose-dependent decreases in end-diastolic diameter were seen one month after single fractions of 15 or 20 Gy, and death due to cardiac failure occurred after 22.5 Gy.[73][82] The impact of atrial irradiation on survival was also demonstrated by the higher survival seen when atria were spared during heart irradiation.[73] Atrial fibrosis is commonly seen in patients with atrial fibrillation (AF) and plays an important role in the pathophysiology of AF.[249][250][251][252] Continuous AF can lead to LV dysfunction, increased LA pressure and impaired atrial contractility, and has been associated with worse clinical outcomes including stroke.[253] A surrogate for fibrosis, late gadolinium enhancement (LGE) on MRI, has been seen in LA walls of patients with AF. In patients with oesophageal cancer LGE has been seen in areas of heart receiving 40 Gy, and more so in regions receiving 60 Gy.[254] This dose-effect is supported by evidence from another oesophageal cancer study which found microvasculature circulation obstruction in 0%, 43% and 68% of myocardial segments receiving 0, 40 and 60 Gy respectively.[255][256] In another study, 14% of oesophageal cancer patients had symptomatic cardiac disease 5 years after RT, the risk varying with heart volumes receiving ≥ 45 , 50 and 55 Gy.[257]

However, the early difference in OS seen before 6 months in patients with higher volume of LA wall receiving higher doses indicates a potentially more acute mechanism of radiation induced damage than fibrosis. In fact in patients acute inflammation has been seen to induce arrhythmias[258]. A recent review of molecular mechanisms in early cardiovascular response of heart irradiation show a sequence of overlapping events orchestrated by a large number of interacting molecular signals, including cytokines, chemokines, and growth factors.[259] This complex process is reflected by changes in cardiac functional parameters, morphology, inflammatory markers, endothelial dysfunction, expression of von Willebrand factor, Mg^{2+} -ATPase and Na, K-ATPases, miRNAs, connexins, and matrix metalloprotenases in animals.[259] Increased expression of pro-inflammatory and other genes has been demonstrated within hours following irradiation. These include genes of transcription factors such as nuclear factor- κ B (NF- κ B), cytokines such as tumour necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and basic fibroblast growth factor (bFGF) involved in inflammatory processes. Also, it has been suggested that radiation may cause direct damage to blood vessels due to reactive oxygen species (ROS) generation that disrupt DNA strands, leading to an inflammatory cascade. In animals, myocardium has been seen to be more susceptible to arrhythmias at the onset of reperfusion associated with a burst of ROS production after irradiation. Radiation is associated with the induction of acute inflammatory markers, including cytokine expression, an increase in cyclooxygenase-2 (COX-2) expression and COX-2-mediated prostanoid production, acute phase proteins such as CRP and TNF alpha. In patients with LA-NSCLC with potential other underlying cardiac problems associated with their smoking history

and age, arrhythmias induced acutely by radiation induced cardiac damage may result in sudden death.

In summary, imaging studies and animal work have demonstrated radiation dose-related cardiac changes, but further work is required to directly associate these changes with morbidity and mortality.

3.4.3 Limitations

Some limitations of this work must be acknowledged. Firstly, although a prospective study, this was a post-hoc analysis and lacked comorbidity or smoking status data, which may be additive risk factors for RIHD. Secondly, the resting 12-lead-ECG has limited value as an indicator of subtle pathological changes within the heart.[260][261] However, in a similar population over the age of 65 without lung malignancies but with baseline ECG changes, the rate of non-fatal and fatal cardiovascular events at 6 months was only around 2%.[262] Thus the higher rate of ECG changes (38%) observed at 6 months in this study is likely due to RT effect. Thirdly, the study is relatively small, and its findings must consequently be interpreted with caution and it needs validation in an independent data set. Although associations between DR and dosimetry and ECG changes were found, it could not be distinguished whether this was truly cardiac-related deaths or cancer-related deaths, as there was a lack of cardiac-specific morbidity or mortality data, and all patients with early death had tumor relapse. Cause of death recording is complicated, since deaths of patients receiving RT for NSCLC following cardiac arrest could be scored as cancer-related death. Fourthly, although an association

between high LA wall doses and poorer OS was found, the mechanism remains unclear. Although a validated atlas [186] was used to define the cardiac substructure, there remains some uncertainty in the substructure outlines due to lack of consistent use of iv contrast and heart motion, though heart motion during a fraction may average out due to regular beating. Anatomic and positional variations during RT can induce changes in radiation doses to lung and heart.[263] Though a margin was added for small substructures, evaluation of 4DCT and use of cardiac MRI would be useful to provide a better estimate of the actual delivered dose to improve on normal tissue toxicity models. Finally, while PCA provides a very efficient way of reducing many highly correlated dosimetric variables to a few factors, the clinical interpretation of the resulting varimax-rotated PCs can be challenging.

3.5 Conclusion

In this cohort of NSCLC patients significant associations between all-cause death-rate and higher heart volumes receiving 63-69 Gy (particularly LA wall) were seen. The observed associations suggest that small heart volumes receiving high radiation doses negatively impact survival, to a greater extent and more acutely than that seen in breast cancer and lymphoma patients who are treated with lower radiation doses. With each 1cm³ of LA wall receiving 63-69 Gy, the risk of death increases by 4% at any particular point in time. This work is hypothesis-generating and requires validation in an independent dataset. The pathophysiology of acute RIHD needs to be determined in prospective functional imaging studies before recommending modification of treatment plans based on these initial results, if this compromises dosimetric tumour coverage. The finding of an association between DR and Any

ECG change at 6 months after RT does, however, tentatively suggest a link between DR and RT-induced cardiac damage. Given the armoury of RT technology available, dose-escalated NSCLC treatment outcome may be improvable in the future via cardiac substructure-sparing dose-escalation techniques, given greater knowledge of links between survival, cardiac pathophysiology, and cardiac substructure dosimetry.

4. VALIDATION AND REFINEMENT OF THE SURVIVAL MODEL AND PROGNOSTIC INDEX DEVELOPED IN IDEAL-6 DATASET IN A NON-DOSE ESCALATED COHORT: OXFORD

4.1 Introduction

Recently there has been increasing interest in radiation induced cardiac damage impacting survival in patients with lung cancer. However there have been very few successful attempts to validate OS models including heart dosimetry in independent lung cancer datasets. Recently, two studies failed to validate the RTOG-0617 finding of heart V5 being a prognostic factor for early OS in patients with LA-NSCLC treated with CRT, especially once lung mean dose was taken into account in one study.[24][264][265] Without model validation there is a risk of overfitting and difficulties with generalisability. Attempts to validate and refine findings in chapter 3 were made here.

In this chapter, the following hypotheses were tested on a retrospective 'Oxford' cohort treated in the Oxford clinic:

- ***The prognostic index (PI) developed in chapter 3 including cardiac factors can be validated and model findings corroborated in this independent cohort.*** Associations between all-cause death-rate (DR) and higher LA wall volumes receiving 63-69 Gy ($V_{LAwall-63-69}$), Any ECG change at 6 months after RT and larger PTV were found in the analysis of IDEAL-6 in chapter 3. Here, the aim is to validate the PI based on these factors in an independent dataset of LA-

NSCLC patients treated with radical RT in a different centre (Oxford), and to corroborate hazard ratios seen in the best MV model for DR in chapter 3.

➤ ***Heart irradiation impacts cardiac event rate and cardiac related death rate.***

In the SEER database, heart-disease specific survival rate was lowest in lung cancer when compared to other causes of death in 10 most common cancers.[266] Therefore identification of associations between cardiac irradiation and cardiac death rate warrants special interest in these patients with poor prognosis. A limitation of the work in chapter 3 was that the association between cardiac dosimetry and OS was assessed instead of cardiac death rate directly. In this work, direct association between cardiac death rate and cardiac dosimetry is assessed. ECG data is not routinely collected in the clinical setting unlike in IDEAL-6 trial in chapter 3. So, here data regarding new or worsening cardiac events since RT were collected and association with cardiac dosimetry assessed.

➤ ***Smoking and baseline cardiac comorbidity increases DR.*** Smoking is responsible for 10% of all cardiovascular diseases.[267] A higher proportion of lung cancer (89%) than breast cancer patients (45%) are smokers and are therefore more likely to have baseline cardiovascular disease.[268][269] Cardiac mortality after RT is also higher in smokers. For example, in a recent large study of breast cancer patients receiving RT, cardiac mortality was 1% for smokers and 0.3% for nonsmokers.[270] In lung cancer patients treated with RT, higher Charlson Comorbidity index, which includes cardiac comorbidity at baseline, has been associated with worse OS.[271] In this chapter the impact on DR of these

potential confounders (smoking history and baseline cardiac comorbidity) which were missing in IDEAL6 dataset in chapter 3 are assessed.

- **Heart dose-response effect exists for DR.** The current standard RT dose delivered in UK for LA-NSCLC is 64-66 Gy in 32-33 fractions or 55 Gy in 20 fractions.[272] The patients in this cohort were prescribed 66 Gy in 33 fractions which is lower than the doses prescribed in IDEAL-6 in chapter 3 (63-73 Gy in 30 fractions, equivalent to 64-79 Gy in 2 Gy per fraction with α/β of 3). The mean heart dose in breast cancer patients treated between 1977-2001 was around 6-7 Gy and 2-3 Gy for left and right sided tumours respectively.[273] This has reduced to 2.3 Gy and 1.2-2 Gy in left and right sided tumours respectively with contemporary tangential breast or chest wall RT.[274] The mean heart dose in lung cancer patients can be around 15.5 Gy [60] and this can be improved for left and right lung tumours to 4.1 Gy and 4.8 Gy respectively with modern techniques such as dynamic conformal arc therapy, intensity-modulated RT (IMRT) and volumetric modulated arc therapy.[275] Despite lower tumour doses being prescribed for breast cancer (50 Gy) and lymphoma (40 Gy) than for lung cancer, heart irradiation impacts OS in these patients.[276][30] The combination of smoking associated higher underlying and post-treatment cardiac risk and higher radiation doses delivered to the heart in lung cancer than breast cancer patients could result in a more acute effect of heart irradiation on OS in lung cancer than breast cancer patients. Therefore, another aim of this work is to identify the impact of cardiac dosimetric parameters other than high doses on OS using DVH-wide analysis based on PCA and localise these to cardiac substructures.

4.2 Summary of methods

4.2.1 Population (described in section 2.1.3)

64 patients treated with radical RT or CRT to 66 Gy in 33 fractions delivered once daily 5 days a week for LA-NSCLC in the Oxford cohort with or without sequential 3-4 cycles of chemotherapy or 2 cycles for concurrent CRT (details in section 1.1.3).

4.2.2 Data collection

Treatment and disease parameters, time to last follow-up or death, smoking history, and pre-existing baseline cardiac co-morbidities at start of RT (ischaemic heart disease (acute myocardial infarction, coronary artery bypass graft, angioplasty or stent, coronary artery disease), cardiomyopathy, heart failure, pericardial disease, arrhythmias) were collected. Cardiac-morbidity identified from medical notes were defined as new or worsening of cardiac events listed above within 1 year of completion of RT, both symptomatic and asymptomatic. As 'Any ECG change' in IDEAL-6 in chapter 3 was missing in this cohort, cardiac-morbidity effectively substituted for this variable in the MV model. Death certificates were reviewed to determine whether cardiac cause was recorded in any part of the certificate to assess cardiac-related-death rate.

4.2.3 Processing of RT dosimetric data (details in section 2.3 & 2.4)

GTV, ITV, CTV, PTV and OARs were outlined as described in section 1.1.3 and Appendix 3. Heart contours delineated by clinical oncologists at our centre were edited by myself and LA-Wall volumes were delineated by myself using the validated atlas.[186] LA-Wall receiving 63-69 Gy in 30 fractions in IDEAL-6 equates to 64.3-

73 Gy in 2 Gy fractions (EQD2) ($\alpha/\beta = 3$ Gy). In the Oxford cohort RT was delivered in 33 fractions so the equivalent dose is 65-71 Gy. Therefore, LA-Wall volumes receiving 65-71 Gy ($V_{\text{LAWall-65-71}}$) as well as mean heart doses were extracted for all patients. PCA was performed to extract the 10 highest-ranked varimax rotated heart PCs describing at least 95% variance of the heart DVH data.

4.2.4 Validation of the prognostic index (PI) derived from IDEAL-6 dataset

Performance of the PI developed in chapter 3 (section 3.3.6) was assessed in this independent cohort. First, differences in patient and treatment characteristics between the 2 cohorts were compared using Mann-Whitney, t and chi-square tests. Regression coefficients for the covariates in MV model 5 in IDEAL-6 ($V_{\text{LAWall-63-69}}$, Any ECG change and PTV) were used to calculate the linear-predictor values for Oxford patients as shown in the equation [1] below. Any ECG change was substituted by cardiac-morbidity and $V_{\text{LAWall-63-69}}$ was substituted by $V_{\text{LAWall-65-71}}$ in equation [1].

$$\text{Linear Predictor} = (.002 * \text{PTV}) + (.888 * \text{cardiac-morbidity}) + (.039 * V_{\text{LAWall-65-71}}) \quad [1]$$

PTV is measured in cm³; Score for patients with cardiac-morbidity = 1;

Score for patients with no cardiac-morbidity = 0;

Score for patients with cardiac-morbidity data missing = .5;

$V_{\text{LAWall-65-71}}$ measured in percentage of total LA Wall volume

Patients with linear-predictor values $<$ or ≥ 1.345 (cut point from section 3.3.6) were classified as low and high-risk respectively. KM curves for low and high-risk patients

were generated and difference in survival between the groups tested using log rank test with a p value of $<.05$ considered significant. Performance of the PI in discriminating between high and low risk patients was assessed using Harrell's-c-statistic.

4.2.5 Corroboration of model for all cause death rate (DR) from Chapter 3

MV model 5, the best MV model containing cardiac substructure, from chapter 3 (Section 3.3.4 Table 11) was refitted on Oxford data. Univariable and multivariable cox regression analyses (UVA/MVA) of the covariates in MV model 5 (PTV, $V_{\text{LAWall-65-71}}$ substituting for $V_{\text{LAWall-63-69}}$ and cardiac-morbidity substituting for Any ECG change) for DR measured from the start of RT were performed to corroborate hazard ratios (HRs) for the covariates seen in MV model 5 in chapter 3.

4.2.6 Refinement of the MV model for DR (Details in section 2.6)

UVA/MVA cox regression analyses for DR measured from the start of RT were performed for association with: patient and treatment characteristics, smoking history, baseline cardiac comorbidity, cardiac-morbidity, and scores of 10 heart PCs. Clinically significant factors and factors with p-value $\leq .2$ on UVA were included in MV models, and model selection carried out as described in section 2.6.2.3. Model diagnostics, performance assessment, multiple hypotheses correction and multicollinearity check were performed as described in section 2.6. Scale of survival variation was assessed by evaluating median volumes of significant dosimetric parameters by Kaplan Meier analysis with a log rank test p-value of $<.05$ considered

statistically significant. Internal validation and calculation of bias corrected 95% CI for HRs was carried out using bootstrap of 1000 samples.

4.2.7 Localisation of heart doses represented by heart PC to substructure

The graphical approach validated in chapter 3 was used to localise the significant heart dose bins represented by the peaks in Heart PCs significantly associated with DR found in the best MV model from section 4.2.6 ($\text{Heart}_{\text{maxpeak}}$) to relevant region of the heart (details in Appendix 5). Once the $\text{Heart}_{\text{maxpeak}}$ was localised to a specific region of the heart, the cardiac substructures contained in this region were delineated in all patients using the validated cardiac atlas [186] and DVHs extracted. Volumes of this substructure receiving $\text{Heart}_{\text{maxpeak}}$ then replaced Heart PC in the best MV model from section 4.2.6. If a substructure was found to be significantly associated with DR on MVA in Oxford cohort, this substructure was then delineated in IDEAL-6 patients and volumes receiving the equivalent doses extracted and replaced heart PC in the MV model to ascertain association with DR.

4.2.8 Modelling of cardiac-related-death and cardiac-morbidity

Cardiac-related-death was modelled from the start of RT using Cox regression. Clinically significant factors i.e. cardiac-morbidity, baseline cardiac comorbidity and variables identified in the best MV model for DR were included in the MV model for cardiac-related-death. Associations between cardiac-morbidity and clinically significant factors such as baseline cardiac comorbidity and covariates in the best MV model for DR were tested using logistic regression. The predictive abilities of the MV models were characterised using AUC of ROC curves.

4.3 Results

4.3.1 Patient and treatment characteristics

Table 1. Patient characteristics

Characteristic	No of patients (%)
WHO performance status	
0	17 (26.6)
1	34 (53.1)
2	5 (7.8)
3	1 (1.6)
Missing	7 (10.9)
Gender	
Female	25 (39.1)
Male	39 (60.9)
Nodal status	
N 2 or 3	32 (50.0)
N 0 or 1	29 (45.3)
Missing	3 (4.7)
Stage	
1	3 (4.7)
2	17 (26.6)
3	40 (62.5)
Missing	4 (6.3)
Histology	
Squamous	36 (56.3)
Non-squamous	24 (37.5)
Missing	4 (6.3)
Smoking history	
Ex/Current Smoker	51 (79.7)
Non-smoker	2 (3.1)
Missing	11 (17.2)
Pack year history (Mean; Range)	45 (0-174)
Cardiac comorbidity at baseline	
Yes	17 (26.6)
No	36 (56.3)
Missing	11 (17.2)

Table 2. Treatment characteristics

Characteristic	No of patients (%)
Prescribed tumour dose	
66Gy in 33#	56 (87.5)
64Gy in 32#	3 (4.7)
62Gy in 31#	2 (3.1)
60Gy in 30#	2 (3.1)
58Gy in 29#	1 (1.6)
Chemotherapy	
Concurrent	17 (26.6)
Sequential	16 (25.0)
No chemotherapy	29 (45.3)
Missing data	2 (3.1)

Patient and treatment characteristics are detailed in Table 1 and 2. Median age was 71 (range 48 - 89). Median OS was 28 months. Median PTV was 319 cm³ (range

82-1120). 88% had 4DCT for RT planning. All patients were prescribed 66 Gy in 33 fractions to the tumour, however 12% did not complete 66 Gy in 33 fractions due to toxicity. The mean delivered dose to the prescription point was 65.5 Gy. The median mean heart EQD2 was 7.6 Gy (range 0.5-32.2 Gy) and median mean LA wall EQD2 was 12.5 Gy (range 0.5-36.2 Gy). 10 varimax-rotated heart PCs which describe >95% total variance are plotted in Appendix 10. Nine patients had cardiac-morbidity and this information was missing for 9 patients. 15 patients had Cisplatin and Etoposide, 5 had Gemcitabine and Carboplatin, 4 had Gemcitabine and Cisplatin, 3 had Pemetrexed and Cisplatin, 2 had Vinorelbine and Carboplatin, 1 had Vinorelbine and Cisplatin, and chemotherapy details were missing for 3 patients.

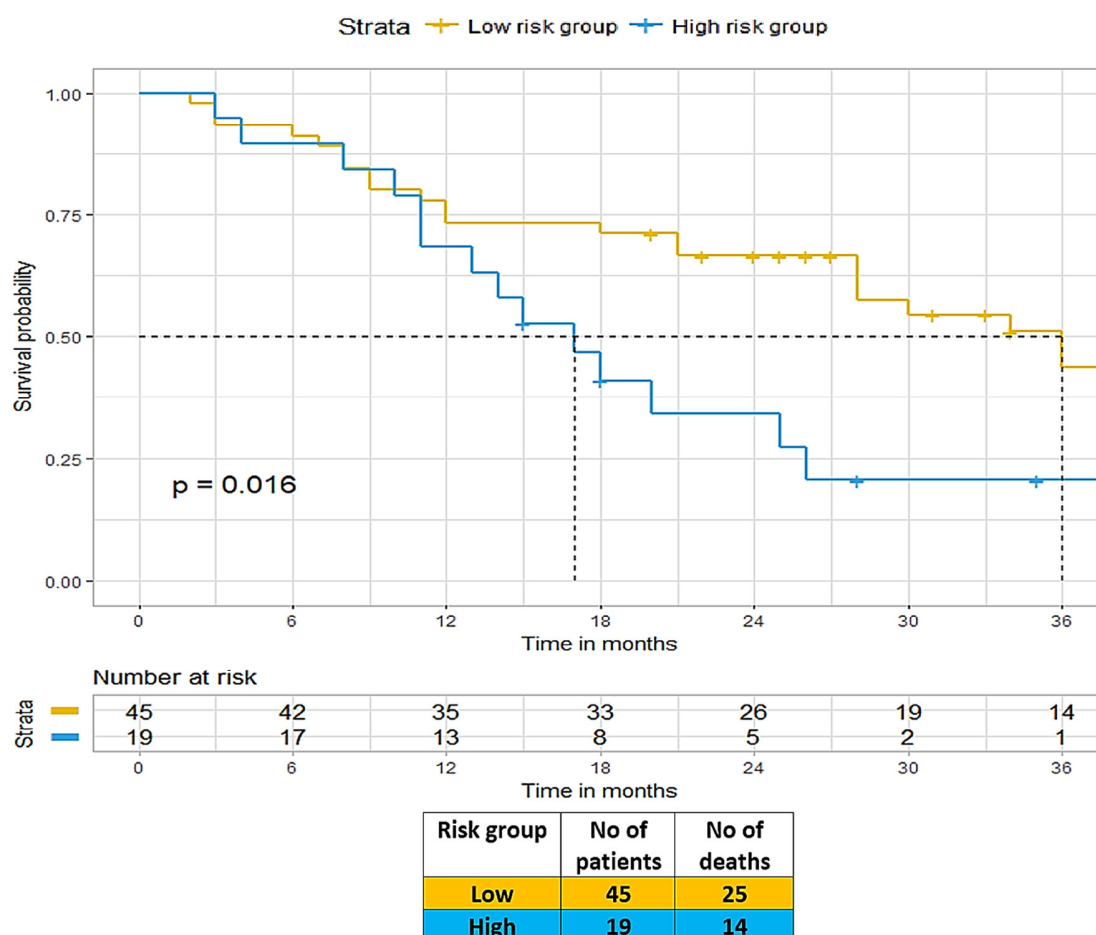
Patient and treatment characteristics compared to IDEAL-6

A comparison between the patient and treatment characteristics of the IDEAL-6 and Oxford datasets is presented in the table shown in Appendix 9. In the Oxford cohort a higher proportion had lower N stage and were older. Though there were less PS 0 patients in the Oxford cohort, the proportion of PS 1 patients was similar to IDEAL-6. PTVs were smaller in Oxford cohort possibly partly due to the higher rate of 4DCT use for planning compared to IDEAL-6 (88% V 44%). All patients in IDEAL-6 received concurrent chemotherapy, whereas only 26.6% patients received concurrent chemotherapy in the Oxford cohort. Lower RT doses were prescribed in the Oxford cohort compared to IDEAL-6. Median OS in IDEAL-6 and Oxford was 39 and 28 months respectively.

4.3.2 Validation of prognostic index (PI) derived in chapter 3

According to the PI from chapter 3, 45 patients were classified as low-risk and 19 as high-risk. 25 (56%) patients in the low-risk and 14 (74%) in the high-risk group died. KM curves in Figure 1 show a significant difference in OS between the 2 risk groups ($p .02$). Median OS for high and low-risk groups were 17 and 36 months respectively. Risk of death was 2.3 times higher in the high than low-risk group ($HR=2.3$; $95\%CI:1.1-4.5$; $p .02$). Performance based on the PI was good (Harrell-C-statistic = .63). This confirms the PI derived from PTV, volume of LA wall receiving high dose, and Any ECG change linear predictors in chapter 3 performs well in this independent cohort despite cardiac-morbidity substituting Any ECG change.

Figure 1. Kaplan Meier curves for patients dichotomised to high or low risk based on linear predictors.



4.3.3 Corroboration of HRs in MV model 5 in chapter 3 for all cause death rate

MV model 5 from chapter 3 consisting of PTV, $V_{LAwall-63-69}$ in IDEAL-6 equivalent to $V_{LAwall-65-71}$ in Oxford ($V_{LA-Wall-high-dose}$) and Any ECG change substituted by cardiac-morbidity was refitted in the Oxford data and results are shown in Table 3. On UVA, Cardiac event and high $V_{LA-Wall-high-dose}$ were significantly associated with DR ($p .05$ and $p .006$) and $V_{LA-Wall-high-dose}$ retained significance on MVA. B-H test showed that Cardiac event and $V_{LA-Wall-high-dose}$ remained significant after correction for multiple hypotheses testing. HRs for DR were similar for the model in IDEAL-6 and Oxford

(Table 3). In the Oxford cohort PTV was not significantly associated with DR on MVA and the MV model performance was not as good as IDEAL-6 (c-statistic 0.76 for IDEAL-6 v 0.68 for Oxford). Therefore, the impact of other variables was explored to assess whether an improved MV model for DR can be derived from this non-dose escalated cohort.

Table 3. Corroboration of hazard ratios (HR) for the same models fitted in IDEAL-6 and Oxford data for all cause death (DR). *c* = Harrell's-c-statistic

	Univariable modelling				Multivariable modelling			
	IDEAL-6		Oxford Cohort		IDEAL-6 <i>c</i> = .76	Oxford Cohort <i>c</i> = .68		
Co-variate	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
PTV	.04	1.002 (1-1.003)	.17	1.001 (1-1.002)	.08	1.002 (1-1.005)	.87	1.000 (.999-1.002)
V _{LA-Wall-high-dose}	.01	1.04 (1.01-1.06)	.01	1.08 (1.02-1.13)	.02	1.04 (1.01-1.07)	.01	1.09 (1.03-1.15)
Cardiac Event	.03	2.94 (1.12-7.76)	.05	2.29 (1-5.263)	.08	2.43 (.90-6.55)	.07	2.20 (.92-5.29)

50 patients received <2.2% V_{LA-Wall-high-dose} (2.2% being the median level identified in IDEAL-6) of which 29 died. 14 patients received ≥2.2% V_{LA-Wall-high-dose} of which 10 died. Patients with ≥2.2% V_{LA-Wall-high-dose} had a significantly poorer OS compared to patients with <2.2% V_{LA-Wall-high-dose} (HR 2.28; 95% CI 1.05-4.95; p = 0.04). 46 patients had V_{Heart-65-71} >0%; of which 23 had V_{LAwall-65-71} >0%. Patients with cardiac-morbidity had worse OS than those without cardiac-morbidity (HR 2.29; 85% CI 1.00-5.26, p = 0.05). 9 patients had cardiac-morbidity of which 8 died.

4.3.4 Refinement of MV model for DR: Effect of other clinical and dosimetric factors on DR

80% were current or ex-smokers, 27% had baseline cardiac comorbidity and 14% developed cardiac-morbidity (Table 1). 6 patients developed fast AF or tachycardia, 3 developed pericardial effusions, 1 had angina and 2 had heart failure/fluid overload. UVA of clinical factors are shown in Table 4. Older age was significantly associated with better survival. Smoking history, baseline cardiac comorbidity and PTV size were not significantly associated with DR. B-H test showed that cardiac-morbidity and age remained significant after correction for multiple hypotheses testing.

Table 4. Univariable Cox regression models of all cause death rate (DR): clinical factors.

PTV = planning target volume; PS = performance status; cardiac-morbidity = recorded cardiac event within 12 months of radiotherapy (RT)

Covariate	p-value	HR (95% CI)
Age	.03	.97 (.94-1.00)
PTV	.17	1.00 (1.00-1.00)
Prescribed dose	.18	.91 (.78-1.05)
Concurrent chemotherapy	.24	1.53 (.75-3.12)
N0/1 Vs N2/3	.91	1.04 (.54-1.98)
PS0 Vs >0	.90	1.05 (.50-2.18)
Ex/Current smoker V Non-smoker	.46	2.12 (.29-15.65)
Cardiac-comorbidity at baseline	.58	.81 (.38-1.71)
Cardiac-morbidity post RT	.03	2.94 (1.12-7.76)

Larger Heart-PC5 scores were associated with higher DR on UVA (HR 1.44, $p < .01$) (Table 5). Heart-PC5 represents high volume of heart receiving 36-44 Gy and 65-71 Gy ($V_{\text{Heart-36-44}}$ and $V_{\text{Heart-65-71}}$ respectively) (Figure 2). $V_{\text{Heart-36-44}}$ and mean heart dose were significantly associated with DR on UVA. $V_{\text{Heart-65-71}}$ and $V_{\text{Heart-36-44}}$ were weakly correlated and so were $V_{\text{LAWall-65-71}}$ and $V_{\text{LAWall-V36-44}}$ ($r=0.4$; $p=0.004$) (Table 6). Heart mean dose was moderately correlated with $V_{\text{Heart-36-44}}$ ($r = .68$; $p < .01$) and with $V_{\text{Heart-65-71}}$ ($r = .61$; $p < .01$) (Table 6). Due to the correlations between heart mean dose and heart constraints, they were entered into the MV model independently (Table 7).

Figure 2. Heart Principal Component 5 (HEART-PC5) representing high volume of heart receiving 36-44 Gy and 65-71 Gy ($V_{\text{Heart-36-44}}$ and $V_{\text{Heart-65-71}}$)

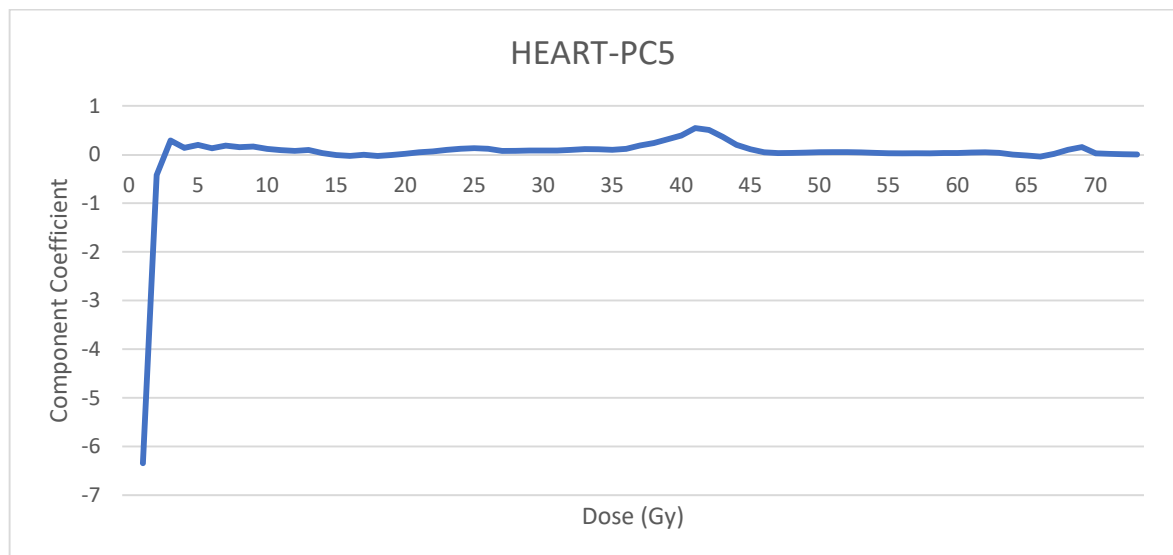


Table 5. Univariable Cox regression models
for all cause death rate (DR): heart dosimetry
(PC = principal component)

Co-variate	p-value	HR (95% CI)
Heart-PC1	.32	1.16 (.87-1.56)
Heart-PC2	.99	1.00 (.75-1.33)
Heart-PC3	.57	1.08 (.83-1.40)
Heart-PC4	.26	1.14 (.91-1.43)
Heart-PC5	<.01	1.44 (1.09-1.90)
Heart-PC6	.16	1.20 (.93-1.54)
Heart-PC7	.34	1.18(.84-1.67)
Heart-PC8	.24	1.20 (.89-1.62)
Heart-PC9	.60	1.09 (.79-1.51)
Heart-PC10	.81	.96 (.71-1.30)
Heart mean dose	.02	1.05 (1.01-1.09)
V _{Heart36-44}	<.01	1.15 (1.05-1.27)
V _{Heart65-71}	.27	1.05 (.97-1.14)

Table 6. Correlations between
heart and LA wall dosimetric
parameters (*r*= Pearson correlation
coefficient; *p*=*p*-value)

		V _{Heart-65-71}	V _{Heart-36-44}	Heart mean dose
V _{LAwall-65-71}	r	.49	.50	.54
	p	<.01	<.01	<.01
V _{Heart-65-71}	r		.30	.61
	p		.02	<.01
V _{Heart-36-44}	r			.68
	p			<.01

MV model 1 was judged best according to AIC, starting with all clinical factors and heart PCs with p-value <.2 on UVA (Age, PTV, Prescribed Dose, cardiac-morbidity, Heart-PC5, Heart-PC6, heart mean dose) plus clinically significant factors (chemotherapy and nodal status), and retained Heart-PC5, cardiac-morbidity and Age as covariates associated with DR (Table 7). This analysis was based on 55 patients due to missing cardiac-morbidity data. VIF and tolerance levels were within set limits, suggesting no multicollinearity.

V_{Heart-36-44} and Heart-PC5 scores were highly correlated (*r* .85; *p* <.01) but V_{Heart-65-71} and Heart-PC5 scores were not correlated (*r* .26; *p* .41). When V_{Heart-36-44} and V_{Heart-}

65-71 were added to Age and cardiac-morbidity, the best AIC selected MV model 2 retained Age, cardiac-morbidity and $V_{\text{Heart-36-44}}$, and the p-values and HRs were similar to MV model 1 (Table 7). VIF for all factors in the model were <4 excluding multicollinearity. Model performance was better (c-statistic improved from 0.69 to 0.71) when $V_{\text{Heart-36-44}}$ replaces Heart-PC5. Heart mean dose and $V_{\text{LAWall-65-71}}$ were correlated to $V_{\text{Heart-36-44}}$ (Table 6), so they were added to the MV model separately with Age and cardiac-morbidity and were found not to be statistically significant (MV models 3 and 4 in Table 7). The best model was MV model 2, which contained cardiac-morbidity, Age and $V_{\text{Heart-36-44}}$. B-H test showed all covariates in the MV models remained significant after correction for multiple hypotheses testing.

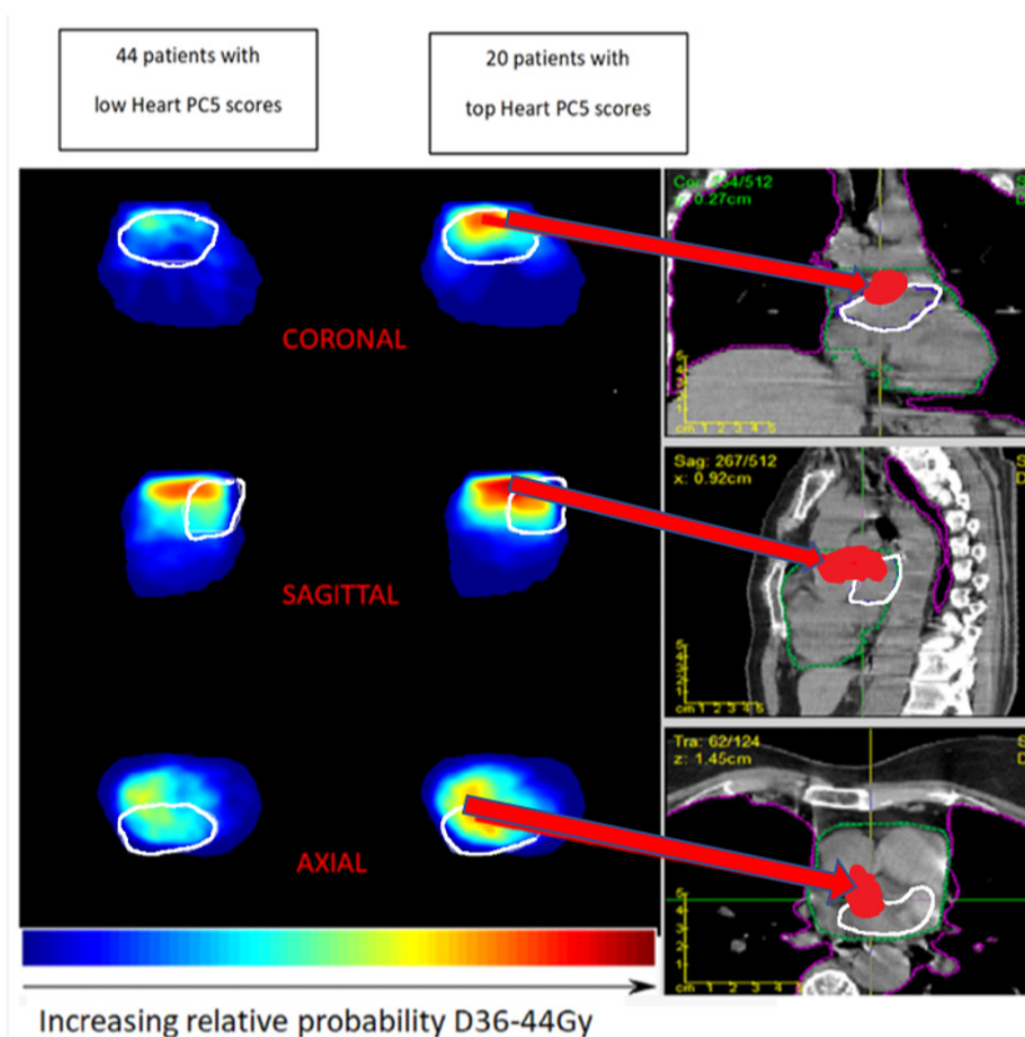
Table 7. Multivariable (MV) Cox models of all-cause death-rate (DR): MV model 1 is the best judged according to AIC. Heart-PC5 is replaced by $V_{\text{Heart-36-44}}$ in MV model 2, $V_{\text{LAWall-65-71}}$ in MV model 3 and Heart mean dose in MV model 4. cardiac-morbidity = *recorded cardiac event within 12 months of radiotherapy*; c=Harrell's-C-statistic.

	MV model 1 including heart PC c = .69		MV model 2 substituting heart PC with $V_{\text{Heart-36-44}}$ c = .71		MV model 3 substituting heart PC with $V_{\text{LAWall-65-71}}$ c=.70		MV model 4 substituting heart PC with Heart mean dose c=.68	
Covariate	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
Age	<.01	.94 (.91-.98)	<.01	.95 (.91-.98)	<.01	.95 (.92-.98)	<.01	.95 (.91-.98)
Cardiac-morbidity	.03	2.58 (1.10-6.04)	.04	2.44 (1.04-5.72)	.03	2.49 (1.07-5.81)	.06	2.3 (.97-5.77)
Heart-PC5	.07	1.33 (.98-1.79)						
$V_{\text{Heart-36-44}}$			.04	1.11 (1.00-1.23)				
$V_{\text{LAWall-65-71}}$					.05	1.07 (1.00-1.14)		
Heart mean dose							.34	1.0 (.98-1.06)

4.3.5 Localisation of heart doses represented by Heart-PC5 to substructure

In 20 patients with high Heart-PC5 scores, 36-44 Gy localised to a region which contains aortic valve (AV), left main coronary artery (LMCA), and coronary ostia (Figure 3). Therefore, these structures were delineated in all patients for further localisation. AV and LMCA were outlined according to the validated atlas.[186] As coronary ostia can be challenging to visualise and outline consistently [277][278][279], AV was grown isotropically by 5mm to create a region (AV+0.5) containing the ostia which have been described to be located just above AV. dDVHs were extracted for these structures and their association with DR was assessed.

Figure 3. Three perspective views of the reference heart and left atria geometry are plotted. Data are shown for 20 patients with highest Heart-PC5 scores and 44 patients with lowest Heart-PC5 scores. The red region indicates the area with high probability of receiving 36-44 Gy. Blue region indicates the area with low probability of receiving 36-44 Gy. The red region localises to the region of aortic valve/left main coronary artery/coronary ostia in patients with high Heart-PC5 scores. (Red arrow and red marker indicates the area on the CT scan with the high probability of receiving 36-44Gy). White outline is the left atria.



4.3.6 Impact of intermediate dose (36-44 Gy) to heart substructures on DR

AV+0.5 volume receiving 36-44 Gy ($V_{AV+0.5-36-44}$) and AV volume receiving 36-44 Gy ($V_{AV-36-44}$) were correlated to $V_{Heart-36-44}$ (r .76 and .65 respectively), and $V_{AV+0.5-36-44}$ and $V_{AV-36-44}$ were strongly correlated to each other ($r=.85$). On UVA, although $V_{AV-36-44}$ was significantly associated with DR, $V_{AV+0.5-36-44}$ containing coronary ostia was more strongly associated with DR (Table 8). The neighbouring left main coronary artery (LMCA) was not statistically significantly associated with DR on UVA, further strengthening the significant finding in MV model 5 of coronary ostia irradiation to 36-44 Gy impacting DR (Table 8). As $V_{AV+0.5-36-44}$ was more significantly associated with DR, this replaced $V_{Heart-36-44}$ (Table 9 MV model 5) and Age, cardiac-morbidity and $V_{AV-36-44}$ remained significant in the MV model.

Diagnostics of MV model 5: B-H test showed that Age, cardiac-morbidity and $V_{AV+0.5-36-44}$ remained significant after correction for multiple hypothesis testing. There was no multicollinearity as VIF was <4 . Plots in Appendix 11 show that there were no influential observations. Assessment of Schoenfeld residuals showed there was no violation of the proportional hazards assumption. Runs test showed residuals displayed random structure. A good model fit was seen on Cox-Snell residual plot (Appendix 11). Performance of MV model 5 was better than MV model 2 where $V_{Heart-36-44}$ was replaced with $V_{AV+0.5-36-44}$ (c-statistic of 0.74 vs 0.71). GND test showed that when censored at 12 and 18 months, there was good model calibration with p-values $<.05$, but calibration was poor at 24 months likely due to less events at this time point due to short follow up. However, the test was conducted after splitting the data into quartiles not deciles as >5 events are needed in each group.

As cardiac-morbidity was missing for 9 patients, the above MV modelling was based on 55 patients. 100 fold multiple imputation was used to generate missing data for the 9 patients so that all 64 patient data were considered. The pooled MV model in the imputed data shown in Table 9 confirms $V_{AV+0.5-36-44}$ remains significant and has similar HR values to MV model 5 generated from the 55 patient cohort, but age was not significant. Internal validation of the MV model using bootstrap of 1000 samples showed a small bias and the HRs did not cross 0. There was no change in the significance levels or HRs when smoking status and baseline cardiac comorbidity was added to the MV model excluding these as confounders for the findings (Details in Appendix 12).

Twenty three patients had 65-71 Gy delivered to their LA Walls and 24 patients had 36-44 Gy delivered to their AV+0.5 region. There was moderate correlation between $V_{LAWall-65-71}$ and $V_{AV+0.5-36-44}$ ($r .59$; $p < .01$) i.e. patients receiving high $V_{LAWall-65-71}$ also had high $V_{AV+0.5-36-44}$ likely due to beam arrangement. So, the impact of $V_{AV+0.5-36-44}$ on DR may be a reflection of $V_{LAWall-65-71}$ effect on DR, so these variables were entered into the MV model separately. The median volume of $V_{LAWall-65-71}$ and $V_{AV+0.5-36-44}$ was 0%. The range for $V_{LAWall-65-71}$ was 0-26% and $V_{AV+0.5-36-44}$ was 0-41%. Patients with $V_{LAWall-65-71}$ and $V_{AV+0.5-36-44}$ of 0 had significantly better OS than those with any $V_{LAWall-65-71}$ or $V_{AV+0.5-36-44}$ (Figure 4). But MV model 3 in Table 7 showed $V_{LAWall-65-71}$ had borderline significance.

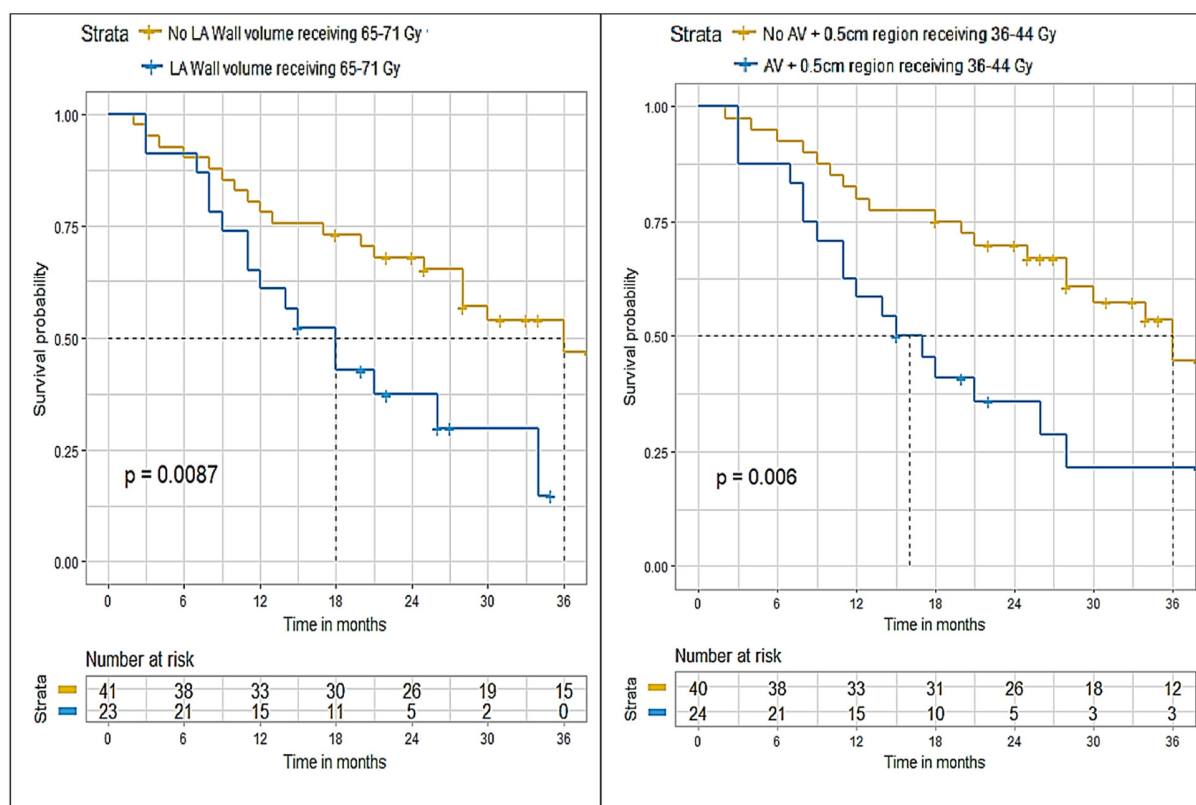
Table 8. UVA of Cox regression models for all cause death rate (DR). *LMCA* = *left main coronary artery*; $V_{AV-36-44}$ = *Aortic Valve receiving 36-44 Gy*; $V_{AV+0.5-36-44}$ = *Aortic Valve + 0.5cm receiving 36-44 Gy*; $V_{LMCA+0.5-36-44}$ = *Left main coronary artery + 0.5cm receiving 36-44 Gy*

Co-variate	p-value	HR (95% CI)
$V_{AV-36-44}$	.002	1.05 (1.02-1.09)
$V_{AV+0.5-36-44}$	<.001	1.07 (1.03-1.10)
$V_{LMCA+0.5-36-44}$	.123	1.02 (1.00-1.04)

Table 9. Multivariable Cox model 5 of all-cause death. $V_{Heart-36-44}$ in MV model 2 in Table 7 replaced by $V_{AV+0.5-36-44}$ with results of bootstrap internal validation and MV model in multiple imputed data. cardiac-morbidity = recorded cardiac event within 12 months of radiotherapy, c=Harrell's-c-statistic

Co-variate	MV model 5 on 55 patients C = .74		Bootstrap 1000 fold		Pooled MV model analysed using multiple imputed data	
	p-value	HR (95% CI)	Bias	Bias corrected 95% CI for HR	p-value	HR (95% CI)
Age	.02	.96 (.92-.99)	-.002	.92-.99	.15	.98 (.94-1.01)
Cardiac-morbidity	.02	2.77 (1.18-6.49)	.058	1.15 – 8.04	.03	2.65 (1.11-6.28)
$V_{AV+0.5-36-44}$	<.01	1.06 (1.02-1.10)	.005	1.02 – 1.13	<.01	1.06 (1.03-1.10)

Figure 4. Kaplan Meier curve for overall survival (OS) dichotomising patients receiving: $V_{\text{LAWall-65-71}} > 0\%$ (blue), 0% (yellow) (Left); and $V_{\text{AV+0.5-36-44}} > 0\%$ (blue), 0% (yellow) (Right). *p-values of log rank test.*



4.3.7 Impact of intermediate dose to heart and AV+0.5: analysis of IDEAL-6 patients

36-44 Gy in 33 fractions delivered in Oxford to heart is equivalent to 35-43 Gy in 30 fractions in IDEAL-6 with alpha/beta of 3 ($V_{\text{Heart-35-43}}$). On UVA, $V_{\text{Heart-35-43}}$ was not significantly associated with DR in IDEAL-6 (HR 1.09, 95%CI .98-1.21, p .13) but AV+0.5 volume receiving 35-43 Gy ($V_{\text{AV+0.5-35-43}}$) was significantly associated with DR (HR 1.04, 95% CI 1.00-1.09, p .04). This adds strength to the significant finding in Oxford of high $V_{\text{AV+0.5-36-44}}$ being associated with poorer OS. When an MV model

was fitted in IDEAL-6 data containing $V_{AV+0.5-35-43}$, Age and covariates from the best MV model from chapter 3 (PTV, Any ECG change and $V_{LAWall-V63-69}$), the dosimetric parameters and PTV remained significant (Table 10) but Any ECG change was not significant. Age was a positive prognostic factor, however when the outliers 42 and 9 are removed, age has a similar negative prognostic effect to that seen in Oxford (Table 10, Model diagnostics in Appendix 13). HR was 1.06 in IDEAL-6 and Oxford for $V_{AV+0.5-35-43}$ and its equivalent $V_{AV+0.5-35-43}$ respectively.

Table 10. Univariable (UVA) and Multivariable (MVA) regression models of all cause death rate (DR) in IDEAL-6 (53 patients). Cardiac-morbidity in MV model 5 is replaced by Any ECG change; $V_{AV+0.5-36-44}$ replaced by $V_{AV+0.5-35-43}$; $V_{LAWall-65-71}$ replaced by $V_{LAWall-63-69}$

Co-variate	UVA IDEAL-6		MVA IDEAL-6		MVA IDEAL-6 after removing 2 outliers	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
Age	.596	1.01 (.97-1.06)	.721	1.01 (.95-1.08)	.82	.99 (.92-1.06)
PTV	.037	1.00 (1.00-1.00)	.039	1.00 (1.00-1.01)	.01	1.00 (1.00-1.01)
Any ECG change	.029	2.94 (1.12-7.76)	.156	2.24 (.74-6.78)	.08	2.80 (.89-10.01)
$V_{AV+0.5-35-43}$	.038	1.04 (1.00-1.09)	.030	1.06 (1.01-1.12)	<.01	1.09 (1.02-1.14)
$V_{LAWall-63-69}$	.012	1.04 (1.01-1.06)	.045	1.04 (1.00-1.07)	.04	1.04 (1.00-1.09)

4.3.8 Refined prognostic index (PI) including PTV, Age, Cardiac event, AV+0.5 receiving intermediate dose and LA wall receiving high dose fitted in IDEAL-6 dataset and validated in Oxford cohort

$V_{LAWall-63-69}$ in IDEAL-6 and $V_{LAWall-65-71}$ in Oxford are equivalent and are described as $V_{LAWall-high-dose}$. Any ECG change in IDEAL-6 is substituted with cardiac-morbidity in Oxford and is described as 'Cardiac event'. $V_{AV+0.5-36-44}$ in Oxford cohort is equivalent to $V_{AV+0.5-35-43}$ in IDEAL-6 and is described as $V_{AV+0.5-Int-dose}$.

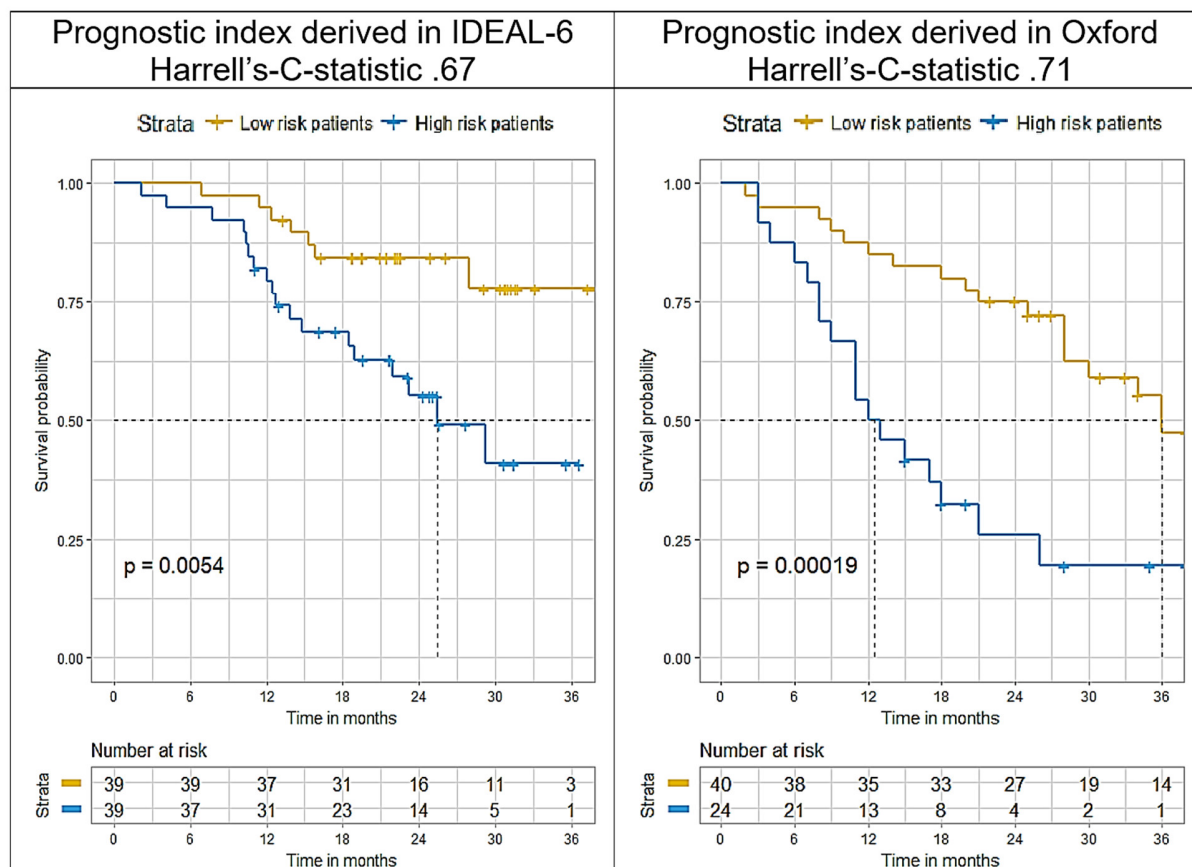
To refine the PI derived from IDEAL-6 defined in section 3.3.6, Age and $V_{AV+0.5-Int-dose}$ were added to the MV model containing Cardiac event, PTV and $V_{LAwall-high-dose}$. The regression coefficients for this MV model from IDEAL-6 after removing the outliers were used to calculate the linear-predictor values for DR for each patient in IDEAL-6 and Oxford cohorts using the equation in Box 1. Patients were classified as high-risk if their linear-predictor value was >1.87 (median linear-predictor for IDEAL-6). K-M curves in Figure 5 show the high-risk group based on the PI have significantly worse OS in IDEAL-6 ($p < .01$) and in the validation Oxford cohort ($p < .01$). The median OS for high and low-risk groups in IDEAL-6 were 25 and 39 months respectively and in Oxford cohort were 12 and 36 months respectively. Patients with high-risk score (PI > 1.87) had 3.4 times higher risk of death than low-risk patients in Oxford cohort (HR 3.4; 95% CI 1.7-6.7; $p < .01$) and 3.2 times higher risk of death than low-risk patients in IDEAL-6 (HR 3.2; 95% CI 1.4-7.8; $p < .01$). Addition of Age and $V_{AV+0.5-Int-dose}$ to the PI from chapter 3 improved its performance in Oxford cohort (c-statistic .63 vs .71).

Box 1. Linear predictor for DR equation

$$\text{Linear Predictor} = (.004 * \text{PTV}) + (-.008 * \text{Age}) + (1.092 * \text{Cardiac event}) + (.085 * [\text{AV}+0.5] \text{receiving intermediate dose}) + (.042 * \text{LA Wall receiving high dose})$$

Covariate	Unit of measure	Value in IDEAL-6	Value in Oxford
PTV	cm3	PTV	PTV
Age	year	Age at start of RT	Age at start of RT
Cardiac event	1 = present; 0 = absent; 0.5 = data missing	Any ECG change	Recorded cardiac event (RCE)
AV+0.5 receiving intermediate dose	% of AV+0.5 total volume	$V_{AV+0.5-35-43}$	$V_{AV+0.5-36-44}$
LA Wall receiving high dose	% of LA Wall total volume	$V_{LAwall-63-69}$	$V_{LAwall-65-71}$

Figure 5. Kaplan-Meier curves for patients dichotomised to high or low risk based on the linear predictor values from the prognostic index. *p-values of log rank test.*



4.3.9 Modelling of cardiac-related-death

Five patients (8%) had cardiac-related-death. 1 of these patients had cardiac-morbidity and cardiac-morbidity data was missing for 1 patient. 3 patients with cardiac-related-death had baseline cardiac morbidity, and for 2 patients this data was missing. To avoid multiple hypotheses testing in this cohort with small event rate, only variables significantly associated with DR were tested. Mean $V_{LAWall-65-71}$ was higher in patients with cardiac-related-death (4.3%) than in patients who had non-cardiac-related-death death (2.9%) and in patients who were alive at the end

of the study (1.1%). Mean $V_{AV+0.5-36-44}$ was also higher in patients with cardiac-related-death (7.4%) than in patients who had non-cardiac-related-death (6.0%) and in patients alive at the end of the study (1.8%). On MVA high $V_{AV+0.5-36-44}$ and $V_{LAwall-65-71}$ volumes were associated with higher DR but were borderline significant (Table 11). Cardiac-morbidity was not significantly associated with cardiac-related-death.

Table 11. Univariable (UV) and Multivariable (MV) regression models for recorded cardiac-related-death

Co-variate	UV model		MV model 1 (Harrell's-C-statistic: .92)		MV model 2 (Harrell's-C-statistic: .88)	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
Age	.77	.99 (.90-1.08)	.74	.98 (.89-1.09)	.59	.97 (.87-1.08)
Cardiac-morbidity	.35	3.19 (.28-36.65)	.47	2.62 (.19-35.34)	.45	2.56 (.23-28.75)
$V_{AV+0.5-36-44}$	.03	1.14 (1.01-1.28)	.05	1.41 (.99-1.99)		
$V_{LAwall-65-71}$	.06	1.13 (1.00-1.29)			.05	1.20 (1.00-1.43)

4.3.10 Modelling cardiac-morbidity within 12 months of RT

27% patients had documented baseline cardiac comorbidity prior to starting treatment. 9 patients (14%) developed cardiac-morbidity. 6 patients had fast AF or tachycardia, 3 had pericardial effusion, 1 had angina and 2 had heart failure/fluid overload. 8 of the 9 patients with cardiac-morbidity died but only 1 had cardiac-related-death (due to myocardial infarction). Cardiac-morbidity was significantly associated with DR ($p = 0.03$) as shown in Table 4. 89% patients with cardiac-morbidity died; whereas only 57% without cardiac-morbidity died. Despite more deaths in patients with cardiac-morbidity, most of these were recorded as non-

cardiac related deaths, likely due to overlap of symptoms of lung cancer and cardiac morbidities. Baseline cardiac comorbidity was significantly associated with cardiac-morbidity (Table 12). There was no significant association between $V_{\text{LAWall-65-71}}$ and $V_{\text{AV+0.5-36-44}}$ and cardiac-morbidity.

Table 12. Univariable (UV) and multivariable (MV) logistic regression models of cardiac-morbidity. *AUC = area under curve*

Co-variate	UV		MV model 1 (AUC .79)		MV model 2 (AUC .81)	
	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
Age	.97	1.00 (.93-1.07)	.37	.96 (.89-1.05)	.48	.97 (.89-1.05)
Baseline cardiac comorbidity	.02	6.00 (1.28-28.12)	.02	8.15 (1.42-46.84)	.02	8.57 (1.48-49.73)
$V_{\text{AV+0.5-36-44}}$	.81	1.02 (.89-1.16)	.99	1.00 (.90-1.11)		
$V_{\text{LAWall-65-71}}$	.71	.98 (.90-1.07)			.57	1.05 (.90-1.23)

4.3.11 Summary of key findings

$V_{\text{LAWall-63-69}}$ in IDEAL-6 and $V_{\text{LAWall-65-71}}$ in Oxford are equivalent and is described as $V_{\text{LAWall-high-dose}}$. Any ECG change in IDEAL-6 is substituted with cardiac-morbidity in the Oxford cohort and is described as 'cardiac event'. $V_{\text{AV+0.5-36-44}}$ in Oxford is equivalent to $V_{\text{AV+0.5-35-43}}$ in IDEAL-6 and is described as $V_{\text{AV+0.5-Int-dose}}$.

- Prognostic index derived from IDEAL-6 consisting of PTV, $V_{\text{LAWall-high-dose}}$ and cardiac event was validated in the Oxford cohort despite cardiac-morbidity substituting Any ECG change and other differences in patient and treatment characteristics between the 2 cohorts.
- MV model consisting of PTV, $V_{\text{LAWall-high-dose}}$ and cardiac event fitted independently in Oxford had similar HRs to IDEAL-6, corroborating the findings

in chapter 3 of high $V_{\text{LAWall-high-dose}}$, cardiac event and larger PTV being associated with worse OS.

- PTV was not significantly associated with OS in the Oxford cohort, unlike in IDEAL-6.
- Older age was associated with better OS possibly due to earlier presentation due to screening and lower cardiopulmonary reserve.
- Smoking history and baseline cardiac comorbidity were not significantly associated with OS and were not confounders for the dosimetric findings.
- Higher coronary ostia region receiving intermediate doses was significantly associated with worse OS.
- $V_{\text{LAWall-high-dose}}$ and $V_{\text{AV+0.5-Int-dose}}$ were correlated in Oxford likely due to beam arrangement, raising the possibility of $V_{\text{AV+0.5-Int-dose}}$ effect on OS being partly due to $V_{\text{LAWall-high-dose}}$ effect on OS. However, in IDEAL-6, these were found to be independent significant factors associated with OS.
- A refined prognostic index (PI) was developed in IDEAL-6 combining the factors identified in IDEAL-6 and Oxford (Age, PTV, cardiac event, $V_{\text{AV+0.5-Int-dose}}$ and $V_{\text{LAWall-high-dose}}$) which performed well at classifying patients into high and low-risk prognostic groups when tested independently in the Oxford cohort.
- Higher $V_{\text{AV+0.5-36-44}}$ and $V_{\text{LAWall-65-71}}$ were associated with higher cardiac-related-death rate, but these were not statistically significant likely due to the low event rate.
- Higher $V_{\text{AV+0.5-36-44}}$ and $V_{\text{LAWall-65-71}}$ were significantly associated with worse OS, but were only borderline significantly associated with cardiac-related-death and not associated with cardiac-morbidity. However, baseline cardiac comorbidity

was associated with higher cardiac-morbidity as expected, so the data is not unusual.

4.4 Discussion of results

4.4.1 Validation and corroboration of IDEAL-6 findings

Despite differences in patient and treatment characteristics between the datasets, the results of IDEAL-6 analysis [280] were corroborated in the Oxford cohort, having found high $V_{\text{LA-Wall-high-dose}}$ and cardiac events were associated with poorer OS with similar HRs to IDEAL-6. Though no direct significant association between cardiac events and dosimetry was seen, there was some association between cardiac death and $V_{\text{LA-Wall-high-dose}}$ and $V_{\text{AV+0.5-Int-dose}}$. A recent study of patients treated with SABR also found no correlation between grade ≥ 3 cardiac events and cardiac dose.[281] However, Allen et al found cardiac events were associated with heart doses of >63 Gy.[282] This high dose effect provides further support for heart toxicity contributing to the poorer OS seen in the high dose arm in RTOG-0617.[24]

In the Oxford cohort >65 Gy was delivered to LA wall in 23 patients, RA wall in 12 patients, LV wall in 5 patients and RV wall in 2 patients. This along with the finding that $V_{\text{LAWall-65-71}}$ but not $V_{\text{Heart-65-71}}$ was significantly associated with OS, strengthens the hypothesis that LA wall high dose radiation especially is associated with worse OS. The most frequently observed cardiac-morbidity was arrhythmia which supports the hypothesis that conduction abnormality due to LA inflammation or fibrosis secondary to LA wall high dose may be the mechanism of damage as discussed in chapter 3.

In the Oxford cohort, PTV was not significantly associated with DR on MVA, and the performance of the best MV model from IDEAL-6 containing PTV, $V_{LA-Wall-high-dose}$ and cardiac event was lower than seen in IDEAL-6 (c-statistic .76 v .68). The lower performance could be due to cardiac-morbidity not being as good a predictor for DR as Any ECG change. Also, PTVs were smaller here than in IDEAL-6 (mean of 401cm^3 Vs 319cm^3) possibly due to higher 4DCT use (88% Vs 44%), and this lower variance may impact its ability to be a good predictor. The poorer model performance may also be due to intermediate heart doses impacting OS when lower tumour doses are prescribed than in IDEAL-6. This is supported by the finding that performance was better in the Oxford cohort when the MV model contained $V_{AV+0.5-Int-dose}$ (C-statistic =.74).

As cardiac-morbidity data were collected retrospectively some data may be missing and this is a limitation of this data set. However, cardiac-morbidity rate in Oxford cohort of 14% is not hugely dissimilar to the 11% grade ≥ 3 cardiac events seen within 24-months in two other studies.[283][281] In another post hoc analysis, though, 23% patients had one or more symptomatic cardiac events with a median of 26 months to first event.[284] These rates are much higher than the combined fatal and non-fatal cardiac event rate of 4% seen in patients with baseline ECG changes in the general population not receiving treatment for lung cancer at 1 year follow up and 2% in patients without baseline ECG change.[262] Therefore the higher cardiac-morbidity rate in the Oxford cohort is likely due to the additional lung cancer treatment effect.

4.4.2 Other clinical factors affecting OS

Younger age was significantly associated with worse OS. Older patients had smaller tumours (correlation coefficient -0.12) perhaps due to earlier presentation secondary to lower cardiopulmonary functional reserve due to comorbidities or earlier detection through screening. This finding was also noted in another recent study where younger age was associated with poorer OS in lung cancer patients treated with RT [283], therefore though the finding was not in keeping with majority of the literature, it is not completely unusual in areas where there are perhaps better screening programmes or higher pick up rates in older patients. Smoking is associated with cardiovascular disease [267] and higher cardiac mortality after RT.[270] In the Oxford cohort, smoking was not significantly associated with OS and was not a confounder for the dosimetric findings. However, 89% of patients were smokers.

Cardiac comorbidity is included in Charlson comorbidity index, and a higher index score is associated with worse OS.[271] In a post hoc analysis of 127 patients in prospective trials, 14% had baseline coronary artery disease (CAD).[284] 27% of Oxford patients had baseline cardiac comorbidity and there was no significant direct association between baseline cardiac comorbidity and OS or cardiac-related-death and it was not a confounder for the dosimetric findings. This suggests RT related cardiac damage leading to death may be due to an alternate mechanism to worsening of existing problems such as ischaemic heart disease, the most common baseline cardiac comorbidity. This is further supported by the finding that the most frequent cardiac-morbidity was arrhythmia possibly due to high dose related LA Wall inflammation or fibrosis.[252][251][249]

Though baseline cardiac comorbidity wasn't directly related to OS, it was associated with cardiac-morbidity as seen previously [284], and cardiac-morbidity was significantly associated with OS. Dess et al had similar findings where pre-existing cardiac disease was significantly associated with grade ≥ 3 cardiac events (HR 2.96; 95% CI, 1.07 to 8.21) and grade ≥ 3 cardiac events were associated with higher risk of death (HR 1.76; 95% CI, 1.04 to 2.99).[283] But no direct associations between dosimetric factors and cardiac-morbidity were seen in the Oxford cohort likely due to small event rates. However another study found mean heart dose ≥ 20 Gy had a 21% 2-year cardiac event rate after adjustment for competing risk of death.[284] But they did not find an association between heart dosimetry and OS unlike the Oxford cohort, and this was thought to be due to small sample size and the competing risk of death from lung cancer.

In the general population, at 1 year follow up, the rate of fatal cardiovascular event is around 1% in patients with baseline ECG changes and 0.3% in patients without baseline ECG changes.[262] In the Oxford cohort the fatal cardiovascular event rate at 1 year (cardiac-related-death) was higher at 8%, suggesting this excess risk is likely due to lung cancer treatment. In comparison, in a recent study of SABR patients cardiac-related-death rate was 4.5% and they all had pre-existing cardiac disease.[281] In the Oxford cohort, $V_{LAWall-65-71}$, $V_{AV+0.5-36-44}$, baseline cardiac comorbidity and cardiac-morbidity were not statistically significantly associated with cardiac-related-death likely due to low event rates. 89% of patients with cardiac-morbidity died and only 57% without cardiac-morbidity died, yet only 1 patient with cardiac-morbidity was reported to have had cardiac-related-death. In contrast in the

SABR study, those who died from known cardiac causes all had preexisting cardiac disease.[281] This suggests there may be under reporting of cardiac-related-death in lung cancer patients in the Oxford cohort due to overlap of symptoms of cardiac morbidity, lung cancer progression and treatment related toxicity, and highlights the need for prospective monitoring of these patients.

4.4.3 Heart substructure dose response effect on OS

In lung cancer patients, high smoking rate and baseline cardiac comorbidity may act synergistically with radiation induced heart damage to expedite cardiac problems which are usually seen much later in breast cancer patients, who are less likely to have cardiac comorbidities as they tend to be younger, have lower smoking rate (45%)[269] and receive lower heart doses due to lower prescribed radiation doses.[31][285] Also patients with lymphoma receiving intermediate radiation doses compared to lung cancer patients have been seen to have damage to substructures such as the valve at >30 Gy, and their OS is affected earlier than in breast cancer patients.[286] In fact, in a recent large study of Hodgkin lymphoma survivors aged over 60 years, almost 30% of the total excess deaths observed were due to heart disease.[287] As the effect on OS is more acute in lung cancer than breast cancer patients despite similar mean heart doses, this difference in OS may be due to higher peak heart doses in lung cancer patients, due to higher prescribed doses.

In the Oxford cohort, patients received a standard radiation dose which is lower than the doses delivered in IDEAL-6 and the best AIC selected MV model with the best performance contained $V_{AV+0.5-Int-dose}$. A lower proportion of patients in Oxford

received $V_{\text{LA-Wall-high-dose}}$ compared to IDEAL-6 (36% Vs 62% respectively). Also, the mean and range of $V_{\text{LA-Wall-high-dose}}$ were lower in Oxford cohort than in IDEAL-6 (2.2% (Range 0-25.5) and 6.8% (Range 0-76%) respectively). This lower number of patients receiving lower $V_{\text{LA-Wall-high-dose}}$ may partly explain why $V_{\text{AV}+0.5\text{-Int-dose}}$ was more significant in this cohort. Also, $V_{\text{AV}+0.5\text{-Int-dose}}$ and $V_{\text{LA-Wall-high-dose}}$ were correlated in Oxford likely due to beam arrangement, so the effect of $V_{\text{AV}+0.5\text{-Int-dose}}$ on OS may partly be a reflection of the $V_{\text{LA-Wall-high-dose}}$ effect. However, in IDEAL-6, $V_{\text{AV}+0.5\text{-Int-dose}}$ and $V_{\text{LA-Wall-high-dose}}$ were not correlated, and both remained significant in the MV model suggesting these are independent factors impacting OS.

4.4.4 Mechanism of substructure damage due to high and intermediate dose

High dose radiation induced LA wall damage may lead to LA wall inflammation acutely, or fibrosis in the longer term and arrhythmias impacting OS as described in chapter 3. Intermediate radiation dose induced coronary ostia damage is rarely described, but the mechanism is also thought to be related to fibrosis but could also be related to acute inflammation. A recent study of over 1000 patients showed that base of heart containing coronary ostia receiving >8.5 Gy was associated with increased risk of death, and this was validated in another smaller cohort of SABR patients.[288] In this study, MV modelling had many variables with the associated risk of overfitting and there was no correction for multiple hypotheses testing. There was also no indication of mechanism of damage impacting OS due to this relatively low dose.[288] In a report by Grollier et al [289] left coronary ostial stenosis was seen 5 years after mediastinal irradiation for breast cancer. A pressure drop and marked narrowing was observed in the left coronary ostia with severe intimal thickening

consisting of fibrous tissue without any lesion of the media. In another study pulmonary artery $V_{45} > 70\%$ was associated with poorer OS in patients with LA-NSCLC.[271][290] This suggests that intermediate dose rather than low dose to large vessels can cause an early effect on OS, and also supports our finding of intermediate dose to coronary ostial region impacting OS. So high volume of different substructures receiving different doses may impact OS, highlighting the complexity of the heart. This suggests there may not be a threshold 'safe' heart dose, but there may be a continuous heart dose-volume-time effect on OS. This is explored further in chapter 5. At this point, measures to reduce both $V_{LA-Wall-high-dose}$ and $V_{AV+0.5-Int-dose}$ should be considered without compromising PTV coverage as the exact mechanisms of damage remain unclear. Reducing $V_{LA-Wall-high-dose}$ may consequently lower $V_{AV+0.5-Int-dose}$ due to the delivery technique and needs further exploration in a planning study. Uncertainties of the impact of cardiac irradiation to substructures should also encourage prospective functional imaging studies to further our understanding.

4.4.5 Limitations

This analysis was subject to the limitations of the uncertainties over retrospectively identifying cardiac-morbidity from medical records, attributing cardiac-related-death from certificates and from a lack of routine follow-up cardiac testing. Therefore, there may be under recording of cardiac-morbidity and cardiac-related-death. But this is a problem that is faced by many in this situation as often when patients with lung cancer die in the community the cause of death is attributed to their lung cancer and documented as such on death certificates. Also, due to the overlap of symptoms of

lung cancer, treatment related toxicity and cardiac-morbidity, inevitably there will be difficulty in teasing out the actual cause of symptoms retrospectively, resulting in under reporting of cardiac-morbidity. On the other hand, arrhythmias recorded as cardiac-morbidity may be more subject to confounding by concurrent illnesses and therefore may result in over recording of cardiac-morbidity. Here, only hospital records were examined to collate cardiac toxicity data. In future work to reduce cardiac toxicity data loss, examining GP records may also be helpful. The numbers of cardiac-related-death and cardiac-morbidity were low here, limiting the examination of multiple covariates. This cohort had different patient and treatment characteristics to IDEAL-6. Despite these differences the heart substructure dosimetric findings in IDEAL-6 were reproducible in this cohort. The refined PI derived in this work needs validation in a further independent cohort. In patients treated for lung cancer there is overlap between cardiac symptoms, treatment toxicity and disease recurrence i.e. chest pain and shortness of breath. Therefore, it is difficult to differentiate cardiac morbidity from disease progression and treatment toxicity which could result in mis-recording of cardiac death as cancer related death.

4.5 Conclusion

Findings of previous work of high LA wall volume receiving high dose (EQD2 64-73Gy) and cardiac events post RT being associated with poorer OS were corroborated in this independent data set despite differences in patient and treatment characteristics. The prognostic index derived in the last chapter from the isotoxically dose escalated cohort consisting of PTV, LA wall volume receiving EQD2 64-73Gy and cardiac event post RT was refined by adding volume of coronary ostia

region receiving intermediate dose (EQD2 29-38 Gy) and age. Closer monitoring for cardiac problems after stratifying patients into low and high-risk groups using prognostic indices as described here may allow earlier intervention for cardiac problems to improve OS. Closer cardiac monitoring and earlier specialist input for patients deemed to have higher risk instead of all patients is also likely to be more cost effective. Radiotherapy planning studies assessing the feasibility of lowering LA wall volume receiving EQD2 64-73Gy and coronary ostia region receiving EQD2 29-38 Gy without compromising PTV would be useful, as well as prospective functional studies to study the mechanism of damage and differentiate cardiac related and disease related deaths.

5. Refinement of the survival model including heart dosimetry in a large cohort of patients: IDEAL-5, IDEAL-6 AND OXFORD

5.1 Introduction

Significant associations between all-cause death-rate (DR) and greater LA Wall volumes receiving EQD2 64-73 Gy and whole heart volumes receiving EQD2 29-38 Gy (α/β 3) were found in the post-hoc analysis of the prospective IDEAL-6 data in chapter 3 and retrospective Oxford data in chapter 4. Here, the prognostic index (PI) derived from the refined MV model for DR containing high and intermediate heart doses in chapter 4 is tested in an independent isotoxically dose escalated cohort, IDEAL-5.

Small sample size is a limitation of studies exploring radiation induced cardiac disease in lung cancer. Here, following independent testing in the IDEAL-5 cohort, patients treated in IDEAL-5, IDEAL-6 and Oxford cohorts were combined to address this limitation of small sample size, and this larger merged cohort of patients with LA-NSCLC treated with radical RT was used to assess clinical and dosimetric factors impacting DR. The combined cohort had 2 isotoxic dose escalation studies and 1 standard radiation dose study. So principal component analysis (PCA) of this combined cohort provides more covariate patterns in the PCs against which a dose-volume-time effect can be assessed.

5.2 Summary of methods

5.2.1 Data collection

Treatment details for the 36 patients in IDEAL-5, 78 in IDEAL-6 and 64 in Oxford cohorts are outlined in chapter 2. Data were analysed for the combined cohort of 178 patients with LA-NSCLC. Correlations between variables which were not normally distributed according to the Shapiro Wilk test were tested using Spearman test. Kruskal-Wallis H test was used to determine statistically significant differences between the three cohorts.

5.2.2 Processing of radiotherapy dosimetric data

Processing of RT dosimetric data is described in detail in chapter 2 and summarised in chapters 3 and 4. To account for differences in fractionation schemes between the IDEAL and Oxford schedules, biologic effective corrections to equivalent dose in 2 Gy fractions (EQD2) were performed using the linear quadratic model assuming an α/β ratio of 3 Gy for heart. Dosimetric parameters were extracted from the DVHs after conversion from physical dose to EQD2. EQD2 DVHs were extracted for all 178 patients and PCA was carried out for heart on the combined DVH data as described in section 2.4.2 and 10 highest-ranked varimax rotated PCs obtained describing at least 95% variance. Tumour dose was converted to EQD2 for consistency using the linear quadratic model assuming an α/β ratio of 10 Gy and a repopulation rate of .66 EQD2 per day. Time correction tumour EQD2 equation [1]:

$$\text{EQD2Tumour} = \{D * ((d+10)/12)\} - \{.66 * (\text{Total schedule time in days} - 33 \text{ days})\} \quad [1]$$

*Shortest total schedule time in days: 33 days for 30 fractions in 5 weeks in IDEAL-5;
40 days for 30 fractions in 6 weeks in IDEAL-6; 45 days for 33 fractions in 6.5 weeks in Oxford.
D=total dose; d=dose per fraction*

5.2.3 Validation of the refined prognostic index (PI) derived from chapter 4 (section 4.3.8 Box 1): PTV, Age, Any ECG change, AV+0.5 receiving intermediate dose and LA wall receiving high dose

Performance of the PI developed in chapter 4 (section 4.3.8) was assessed in the independent cohort of IDEAL-5. Regression coefficients for the covariates in MV model containing PTV, Age, Any ECG change, AV+0.5 receiving intermediate dose and LA wall receiving high dose were used to calculate the linear-predictor values for IDEAL-5 patients using the equation below. As Cardiac event data was missing, a score of 0.5 was given to all patients for this variable. As AV+0.5 region corresponding to the coronary ostia was not delineated in this cohort, AV+0.5 receiving intermediate dose was substituted with whole heart receiving intermediate dose in the equation. Patients with linear-predictor values $<$ or ≥ 1.87 (cut point from chapter 4) were classified as low and high-risk groups respectively. KM curves for these groups were generated and difference in survival between the groups tested using log rank test with a p-value of $<.05$ considered significant.

$$\text{Linear Predictor} = (.004 * \text{PTV}) + (-.008 * \text{Age}) + (1.092 * \text{Cardiac event}) + \\ + (.085 * [\text{AV}+0.5] \text{receiving intermediate dose}) + (.042 * \text{LA Wall receiving high dose})$$

PTV was measured in cm^3 , age in years, LA wall receiving high dose was percent of LA wall volume receiving 63-69 Gy ($V_{\text{LAwall}63-69}$) and AV+0.5 receiving intermediate dose was percent of heart volume receiving 35-43 Gy ($V_{\text{Heart}35-43}$).

5.2.4 Corroboration of model for all cause death rate (DR) from Chapter 4

LA-Wall receiving 63-69 Gy in 30 fractions in IDEAL-6 and IDEAL-5 or 64-71 Gy in 33 fractions in Oxford equates to 64.3-73 Gy EQD2 for α/β of 3Gy ($V_{\text{LAWall64-73EQD2}}$). Heart receiving 36-44 Gy in 33 fractions in Oxford equates to 29-38 Gy EQD2 ($V_{\text{Heart29-38EQD2}}$). $V_{\text{LAWall64-73EQD2}}$, and $V_{\text{Heart29-38EQD2}}$ and mean EQD2 heart doses were extracted for all patients. To corroborate the UVA HRs from chapter 4, UV Cox regression models for DR were refitted in this combined cohort for $V_{\text{Heart29-38EQD2}}$, $V_{\text{LAWall64-73EQD2}}$, PTV, and age. As cardiac event data was missing in IDEAL-5, it was not possible to corroborate the MV model from chapter 3 and 4 here.

5.2.5 Refinement of MV model for DR - effect of clinical and dosimetric factors

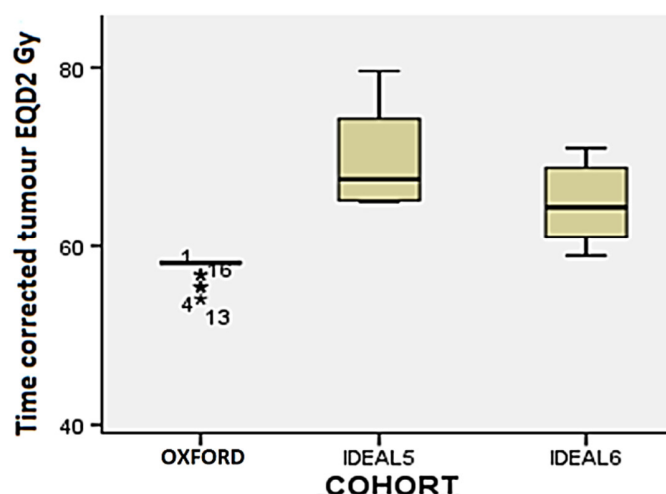
Exploratory UVA and MVA were carried out to assess the impact of dosimetric and clinical factors on DR measured from the start of RT using cox regression. Factors analysed for association with DR were: any clinically significant factors associated with DR, factors statistically significantly different between the 3 cohorts, and scores of the 10 highest-ranked heart PCs. Clinically significant factors and heart PCs with p-values $\leq .2$ on UVA were included in MV model, and stepwise bi-directional variable elimination performed to find the best MV model with the lowest AIC score. Model diagnostics, performance assessment, multiple hypotheses correction and multicollinearity check were performed as described in section 2.6.

5.3 Results

5.3.1 Total population

93% patients were PS 0 or 1 (54% PS1 and 39% PS0). Median age was 67 (range 43-89). 74% received concurrent chemotherapy, 25% did not and this information was missing for 2 patients. Median OS was 34 months (95% CI: 28-40). Median PTV was 359cm³ (range 82-1262). Tumour mean time corrected EQD2 with an α/β ratio of 10 was 63.3 Gy (Range 54-79.6) and the highest was in IDEAL-5 (Figure 1). 57% had squamous cell carcinoma (57%). 63% had N2 disease and 9 patients had N3 disease.

Figure 1. Box and whisker plots showing the distribution of time corrected tumour dose in equivalent 2 Gy per fraction (EQD2) with an alpha/beta ratio of 10 in the 3 cohorts (OXFORD, IDEAL-5 and IDEAL-6). The mean tumour EQD2 for each cohort is the horizontal line inside the box. The Asterix represent outliers and the number associated with each Asterix represent the ID number of the patient.



Patient and tumour characteristics in the cohorts are compared in Table 1. Age, nodal status, PS, GTV, PTV, IMRT, prescribed doses and concurrent chemotherapy use were significantly different between the cohorts. Oxford patients were older and a higher proportion had lower nodal stage. There were less PS0 patients in the Oxford cohort. The smaller PTV size in Oxford cohort is likely due to a combination of smaller GTVs and a higher rate of 4DCT use. All patients in IDEAL-5 and 6 received concurrent chemotherapy, whereas only 26.6% received concurrent chemotherapy in the Oxford cohort. Lower radiation doses were delivered to the tumour in Oxford cohort compared to IDEAL-5 and IDEAL-6. Median OS was not significantly different (p .18).

Table 1. Characteristics of IDEAL-5, IDEAL-6 and OXFORD.

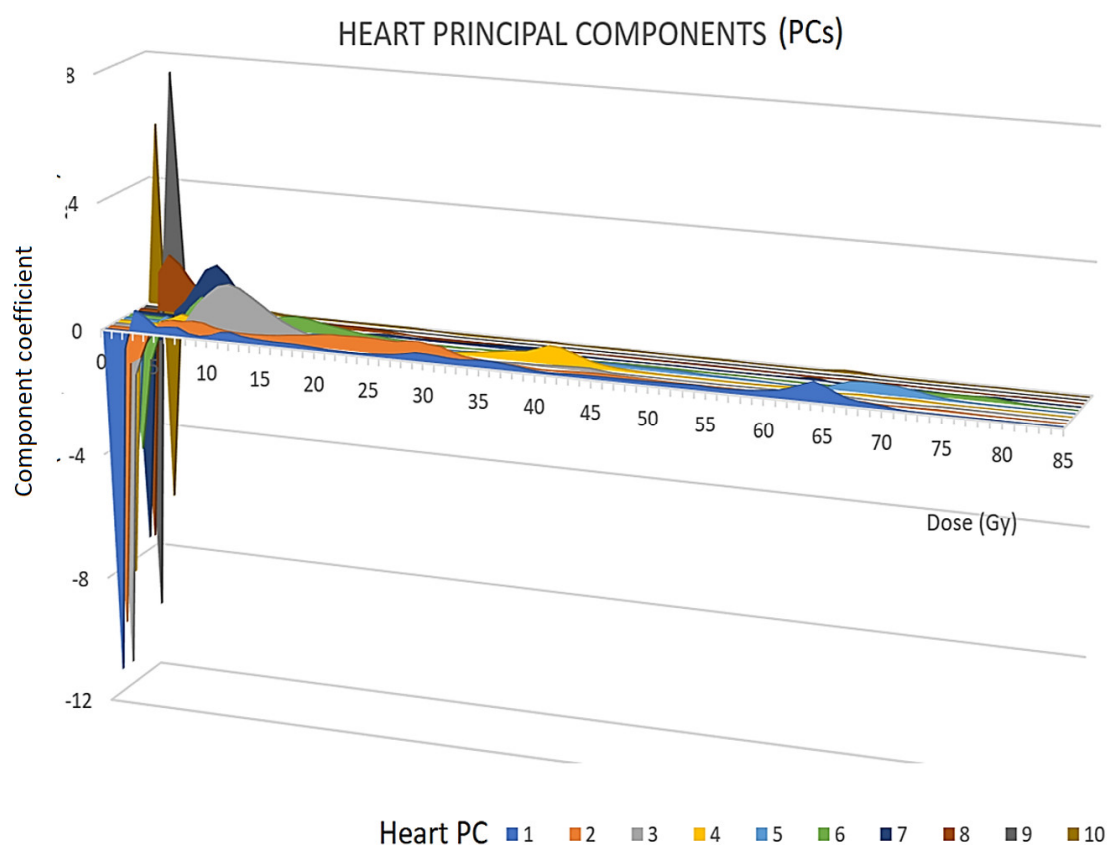
Kruskall Wallis (KW) and log rank test to compare the 3 cohorts

Characteristic	IDEAL-5 (n=36)	IDEAL-6 (n=78)	OXFORD (n=64)	KW/log rank
Data type	Prospective	Prospective	Retrospective	
Age (years; median (range))	67 (46-76)	66 (43-84)	71 (44-89)	<.01
WHO® performance status No (%)				.01
0	20 (55.6)	32 (41.0)	17 (26.6)	
1	16 (44.4)	46 (59.0)	34 (53.1)	
2	-	-	5 (7.8)	
3	-	-	1 (1.6)	
Missing	-	-	7 (10.9)	
Gender No (%)				.21
Female	13 (36.1)	20 (25.6)	25 (39.1)	
Male	23 (63.9)	58 (74.4)	39 (60.9)	
Nodal status No (%)				<.01
N 2 or 3	29 (80.6)	65 (83.3)	32 (50.0)	
N 0 or 1	7 (19.4)	13 (16.7)	29 (45.3)	
Missing	-	-	3 (4.7)	
Histology No (%)				.56
Squamous	23 (63.9)	42 (53.8)	36 (56.3)	
Non-squamous	13 (36.1)	36 (46.2)	24 (37.5)	
Missing	-	-	4 (6.3)	
Gross tumour volume (cm³; median (range))	82.6 (21-217)	103.9 (14.3-598.3)	53.2 (5.2-396.5)	<.01
Planning target volume (cm³; median (range))	353 (181-720)	400.6 (138.7-1262.1)	319 (82 – 1120)	.01
4-Dimensional CT for planning No (%)	Unknown	34 (44)	56 (88)	-
Intensity modulated radiotherapy (IMRT) No. (%)	10 (28)	3 (4)	16 (25)	<.01
Prescribed dose (Gy) (No.)	63-65 in 30# (20) 65.1-67 in 30# (6) 67.1-69 in 30# (2) 69.1-71 in 30# (8) -	63-65 in 30# (22) 65.1-67 in 30# (15) 67.1-69 in 30# (10) 69.1-71 in 30# (11) 71.1-73 in 30# (20)	66Gy in 33# (56) 64Gy in 32# (3) 62Gy in 31# (2) 60Gy in 30# (2) 58Gy in 29# (1)	
Prescribed tumour EQD2 $\alpha/\beta=10$ Gy		No.		<.01
≤ 66 Gy	20	22	64	
>66 Gy	16	56	0	
Mean Time adjusted tumour EQD2 (Gy)	69.9	64.7	57.8	<.01
Concurrent Chemotherapy		No.		<.01
Yes	36	78	17	
No (sequential; no chemotherapy)	0	0	45 (16;29)	
Missing	0	0	2	
Mean EQD2* Gy		median (range)		
Heart	8.3 (.72-22.3)	8.0 (0.4-29.2)	7.6 (0.5-32.2)	.90
Left atrium wall	15.8 (.85-43.8)	17.1 (0.5-64.2)	12.5 (0.5-56.2)	.23
Median OS (months)	Not reached	39	28	.18 (Log rank)

5.3.2 Radiotherapy dosimetric data

10 heart differential DVH (dDVH) varimax-rotated PCs describing >95% of total variance are plotted in Figure 2. Median mean heart EQD2 was 8.2 Gy (range .4–32.2 Gy) and median mean LAwall EQD2 was 16.1 Gy (range .5–64.2 Gy) and these quantities were not statistically significantly different between the 3 cohorts (Table 1).

Figure 2. 10 varimax-rotated principal components (PCs) describing >95% of heart dDVH variance



5.3.3 Validation of the prognostic index (PI) developed in section 4.3.8 consisting of Age, PTV, Heart receiving intermediate and high dose in IDEAL-5 patients

According to the PI from chapter 4, 16 IDEAL-5 patients were classified as low-risk and 20 as high-risk. Two patients (13%) in the low-risk and 9 (45%) in the high-risk group died. KM curves in Figure 3 show a significant difference in OS between the two risk groups ($p = .03$). Median OS for high risk group was 17 months and had not been reached for low risk group (HR 4.6; $p = .05$). Performance based on linear-predictor was good (c-statistic .69) confirming the PI derived from higher PTV, Age, $V_{\text{Heart35-43}}$ and $V_{\text{LAWall63-69}}$ in chapter 4 performs well in this independent cohort despite missing cardiac event data and substituting $V_{\text{Heart35-43}}$ for $V_{\text{AV+0.5-35-43}}$.

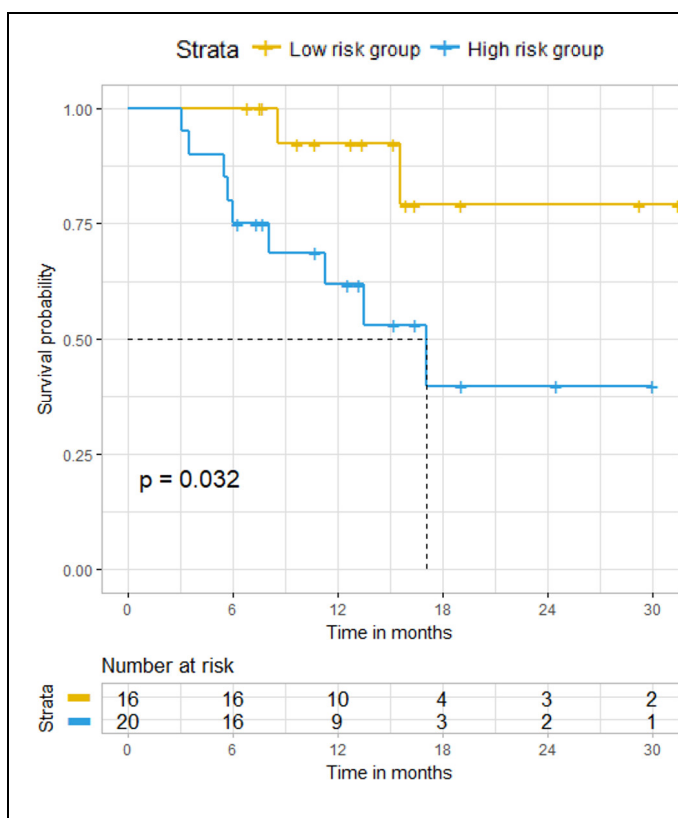


Figure 3. Kaplan Meier curves for patients dichotomised to high or low risk based on the linear predictor from model from chapter 4 section 4.3.8 Box 1. p-value of log rank test.

Risk group	Total no. of patients	No. of deaths
Low	16	2
High	20	9

5.3.4 Corroboration of HRs for variables in the UV model in chapter 4 for all cause death rate (DR) in the merged cohort of 178 patients

Results of UVA are shown in Table 2. On UVA, larger PTV, $V_{\text{LAWall64-73EQD2}}$ and $V_{\text{Heart29-38EQD2}}$ were significantly associated with higher DR and these remained significant after correction for multiple hypotheses testing with an false-discovery-rate of 20%. The p-values indicate greater significance for $V_{\text{LAWall64-73EQD2}}$ in this larger cohort (p .005) than in the IDEAL-6 (p .012) or Oxford (p .006) alone but HRs were similar (1.03, 1.04, 1.08 respectively). Significance level of $V_{\text{Heart29-38EQD2}}$ was similar in the combined cohort and Oxford cohort (p .003), but was lower in IDEAL-6 (p .13) and HRs were similar (1.10, 1.15, 1.09 respectively).

Table 2. Univariable cox regression models for all cause death rate in IDEAL-6, Oxford and combined cohorts (IDEAL-5, IDEAL-6 and Oxford)

Variables	Univariable model IDEAL-6		Univariable model OXFORD		Univariable model COMBINED COHORT	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
Age	.60	1.01 (.97-1.06)	.03	.97 (.94-1.00)	.43	.99 (1.00-1.02)
PTV	.04	1.00 (1.00-1.00)	.17	1.00 (1.00-1.00)	.02	1.00 ((1.00-1.00)
$V_{\text{Heart29-38EQD2}}$	.13	1.09 (.98-1.21)	<.01	1.15 (1.05-1.27)	<.01	1.10 (1.03-1.17)
$V_{\text{LAWall64-73EQD2}}$	.01	1.04 (1.01-1.06)	<.01	1.08 (1.02-1.13)	<.01	1.03 (1.01-1.05)

5.3.5 Exploratory analysis: effect of clinical and dosimetric factors on DR

UVA and MVA are shown in Table 3. On UVA, PTV, Heart-PC4 and Heart-PC5 were significantly associated with DR and these associations remained positive discoveries after correction for multiple testing. The best AIC selected MV model 1 retained PTV, cohort, Heart-PC4, PC5 and PC7 (Table 3).

Table 3. Univariable and multivariable (MV) Cox model for all cause death rate.

c=Harrell's-c-statistic

	Univariable model		AIC selected best MV model 1 c=.67	
	p-value	HR (95% CI)	p-value	HR (95% CI)
PTV	.02	1.001 (1.000-1.002)	.07	1.001 (1.000-1.002)
Time adjusted Tumour EQD2	.15	.97 (.92-1.01)		
Age	.43	.99 (.97-1.02)		
COHORT (IDEAL-5 V Oxford)	.96	.98 (.49-1.96)	.95	.97 (.48-1.95)
COHORT (IDEAL-6 V Oxford)	.08	.63 (.38-1.05)	.05	.59 (.35-.99)
N0or1 Vs 2or3	.88	1.04 (.64-1.69)		
Concurrent chemo	.80	.94 (.57-1.54)		
Heart-PC4	<.01	1.25 (1.06-1.47)	.01	1.22 (1.04-1.44)
Heart-PC5	<.01	1.26 (1.06-1.49)	.04	1.20 (1.01-1.44)
Heart-PC7	.07	1.23 (.98-1.55)	.03	1.27 (1.03-1.58)
Heart-PC10	.19	.86 (.68-1.08)		
V _{Heart3-12}	.03	1.02 (1.00-1.04)		
V _{Heart33-44}	<.01	1.09 (1.04-1.14)		
V _{LAWall64-73}	<.01	1.03 (1.01-1.05)		

5.3.6 Replacing Heart PCs with heart dosimetric parameters in the MV model

Heart-PC4, Heart-PC5 and Heart-PC7 have peaks representing high heart volumes receiving 33-44 Gy ($V_{\text{Heart33-44}}$), 64-73 Gy ($V_{\text{Heart64-73}}$) and 3-12 Gy ($V_{\text{Heart3-12}}$) respectively (Figure 4). $V_{\text{Heart64-73}}$ in previous chapters localises to LAWall. Therefore, Heart PCs were replaced by these dosimetric parameters in the MV model. On UVA, high $V_{\text{Heart3-12}}$, $V_{\text{Heart33-44}}$ and $V_{\text{LAWall64-73}}$ were significantly associated with higher DR and these remained significant after B-H correction for multiple hypotheses testing (Table 3). $V_{\text{LAWall64-73}}$, $V_{\text{Heart33-44}}$ and $V_{\text{Heart3-12}}$ were correlated (Table 4), so they were entered separately into the MV models 2-4 including PTV and cohort and all 3

dosimetric parameters remained statistically significantly associated with DR (Table 5). MV Model performance was good with c-statistic of .63-.66 for MV models 2-4.

Figure 4. Top: Heart-PC4 has a peak at 33-44 Gy representing high heart volume receiving 33-44 Gy ($V_{\text{Heart}33-44}$), Middle: Heart-PC5 has a peak at 64-73Gy representing high heart volume receiving 64-73 Gy ($V_{\text{Heart}64-73}$), Bottom: Heart-PC7 has a peak at 3-12 Gy representing high heart volume receiving 3-12 Gy ($V_{\text{Heart}3-12}$)

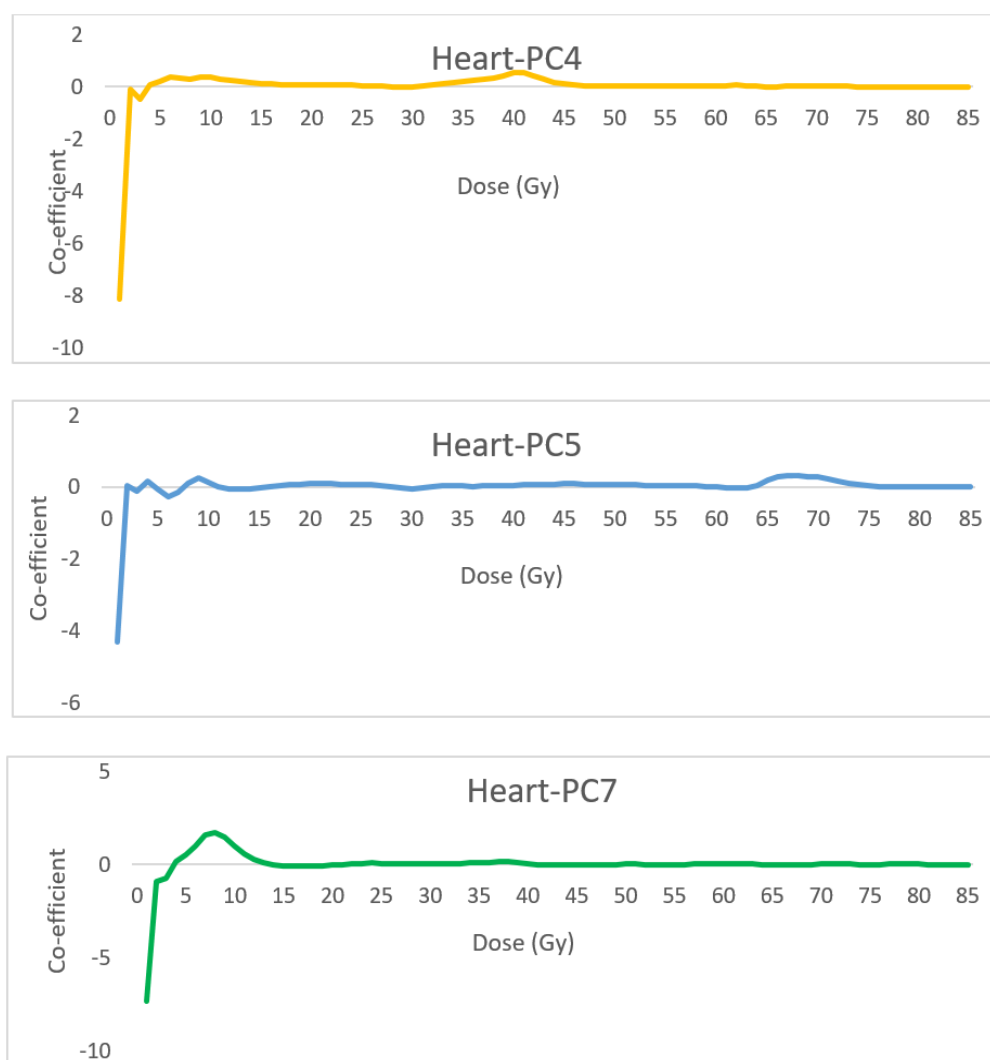


Table 4. Correlation of co-variates (r = correlation coefficient; p = p-value)

Covariate r (p)	V _{Heart3-12}	V _{Heart33-44}	V _{LAWall64-73}
Time adjusted Tumour EQD2	.1 (.33)	-.1 (.26)	.1 (.37)
V _{Heart3-12}		.6 (<.01)	.4 (<.01)
V _{Heart33-44}			.7 (<.01)

Spearman correlation co-efficient >.4 (Green)

Table 5. Multivariable (MV) Cox regression models of all-cause-death-rate (DR). In MV model 2 the uncorrelated V_{Heart3-12} replaces Heart PCs, in MV model 3 V_{Heart33-44} replaces Heart PCs, and in MV model 4 V_{LAWall64-73} replaces Heart PCs

Covariate	MV model 2 V _{Heart3-12} replacing Heart PCs (Harrell C .63)		MV model 3 V _{Heart33-44} replacing Heart PCs (Harrell C .66)		MV model 4 V _{LAWall64-73} replacing Heart PCs (Harrell C .67)	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
PTV	.01	1.00 (1.00-1.00)	.07	1.00 (1.00-1.00)	.02	1.00 (1.00-1.00)
COHORT (IDEAL-5)	.98	1.01 (.50-2.02)	.90	.96 (.48-1.91)	.97	.99 (.50-1.97)
COHORT (IDEAL-6)	.03	.57 (.34-.95)	.04	.61 (.36-1.02)	<.01	.49 (.28-.84)
V _{Heart3-12}	.03	1.02 (1.00-1.04)				
V _{Heart33-44}			<.01	1.07 (1.02-1.12)		
V _{LAWall64-73}					<.01	1.03 (1.01-1.05)
AIC		686.29		683.96		683.06

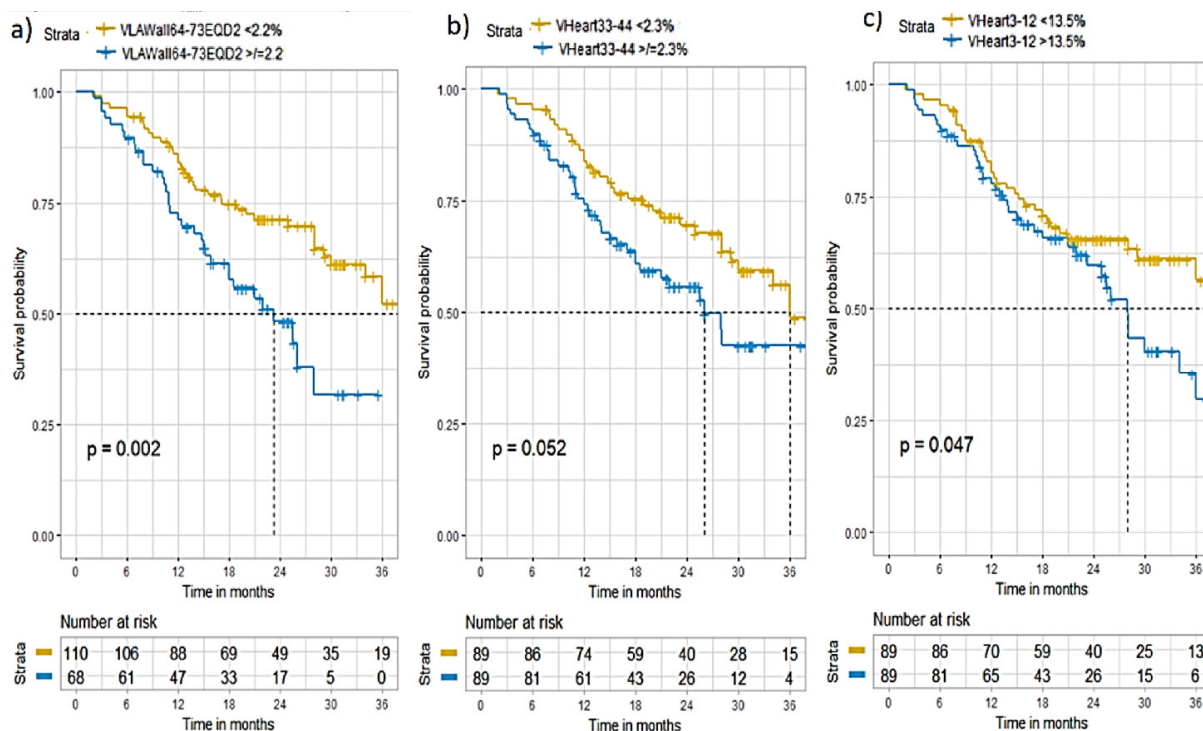
To exclude PTV as a confounder due to overlap of PTV and LA wall and heart, GTV was substituted in the MV model for PTV and the heart dosimetric parameters retained significance, with similar HRs indicating the GTV effect is independent of heart dosimetry (Appendix 14).

5.3.7 Scale of effect of V_{LAWall64-73}, V_{Heart33-44} and V_{Heart3-12}

The cut point identified for V_{LAWall64-73} from chapter 3 of 2.2% was used to dichotomise the 178 patients in the combined cohort. 68 patients had >2.2% V_{LAWall64-73}. There was a significant difference in DR in the 2 groups (Figure 5a).

Median $V_{\text{Heart33-44}}$ of 2.3% was used to dichotomise patients into 2 groups and there was a significant difference in DR (Figure 5b). Median $V_{\text{Heart3-12}}$ of 13.5% was used to dichotomise patients into 2 groups and there was a significant difference in DR (Figure 5c). Though it is difficult to draw conclusions after 2 years due to low number of events, the difference in survival is evident earlier in patients with larger LA wall volumes receiving high dose and larger heart volumes receiving intermediate dose than in patients with larger heart volumes receiving low doses. The survival curves split 1-2 years earlier for high and intermediate doses than for low heart doses (Figure 5). Even small $V_{\text{Heart33-44}}$ and $V_{\text{LAWall64-73EQD2}}$ impact OS, whereas larger $V_{\text{Heart3-12}}$ impact OS suggesting a dose-volume-time effect of heart irradiation on OS.

Figure 5. Kaplan Meier curves for patients dichotomised by (a) $V_{\text{LAWall64-73EQD2}} \geq 2.2\%$ (blue) or $< 2.2\%$ (yellow); (b) $V_{\text{Heart33-44}} \geq 2.3\%$ (blue) or $< 2.3\%$ (yellow); (c) $V_{\text{Heart3-12}} \geq 13.5\%$ (blue) or $< 13.5\%$ (yellow). *p-values of log rank test.*



5.3.8 Summary of results

- The prognostic index from Chapter 4 including heart volume receiving intermediate dose ($V_{\text{Heart}29-38\text{EQD}2}$), LA wall volume receiving high dose ($V_{\text{LAWall}64-73\text{EQD}2}$), PTV and age successfully dichotomised patients in the independent cohort of IDEAL-5 into high and low risk groups despite substituting $V_{\text{AV}+0.5-29-38\text{EQD}2}$ with $V_{\text{Heart}29-38\text{EQD}2}$.
- $V_{\text{Heart}3-12\text{EQD}2}$, $V_{\text{Heart}33-44\text{EQD}2}$ and $V_{\text{LAWall}64-73\text{EQD}2}$ were statistically significantly associated with DR in the overall IDEAL-6, IDEAL-5 and Oxford combined cohort of 178 patients. $V_{\text{LAWall}64-73\text{EQD}2}$ had a greater significance in this larger cohort than in the individual cohorts.
- As high $V_{\text{Heart}3-12\text{EQD}2}$, $V_{\text{Heart}33-44\text{EQD}2}$ and $V_{\text{LAWall}64-73\text{EQD}2}$ were correlated, it was difficult to determine which dosimetric factor impacts DR.
- Larger GTV, a surrogate for tumour burden, negatively impacts OS as GTV size can impact local control and therefore OS. Larger GTVs resulting in larger PTVs, due to the margin, could result in irradiation of larger heart volumes to high dose as part of the PTV, as well as intermediate and low dose which in turn could negatively impact OS. But the impact of heart dosimetry on OS remained significant despite the presence of GTV in the model, suggesting the local control effect of GTV on OS is independent of the heart dosimetry effect on OS.
- A heart dose-volume-time effect on survival may exist with large heart volume receiving low dose impacting OS later and small heart volume receiving high and intermediate dose impacting OS earlier

5.4 Discussion of results

Small sample size is a limitation of most studies exploring radiation induced cardiac problems in patients with lung cancer. This combined data set provided a larger population than the cohorts in chapter 3 and 4 to explore cardiac irradiation impact on DR. Despite differences in patient, tumour and treatment characteristics between the cohorts, in this combined cohort, high LA wall volume receiving high dose (64-73 Gy), and high heart volume receiving intermediate (29-44 Gy) and low doses (3-12 Gy) were associated with DR when controlled for cohort in the MV model. Low dose radiation impact on DR in the individual studies were not detected using PCA, likely due to small sample sizes.

There is evidence to support different heart dosimetric parameters impacting DR, but no consistent dosimetric findings have been found in lung cancer patients. Low (V5) and intermediate (V30) doses to heart were related to OS in RTOG-0617.[24] Low heart doses (V2 >59.7%) was also significantly associated with OS in a retrospective study of 469 patients treated with 66 Gy in 24 fractions with concurrent chemotherapy.[291] In another large cohort, 8.5 Gy to heart base was seen to impact OS.[288] Pericardial events have been associated with heart, right atria (RA), left atria (LA) V30; ischaemic events associated with heart and left ventricle V30; and arrhythmia correlated to RA, LA and heart V30.[292] In a study of 189 patients who had lung stereotactic RT, bilateral ventricle maximum dose was associated with OS.[293] In another study of early lung cancer patients treated with stereotactic RT LA maximum dose was associated with OS.[294]

The impact of low dose heart irradiation on OS appears to occur later than seen with high and intermediate doses suggesting a dose-volume-time effect for radiation induced cardiac damage impacting OS. In support of this hypothesis, patients with breast cancer who receive lower heart doses have been found to have cardiac damage, mainly ischaemic, impacting OS decades after RT.[31][285] Whereas patients with lymphoma receiving intermediate radiation doses (around 30 Gy) have also been seen to have cardiac damage impacting structures such as the valve, earlier than seen in breast cancer patients, which can impact OS.[286] In a recent large study of Hodgkin lymphoma survivors aged over 60, almost 30% of the total excess deaths observed were due to heart disease.[287] Intermediate radiation dose induced major vessel and valvular tissue damage may be related to fibrosis causing stenosis.[289][271][290][286] Higher radiation doses may cause atrial wall inflammation acutely or fibrosis later resulting in arrhythmia as described in chapter 3. Uncertainties regarding the impact of cardiac substructure irradiation should encourage prospective cardiac functional studies to further our understanding.

Larger tumour volume was associated with higher DR which is similar to others' findings.[295][296][297][291][288] In a recent analysis of 868 patients, tumour size of less than 3cm was associated with longer OS.[295] In Oxford cohort, despite the mean GTV size being about half of IDEAL-6, smaller PTVs, more N0 or N1 than N2 or N3 disease, less patients with stage 3 disease (92% versus 73%) and lower mean heart and LA wall doses than IDEAL-6, OS was lower than in IDEAL-6. The lower use of concurrent chemotherapy in Oxford compared to IDEAL-6 and Oxford cohort consisting of less fit patients than in IDEAL-6 (100% PS 0 or 1 in IDEAL-6 versus

80% PS 0 or 1 in Oxford) may contribute to the poorer OS seen in Oxford than IDEAL-6. In Oxford, only 27% of patients received concurrent chemotherapy: 65% of PS 0 patients received concurrent chemotherapy, 15% of PS1, 25% of PS2 and 0% of PS3. In comparison, in IDEAL-6 all patients received concurrent chemotherapy.

Another potential factor that may impact OS is the non-completion rate of RT. The non-completion rate of RT was 12% in Oxford compared to 2% in IDEAL-6. The better OS seen in IDEAL-6 may also be due to this higher RT completion rate possibly due to shorter RT schedule. This is also seen in other shorter schedules with good OS such as CHART[8] delivering 54Gy in 36 fractions over 12 days with a non-completion rate of 1%. The lower mean EQD2 time adjusted tumour dose of <57.8 Gy in Oxford compared to 64.7 Gy in IDEAL-6 may also contribute to the poorer OS seen in Oxford. In fact, higher prescribed radiation tumour doses were associated with better OS in the combined cohort, but not statistically significantly. Impact of high prescribed radiation dose on OS in NSCLC remains controversial. The meta-analysis by Ramroth et al [236] and other studies discussed in section 1.2 have shown a significant trend for better OS with higher dose. But for concurrent CRT, the data is dominated by the negative results of RTOG-0617 trial results, which attempted a large, 22%, across the board dose escalation prescribed to 95% of the PTV from 60 to 74 Gy, equivalent to ICRU reference point doses of 63 and 78 Gy.[24]

The limitations of this combined cohort analysis are outlined here. Firstly, there was a mix of patients with different characteristics, although this was accounted for by

retaining 'cohort' as a variable in the MV model, thus testing the impact of these differences on DR and other variables. Secondly, differing GTV to CTV margins were used in IDEAL compared to Oxford which could affect PTV size, potentially local control, and dose delivered to OAR if resulting in larger PTV. However, when GTV and PTV were entered into the model with heart dosimetry, they remained independently significantly associated with OS indicating a separate effect of margins on local control impacting OS to OAR irradiation effect on OS. Again, despite adding cohort as a variable in the model to take into account variations such as differing margins used in the different cohorts, heart dosimetric parameters remained significant. Thirdly, RT practice is subject to continual innovation, so models from retrospective data may not be as useful in practice. For example, 4DCT and IMRT use has increased a great deal since start of recruitment of IDEAL-6. Fourthly, the correlation between heart volume receiving intermediate and low doses and LA wall volume receiving high dose complicates the interpretation of the impact of each individual factor on survival. Avoiding LA wall receiving high dose may consequently reduce heart volume receiving intermediate and low doses and this needs to be studied in a radiotherapy planning study.

5.5 Conclusions

The prognostic index combining clinical (Age, PTV, cardiac event) and heart dosimetric factors (high volume of LA wall receiving high dose and high volume of heart receiving intermediate dose) was validated in an independent cohort, IDEAL-5. A heart dose-volume-time effect on survival may exist with heart volumes receiving low dose impacting OS later, and even small volumes receiving high and

intermediate dose impacting OS earlier, potentially due to different mechanisms due to damage to different cardiac substructures and needs investigation utilising prospective functional cardiac studies.

6. IMPACT OF LUNG AND LUNG SUBSECTION DOSIMETRY ON RADIATION PNEUMONITIS IN ISOTOXICALLY DOSE ESCALATED COHORTS: IDEAL-5 AND IDEAL-6

6.1 Introduction

The results of the previous chapters and recent evidence indicate that cardiac irradiation may impact cardiac events and OS in patients with lung cancer being treated with radical RT.[298][291][288][280][283][284][299][294] However, due to the proximity of heart and lungs, cardiac sparing RT may result in higher radiation doses being delivered to the lungs which in turn could increase the risk of radiation induced lung toxicity. As delivery of high radiation doses to the tumour is limited by radiation pneumonitis (RP) and radiation fibrosis (RF), refocusing on radiation induced lung toxicity is also important in RT dose escalation. The ability to predict radiation related lung toxicity risk more precisely is not only an essential prerequisite for tumour dose escalation but would also further enable personalised dose prescription.

Various predictive models exist for RP risk, with various lung dosimetric and clinical parameters being implicated which are summarised in chapter 1 section 1.3.2.2.4. Mean lung dose (MLD) has been identified as the most consistent predictor for RP incidence in studies of breast, lymphoma and NSCLC patients.[132][127][133] Consequently, MLD was used as the lung dosimetric parameter limiting isotoxic dose escalation in IDEAL-5 and IDEAL-6 clinical trials.[7]

Here, the following hypotheses were tested in NSCLC patients treated in prospective isotoxic dose escalation trials of CRT who received different prescribed tumour doses with a relatively constant MLD and chemotherapy:

- ***MLD has limited predictive ability for RP in isotoxically dose escalated patients.*** MLD is one of the most consistently used lung dosimetric parameter for RP prediction. In the isotoxic setting where MLD is controlled, MLD will have a limited predictive ability for G2RP. The effectiveness of MLD as a predictor for G2RP in the isotoxic dose escalation setting with potentially low MLD variance was explored here. The higher than expected G2RP incidence of 26% seen in IDEAL-6 despite controlled MLD indicates there are other factors impacting G2RP in the isotoxic setting.
- ***Additional lung and lung subsection dosimetric factors impact RP in isotoxically dose escalated patients.*** As the patients received different prescribed tumour doses with a relatively constant MLD and chemotherapy, this provided a good opportunity to explore other dosimetric and clinical parameters that may impact G2RP risk. There have been conflicting reports of impact of irradiation of upper versus lower tumour and lung lobes on RP.[119][121][120][124][111][102][300][301][176] Since avoidance of whole normal lung surrounding tumour would not be feasible without compromising PTV coverage, here attempts were made to localise lung subsection irradiation most impacting G2RP.
- ***RP models combining dosimetric and non-dosimetric parameters are more robust than dosimetric models alone.*** Studies have suggested that models

incorporating clinical characteristics with dosimetric parameters may better predict RP than models comprising dosimetric parameters alone.[302]

➤ ***There is a synergistic effect between heart and lung irradiation and RP risk.***

Studies have suggested that cardiac and pulmonary damage may act synergistically on cardiopulmonary function i.e. heart irradiation may increase lung toxicity, as detailed in section 1.3.3.[176][177][178][175][179][303][180] This effect may be greater in patients with lung cancer who may have underlying cardiac and lung problems due to smoking. Consequently, the impact of heart irradiation on G2RP and interaction with lung and lung-subvolume dosimetry was also studied here.

To my knowledge, this is the first study to prospectively explore clinical factors and heart substructure and lung subvolume dosimetric interactions impacting G2RP in an isotoxically dose escalated cohort in which the most consistent dosimetric predictor, MLD, is controlled as well as the chemotherapy effect.

6.2 Summary of methods

6.2.1 Population

Data were analysed for 114 patients with stage IIB/III NSCLC: 78 patients treated radically with CRT in IDEAL-6 and 36 in IDEAL-5 (details in section 2.1 and Appendix 3b [7]). The mean and range of prescribed doses were 65.7 Gy (63-71 Gy) in 30 fractions over 5 weeks and 67.8 Gy (63-73 Gy) in 30 fractions over 6 weeks in IDEAL-5 and IDEAL-6 respectively.

6.2.2 Isotoxic dose escalation in IDEAL

For each patient an initial prescribed tumor dose was selected to achieve a target of 18.2 Gy ML-EQD2 (average equivalent dose in 2 Gy fractions delivered to lungs excluding GTV (Lung-GTV)) which is associated with 20% SWOG $\geq$ grade 2 RP rate and 10% $\geq$ grade 3 RP rate according to the NKI model.[304] In this study[304] 7 of 62 trial patients developed grade ≥ 2 RP. The NTCP was calculated assuming a sigmoid (cumulative normal distribution) relation between the complication probability and the MLD. This sigmoid relation is characterised by a TD_{50} and a steepness parameter m . In a maximum likelihood analysis, the parameter values (TD_{50} and m) of the Lyman NTCP model[172] with $n=1$ [132] were fitted to the patient data and automatically optimised so that the agreement between the measured results and the results as predicted by the NTCP model is maximal. In the standard Lyman NTCP model[172], the probability of observing a specified complication after irradiation to dose D of subvolume V is modelled using a cumulative normal distribution, or probit function. TD_{50} is the tolerance dose corresponding to a 50% complication probability after irradiation of the reference volume, m is inversely related to the slope of the dose-response curve for RP, and n is the volume parameter. The Lyman model is fitted to data using maximum likelihood analysis, with the contribution to the likelihood consisting of NTCP or $1 - \text{NTCP}$ for patients experiencing or not experiencing the endpoint, respectively. Figure 3 in this chapter results section shows the incidence of RP grade ≥ 2 as a function of the mean lung dose in 62 evaluable patients. The (- -) line represents the model fitted with $TD_{50} = 29.2$ Gy and $m = 0.45$.

The prescribed tumor dose was reduced by 10% to allow for potential toxicity due to concurrent chemotherapy, and further if necessary to meet other OAR dose constraints (See Appendix 4). If this caused the prescribed tumour dose to fall below 63 Gy, the ML-EQD2 was relaxed to 19.3 Gy, and the patient received 63 Gy provided all OAR constraints were met.[7]

6.2.3 Scoring of radiation pneumonitis (RP)

Maximum RP scores within 6 months of RT were collated using the SWOG scoring system described in section 2.2.2.[93] Patients were dichotomised according to whether or not they experienced grade 2 or higher RP within 6 months of RT (G2RP).

6.2.4 Processing of radiotherapy dosimetric data

Treatment plans were imported into CERR, and Lung-GTV, contralateral lung (CL) and ipsilateral lung (IL) were outlined as described in section 2.3.2. CL and IL were split into equal thirds by dividing the longitudinal extent of each lung into 3 sections to create upper, middle and lower sub-sections (IUL, IML, ILL, CUL, CML, CLL respectively) (see section 2.3.2). Heart was outlined as described in section 2.3.1. dDVHs with 1Gy dose-bins were constructed for all structures. No fractionation correction was required as all patients received 30 fractions. As previous work have shown that the time effect is minimal on lung toxicity between the regimens of IDEAL 5 and 6 treated with 30 fractions in 5 weeks and 6 weeks respectively, time correction was not carried out for lung toxicity modelling work here.[305] Mean Lung-GTV dose (MLD) was extracted and converted to ML-EQD2 using the linear quadratic equation with an alpha/beta ratio of 3 Gy. Lung-GTV MLD was collated as this was the

dosimetric parameter used for isotoxic dose escalation in IDEAL. Using single point metrics such as MLD can be limiting as explained in section 2.4.2. Reducing dose distribution to DVH, and subsequently DVH to a single metric, potentially critical dose-volume information which may help best discriminate between plans at high or low risk for complications might be lost. Therefore, PCA was carried out for Lung-GTV and heart DVH data (details in section 2.4.2) to utilise all DVH data.

6.2.5 Impact of clinical factors and lung dosimetry on G2RP

Mean ML-EQD2 of patients with and without G2RP were compared using the Mann Whitney U test. UV logistic regression models of G2RP incidence were constructed to assess clinical and lung dosimetric factor effects. Variables with p value $\leq .2$ level on UVA as well as clinically significant factors (ML-EQD2, dose, tumour size) were included in a MV logistic regression model, with stepwise bi-directional variable elimination carried out to derive the best model with the lowest AIC score (see section 2.6.2.3). Lung-GTV volumes receiving doses represented by the peak in the Lung-GTV PC that remains significant in the best MV model (Lung-PC_{max}) replaced Lung-PC_{max} in the MV model.

6.2.6 Localisation of relevant Lung-GTV dose bin to lung sub-volume

To localise the relevant lung subvolume receiving receiving doses represented by the peak in the Lung-PC_{max} (PC-dp), the graphical approach described in Appendix 5 was used. 20 patients with G2RP (group P1) and 20 patients without (Group P0) but with the largest coefficients for Lung-PC_{max} were examined. 20 patients were

selected as this was the sample size in the heart localisation work in chapter 3. For these 40 patients the lung subsection receiving PC-dp was also identified by visual inspection of each patient's plan to verify the results of the graphical approach. The extent of the sub-volume receiving PC-dp then replaced Lung-PC_{max} in the best MV model. If subvolume dosimetric factors were significantly correlated ($VIF > 4$ or $r > .4$)[225], they were entered into separate MV models.

6.2.7 Effect of heart dosimetry on G2RP

UVA was used to assess associations between G2RP and the top 10 heart-PCs and mean doses. Interaction terms between Heart-PCs and lung sub-volumes found to be significant in the MV model above were tested. Heart-PCs with p-values $\leq .2$ on UVA and their lung sub-volume interaction terms with p-value $< .2$ were initially included and stepwise bi-directional variable elimination was performed to find the best MV model with the lowest AIC score.

6.2.8 Multivariate Model diagnostics (details in section 2.6.1.1)

Residuals were examined for randomness, goodness of fit, non-linearity, outliers and influential cases using a runs test, lack-of-fit test, hat values, Cook's distance and influence plots. Potential influential observations were removed to assess the impact on coefficient estimates in the model. MV model performance was tested for discrimination using the AUC of the ROC curve and Nagelkerke's R² test. Model calibration was assessed using calibration plots and the Hosmer-Lemeshow goodness of fit test. A 6-fold internal cross validation was performed. Multicollinearity

was excluded if VIF was <4 and correlation co-efficient $<.4$ (section 2.6.2.4).[226]
Multiple hypotheses testing correction was conducted using the B-H procedure with an false-discovery-rate of 20% (section 2.6.2.6).

6.3 Results

6.3.1 Patient characteristics

114 patients were analysed. Patient and treatment characteristics of IDEAL-5 are detailed in Table 1 below, IDEAL-6 are detailed in Table 1 in Section 3.3.1, and characteristics of the combined IDEAL-5 and IDEAL-6 cohort are detailed in Table 2 below. There were 11 deaths in IDEAL-5 and 26 in IDEAL-6 at a median follow up of 13.6 and 21.6 months respectively. IDEAL-5 patients had smaller PTVs than IDEAL-6 (median 353cm^3 (range 181 - 720) and 401cm^3 (range 139 - 1262) respectively). The mean PTV size of the combined cohort was 428cm^3 . The median ages of IDEAL-5 and IDEAL-6 patients were 67 (range 46 - 76) and 66 (range 43 - 84) respectively. The median prescribed dose was lower for IDEAL 5 than IDEAL-6 patients (64.5 Gy (range 63 – 71) and 67.6 Gy (range 63 - 73 Gy) respectively). 26% had Grade 2 or higher RP (G2RP) in the combined cohort, greater than the 20% target (Table 3).

Table 1. Patient and treatment characteristics of IDEAL-5

Characteristic	No (%)
Age	
<65	16
>65	20
WHO performance status[*]	
0	20
1	16
Gender	
Female	13
Male	23
Nodal status	
N 2 or 3	29
N 0 or 1	7
Histology	
Squamous	23
Non-squamous	13
Laterality	
Right	22
Left	14
Tumour location	
Upper	32
Lower	4
Treatment delivery	
3DCRT	26
IMRT	10
Baseline lung function	
Mean Predicted FVC (FVC0) (%)	97
Mean Predicted FEV (FEV0) (%)	79
Mean Predicted DLCO (DLCO0) (%)	73
Baseline *MRC Dyspnoea Score (No.)	
0	16
1	17
2	2
3	1

No. = number of patients

IMRT = intensity modulated radiotherapy;
3DCRT = 3 dimensional conformal radiotherapy

^{*}WHO Performance Status: Appendix 2a

*MRC dyspnoea scale: Appendix 2b

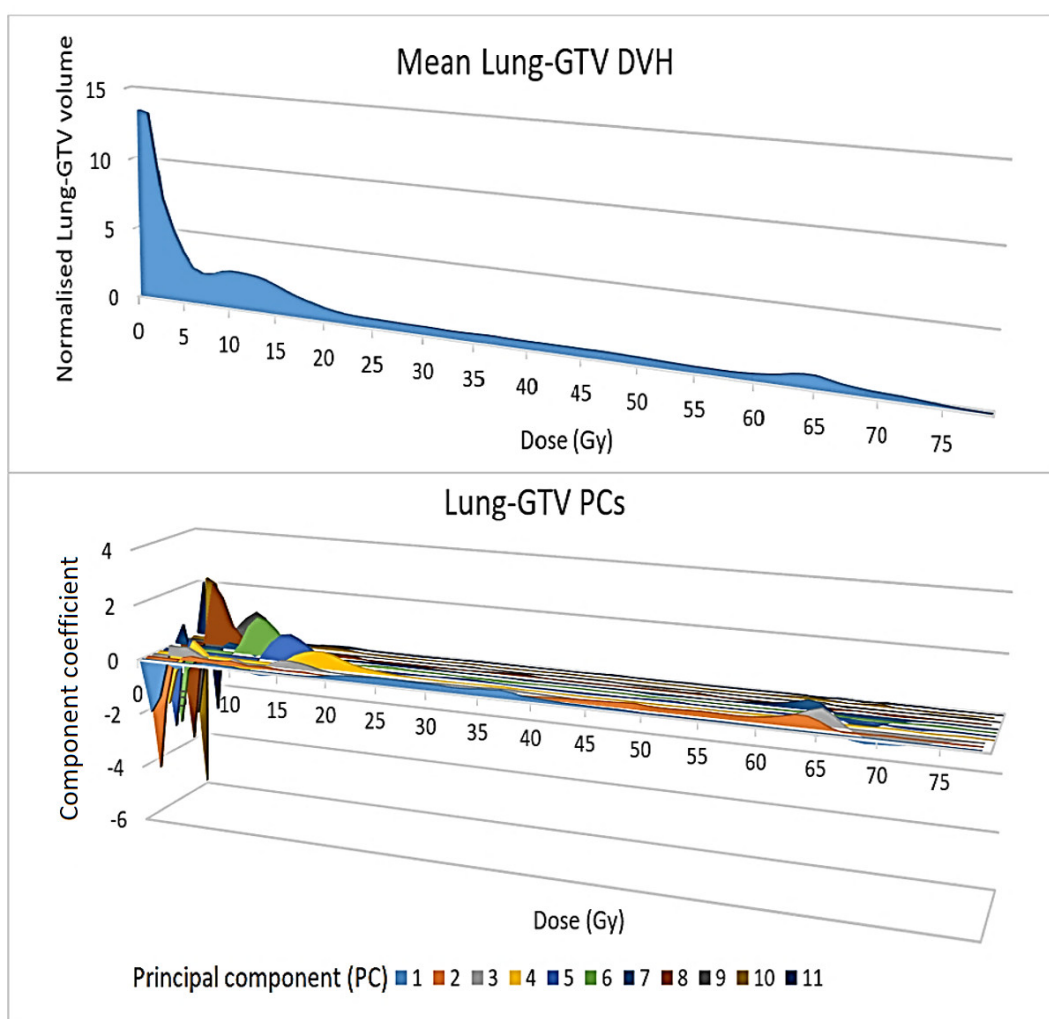
Table 2. Characteristics of combined IDEAL-5 (36 patients) and IDEAL-6 (78 patients) cohort

Characteristic	No
Age	
<65	47
>65	67
WHO performance status[*]	
0	52
1	62
Gender	
Male	81
Female	33
Nodal status	
N 2 or 3	94
N 0 or 1	20
Histology	
Squamous	65
Non-squamous	49
Laterality	
Right	66
Left	48
Tumour location	
Upper	101
Lower	13
Treatment delivery	
3DCRT	101
IMRT	13
Baseline lung function	
Mean Predicted FVC (FVC0) (%)	95
Mean Predicted FEV (FEV0) (%)	77
Mean Predicted DLCO (DLCO0) (%)	70
Baseline *MRC Dyspnoea Score (No.)	
0	40
1	47
2	15
3	5

Table 3. Radiation pneumonitis seen within 6 months of radiotherapy using SWOG grading system

Grade	No of patients
0	65
1	19
2	26
3	4
4	0
5	0

Figure 2. Mean lung minus GTV (Lung-GTV) dDVH of 114 patients, plotted together with the 11 varimax-rotated principal components (PCs) describing >95% of the Lung-GTV dosimetric variance.



6.3.2 Radiotherapy dosimetric data

The mean Lung-GTV dDVH is plotted in Figure 1, alongside the 11 varimax-rotated Lung-GTV PCs which describe more than 95% of Lung-GTV DVH variance. Lung-GTV mean volume was 3.8 litres (Range 1.8 - 7.2).

6.3.3 Impact of ML-EQD2 on G2RP

The mean tumour dose prescribed to all 114 patients was 67.1 Gy. Figure 2 shows the distribution of ML-EQD2 for the 114 patients, together with the distribution of ML-EQD2s calculated for all the patients when they were prescribed an across-the-board mean tumour dose of 67.1 Gy delivered according to the same plan as in IDEAL, rather than the actual IDEAL prescribed doses. Though the mean, median and range of ML-EQD2 were similar in patients prescribed isotoxic doses in IDEAL and all patients were prescribed 67.1 Gy, the variance was smaller in patients prescribed isotoxic doses in IDEAL than if they had been prescribed 67.1 Gy across the board. Only 5 patients were protocol deviators, receiving >18.2 Gy ML-EQD2 in the IDEAL 5 & 6 combined cohort, of which only 1 patient had G2RP and this patient received MLD-EQD2 of 18.7 Gy. The mean delivered ML-EQD2 was 14.4 Gy (95% CI 13.9-14.9).

The expected G2RP rate is 12% for the delivered mean ML-EQD2 of 14.4 Gy according to the NKI model (Figure 3).[304] However, the observed G2RP rate was higher at 26%. The NKI model was not however based on patients receiving concurrent CRT, and therefore RP rates in IDEAL may partly be higher than expected due to the chemotherapy effect. Even if concurrent chemotherapy

effectively raised doses by 10%, this still wouldn't be enough to account for the higher G2RP rate seen. There was no statistically significant difference in ML-EQD2 between patients with or without G2RP (Mann Whitney U p 0.93). ML-EQD2 differences between patients with and without G2RP are described in Table 4.

Figure 2. Distribution of ML-EQD2 in the 114 patients treated in IDEAL-6 (orange) and IDEAL-5 (green); calculated ML-EQD2 if 67.1 Gy (the mean prescribed dose in 114 patients) were prescribed using the same plan as in IDEAL (blue). Box-plot shows larger variance in ML-EQD2 if all patients received 67.1 Gy (blue) delivered according to the same plan as IDEAL than in isotoxically dose escalated IDEAL-6 patients (orange) and IDEAL-5 (green). Median ML-EQD2 for both groups was 15 Gy (pink line).

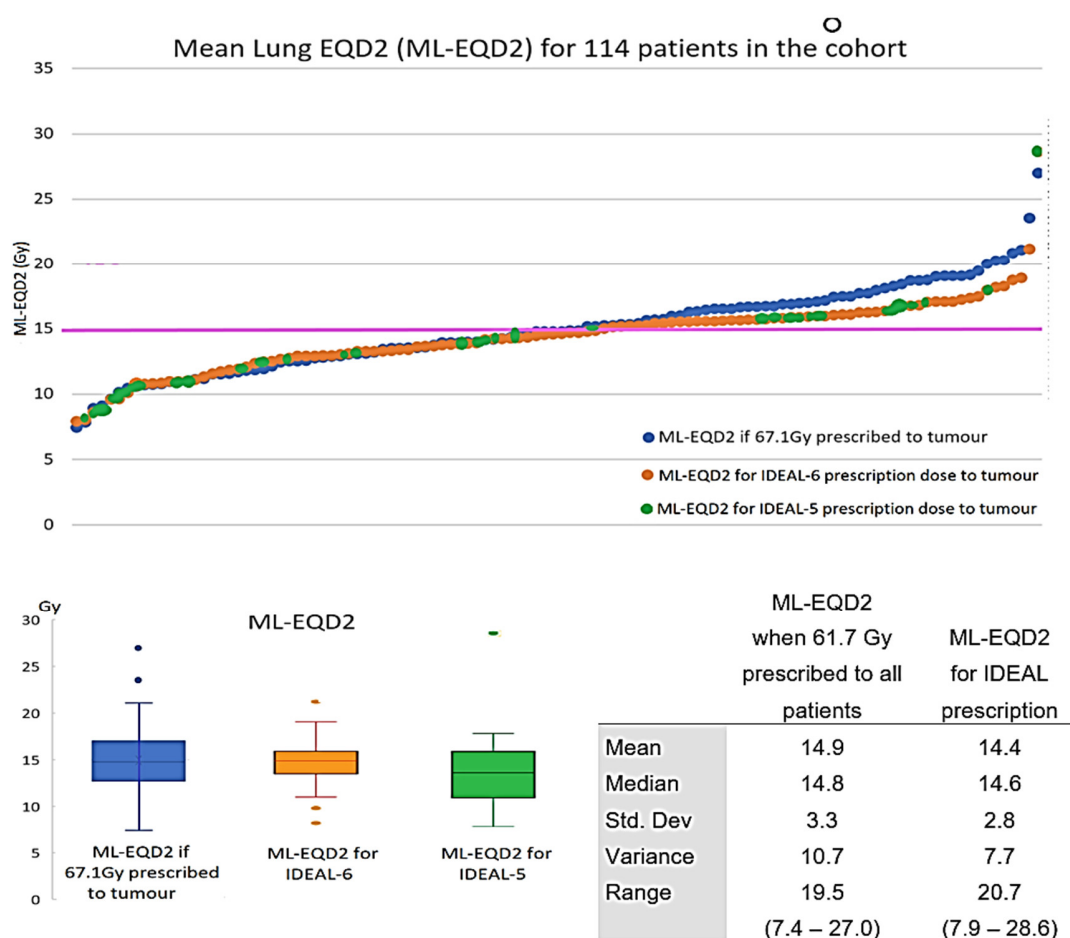


Figure 3. Incidence of radiation pneumonitis (RP) grade 2 or higher as a function of the mean lung dose (MLD) in 62 evaluable patients (Adapted from [304]). The (- Δ -) line represents the NTCP model fitted with $TD_{50} = 29.2$ Gy and $m=0.45$ for dose computation. The error bars represent the 68% confidence intervals of data bins. Blue line indicates 20% predicted G2RP rate for 18.2 Gy MLD; Orange line shows 12% predicted G2RP rate for delivered 14.4 Gy MLD in IDEAL.

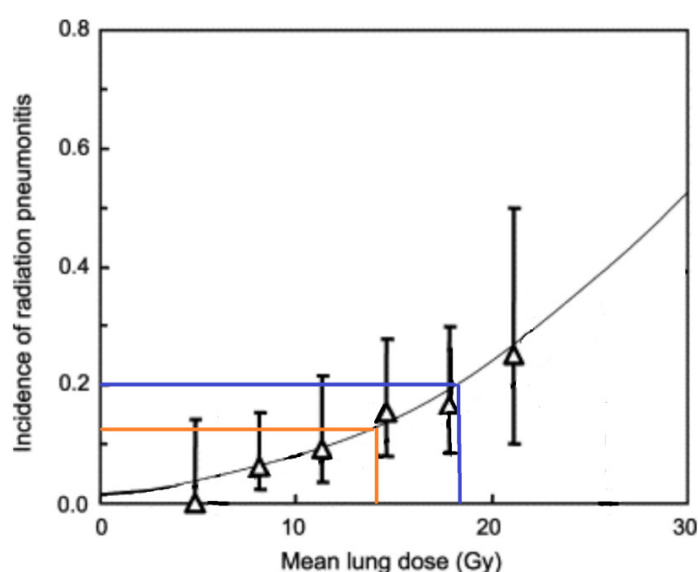


Table 4. Summary statistics of ML-EQD2 in patients with and without G2RP

ML-EQD2	Patients with G2RP (n = 30)	Patients without G2RP (n = 84)
Mean	14.2 Gy	14.5 Gy
Median	14.5 Gy	14.7 Gy
Range (Min-Max)	10.1 Gy (8.6-18.7)	20.7 Gy (7.9-28.6)
95% CI	13.2-15.2 Gy	13.9-15.1 Gy
SD	2.7 Gy	2.8 Gy

6.3.4 Effect of clinical factors on G2RP

On UVA, patients with performance status (PS) 1 had significantly higher odds ratio (OR) (2.45 times the risk for G2RP) than patients with PS0 (See Table 5).

Table 5. Univariable logistic regression models of G2RP versus clinical factors

Covariate	p-value	OR (95% CI)
Age Over 65 Vs Age Under 65	.56	1.30 (0.55 - 3.06)
PS 1 Vs 0	.05	2.45 (1.01 - 5.96)
Male vs Female	.88	0.93 (0.38 - 2.33)
Right Vs Left	.87	0.93 (0.40 - 2.17)
Upper Vs Lower tumour	.70	0.78 (0.22 - 2.75)
Delivered dose	.30	1.06 (0.95 - 1.20)
IMRT	.30	1.90 (0.57 - 6.34)
PTV	.51	1.00 (1.00 - 1.00)
Lung-GTV Volume	.38	1.00 (1.00 - 1.00)
IDEAL-5 Vs IDEAL-6	.83	0.91 (0.37 - 2.24)
Baseline FVC (%)	.15	1.02 (0.99 - 1.04)
Baseline FEV (%)	.17	1.02 (0.99 - 1.04)
Baseline DLCO (%)	.75	1.00 (0.97 - 1.02)
Baseline dyspnoea score 0	.43	
Baseline dyspnoea score 1	.13	2.21 (0.80 - 6.13)
Baseline dyspnoea score 2	.45	1.71 (0.42 - 6.99)
Baseline dyspnoea score 3	.25	3.14 (0.44 - 22.45)

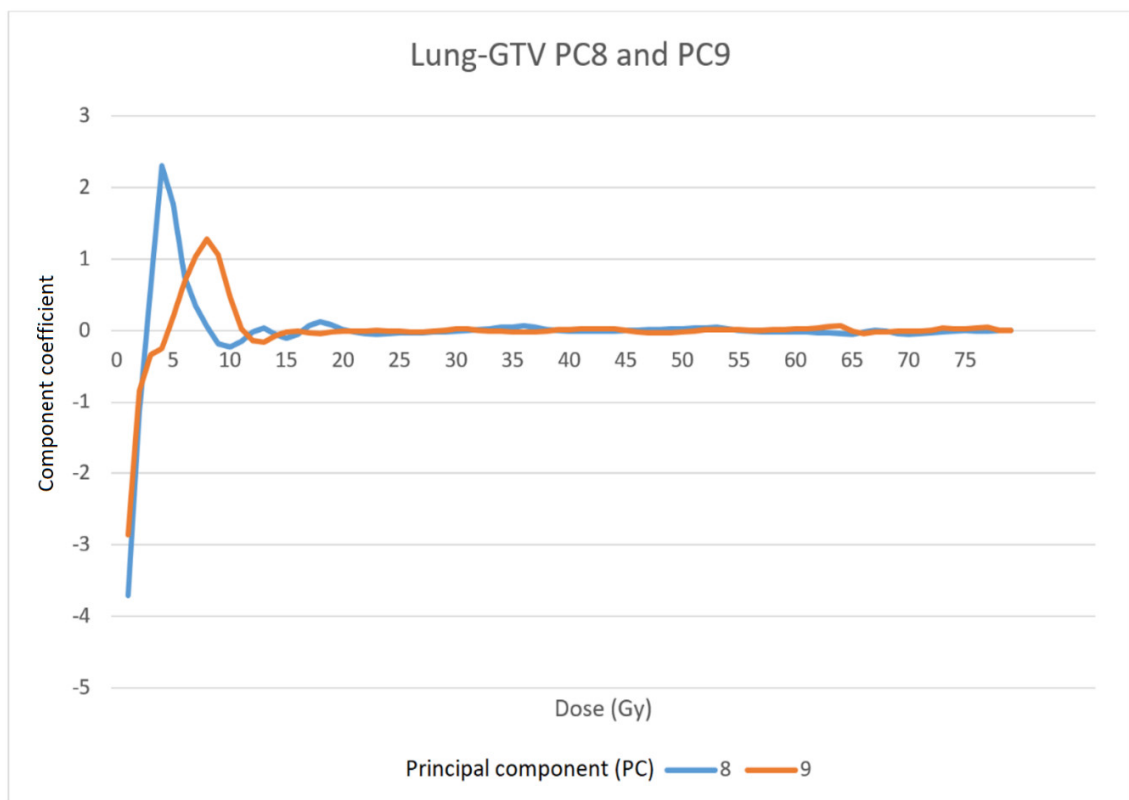
Table 6. Univariable logistic regression models of G2RP versus Lung-GTV dosimetric factors. *PC-principal component*

Covariate	p-value	OR (95% CI)
Mean Lung EQD2	.62	0.96 (0.82 - 1.12)
Lung-GTV-PC1	.66	0.91 (0.59 - 1.40)
Lung-GTV-PC2	.79	0.94 (0.61 – 1.45)
Lung-GTV-PC3	.23	0.77 (0.50 – 1.18)
Lung-GTV-PC4	.56	1.13 (0.75 – 1.70)
Lung-GTV-PC5	.60	0.89 (0.58 – 1.37)
Lung-GTV-PC6	.32	0.80 (0.52 – 1.24)
Lung-GTV-PC7	.84	1.04 (0.69 – 1.59)
Lung-GTV-PC8	.09	1.41 (0.95 – 2.10)
Lung-GTV-PC9	.03	1.56 (1.04 – 2.34)
Lung-GTV-PC10	.70	0.92 (0.60 – 1.40)
Lung-GTV-PC11	.51	0.87 (0.57 – 1.32)

6.3.5 Lung-GTV principal component effect on G2RP

Higher scores of Lung-GTV-PC9 (p .03) and Lung-GTV-PC8 (p .09) were associated with higher G2RP risk on UVA (Table 6). Lung-GTV-PC8 and 9 have prominent peaks which represent doses of 2-8 Gy and 3-11 Gy respectively. Therefore, in patients with high Lung-GTV-PC8 and 9 scores, greater Lung-GTV volumes receive 3-8 Gy ($V_{\text{Lung-GTV}3-8}$) (overlap region of the 2 PC peaks) (Figure 4).

Figure 4. Lung-GTV principal components 8 (PC8) and 9 (PC9) plots showing the overlap positive region lies between the peaks (4–8 Gy) which represents high volume of Lung-GTV receiving 3-8 Gy due to binning



6.3.6 G2RP Multivariable (MV) model combining clinical and dosimetric factors

113 patients were included in MV modelling as one patient did not have a baseline FVC measurement and was excluded. MV model 1 was judged best according to AIC, and was obtained by starting with all factors considered clinically relevant (dose, PTV, ML-EQD2, Age, Cohort, Upper or Lower tumour, Laterality of tumour, Lung-GTV volume) or found to have p-values <.2 on UVA (PS, Baseline percentage predicted FVC (FVC0) and Lung-GTV-PC8 and PC9. The best model retained Lung-GTV-PC8, Lung-GTV-PC9, FVC0 and PS as factors associated with G2RP, and had an AIC of 124. The performance of the model, based on an AUC of .73 was good. A Hosmer-Lemeshow test with an insignificant goodness-of-fit p value suggests the model adequately describes the data (Table 7). When Lung-GTV-PC8 and PC9 were replaced in MV Model 2 by the Lung-GTV volume receiving 3-8 Gy ($V_{\text{Lung-GTV3-8}}$), this volume retained significance (p .02), and the AIC and AUC values did not vary a great deal (Table 7).

Table 7. Multivariable (MV) models for G2RP: MV model 1 consists of clinical factors and Lung PCs; in MV model 2 Lung-GTV PCs are replaced by $V_{\text{Lung-GTV3-8}}$

	MV model 1 containing Lung-GTV PCs		MV model 2: Lung-GTV PCs replaced by $V_{\text{Lung-GTV3-8}}$	
	p-value	OR (95% CI)	p-value	OR (95% CI)
PS	.02	3.44 (1.26-9.40)	.02	2.97 (1.15-7.68)
FVC0	.05	1.03 (1.00-1.05)	.06	1.02 (1.00-1.05)
L-GTVPC8	.13	1.39 (0.91-2.13)		
L-GTVPC9	.01	1.76 (1.14-2.72)		
$V_{\text{Lung-GTV3-8}}$			.02	1.08 (1.02-1.17)
Constant	<.01	.014	.00	.005
AIC		124		125
AUC (95% CI)		.73 (.62-.84)		.70 (.59-.82)
Nagelkerke R2		.20		.17
Hosmer-Lemeshow test		Chi Sq = 7.13; p = .52		Chi Sq = 13.34; p = .10

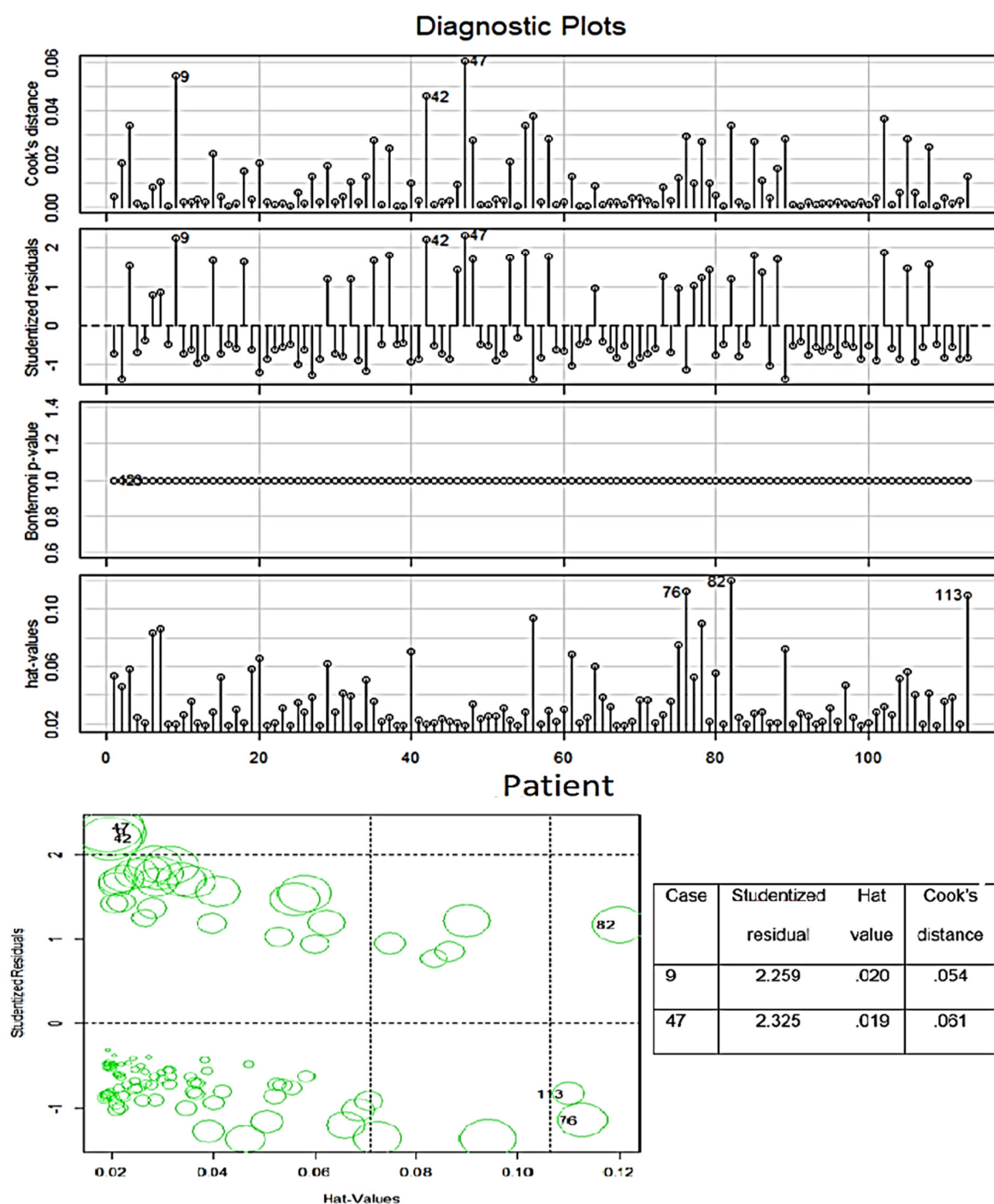
Diagnostics of the best G2RP MV model containing lung dosimetry + clinical factors (MV model 2: PS, FVC0 and V_{Lung-GTV3-8})

MV model 2 consisting of PS, FVC0 and V_{Lung-GTV3-8} had an AUC based on 6-fold internal cross validation of .69, demonstrating good discrimination (Table 8). It was a good fit for the data with an Hosmer-Lemeshow test $p > .05$ and accounted for 17% outcome variation (Nagelkerke R² in Table 7). Model calibration plots (Figure 8) comparing predicted and observed G2RP rates for each risk group were very close. B-H analysis of effects of multiple hypotheses testing showed V_{Lung-GTV3-8} and PS remained positive discoveries allowing for a false-discovery-rate of 20%, and there was no multicollinearity. There was randomness of residuals based on the runs test. There was no correlation between Pearson residuals and predictors and fitted values according to the lack-of-fit test ($p > .05$). There were no studentized residuals with Bonferroni $p < .05$ suggesting there were no outliers. Patient 47 had the largest studentized residual and Cook's distance and patient 82 had the largest hat value, but all Bonferroni p values were close to 1 suggesting no influential patients (Figure 5). Patients 9 and 47 had the highest Cook's distances ($> .05$), but their hat values were small ($< .02$) and the regression coefficients remained similar when these patients were removed showing they were not influential cases.

Table 8. 6-fold internal cross validation of MV model 2 (PS, FVC0, V_{Lung-GTV3-8})

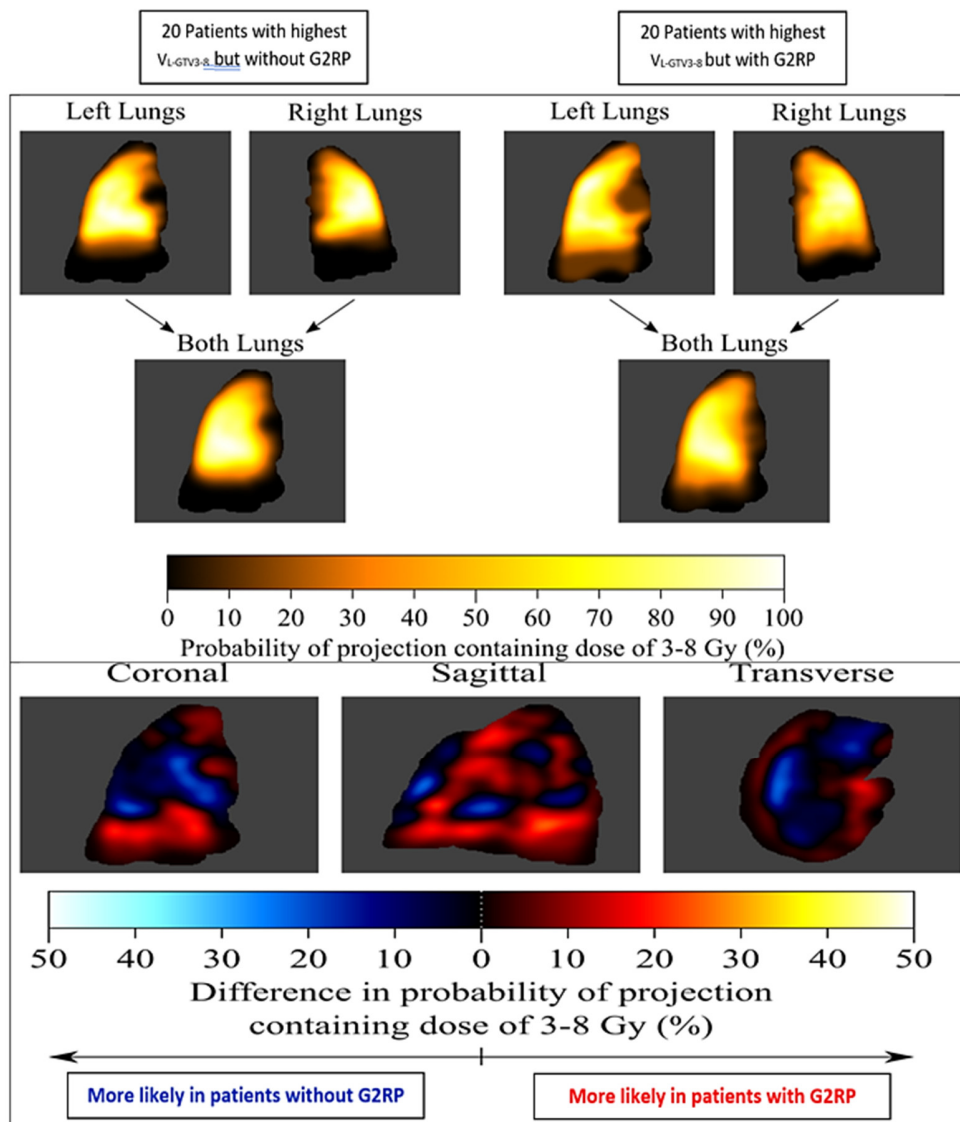
	Percentage Correct		AUC of ROC	
	Training Set	Validation Set	Training Set	Validation Set
Cohort 1	75.5	84.2	.70 (.58-.82)	.71 (.36-1.0)
Cohort 2	74.5	84.2	.68 (.55-.80)	.85 (.66-1.0)
Cohort 3	76.8	66.7	.72 (.60-.85)	.64 (.34-.93)
Cohort 4	73.4	84.2	.69 (.57-.82)	.74 (.44-1.0)
Cohort 5	74.5	78.9	.72 (.60-.85)	.50 (.21-.79)
Cohort 6	81.9	52.6	.71 (.58-.84)	.67 (.41-.92)
Mean	76.1	75.1	.70	.69

Figure 5. Top: Diagnostic plots of Cook's distance, studentized residuals, Bonferonni p and hat-values for MV model 2 (PS, FVC0 and V_{Lung-GTV3-8}). Bottom: Studentized residuals plotted against hat-values: circle size proportional to Cook's distance. Patients 9 and 47 have the largest Cook's distance, but have small hat-values (table adjacent).



6.3.7 Localisation of $V_{\text{Lung-GTV3-8}}$ to lung subvolume

Figure 6. 20 patients with high $V_{\text{Lung-GTV3-8}}$ and G2RP compared to 20 patients with high $V_{\text{Lung-GTV3-8}}$ but without G2RP. Contralateral lungs are plotted in the figure. In patients with G2RP, there is a greater probability of the lower half of the contralateral lung receiving doses of 3-8Gy. *Figure courtesy of Dr D Warren.*



40 patients with the highest $V_{\text{Lung-GTV3-8}}$ volumes were separated into two groups: 20 with G2RP and 20 patients without G2RP for comparison. Then these groups were

separated into 2 subgroups, depending on whether their contralateral lung was left or right sided. Regions receiving 3-8 Gy extended more inferiorly for patients with G2RP than for those without, in both right and left lungs, and were concentrated in the contralateral lung middle and lower lobes (Figure 6). It should be noted that some of the patient numbers are small though – for example, there are only 7 pts in the G2RP left lung group. Direct visual inspection of these 40 patients' RT plans also verified the results of the graphical approach, with 3-8 Gy regions extending further in the inferior direction of contralateral lung for patients with G2RP than for those without. Additionally, mean $V_{\text{Lung-GTV3-8}}$, $V_{\text{CL3-8}}$, $V_{\text{CLL3-8}}$ and $V_{\text{CML3-8}}$ volumes were all higher in patients with G2RP than in those without G2RP (Table 10).

UVA of contralateral and ipsilateral lung volumes receiving 3-8 Gy ($V_{\text{CL3-8}}$ and ($V_{\text{IL3-8}}$) respectively) showed $V_{\text{CL3-8}}$ to be significantly associated with G2RP (OR 1.04, 95% CI 1.00-1.09; p .07), although $V_{\text{IL3-8}}$ was not (OR 1.03, 95% CI .97-1.10; p .29). $V_{\text{CL3-8}}$ remained significant when it replaced $V_{\text{Lung-GTV3-8}}$ in MV model 3 (Table 9).

When $V_{\text{CL3-8}}$ was substituted by CUL, CML and CLL volumes receiving 3-8 Gy ($V_{\text{CUL3-8}}$, $V_{\text{CML3-8}}$, $V_{\text{CLL3-8}}$ respectively), the best MV model selected by AIC included PS, FVC0 and $V_{\text{CML3-8}}$ and $V_{\text{CLL3-8}}$ (MV model 4 in Table 9). Compared to MV model 2 which contained $V_{\text{Lung-GTV3-8}}$, MV model 4 which contained $V_{\text{CML3-8}}$ and $V_{\text{CLL3-8}}$ had a lower AIC (125 and 124 respectively) and higher AUC (.70 vs .74 respectively), indicating MV model 4 was better at predicting G2RP.

Table 9. Localisation of Lung-GTV receiving 3-8 Gy ($V_{\text{Lung-GTV3-8}}$) to lung subunit. In multivariable (MV) model 3 for G2RP $V_{\text{Lung-GTV3-8}}$ is replaced by contralateral lung receiving 3-8 Gy ($V_{\text{CL3-8}}$); in MV model 4 $V_{\text{CL3-8}}$ is replaced by contralateral lower and middle subunits receiving 3-8 Gy ($V_{\text{CLL3-8}}$ and $V_{\text{CML3-8}}$ respectively)

	MV model 3 replacing $V_{\text{Lung-GTV3-8}}$ with $V_{\text{CL3-8}}$		MV model 4 replacing $V_{\text{CL3-8}}$ with $V_{\text{CLL3-8}}$ and $V_{\text{CML3-8}}$	
	p-value	OR (95% CI)	p-value	OR (95% CI)
PS	.01	3.58 (1.35-9.50)	<.01	4.20 (1.51-11.68)
FVC0	.06	1.02 (1.00-1.05)	.05	1.03 (1.00-1.05)
$V_{\text{CL3-8}}$	.03	1.06 (1.01-1.11)		
$V_{\text{CLL3-8}}$			.03	1.05 (1.01-1.09)
$V_{\text{CML3-8}}$			.04	1.04 (1.00-1.08)
Constant	<.01	.006	<.01	
AIC		126		124
AUC (95% CI)		.70 (.59-.81)		.74 (.63-.85)
Nagelkerke R2		.16		.20
Hosmer-Lemeshow test		Chi ² 14.67; p = .07		Chi ² 10.23; p = .25

Table 10. Summary statistics for the variables in the MV models 2,3,4

	All patients n = 113	Patients with G2RP n = 30	Patients without G2RP n = 83
(%)			
Mean FVC0	95.5	99.7	94.0
Mean $V_{\text{Lung-GTV3-8}}$	15.6	18	15
Mean $V_{\text{CL3-8}}$	17.2	20	16
Mean $V_{\text{CML3-8}}$	21.9	25	21
Mean $V_{\text{CLL3-8}}$	5.9	9	5

Diagnostics of the best MV model for G2RP containing lung subvolume dosimetry + clinical factors (MV model 4: PS, FVC0, $V_{\text{CML3-8}}$ and $V_{\text{CLL3-8}}$)

AUC for MV model 4 containing PS, FVC0, $V_{\text{CML3-8}}$ and $V_{\text{CLL3-8}}$ based on 6-fold internal cross validation was 0.74, demonstrating good discrimination (Table 11).

This model accounted for the highest variation in outcome (20.1% in Nagelkerke R2 score) compared to MV models 2 and 3 containing $V_{\text{Lung-GTV3-8}}$ or $V_{\text{CL3-8}}$ respectively.

So, high volume of lower half of the contralateral lung receiving 3-8 Gy seems to be

associated with increased risk of G2RP. Using the B-H process to hold the false-discovery-rate to 20% after allowing for multiple hypotheses testing, V_{CML3-8} , V_{CLL3-8} and PS remained significantly associated with G2RP incidence and there was no multicollinearity. The model described the data adequately with Hosmer-Lemeshow test $p > .05$ suggesting no significant difference between predicted and observed rates for G2RP. Model calibration plots (Figure 8) comparing predicted and observed G2RP rates for each risk group were very close. There was randomness of residuals based on runs test. There was no correlation between Pearson residuals and predictors and fitted values according to the lack-of-fit test ($p > .05$). There were no studentized residuals with Bonferroni-adjusted $p < .05$, suggesting there were no outliers. Patients 9 and 47 had the largest studentized residuals and Cook's distances, and patient 108 had the largest hat value, but all Bonferroni-adjusted p -values were close to 1 (Diagnostic plot shown in Figure 7 top). The highest Cook's distance and studentized residual were for case 9 ($p > .05$); but for this case the hat values were very small (.025), so it was unlikely to be an influential case, and this was proven correct when the MV regression coefficients remained similar despite removing patient 9 (PS 1.4 Vs 1.7, FVC0 .03 for both, V_{CML3-8} .04 vs .05 and V_{CLL3-8} .05 for both).

Table 11. 6-Fold Cross validation of MV model 4 (PS, FVC0, V_{CLL3-8} & V_{CML3-8})

	Percentage Correct		AUC of ROC (95% CI)	
	Training Set	Validation Set	Training Set	Validation Set
Cohort 1	73.4	89.5	.74 (.62-.85)	.88 (.65-1.0)
Cohort 2	73.4	84.2	.73 (.61-.85)	.81 (.60-1.0)
Cohort 3	78.9	66.7	.76 (.65-.88)	.64 (.34-.93)
Cohort 4	75.5	68.4	.73 (.61-.85)	.73 (.48-1.0)
Cohort 5	74.5	68.4	.75 (.63-.87)	.67 (.42-.92)
Cohort 6	81.9	57.9	.74 (.63-.86)	.72 (.48-.97)
Mean	76.3	72.5	.74	.74

Figure 7. Top: Diagnostic plots of Cook's distance, studentized residuals, Bonferonni p and hat-values for MV model 4 (PS, FVC0 and V_{CML3-8} and V_{CLL3-8}). Bottom: Studentized residuals plotted against hat-values: circle size proportional to Cook's distance. Patient 9 has the highest Cook's distance and studentized residual but has small hat-value (table adjacent).

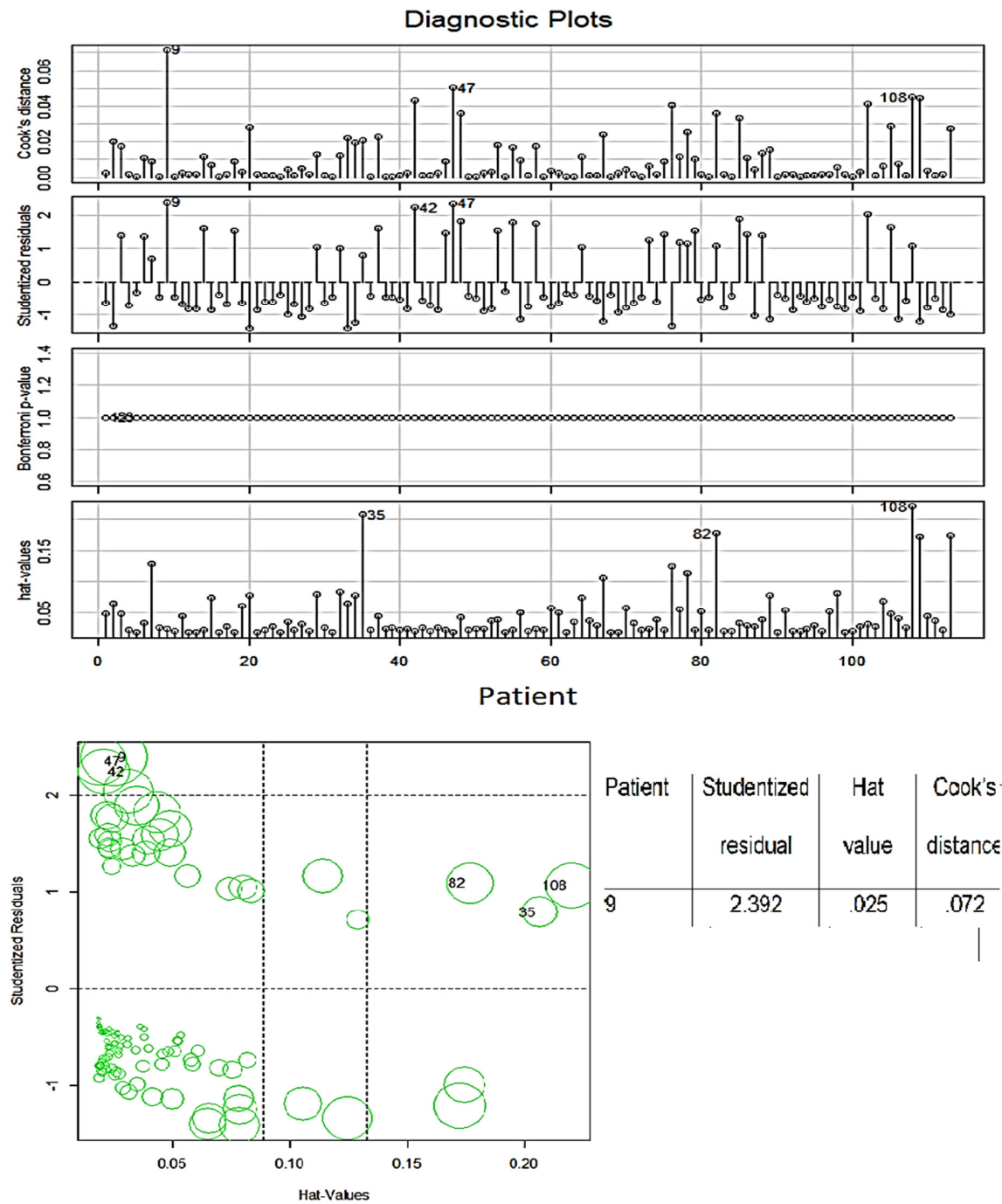
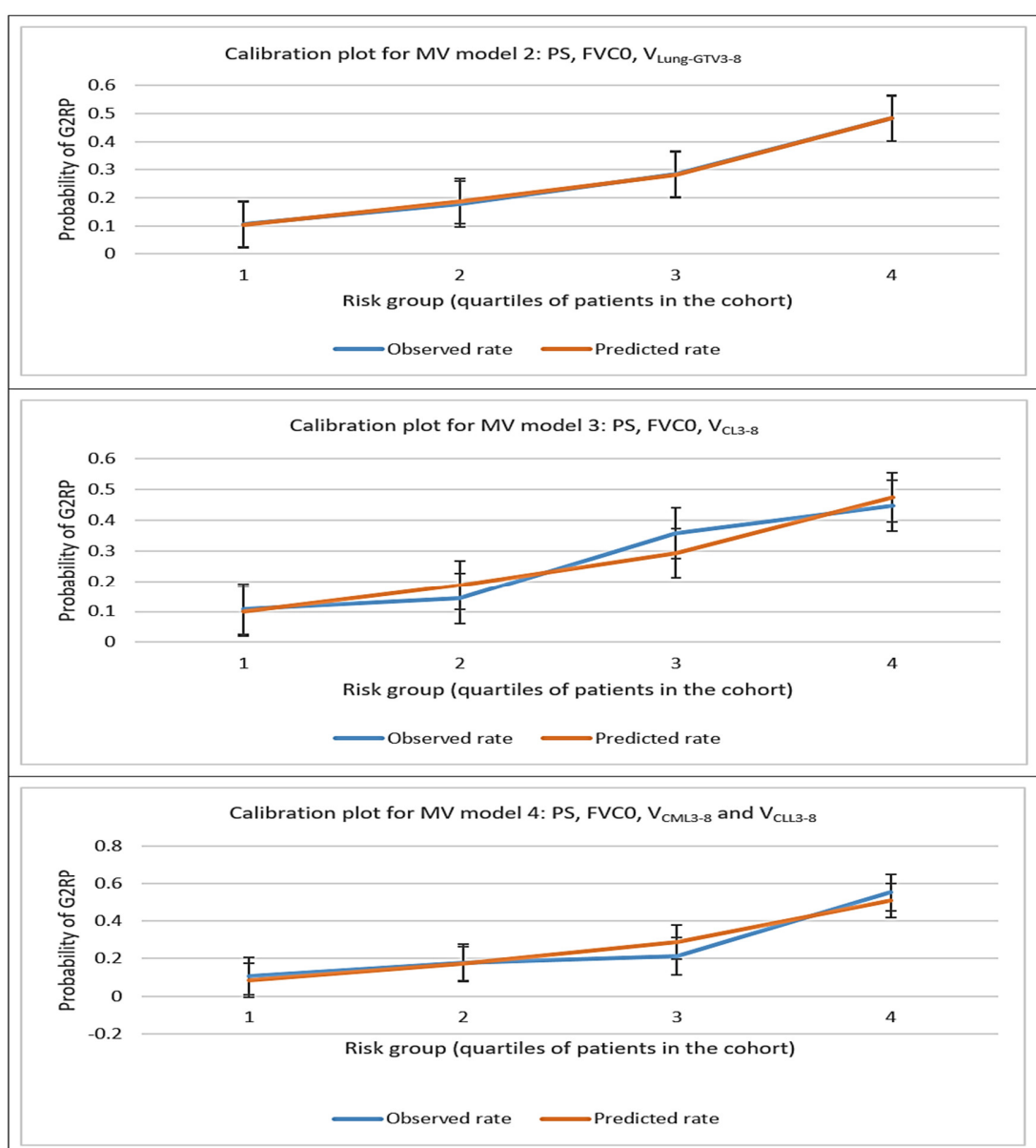


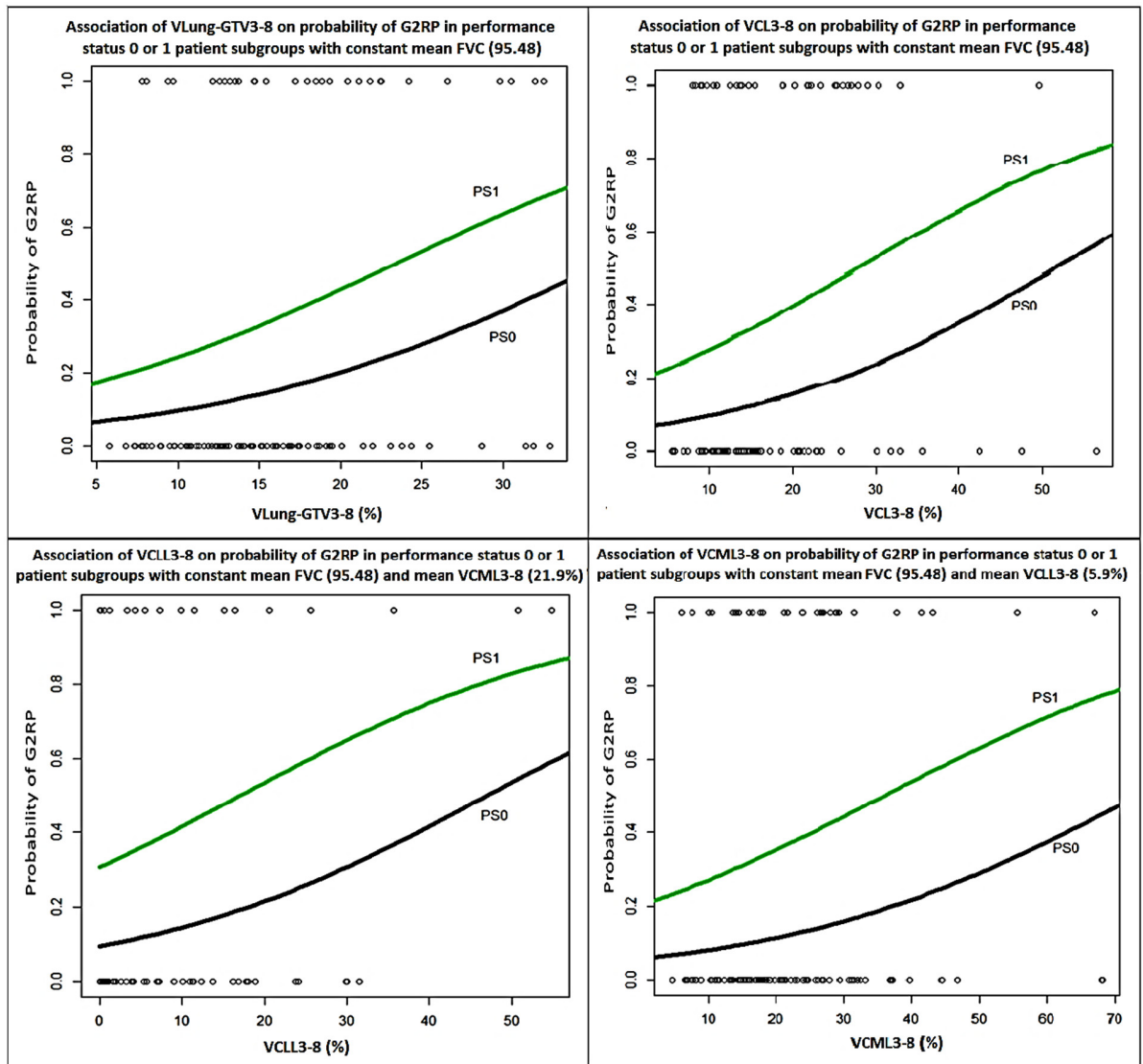
Figure 8. Calibration plot for MV models – Observed versus predicted G2RP incidence: Mean predicted G2RP rates calculated from each MV model vs observed rates; 28 patients in risk groups 1 (low risk), 2 (low-medium risk) and 3 (medium-high risk); and 29 patients in risk group 4 (high risk). The risk groups are grouped according to ascending predicted probability of G2RP according to the MV model. The lines connecting bins are intended as a visual guide. All plots had overlap of standard error bars between observed and predicted G2RP.



6.3.8 G2RP variation with PS, FVC0, $V_{\text{Lung-GTV3-8}}$, $V_{\text{CL3-8}}$, $V_{\text{CML3-8}}$ & $V_{\text{CLL3-8}}$

The MV models are plotted in Figure 9 to demonstrate the scale of association between increasing $V_{\text{Lung-GTV3-8}}$, $V_{\text{CL3-8}}$, $V_{\text{CML3-8}}$ and $V_{\text{CLL3-8}}$ and G2RP incidence. As volume of lung, especially CLL and CML receiving 3-8 Gy increases, the risk of G2RP increases steeply in both patients with PS 0 and PS1, but this is particularly evident in PS1 patients.

Figure 9. MV models from Table 7 and 9 plotted to demonstrate the scale of association between $V_{\text{Lung-GTV3-8}}$, $V_{\text{CL3-8}}$, $V_{\text{CML3-8}}$ and $V_{\text{CLL3-8}}$ and G2RP risk.



6.3.9 Impact of heart dosimetry on G2RP

Mean (MH-EQD2) and median heart EQD2s were 9.2 and 8.2 Gy respectively (Range .4-29.1 Gy). On UVA, no Heart-PCs or MH-EQD2 were statistically significantly associated with G2RP (Table 12), although Heart-PC1, PC3 and PC10 had p values of $<.2$ on UVA. There were no strong correlations between these three Heart-PCs and $V_{\text{Lung-GTV3-8}}$, $V_{\text{CL3-8}}$ or $V_{\text{CML3-8}}$ ($r <.04$), but Heart-PC1 and $V_{\text{CLL3-8}}$ were correlated ($r 0.50$). Therefore, Heart-PC1 and $V_{\text{CLL3-8}}$ were entered into the G2RP MV models separately. Heart-PC1, 3 and 10 were entered together with $V_{\text{Lung-GTV3-8}}$, FVC0 and PS; the best AIC-based MV model did not retain either Heart-PC1 or 10. Consequently Heart-PC1 and 10 were not taken forward to test with lung subunit dosimetry. Heart-PC3 was entered in the MV model 5 with FVC, PS and $V_{\text{Lung-GTV3-8}}$ and it remained significant (Table 12). Heart-PC3 (Figure 10) represents high heart volume receiving 6-36 Gy, 42-56 Gy and 67-75 Gy ($V_{\text{Heart6-36}}$, $V_{\text{Heart42-56}}$, $V_{\text{Heart67-75}}$ respectively). UVA of these heart dose bins showed $V_{\text{Heart42-56}}$ had a p value $<.2$. When $V_{\text{Heart42-56}}$ replaces Heart-PC3 in MV model 6 (Table 13) containing FVC0 and PS, $V_{\text{Heart42-56}}$ remained significant.

Figure 10. Heart PC3 representing high volume of heart receiving 6-36 Gy, 42-56 Gy and 67-75 Gy ($V_{\text{Heart6-36}}$, $V_{\text{Heart42-56}}$, $V_{\text{Heart67-75}}$ respectively)

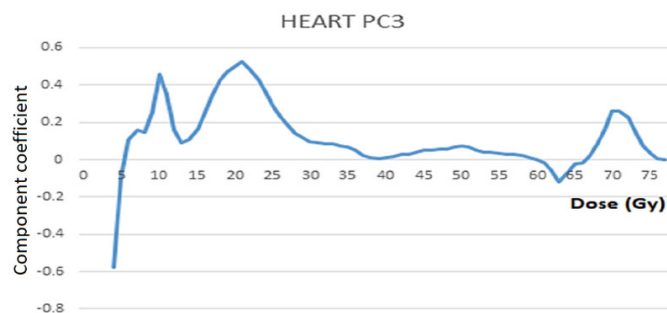


Table 12. Univariable and multivariable logistic regression models of G2RP: whole heart dosimetric factors. MV model 5: including Heart-PC3 + $V_{\text{Lung-GTV3-8}}$

Variable	UVA (n=114)		MV model 5 with Heart-PC3 and $V_{\text{Lung-GTV3-8}}$	
	Sig.	OR (95% CI)	Sig.	OR (95% CI)
Mean Heart EQD2	.23	1.05 (.98-1.10)		
Heart PC1	.15	1.34 (.90-2.00)		
Heart PC2	.41	.80 (.47-1.36)		
Heart PC3	.07	1.54 (.97-2.44)	.05	1.80 (1.01-3.20)
Heart PC4	.96	1.01 (.67-1.53)		
Heart PC5	.96	.99 (.65-1.51)		
Heart PC6	.43	.82 (.50-1.35)		
Heart PC7	.88	1.03 (.68-1.56)		
Heart PC8	.29	.79 (.51-1.22)		
Heart PC9	.33	.80 (.51-1.25)		
Heart PC10	.08	.68 (.45-1.05)		
PS	.05	2.45 (1.01-5.96)	<.01	4.42 (1.52-12.86)
FVC0	.15	1.02 (.99-1.04)	.05	1.03 (1.00-1.05)
$V_{\text{Lung-GTV3-8}}$	.02	1.08 (1.02-1.16)	.07	1.07 (.99-1.15)
$V_{\text{CL3-8}}$	.07	1.04 (1.00-1.09)		
Constant			.000	.004
AIC				121.6
AUC				.75
Hosmer-Lemeshow test				Chi sq 14.2; p .08
Nagelkerke R Sq				.23

There was poor correlation between $V_{\text{Heart42-56}}$ and $V_{\text{Lung-GTV3-8}}$, $V_{\text{CL3-8}}$ and $V_{\text{CML3-8}}$ ($r < .4$). $V_{\text{Heart42-56}}$ remained significant when $V_{\text{Lung-GTV3-8}}$, $V_{\text{CL3-8}}$ or $V_{\text{CML3-8}}$ were added to the MV model also containing FVC0 and PS (Table 13 - MV model 6, 7, 8 respectively). Interaction terms between $V_{\text{Heart42-56}}$ and $V_{\text{Lung-GTV3-8}}$, $V_{\text{CL3-8}}$ and $V_{\text{CML3-8}}$ were tested and found not to be significant and did not remain in the best AIC selected MV model.

$V_{\text{Heart42-56}}$ and $V_{\text{CLL3-8}}$ were moderately correlated ($r=.51$), and both became insignificant in the MV model when entered together (MV Model 9 in Table 13). Due

to the correlation between $V_{\text{CLL3-8}}$ and $V_{\text{Heart42-56}}$, it is difficult to determine which has the highest impact on G2RP incidence. In contrast, $V_{\text{CML3-8}}$ and $V_{\text{Heart42-56}}$ were not significantly correlated and in MV model 8 both remain significant with independent effects on G2RP (Table 13). AIC score was smaller and AUC similar for MV model 8 containing $V_{\text{CML3-8}}$, $V_{\text{Heart42-56}}$, FVC0 and PS compared to MV model 4 containing $V_{\text{CML3-8}}$, $V_{\text{CLL3-8}}$, FVC0, PS (AIC 123 and 124 respectively; and AUC .74) (Table 9 & 13). So, MV model 8 containing PS, FVC0, $V_{\text{CML3-8}}$, $V_{\text{Heart42-56}}$ was a slightly better model for G2RP.

Table 13. MV model with $V_{\text{Heart42-56}}$ and lung and subunits

	UVA (n=114)		MV model 6 adding, $V_{\text{Lung-GTV3-8}}$ to model with $V_{\text{Heart42-56}}$		MV model 7 replacing $V_{\text{Lung-GTV3-8}}$ with $V_{\text{CL3-8}}$ in model with $V_{\text{Heart42-56}}$		MV model 8 replacing $V_{\text{CL3-8}}$ with $V_{\text{CML3-8}}$ in model with $V_{\text{Heart42-56}}$		MV model 9 replacing $V_{\text{CL3-8}}$ with $V_{\text{CML3-8}}$ and $V_{\text{CLL3-8}}$ in model with $V_{\text{Heart42-56}}$	
	Sig.	OR (95% CI)	Sig.	OR (95% CI)	Sig.	OR (95% CI)	Sig.	OR (95% CI)	Sig.	OR (95% CI)
PS	.05	2.45 (1.01-5.96)	.01	3.63 (1.34-9.86)	<.01	4.33 (1.55-12.10)	<.01	4.31 (1.55-11.96)	<.01	4.82 (1.66-13.98)
Baseline FVC (% predicted)	.15	1.02 (.99-1.04)	.09	1.02 (1.00-1.05)	.08	1.02 (1.00-1.05)	.05	1.03 (1.00-1.05)	.06	1.03 (1.00-1.05)
$V_{\text{Lung-GTV3-8}}$	.02	1.08 (1.02-1.16)	.03	1.08 (1.01-1.17)						
$V_{\text{CL3-8}}$	.07	1.04 (1.00-1.09)			.04	1.05 (1.00-1.01)				
$V_{\text{CML3-8}}$	.17	1.02 (.99-1.06)					.03	1.04 (1.00-1.08)	.03	1.04 (1.01-1.08)
$V_{\text{CLL3-8}}$	.07	1.04 (1.00-1.08)							.17	1.03 (.99-1.08)
$V_{\text{Heart42-56}}$	.05	1.10 (1.00-1.20)	.04	1.12 (1.01-1.24)	.04	1.12 (1.01-1.24)	.01	1.14 (1.03-1.27)	.09	1.11 (.99-1.24)
$V_{\text{Heart6-36}}$	.40	1.01 (.99-1.03)								
$V_{\text{Heart67-75}}$	.46	1.06 (.90-1.25)								
Constant			.000	.003	.000	.004	.000	.003	.000	.002
AIC				122.6		123.5		123.0		123.1
AUC (95% CI)				.74 (.63-.85)		.74 (.63-.84)		.74 (.63-.84)		.76 (.65-.86)
Hosmer-Lemeshow test				Chi sq 7.9; p .44		Chi sq 2.4; p .96		Chi Sq 5.3; p.73		Chi Sq 8.6; p .38
Nagelkerke R Sq				.22		.21		.21		.23

Diagnostics of the best MV model for G2RP containing lung subvolume and heart dosimetry and clinical factors (MV model 8:PS, FVC0, V_{CML3-8}, V_{Heart42-56})

AUC for MV model 8 based on 6-fold cross validation was also .75, demonstrating good discrimination (Table 14). V_{CML3-8}, V_{Heart42-56} and PS remained positive discoveries after allowing for multiple hypothesis testing, and there was no indication of multicollinearity. MV model 8 accounted for 21% variation in outcome (Nagelkerke R² score). MV model 8 describes the data adequately with an Hosmer-Lemeshow test $p > .05$ suggesting no significant difference between predicted and observed rates for G2RP, and the calibration plot in Figure 11 also showed that predicted and observed rates of G2RP for each risk group were very close. There was randomness of residuals based on runs test and there was no correlation between Pearson residuals and predictors and fitted values according to the lack-of-fit test ($p > .05$). There were no studentized residuals with Bonferroni-adjusted $p < .05$ suggesting there were no outliers. The highest Cook's distances and hat values were in patients 9 and 109, but no studentized residuals were very large or small and all Bonferroni-adjusted p values were close to 1 (Diagnostic plot Figure 12 top). Regression coefficients were similar after removing these cases, further supporting that there were no influential cases (PS 1.5 Vs 1.6, FVC0 .03 for both, V_{CML3-8} .04 vs .06 and V_{Heart42-56} .13 for both).

Table 14. 6-Fold Cross validation of MV model 8 including heart and lung sub volumes (PS, FVC0, $V_{\text{Heart42-56}}$ and $V_{\text{CML3-8}}$)

	Percentage Correct		AUC of ROC (95% CI)	
	Training Set	Validation Set	Training Set	Validation Set
Cohort 1	77.7	84.2	.734 (.623-.845)	.896 (.744-1.00)
Cohort 2	75.5	94.7	.708 (.591-.826)	.938 (.808-1.00)
Cohort 3	78.9	72.2	.771 (.659-.882)	.584 (.294-.875)
Cohort 4	79.8	73.7	.712 (.585-.839)	.814 (.622-1.00)
Cohort 5	77.7	73.7	.763 (.652-.874)	.521 (.174-.867)
Cohort 6	78.7	57.9	.746 (.625-.868)	.733 (.488-.979)
Mean	78.1	76.1	.74	.75

Figure 11. Calibration plot for MV model 8 – Observed versus predicted G2RP incidence: Mean predicted G2RP rates calculated for MV model 8 vs observed rates; 28 patients in risk groups 1 (low risk), 2 (low-medium risk) and 3 (medium-high risk); and 29 patients in risk group 4 (high risk). Patients are assigned to risk groups via ascending predicted probability of G2RP according to the MV model. The lines connecting bins are intended as a visual guide. Standard error bars overlap between observed and predicted G2RP.

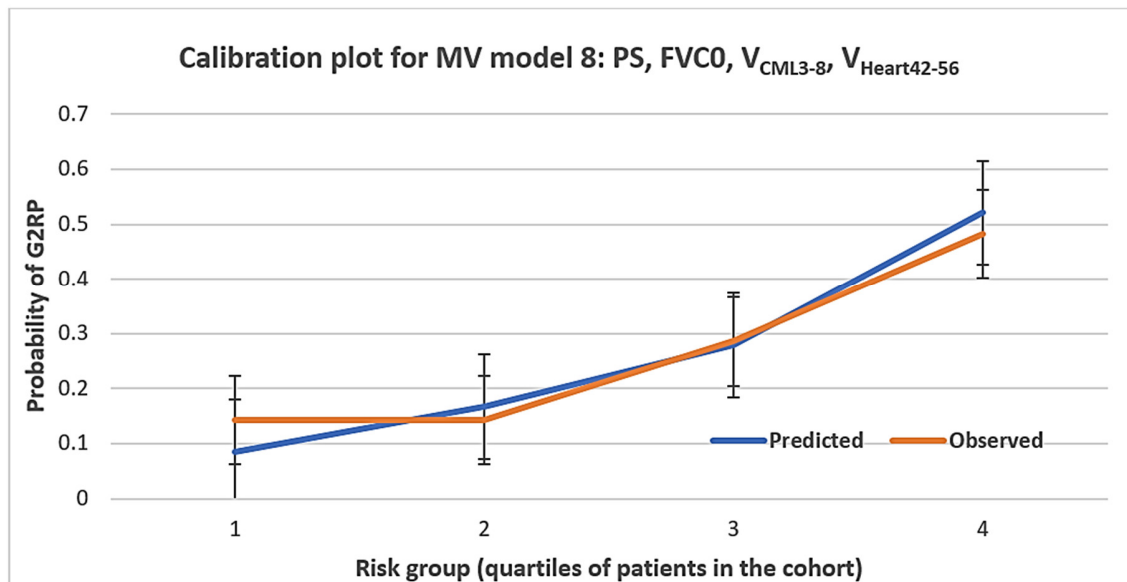
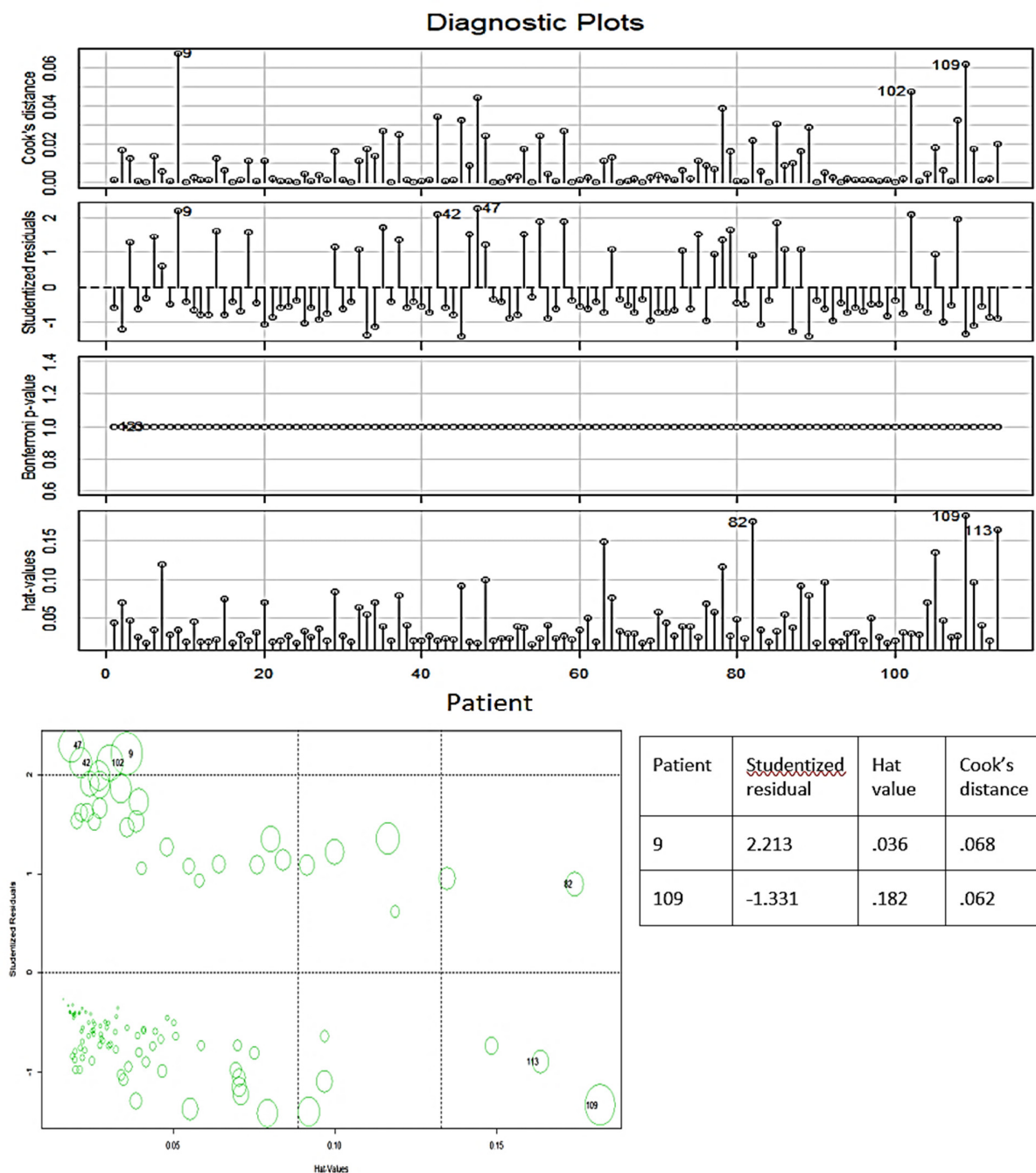


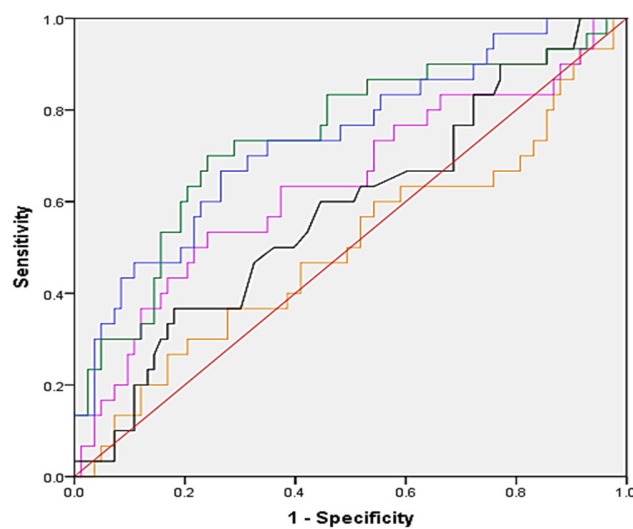
Figure 12. Top: Diagnostic plots of Cook's distance, studentized residuals, Bonferonni p and hat-values for MV model 8 (PS, FVC0, $V_{\text{Heart42-56}}$ and $V_{\text{CML3-8}}$). Bottom: Studentized residuals

plotted against hat-values: circle size proportional to Cook's distance. Patients 9 and 109 have the highest Cook's distance and studentized residual but small hat-values (table embedded in figure).



6.3.10 Combining dosimetric and clinical parameters in MV models for G2RP: comparing model performance

Figure 13. Receiver operator characteristic (ROC) curves for the performance of G2RP MV models with combined dosimetric and clinical factors (MV model 4 and 8) and dosimetric factors only. The area under the curves (AUC) for the models are in the table with 95% confidence intervals. *Red diagonal line: reference line.*



Covariates		AIC	AUC	95% CI
ML-EQD2	—	134.6	.50	.37-.63
$V_{\text{Lung-GTV3-8}}$	—	128.9	.64	.51-.76
FVC0	—	132.6	.58	.46-.70
MV model 4: PS+FVC0+ $V_{\text{CML3-8}}$ + $V_{\text{CLL3-8}}$	—	124.0	.74	.63-.85
MV model 8: PS+FVC0+ $V_{\text{CML3-8}}$ + $V_{\text{Heart42-56}}$	—	123.0	.74	.63-.84

Predictive performance of the two best combined MV models (MV model 4 consisting of PS, FVC0, $V_{\text{CML3-8}}$ and $V_{\text{CLL3-8}}$ and MV model 8 consisting of PS, FVC0, $V_{\text{CML3-8}}$ and $V_{\text{Heart42-56}}$) found in this chapter were better than conventional dose–volume metric (ML-EDQ2) and single parameters (FVC0 or $V_{\text{Lung-GTV3-8}}$) according to AUC scores (Figure 13). Model 8 had the lowest AIC score, suggesting this was the best model for G2RP.

6.3.11 Summary of key findings

- ML-EQD2 alone is not a good G2RP predictor in this isotoxically dose escalated cohort treated with concurrent CRT where ML-EQD2 variance is low.
- When ML-EQD2 is controlled and chemotherapy is delivered to all patients, high $V_{\text{Lung-GTV3-8}}$, poorer PS and higher baseline FVC (FVC0) were associated with higher G2RP risk.
- High $V_{\text{Lung-GTV3-8}}$ localising to contralateral lower and middle lung was associated with higher G2RP risk.
- Models combining clinical and dosimetric parameters predicted G2RP better than models with dosimetric or clinical parameters alone.
- Due to the correlation between $V_{\text{Heart42-56}}$ and $V_{\text{CLL3-8}}$, the effect of high $V_{\text{CLL3-8}}$ impacting G2RP may be a reflection of high $V_{\text{Heart42-56}}$ or vice versa secondary to RT delivery technique. The best MV model for G2RP consisted of PS, FVC0, $V_{\text{Heart42-56}}$ and $V_{\text{CML3-8}}$.

This is the first prospective study of an isotoxically dose escalated cohort resulting in a model for G2RP combining patient characteristics and heart and lung sub volume dosimetry when chemotherapy and ML-EQD2 effect is controlled.

6.4 Discussion of results

6.4.1 ML-EQD2 not a good G2RP predictor in isotoxic dose escalation

Exposure of various lung volumes to various radiation doses may be associated with increased RP risk, but the most consistently described predictor is ML-EQD2.[127][128][129][126][130][131][132][133] ML-EQD2 was the lung dosimetric

parameter used in IDEAL for isotoxic dose escalation. This is the reason for exploring the impact of ML-EQD2 alone on G2RP firstly here. By reducing dose distribution to DVH, and subsequently DVH to a single metric such as ML-EQD2, potentially critical dose-volume information which may help to best discriminate between plans at high or low risk for complications might be lost. The first results section in this chapter demonstrates this limitation of ML-EQD2, as ML-EQD2 was not a good predictor for G2RP in this cohort of isotoxically dose escalated patients with good baseline lung function. The expected G2RP rate for ML-EQD2 of 18.2 Gy was 20% excluding the effect of concurrent chemotherapy[304], but the observed rate was higher at 26% for delivered 14.4 Gy mean ML-EQD2. The lack of significant difference in ML-EQD2 between patients with and without G2RP may reflect the lack of ML-EQD2 variation in this cohort rather than an underlying lack of correlation between ML-EQD2 and G2RP. Yorke et al[303] also found that once MLD (median 19.9 Gy) was capped at 20 Gy, it was no longer a significant predictive factor for G2RP. They also postulated that these results may be due to the small MLD range resulting from strict planning constraints, similar to my findings.

Though IDEAL-6 used MLD-EQD2 for isotoxic dose escalation, another single point lung dosimetric parameter frequently used to predict RP incidence is lung-GTV V20 [133][124][154]. 39 patients had lung-GTV V20 >30% in this cohort, of whom 10 had G2RP, but there was no significant difference in mean V20 between patients with and without G2RP (Mann Whitney U p .78). So, lung-GTV V20, another single point dosimetric parameter was also not a good predictor for G2RP in this isotoxic setting

strengthening the need to explore the impact of patient characteristics and whole DVH data using PCA on G2RP.

6.4.2 Association of low dose irradiation with risk of G2RP

The higher than expected G2RP rate despite controlled ML-EQD2 suggests other clinical and dosimetric parameters play an additional role in G2RP. Here, low dose radiation (3-8 Gy EQD2 of 2-5 Gy) to larger volumes of the lower and middle sub-sections of the contralateral lung was associated with higher G2RP risk. In fact, low dose irradiation to lungs in many studies have been associated with RP incidence, with various suggested optimal threshold volumes. Doses as low as 2.5 Gy have been implicated in increased RP risk after SBRT.[306] Lung V5 has been associated with increased RP incidence in many studies [135][136][137], and it has been suggested to constrain V5 to <65% [138][139][140][141], <55% [142] [143], <50% [97] or <40% [144] to limit RP risk. High mean V5 has also been seen to impact radiation induced lung disease in a small study of early stage lung tumours treated with SABR.[107] The range of suggested constraint levels for the low doses suggest a possible interplay with clinical factors, as suggested in other studies.[89]

The association between the 3-8 Gy and G2RP risk could reflect potential shunting of perfusion from adjacent areas damaged by >8 Gy, resulting in better oxygenation in areas receiving <8 Gy, increasing free radical formation and more damage in areas receiving <8 Gy than >8 Gy. This hypothesis is supported by the SPECT study results of Farr et al [307], which showed dose-dependent lung perfusion changes, with small function increases in low dose areas and function reductions in high dose

areas, possibly due to function being shunted to areas receiving low dose. It has also been hypothesised that lung may be sensitive to large volumes exposed to low doses in proximity to high-dose regions. The putative mechanism is likely an inflammatory mechanism similar to that seen in spinal cord, where a large decrease in tolerance dose is seen if a short segment of cord is irradiated to high dose when surrounded by a low-dose bath compared with irradiating the segment alone.[308][309] In lung the inflammatory response due to low dose may result in hypersensitivity RP that extends outside the high dose volume.[310]

6.4.3 Association of contralateral lower lung irradiation with risk of G2RP

A high volume of contralateral middle-to-lower lung receiving low doses of 3-8 Gy was associated with increased G2RP risk. Other studies have found similar results, with contralateral lung V5 being associated with G2RP.[147] Specifically, keeping contralateral lung V5 to below 55.5% has been suggested to reduce G2RP risk.[147][146] High volume of contralateral lung receiving low doses could however reflect RT planning techniques, with ipsilateral lung receiving high doses to ensure PTV coverage. But contralateral lung function may be of particular importance in compensating for ipsilateral RP due to high dose.

Some studies have reported an increased risk of G2RP in patients with lower tumours, resulting in increased middle or lower lobe of lung irradiation, but other studies have failed to confirm this finding.[89][119][120][121][95][102][122][123][113] One hypothesis for the potential correlation of anatomic location and RP is a

variation in target cell density within individuals between the lobes, or interaction of the radiation response of adjacent organs, such as the heart which is described below. A second hypothesis is that lower lung irradiation induces inflammatory cytokines resulting in a greater inflammatory response and RP than upper lung irradiation, and this has been seen in animals.[300] The protective effects of superoxide dismutase (SOD) and L-N^G-nitroarginine methyl ester (L-NAME) also suggest that inflammatory cytokines induced by the irradiation may initiate indirect DNA damage both in and out of the radiation field.[300] Thirdly, respiration-dependent motion alters lung tumour position and normal lung geometry, especially in the lower lung, so that a higher volume of lung tissue is actually irradiated to low doses than estimated from the static dose distribution.[311]

There were no differences in G2RP risk in patients treated with IMRT or 3D conformal RT in this work, perhaps due to the small number of patients (13 out of 114 patients) being treated with IMRT. However, effects of low doses are of increasing interest now with increasing use of rotational IMRT, which may result in higher lung volumes receiving low doses.

6.4.4 Association of high baseline FVC with increased risk of G2RP

Patients treated in IDEAL had better baseline lung function than the standard LA-NSCLC patients treated with CRT in other cohorts. For example, the baseline mean FVC, FEV and DLCO in patients receiving CRT in a study by Wang et al were 67.2%, 76.3% and 65% respectively. In IDEAL, these were 95%, 77% and 70% respectively. One hypothesis is that ML-EQD2 may be a good predictor in the more standard

patients with poorer baseline lung function, but in patients with better baseline lung function, such as in IDEAL, a G2RP model combining lung function, patient characteristics and lung dosimetric parameters perform better than ML-EQD2 alone as shown in Figure 13.

Here, high baseline FVC representing better lung function prior to RT was significantly associated with G2RP in the MV model. The impact of baseline lung function on RP incidence has been controversial, as some studies have reported an effect and others have not.[102][104][105][106][107][108] Some studies have shown that RP can be milder in patients with more severe COPD than in patients with normal lung function.[109][108] A prospective study with 12 months follow-up in 135 patients with unresectable NSCLC showed patients with good pretreatment pulmonary function ($FEV_1 \geq 50\%$ predicted) experienced larger decrease in lung function tests than patients with poor function at baseline ($FEV_1 < 50\%$ predicted); however the presence or absence of symptoms of RP were not reported in that study.[110]

There are many hypotheses for mechanisms by which higher baseline lung function may increase RP risk. Firstly, better lung function reflects a larger functioning lung volume and higher level of cellular oxygenation, so likely increased free radical formation and damage due to radiation, and greater radiation sensitivity of alveolar cells and more significant lung injury. The second hypothesis is that patients with poor baseline lung function are more likely to experience significant symptoms which may be at a maximum level prior to treatment, therefore the post-treatment score

would be less likely to decrease by one grade, resulting in G2RP potentially being missed. Thirdly, tumor shrinkage after treatment could alleviate airway occlusion and improve ventilation improving symptoms. Fourthly, patients with low baseline lung function may have emphysema. Since emphysema is anatomically equivalent to the lack of functioning lung tissue, less risk of lung toxicity may be seen if there is less lung tissue to injure. In this study lung comorbidity was not collected. However, high baseline FVC may reflect worse COPD, as diagnosis of COPD is based on the forced expiratory volume in 1 s (FEV_1)/FVC < 0.70 ratio. Patients with COPD are often prescribed bronchodilators and steroids which may also prevent radiation-induced lung toxicity. A retrospective study showed irradiated lung volume without emphysema leads to more accurate dosimetric prediction of RP than traditional parameters.[312] A recent planning study showed significant reductions in functional lung volume receiving ≥ 20 Gy and mean functional lung dose when SPECT or hyperpolarised helium-3-MRI is incorporated into IMRT planning.[313] This phenomenon is being studied in detail in the FLAIR study which incorporates functional imaging in RT to avoid functioning lung.[314]

6.4.5 Association of poor PS with increased risk of G2RP

Patients with PS 1 had a higher risk of G2RP than patients with PS0. Poor PS may reflect less fit patients with comorbidities, and comorbidity is associated with increased RP risk.[95] Poor PS has also been associated with RP risk in other studies[102][96] and can be associated with increased inflammatory markers including IL-6 [315], which has been seen to increase the risk of RP.[316]

6.4.6 Influence of heart dosimetry on G2RP

High $V_{\text{Heart}42-56}$ was associated with increased G2RP risk. This effect was independent of $V_{\text{Lung}3-8}$, $V_{\text{CL}3-8}$ and $V_{\text{CML}3-8}$, however due to the correlation between $V_{\text{Heart}42-56}$ and $V_{\text{CLL}3-8}$ it was difficult ascertain whether the effect is due to $V_{\text{Heart}42-56}$ or $V_{\text{CLL}3-8}$. A similar effect of intermediate dose to heart on RP was seen in a recent study of 103 mesothelioma patients receiving 50.4 Gy in 28 fractions.[303] A significant correlation between volume of heart receiving 35-47Gy and G2RP was seen, but no significant correlations were found for lung dose-volume metrics. Because the MLD planning constraint was strictly enforced and prescription dose was capped at 50.4 Gy, MLD was close to 20 Gy for most patients and controlled similar to the cohort in this chapter.

Huang et al found in 209 NSCLC patients, RP model including heart D10 (minimum dose to the hottest 10% of the heart), lung D35, and maximum lung dose performed better than RP models with lung variables alone.[175] However another study found no evidence of heart irradiation impacting moderate or severe RP in a study of 629 NSCLC patients.[183] Also, in another dose escalation study of 78 patients, heart dosimetry was not significantly related to RP, however only a selected few heart variables were tested here.[174] In a recent study which utilised PCA, some heart variables including mean heart dose, $V_{\text{Heart}5}$ and $V_{\text{Heart}30}$ were associated with RP on UVA, however only MLD remained significant on MVA.[184] In a recent study of NSCLC patients treated using IMRT with a mean heart dose of 10.4 Gy, heart and chamber dosimetry was not found to be significantly associated with Grade 3 or higher RP.[317] However, these patients were retrospectively reviewed, received

either 66 or 60 Gy, and only the following variables were tested in the MV model: heart V30, left atria V5, left ventricle V40, right atria V50, and right ventricle V55. The discrepancies between our results and those reported in some other studies may be due to a combination of different endpoints being studied and heart parameters being tested, MLD and chemotherapy effect not being controlled, or possible bias due to the retrospective nature of data collection.

6.4.7 Combined clinical and dosimetric models are better than single parameter models

Here, MV models of G2RP incidence incorporating clinical and dosimetric factors had better predictive performance than MV models based on clinical or dosimetric factors alone. It is important to consider clinical factors so that personalised OAR dose constraints can be determined to develop better isotoxic dose escalation strategies. For example, since G2RP risk may be higher in patients with poorer PS and higher baseline FVC, more stringent lung and heart dosimetric constraints may be needed to maintain an acceptable G2RP risk. A few studies have attempted to consolidate dosimetric and clinical factors into a single predictive model for RP, and these are discussed in section 1.3.2.2.5. However there appears to be no consensus on the best model likely due to the different datasets being used with different dosimetric constraints, dose delivery, and other differences in treatment.

6.4.8 Limitations

Though the model derived here was internally validated, it needs external validation. Smoking can be a preventive factor [111] and baseline comorbidity a causative factor

[95][168]. However, these data were missing in this cohort. RP is a “noisy” endpoint and therefore a limitation, as it is subject to considerable uncertainty. As noted in the QUANTEC report,[127] many factors can cause dyspnoea including anaemia, cardiac arrhythmia, infection, and tumour recurrence. Also, treatment-induced tumor shrinkage can improve lung function and thereby mask normal lung injury. The unique features of the work presented here, however, is the isotoxic dose escalation strategy with no treatment time protraction, the controlled ML-EQD2, consistent chemotherapeutic agents, prospective data collection with clear RP scoring system and availability of baseline dyspnoea scores. This uniformity made the dataset ideal for detecting subtle influences of other clinical and dosimetric factors on G2RP risk. Another limitation of this work was the use of the more pragmatic approach of geographical instead of anatomical segmentation of the lungs as anatomical segmentation of the lungs was thought to be more labour intensive if implemented in the clinical setting in the future. Though it is reasonable to use the geographical segmentation approach to study G2RP, as other studies have also indicated that lower location of tumours tend to be associated with increased RP risk, in future work to better understand links between lung lobe irradiation and the pathophysiology of G2RP an anatomical segmentation approach should also be explored.

6.5 Conclusion

Mean lung dose has limited predictive ability for G2RP in isotoxically dose escalated patients due to minimal MLD variance. Poor performance status, high baseline FVC and high volume of tumour-free lung receiving low doses of 3-8 Gy (EQD2 2-5 Gy) especially contralateral lung lower and middle sections, and high heart volume

receiving intermediate doses of 42-56 Gy (EQD2 37-55 Gy), were associated with higher G2RP risk. This study supports the merit of combining clinical and dosimetric parameters in G2RP predictive models. Further exploration with functional imaging and in-silico modelling studies are required to assess feasibility of avoiding low dose to high volume of contralateral lower and middle lung sections with good function, especially in patients with poor PS and high baseline FVC.

7. FINAL CONCLUSIONS AND FUTURE DIRECTIONS

Radiation-induced normal tissue toxicity limits attempts to improve OS in LA-NSCLC via radiotherapy dose escalation. This work derives novel models for survival and cardiopulmonary toxicity, combining patient, tumour and dosimetric factors, potentially allowing the therapeutic index of LA-NSCLC RT to be widened by improving understanding of radiation induced cardiopulmonary toxicity and aiding personalised tumour dose prescription.

The work in **chapter 3** was the first study to explore associations between OS, heart and cardiac substructure irradiation, and ECG changes representing cardiac damage in an isotoxically dose escalated cohort of LA-NSCLC patients. Larger PTV size, high volume of heart especially LA wall receiving high doses of EQD2 64-73 Gy ($V_{LAWall-64-73EQD2}$) and any ECG change within 6 months of RT were associated with poorer OS. Grouping of patients in high and low risk groups on the basis of prognostic index (PI) provided good discrimination between patients with shorter and longer survival. No direct significant associations between baseline ECG changes, heart or LA wall dosimetric parameters and any ECG change within 6 months of RT were seen, likely due to low event rates. The observed associations suggest that even small LA wall volume (2.2%) receiving high radiation doses may negatively impact OS, more acutely and greatly than the negative association between OS and heart irradiation seen in breast cancer and lymphoma patients, who are treated using lower radiation doses. The pathophysiology of acute radiation-induced cardiac damage needs to be determined in prospective functional studies, but the finding of

an association between OS and Any ECG change at 6 months after RT tentatively suggests a link between OS and radiation-induced cardiac damage. Though the sample size was small, higher $V_{\text{LAWall-64-73EQD2}}$ and Any ECG change were also associated with worse post-disease progression survival, which may reflect radiation-induced cardiac damage limiting tolerability of further treatment on progression of disease, thereby resulting in poorer survival.

In **chapter 4**, the hazard ratios for $V_{\text{LAWall-64-73EQD2}}$ and cardiac-morbidity, substituting for Any ECG change in the survival model from chapter 3, were corroborated in an independent standard dose retrospective cohort, despite differences in patient and treatment characteristics. The PI derived in chapter 3 was also validated in this independent cohort despite cardiac-morbidity substituting Any ECG change. However, the performance of the PI was not as good in this standard dose cohort as it was in the dose escalated cohort of chapter 3. So, the impact of other factors on OS were explored and younger age and high coronary ostia region receiving intermediate doses of 29-38 Gy EQD2 ($V_{\text{AV+0.5-29-38EQD2}}$) were found to be associated with worse OS. A refined PI was developed by combining factors identified in both cohorts (Age, PTV, cardiac event, $V_{\text{LAWall-64-73EQD2}}$ and $V_{\text{AV+0.5-29-38EQD2}}$), and classified patients into low and high-risk prognostic groups well when tested in both cohorts. In **chapter 5**, this refined PI successfully dichotomised patients in another small independent cohort into low and high-risk groups, despite substituting $V_{\text{AV+0.5-29-38EQD2}}$ with $V_{\text{Heart29-38EQD2}}$ and missing cardiac-event data. Closer monitoring for cardiac problems after stratifying patients into low and high-risk groups using PIs may allow earlier intervention for cardiac problems, potentially improving OS.

In **chapter 4**, higher $V_{\text{LAWall-64-73EQD2}}$ and $V_{\text{AV+0.5-29-38EQD2}}$ were significantly associated with worse OS, but were not statistically significantly associated with cardiac deaths or cardiac events directly likely due to low event rates. Baseline cardiac comorbidity was associated with higher cardiac event risk after RT as expected, which in turn was associated with poorer OS. Cardiac deaths were more common in patients with cardiac events. $V_{\text{LAWall-64-73EQD2}}$ and $V_{\text{AV+0.5-29-38EQD2}}$ were associated with a higher cardiac death rate, although this was not statistically significant. Rates were low in this retrospective study, possibly partly due to under-recording of cardiac events and deaths due to overlap of symptoms of disease progression and treatment toxicity.

In **chapter 5**, the larger combined cohort allowed identification of further factors associated with OS, which were not significant in the smaller individual cohorts. High $V_{\text{Heart3-12EQD2}}$, $V_{\text{Heart33-44EQD2}}$ and $V_{\text{LAWall64-73EQD2}}$ were statistically significantly associated with poorer OS in the combined cohort. As high $V_{\text{Heart3-12EQD2}}$, $V_{\text{Heart33-44EQD2}}$ and $V_{\text{LAWall64-73EQD2}}$ were correlated, it was difficult to determine which dosimetric factor impacted OS most. But a dose-volume-time effect was seen with heart volumes receiving low dose impacting OS later, and heart volumes receiving high and intermediate dose impacting OS earlier, potentially due to different cardiac substructure radiation damage affecting OS at different time points. This needs investigation utilising prospective functional cardiac studies. However, this is in line with the findings in breast cancer, lymphoma and oesophageal cancer patients where low, intermediate and high doses are delivered respectively resulting in late, intermediate and early impact on OS as discussed in chapter 1.

In RTOG-0617, there was a 37% increase in local progression in the higher dose arm where lower OS was also seen, raising the question whether local control is a potential confounder for the cardiac dosimetric effect on OS seen. In chapter 5, the effect of GTV size on OS was also assessed as larger GTV is a surrogate for tumour burden and can impact local control. But the heart dosimetric effect on OS was found to be independent of GTV size and therefore local control. Also, post progression survival was lower in patients with higher volume of LA wall receiving high dose in IDEAL-6 in chapter 3, which also indicates that the impact of heart dosimetry on OS is independent of local control effect.

The results of Chapters 3, 4 and 5 results make a case for cardiac substructure sparing in lung cancer RT. However, cardiac substructure sparing could potentially increase lung irradiation due its proximity to heart. The work in **chapter 6** is the first to my knowledge to derive combined dosimetric and clinical predictive models for G2RP using lung-GTV DVH wide analysis and lung sub volume localisation in an isotoxic dose escalation cohort. ML-EQD2 has been described as the most consistent predictor for G2RP. However, in an isotoxically dose escalated cohort with minimal ML-EQD2 variance and consistent chemotherapy effect, ML-EQD2 was found to have limited predictive ability for G2RP in my work. A model consisting of poor performance status, high baseline FVC, high volume of tumour free lung receiving low doses of 3-8 Gy (EQD2 2-5 Gy), especially contralateral lung middle subsection, and high heart volume receiving intermediate doses of 42-56 Gy (EQD2 37-55 Gy), was associated with higher G2RP risk suggesting a possible synergistic effect of lung and heart irradiation on G2RP. This study supports the merit of

combining clinical and dosimetric parameters in G2RP predictive models. Further exploration with functional imaging and in-silico modelling studies are required to assess the feasibility of avoiding low doses to high volumes of contralateral lower and middle lung sections with good function especially in patients with poor PS and high baseline FVC.

Future directions

A recent review found no consensus on heart dose-constraints used in NSCLC treatments, with most studies setting very lenient constraints especially at higher heart dose-levels.[318] The findings from my work suggest that low, intermediate and high dose to heart could all potentially impact OS. An in-silico modelling study is currently being undertaken to assess the feasibility of lowering the volume of heart and LA wall receiving the dosimetric parameters identified in this work as being significantly associated with OS, without compromising PTV coverage, and assessing whether lowering high dose to LA wall would consequently reduce intermediate dose to coronary ostia region and low dose to whole heart due to their correlations. Combined lung functional imaging and in-silico modelling studies are required to assess feasibility of avoiding low doses to large volume of contralateral lower and middle lung subsections with good function especially in patients with poor PS and high baseline FVC.

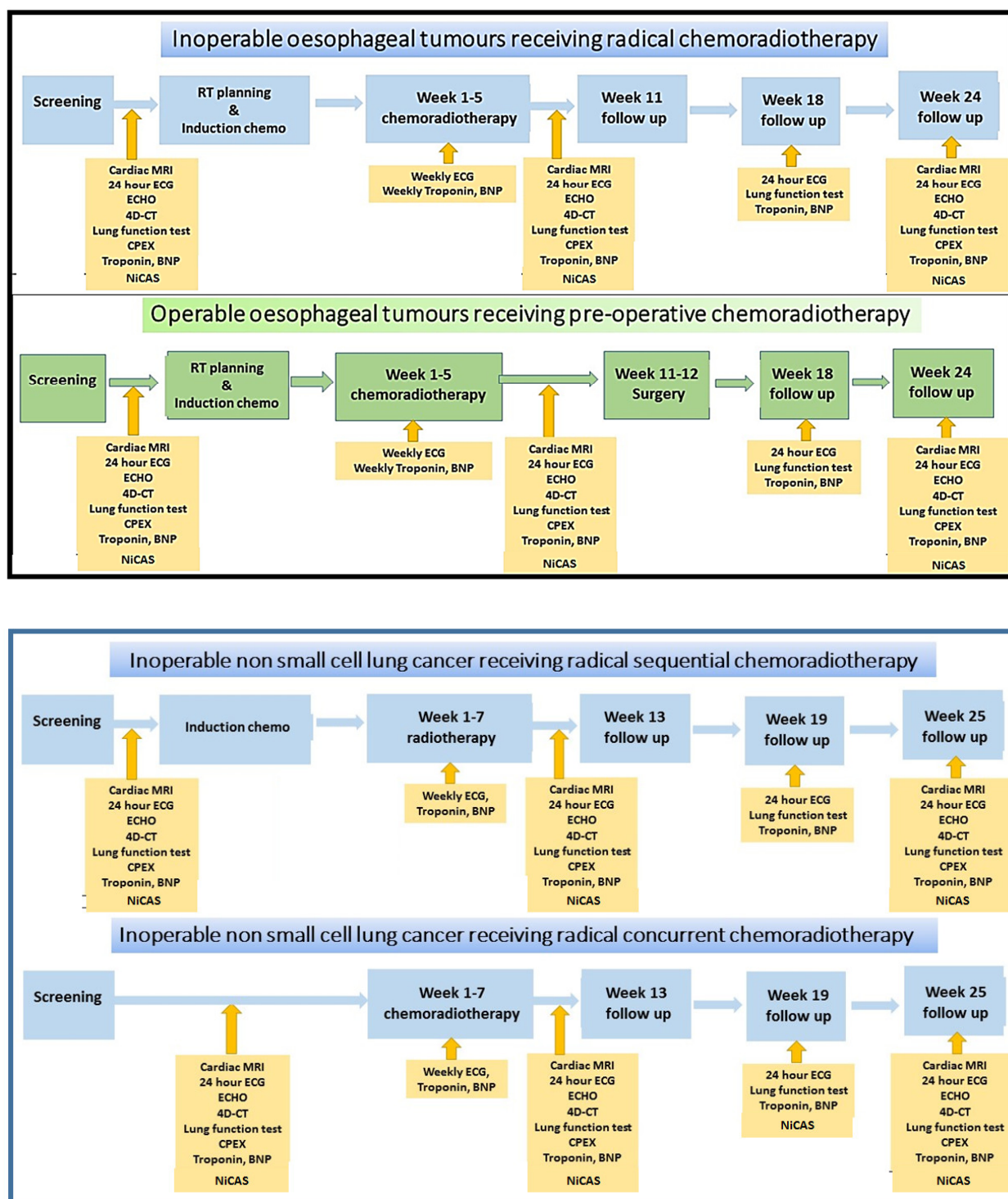
The pathophysiology of cardiopulmonary radiation damage needs further investigation. A prospective exploratory cardiopulmonary functional study of 25 patients incorporating serial cardiopulmonary functional tests before and after RT in

the acute and subacute setting has been planned to investigate the mechanism of damage and better differentiate between cardiac related and disease related deaths. The planned objectives and endpoints are listed in Table 1 and the proposed trial schema is detailed in Figure 1. Early detection of subclinical cardiopulmonary changes may allow preventative measures to be implemented. So, it may be useful to incorporate functional investigations such as cardiopulmonary exercise (CPEX) testing, cardiac MRI and 4D-CT into the RT planning process and subsequent follow up, initially to improve the predictive power of dose-volume-based models of respiratory and cardiac tolerance, and ultimately to further individualise dose-prescription and delivery according to these models.

Table 1. Proposed objectives and endpoints for the planned prospective cardiopulmonary functional study

Primary Objective	Endpoints
Identify associations between cardiac damage and RT	Changes in ECGs from baseline to 6 months after RT seen in >40% patients
Secondary Objective	Endpoints
1)Identify associations between heart substructure pre-defined dosimetric parameters and changes in heart function seen on Cardiac MRI or 24 hour ECG	1) Late gadolinium enhancement of cardiac subendothelium and adenosine stress perfusion changes on cardiac MRI and conduction or ischaemic changes seen on ECG associated radiation dosimetry
2)Identify associations between heart substructure pre-defined dosimetric parameters and changes in functional status of the patient Assess whether 24 hour ECG is an adequate surrogate for MRI changes associated with RT	2)Deterioration on CPEX test results compared to baseline
3)Assess whether blood cardiac biomarkers are surrogates for MRI and 24 hour ECG changes associated with RT	3)Strong correlation between 24hour ECG conduction or ischaemic changes and MRI changes stated in primary endpoint
4)Identify associations between lung and heart substructure pre-defined dosimetric parameters and changes in lung and heart function to explore the synergistic effect seen on functional imaging	4)Strong correlation between Troponin and BNP and conduction or ischaemic changes on 24 hour ECG or MRI changes stated in primary endpoint
5)Assess feasibility of achieving the cardiac substructure and lung dosimetric parameters identified above by incorporating functional imaging	5)Higher percentage decrease in lung function in areas of lung irradiation to predefined dosimetric parameters when heart substructures also irradiated to pre-defined dosimetric parameters compared to when lung only irradiated to predefined dosimetric parameter
Tertiary/ Exploratory Objective	Endpoints
Exploration of other relationships heart substructure and lung irradiation and heart and lung toxicities	Novel heart substructure and lung dosimetric parameters identified to be correlated to - increased cardiac changes seen on cardiac MRI or 24 hour ECG such as ischaemic changes, conduction abnormalities or left ventricular dysfunction or - lung changes such as pneumonitis seen on 4D-CT - cardiopulmonary functional deterioration based on CPEX

Figure 1. Proposed schema for the prospective cardiopulmonary functional study



Patients in the control arms will have Cardiac MRI, 24-hour ECG, ECHO, 4D-CT, Lung function test, CPEX, Troponin, BNP at screening pre-chemotherapy and also 2 weeks after completion of course.

Concluding remarks

This work adds to the knowledge about the nature, magnitude and timing of whole heart and cardiac substructure irradiation on overall survival. Novel survival and lung toxicity models have been obtained combining clinical and dosimetric factors. This will aid future management of LA-NSCLC, further personalising radiation dose escalation strategies. The planned in-silico and prospective cardiopulmonary functional studies will contribute additional knowledge regarding practical implications and underlying mechanism of damage in the heart and lungs. Given the armoury of intensity-modulated photon, proton and ion beam RT technology and functional imaging techniques available, outcomes of dose-escalated NSCLC treatments may be improvable in the future via cardiac substructure and lung subvolume sparing dose-escalation techniques, given greater knowledge of cardiopulmonary toxicity.

APPENDICES

Appendix 1. Staging of lung cancer used at the time of data collection in this work

Table 1. Seventh edition of the TNM classification for lung cancer by the International Association for the Study of Lung Cancer (IASLC) staging committee in 2009.[319]

	Tumour (T)	Nodal status (N)	Metastases (M)
X	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy	Regional lymph nodes cannot be assessed	Distant metastasis cannot be assessed
is	Carcinoma in situ		
0	No evidence of primary tumour	No regional lymph node metastasis	No distant metastasis
1	Tumour < 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus) 1a: Tumour < 2 cm in greatest dimension 1b: Tumour > 2 cm but < 3 cm in greatest dimension	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	Distant metastasis 1a: Separate tumour nodule(s) in a contralateral lobe tumour with pleural nodules or malignant pleural/pericardial effusion 1b: Distant metastasis
2	Tumour > 3 cm but < 7 cm or tumour with any of the following features (T2 tumours with these features are classified T2a if < 5 cm): Involves main bronchus, > 2 cm distal to the carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung 2a: Tumour > 3 cm but < 5 cm in greatest dimension 2b: Tumour > 5 cm but < 7 cm in greatest dimension	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	
3	Tumour > 7 cm or one that directly invades any of the following: Chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium Tumour in the main bronchus < 2 cm distal to the carina but without involvement of the carina Associated atelectasis or obstructive pneumonitis of the entire lung Separate tumour nodule(s) in the same lobe	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)	
4	Tumour of any size that invades any of the following: Mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina Separate tumour nodule(s) in a different ipsilateral lobe		

T = size of the primary tumour and whether it has invaded nearby tissue; N = regional involved lymph nodes; M = distant metastasis.

Table 2. Seventh edition American Joint Committee on Cancer anatomic stage grouping of lung cancer (adapted from[320])

Anatomic stage	T	N	M
Occult carcinoma	X	0	0
0	is	0	0
1A	1	0	0
1B	2a	0	0
IIA	2b	0	0
	1, 2a	1	0
IIB	2b	1	0
	3	0	0
IIIA	1,2,3	2	0
	3,4	1	0
	4	0	0
IIIB	1,2,3	3	0
	4	2,3	0
IV	Any	Any	1

T = size of the primary tumour and whether it has invaded nearby tissue; N = regional involved lymph nodes; M = distant metastasis.

Appendix 2. Patient characteristics

2a) WHO Performance status (PS)

GRADE	WHO PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

2b) MRC Dyspnoea score

- 1 - not troubled by breathlessness except on strenuous exercise;
- 2 - Short of breath when hurrying on a level or when walking up a slight hill;
- 3 - Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace;
- 4 - Stops for breath after walking 100 yards, or after a few minutes on level ground

Appendix 3. Oxford University Hospitals lung radiotherapy guidelines

Indications for using radical RT

- 1. Patients with T1-3, N0-1, M0 NSCLC who decline surgery or have underlying medical conditions making surgery unacceptable and cannot receive ablative therapy can be treated with radical RT alone.*
- 2. Patients with bulky T3, T4 and / or N2 (occasionally N3 if can be encompassed in a radical RT field) NSCLC can be treated either with concurrent or sequential CRT, or as radical RT alone in those who are not fit for chemotherapy.*

Chemotherapy for CRT

Sequential CRT involves 3-4 cycles of a platinum doublet (induction chemotherapy). For non-squamous tumours a platinum agent plus Pemetrexed is delivered. For squamous tumours a platinum agent plus either vinorelbine or gemcitabine is delivered. A minimum interval of 4 weeks is required between the last dose of chemotherapy and the start of RT.

Concurrent CRT is offered to patients who are WHO PS 0-1 with no significant comorbidities and have localised disease encompassable within a radical RT field. 2 cycles of cisplatin (day 1, day 8) plus etoposide (day 1-5) on a 28 day cycle is delivered, with both chemotherapy and RT beginning on day 1 on a Monday.

RT

For Stage I-II NSCLC, radical RT alone can be used. For patients with borderline lung function but with small and central disease not suitable for stereotactic ablative RT (SABR), 60-66 Gy in 30-33 fractions over 6-6 ½ weeks on consecutive 5 days per week can be prescribed with the final deliverable dose being dependent on organ at risk (OAR) dose constraints (Table) being met. For CRT, similar RT doses are delivered.

Image acquisition

The planning computer tomography (CT) is a free-breathing helical CT scan of contiguous 2.5 mm axial slices from the upper cervical spine to the lower edge of the liver acquired for target and OAR delineation and dosimetry planning. Intravenous (iv) contrast is used for

central tumours to differentiate disease from blood vessels or atelectasis. A free-breathing 4 dimensional CT (4DCT) scan is also acquired to assess respiratory motion. The maximum exhale and maximum inhale datasets on 4DCT are labelled. In the absence of a 4DCT, fluoroscopy may be used to assess motion.

Volume delineation

The gross tumour volume (GTV) is delineated on the helical RT planning CT scan utilising information from bronchoscopy, endobronchial ultrasound, mediastinoscopy and positron emission tomography (PET)-CT scan. Following induction chemotherapy, the GTV is the post-chemotherapy extent of disease in the primary site (GTVp) and pre-chemotherapy involved nodes (GTVn). GTV is defined on the maximum exhale 4DCT dataset (GTVexh) and the maximum inhale 4DCT dataset (GTVinh). A composite of GTVexh and GTVinh generates 4DGTV and the full 4DCT dataset is checked to assess all motion of GTV has been captured within this 4DGTV.

Clinical target volume (CTV) is created by adding a margin to the GTV to account for any subclinical or microscopic disease. CTV is normally a minimum of 0.6 cm for squamous cell carcinomas and 0.8 cm for adenocarcinomas. CTV is edited to exclude anatomical boundaries that limit microscopic spread such as bone and chest wall. CTVinh and CTVexh are created from the GTVinh and GTVexh respectively by adding the above margins. CTVinh and CTVexh are merged to produce the final CTV. If induction chemotherapy is given to shrink the primary tumour to make the disease encompassable within a radical RT portal, treating the post-chemotherapy extent of disease in the GTVp with a margin for CTV is acceptable. If pre-chemotherapy primary tumour size is acceptable, the pre-chemotherapy extent of primary disease respecting anatomical boundaries is treated.

A set-up margin is added to the CTV to create a planning target volume (PTV) to account for variations in set-up with the immobilisation technique employed and corrected for by using daily image guided cone-beam CT. With daily online cone-beam CT imaging and repositioning a 0.5 cm margin is considered sufficient in OUH to account for setup variability. If 4DCT is not available but fluoroscopy is available, the conventional margins below can be modified at the discretion of the clinician.

Conventional CTV to PTV margins where 4DCT or fluoroscopy is unavailable:

Tumour position	Anterior/posterior	Lateral	Superior/Inferior
Upper Lobe	0.8 cm	0.8 cm	1.0 cm
Lower Lobe	1.0 cm	1.0 cm	1.5 cm

The following OARs are delineated: pericardium, oesophagus, brachial plexus (for upper lobe tumours), right lung, left lung, lung-GTV (volume of lung excluding GTV), spinal canal, and stomach and liver for lower lobe tumours.

Treatment planning

A minimum of 95% of the prescribed dose should be delivered to atleast 98% of the PTV, provided all OAR dose constraints are met (Table). PTV coverage of 92% may be acceptable where the PTV overlaps normal tissue. If the planning objectives and OAR dose constraints cannot be met with 3D conformal RT (3DCRT) then intensity modulated RT (IMRT) or Rapid arc is used. Hybrid Rapid arc may be considered for difficult cases where combined 3DCRT and Rapid arc plans are delivered each fraction. Contralateral lung should be spared traversing radiation wherever possible. Lung volume receiving greater than 5Gy (V5) should be less than 42% but 65% may be acceptable if the patient's lung function is adequate as per NCCN guidelines.[321]

Table. Summary of organ at risk (OAR) dose constraints

Organ	Parameter +/- limit	α/β	2Gy/33# or 1.8Gy/25# Parameter or limit	2.75Gy/20# Parameter or limit
0.3cm_PRV_CANAL	D_{max} ie < 0.1cc	2	<45Gy	<38Gy
Lung-GTV	Vx <35%	10	x = 20Gy	x = 19Gy
	Vx <50%		x = 13Gy	x = 12Gy
	Vx <42%		x = 5Gy	x = 5Gy
	MLD		<18Gy	<18Gy
Pericardium	Vx <46%	2.5	x = 30Gy	x = 26Gy
	D_{mean}		<26Gy	<22Gy
Oesophagus	D_{max} (chemo) ie <0.1cc	10	<58Gy	<55Gy
	D_{max} (no chemo) ie <0.1cc		<69Gy	<65Gy
	Vx <30%		x = 50Gy	x = 47Gy
	D_{mean}		<34Gy	<32Gy
Brachial Plexus	D_{max} ie <0.1cc		<60Gy	<50.5Gy
Stomach	D_{max} ie <0.1cc	10	<50Gy	<47Gy
Liver	D_{mean}	2	<28Gy	<24Gy

Vx - volume receiving greater than x Gy; MLD - mean lung dose; D_{max} - maximum dose; D_{mean} - mean dose; # - fraction; chemo – chemotherapy; Non_GTV_Lung* - Lung minus gross tumour volume; PRV - planning risk volume; α/β – alpha:beta ratio of the tissue

Appendix 4. IDEAL CRT chemoradiotherapy

The description from *Landau DB et al* is below [7]

Design

Patients received the highest prescribed tumor doses between 63 and 73 Gy deliverable while meeting the normal tissue dose constraints shown in [Table 1](#). For lungs, spinal cord, brachial plexus, and heart these constraints were held at levels determined from an earlier review ([11](#)). However, insufficient data linking dose to toxicity existed for an esophageal constraint to be defined up front, and so an incrementally increasing esophageal limit was used during the trial. To facilitate this process, patients were split after RT treatment planning but before tumor dose prescription into 2 nonrandomized groups based on dosimetric findings. In group 1, prescribed tumor doses were limited by an escalating esophageal constraint, whereas in group 2 prescribed tumor doses were limited by lung and other normal tissue constraints. Allocation of patients to these groups was therefore determined purely on the basis of dosimetry and not clinician choice.

Table 1

Summary of the radiation therapy planning and dose prescription process

Process steps				
Tumor coverage aim				
PTV	90% isodose to cover 98% of PTV			
Tumor dose prescribed to the ICRU reference point initially selected to achieve				
Lung	EQD _{2mean} 18.2 Gy			
Prescribed tumor dose reduced by 10%, and further if needed to meet the following limits				
Heart	D _{100%} <45 Gy, D _{67%} <53 Gy, D _{33%} <60 Gy			
Spinal cord	D _{0.1cc} ≤ 47 Gy			
Brachial plexus	D _{30%} ≤60 Gy, D _{0.1cc} ≤65 Gy			
Esophagus	Dose to 1 cm ³ =65 Gy	Dose to 1 cm ³ =68 Gy	Dose to 1 cm ³ =71 Gy	Dose to 1 cm ³ ≤63 Gy*
Limit for	Group 1: cohort 1	Group 1: cohort 2	Group 1: cohort 3	Group 2

Abbreviations: EQD_{2mean} = equivalent dose in 2-Gy fractions averaged across lung, excluding gross tumor volume (GTV); ICRU = International Commission on Radiation Units and Measurements; PTV = planning target volume.

Prescribed tumor dose finally limited to 63-73 Gy, patients being ineligible for the trial if this causes lung V_{20Gy} (the volume of lung excluding GTV receiving more than 20 Gy) or EQD_{2mean} to exceed 35% or 19.3 Gy, respectively.

*This dose level increased to 65 Gy, and then 68 Gy as safety data became available from group 1.

Group 1 was designed as a phase 1 study to establish an esophageal maximum tolerated dose (MTD), patients' prescribed tumor doses being limited by an escalating experimental constraint on dose delivered to the most highly irradiated 1 cm³ of esophagus. This esophageal dose constraint was progressively raised from 65 Gy to 68 Gy and then 71 Gy, following a 6 + 6 design ([Fig. E1](#); available online at www.redjournal.org), treating 6 or 12 patients at each level. It was initially planned to include a 73-Gy esophageal dose cohort, but the 73-Gy upper limit on prescribed tumor dose meant that in practice it was not feasible to deliver 73 Gy to 1 cm³ of esophagus. Dose-limiting toxicities were grade ≥ 3 esophagitis (Common Terminology Criteria for Adverse Events, version 4.0) occurring during or within 4 weeks of completing RT and late esophageal toxicity, which was monitored closely.

Group 2 comprised all trial patients whose prescribed tumor doses were limited by other dose constraints, often lung or cord, and was designed to provide further toxicity data, particularly for radiation pneumonitis (RTPN). For some group 2 patients, however, prescribed tumor dose was limited by a lower esophageal constraint, already known to be safe, initially set at 63 Gy to 1 cm³ ([Table 1](#)). As the trial recruited, this group 2 esophageal limit was progressively raised to levels for which early toxicity had been found to be acceptable in cohorts of 12 patients in group 1.

Feasibility and survival data were analyzed jointly across both groups, comprising the phase 2 element of the study.

Interventions

Concurrent chemotherapy was 2 cycles of intravenous cisplatin (75 mg/m²) on days 1 and 29 of RT, and intravenous vinorelbine (15 mg/m²) on days 1, 8, 29, and 36. No induction or consolidation chemotherapy was allowed.

Radiation therapy planning was the same for groups 1 and 2. Three-dimensional (3D) or 4-dimensional (4D) CT images were collected during quiet breathing, and on 3D-CT images the gross tumor volume (GTV) was contoured and then expanded by 5 mm to create a clinical target volume and by a further 5-mm minimum radial and 10-mm minimum cranio-caudal to form a planning target volume. On 4D-CT, a composite volume was formed by merging GTVs outlined on the different scan phases, then expanded by 5 mm to form a clinical target volume and by 5 mm minimum further in all directions to form a planning target volume. Most patients were treated using 3D conformal plans comprising 3 to 5 photon fields of energy 5 to 8 MV. Some were treated using volumetric modulated arc therapy (VMAT), according to available center resources. Dose distributions were calculated using “type-b” superposition–convolution algorithms ([12](#)), and all tumor doses were prescribed to the International Commission on Radiation Units and Measurements (ICRU) reference point.

The tumor dose prescription process is summarized in [Table 1](#). For each patient an initial prescribed tumor dose was selected to achieve a target value of 18.2 Gy for lung EQD_{2mean}, the average equivalent dose in 2-Gy fractions delivered to all CT voxels of both lungs excluding the GTV [13](#), [14](#). This level is associated with a 20% rate of Southwest Oncology Group grade 2 to 5 RTPN and a presumed grade 3 to 5 rate of <10% [13](#), [15](#). The prescribed tumor dose was then reduced by 10% to allow for toxicity caused by concurrent chemotherapy, and further if necessary to meet the tabulated dose constraints for esophagus, brachial plexus, heart, and spinal cord ([11](#)). If this caused the prescribed tumor dose to fall below the trial minimum of 63 Gy, the lung EQD_{2mean} limit was relaxed to 19.3 Gy, and the patient would still receive a prescribed tumor dose of 63 Gy provided this relaxed lung limit and all the other normal tissue constraints listed in [Table 1](#) could be met. Prescribed tumor doses were capped at 73 Gy to limit damage to central blood vessels and airways.

Quality assurance was overseen by the Radiotherapy Trials Quality Assurance Group of the National Cancer Research Institute. Before starting the trial, clinicians and physicists from each center attended an outlining and dose prescription workshop. Clinicians outlined 2 benchmark cases (16), which were checked against contours drawn by the principal investigator, and planned 2 pre-outlined benchmark cases, which were reviewed to ensure that trial dosimetric aims were met. An additional arc-planned case was checked for centers introducing VMAT. Equipment details were collected via an online questionnaire. Contouring and dosimetry of each center's first recruited case was independently reviewed before treatment. Further reviews were requested, where deemed necessary, to ensure protocol compliance. Subsequently all treatment plan data were collected centrally and analyzed retrospectively to verify conformance to the trial protocol.

Appendix 5. Localisation of dose bins in a structure to its substructures

Two approaches were used to localise the associations seen between the outcomes and whole heart dosimetry to corresponding cardiac substructures: a graphical interrogation of the shapes of the heart dose-distributions of a sample of 20 patients with top PC scores (for PCs most significantly associated with outcome) mapped to a single reference geometry and a mathematical approach using principal components (PCs) of substructures. Once both methods demonstrated similar results in the cardiac substructure localisation study, only the graphical approach was used to localise the associations seen between lung toxicity and Lung-GTV dosimetry to corresponding lung sub-volumes in the subsequent chapters.

Approach 1: Principal component (PC) approach to localisation to substructure

The first method of localisation involved UVA/MVA of associations between outcomes and the scores of individual cardiac substructure principal components (ss-PCs). To avoid excessive multiple testing, only ss-PCs that closely aligned with 'heart-PC_{max}' (the whole-heart PC most strongly associated with all cause death rate (DR) on MV model) were studied. Normalised dot product criterion was used to assess the closeness of alignment between ss-PCs and heart-PC_{max}. Normalised dot product of ss-PC was defined as:

$$\text{NDP} = \frac{(\sum_j \text{ss-PC}(d_j) \times \text{peak-PC}(d_j)) / \{(\sum_j \text{ss-PC}(d_j)^2)(\sum_j \text{peak-PC}(d_j)^2)\}^{1/2}}{(\sum_j \text{heart-PC}_{\max}(d_j) \times \text{peak-PC}(d_j)) / \{(\sum_j \text{heart-PC}_{\max}(d_j)^2)(\sum_j \text{peak-PC}(d_j)^2)\}^{1/2}}$$

in which j indexes the dose-bins of each PC, and peak-PC is obtained from heart-PC_{max} by setting all bins outside the high-dose peak of heart-PC_{max} to zero. An normalised dot product (NDP) ≥ 1 indicates that the high-dose peak component of the substructure PC is at least as great as that of heart-PC_{max}.

Approach 2: Graphical approach to dose localisation to substructure

This methodology was developed in house by Dr Daniel Warren, and his description of the method is set out below in italics. A summary is detailed here.

Heart substructure localisation: To localise heart dose bins found to be significantly associated with DR to the most relevant heart substructures, a sample of 20 patients were studied with the highest quartile for scores of heart-PC_{max} (representing 20 patients with the largest volumes of heart receiving the doses represented by the peak (*heart-dose-peak*) in heart-PC_{max}) as well as all patients with $>1\text{cm}^3$ heart volume receiving the *heart-dose-peak* in heart-PC_{max}. The shapes of the heart dose-distributions of all patients were mapped to a single reference geometry using an in-house MATLAB program. Binary masks were created from each patient's whole heart, atria and ventricles, and registered to the corresponding masks of a reference patient by affine transformation. 3D dose distributions were mapped to the reference geometry via the same affine transformations, and a threshold was applied to identify the regions where the *heart-dose-peak* in heart-PC_{max} lie for each patient. Two-dimensional projections were created from each of the registered dose-volume masks in the coronal, sagittal and transverse planes. The process is equivalent to casting rays in the posterior-anterior, left-right or inferior-superior directions respectively: if a ray encounters one or more voxels of the mask, a '1' is recorded, and otherwise '0' is recorded. Projections

in a given plane were summed for all hearts analysed and the result was divided by the number of hearts, producing a 2D probability distribution for dose greater than or equal to a set dose level occurring at any point on the projection within the structure of interest. Projections were convolved with a Gaussian smoothing kernel (3mm standard deviation) to avoid identification of features smaller than the typical registration error. This process was carried out for both for the whole heart and for each cardiac substructure, allowing visual localisation of *heart-dose-peak*. The cardiac substructure volume receiving *heart-dose-peak* were then entered into the final MV model as an independent variable to replace heart-PC_{max}. If the correlation between the heart dosimetric factors and substructure dosimetric factors were strong ($r > .4$)[225], these were entered into separate MV models..

Lung sub-volume localisation: To localise Lung-GTV dose bins found to be significantly associated with lung toxicity to the most relevant lung sub-volume, 20 patients with lung toxicity (group P1) and 20 patients without (Group P0), both groups containing patients with the largest volumes of Lung-GTV receiving the doses represented by the peak (*lung-dose-peak*) in the Lung-GTV PC that remains significant in the best AIC selected MV model (lung-PC_{max}). 20 patients was used as this was the random sample number chosen for the heart substructure localisation and therefore taken forward here for consistency. A graphical interrogation of the shapes of the Lung-GTV dose-distributions of these patients was carried out by mapping them to a single reference geometry using an in-house MATLAB program as described above in the heart localisation section and Appendix 5. Binary masks were created from each patient's lung-GTV and IL, CL, IUL, IML, ILL, CUL, CML and CLL volumes and registered to the corresponding masks of a reference patient by affine transformation. Left lungs were flipped to overlay on top of right lungs. The patients were then separated into groups depending on whether their contralateral lung was left or right, and the affine transform to a reference lung on the same side was determined. 3D dose distributions were

mapped to the reference geometry via the same affine transformations, and a threshold was applied to identify *lung-dose-peak*. Lung regions receiving *lung-dose-peak* were visualised by taking 2D projections through the reference geometry in each principal anatomical plane (transverse, coronal, sagittal), producing images with pixel values that represent the percentage of patients for whom *lung-dose-peak* is present at each point projected perpendicular to the plane. Projections were convolved with a Gaussian smoothing kernel (7mm standard deviation reflecting the average distance to agreement of the registered structures) to avoid identification of features smaller than the typical registration error. This process was carried out for both Lung-GTV and for each lung sub-volume, allowing visual localisation of the *lung-dose-peak*. Differences in probabilities between groups P0 and P1 receiving *lung-dose-peak* were calculated producing images with pixel values representing this difference in probability at each point projected perpendicular to the plane.

The volume of CL or IL receiving *lung-dose-peak* were extracted depending on the results of the graphical localisation and they replaced lung-PC_{max} in the MV model if on UVA these were found to be associated with lung toxicity. Volumes of upper, middle or lower sections of CL or IL receiving *lung-dose-peak* were then extracted depending on the results of graphical localisation. Subsection dosimetric variables with p value $\leq .20$ on UVA replaced lung-PC_{max} in the MV model. Lung and sub-volume dosimetric variables with correlation coefficient of $> .4$ were entered into separate MV models.

Details of the graphical localisation method. This section was written by Dr Daniel Warren.

Data preparation

Radiotherapy planning data were exported from the treatment planning system in DICOM-RT format and converted into MATLAB (R2014a; Mathworks, Natick, MA) data-structures using functions from CERR (Computational Environment for Radiotherapy Research). Binary label masks, indicating

whether each voxel of the CT scan lies inside or outside the structure of interest, were extracted for the heart and cardiac substructures (atria and ventricles) of all patients. Planned dose distributions were interpolated on to the same grid as the CT scan and thresholded at greater than or equal to the dose level identified in the whole structure to be associated with outcome (Gy), producing a binary mask of the volume which is dosimetrically similar to the dDVH PC found significant.

Mask registration

One structure set was randomly selected as a reference heart geometry, and a registration procedure was developed to find coordinate transformations that maps each of the other hearts (the test hearts) on to the reference, as follows. Synthetic registration target images were created from binary label masks for the test and reference hearts, with minor intensity variations introduced using the Euclidean distance transform from the surface of each substructure. An example image is presented in Figure 5). The MATLAB function `imregtform` was then used to identify the optimal affine transformation (translation, rotation, scale and shear) to map each test image to the reference image. The registration process used mean square difference as an image similarity metric, and a regular step gradient descent optimizer to perform a maximum of 100 iterations at 3 resolution levels. The resulting transformations were also applied to the thresholded dose distribution, allowing cross-comparison of the high dose volume on the geometry of the reference heart. The average final image following affine registration is presented in Figure 5.

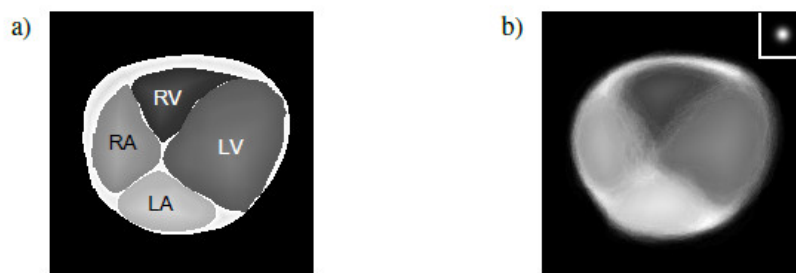


Figure 5: a) Synthetic registration target image for the reference heart, created from the delineated heart and substructures. Each substructure (labelled L/R = left/right, A/V = atrium/ventricle) is assigned an intensity, with individual voxel values modulated by the Euclidean distance transform

from the substructure surface. The voxel value ranges are distinct for each substructure. Image show an axial slice through the centre of the heart. b) Average synthetic image over all test hearts after registration. Insert: Gaussian kernel ($\sigma = 3\text{mm}$) used to smooth final dose projections, to same scale as main image.

Registration performance

Figure 6 illustrates the concordance of heart volumes in three dimensions before and after the registration process. The accuracy of the mapping was assessed quantitatively by comparing the masks for the 78 test hearts after transformation to the mask of the reference heart, using a series of standard metrics as given in Table 5.

The Dice similarity value indicates that, on average, 90% of voxels are correctly mapped from within the test heart to within the reference heart. The mean distance to agreement between the surfaces of the test and reference hearts is typically less than 3mm, as is the average distance between their centres of mass.

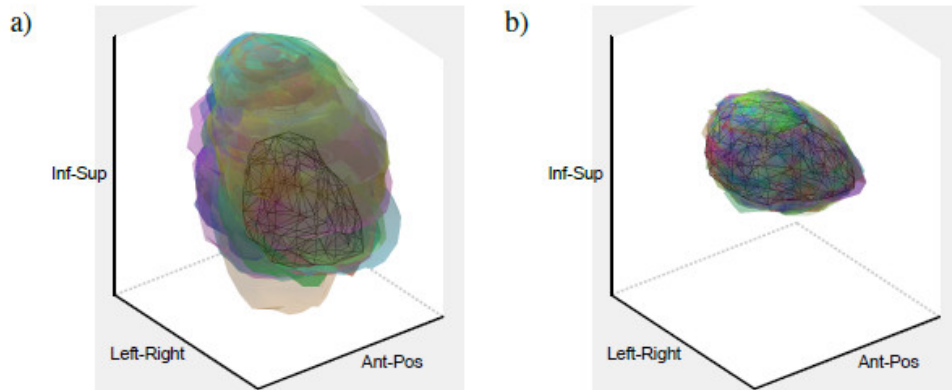


Figure 6: a) Simplified 3D renderings of all hearts in their original coordinate system before registration. Each heart is rendered in a different color. An example heart has been identified by black wireframe rendering. B) Equivalent 3D renderings following the registration process, with the

same heart identified by black wireframe. Visual inspection suggests that for this heart the affine transformation constitutes at least translation, scaling and rotation.

Performance metric	Value (mean $\pm$ s.d.)
Dice similarity coefficient	0.90 $\pm$ 0.02
Jaccard similarity coefficient	0.83 $\pm$ 0.03
Mean distance to agreement	2.6 mm $\pm$ 0.6 mm
Centre of mass displacement	2.5 mm $\pm$ 0.7 mm

Table 5: Standard metrics used to assess the performance of the mask registration process

The overall performance of the process is considered acceptable, given that affine transformations cannot account for local deformation, although the results indicate that the method is not suitable for identifying features of order 3mm and smaller.

Visualisation by projection

Two-dimensional projections were created from each of the registered high-dose volume masks in the coronal, sagittal and transverse planes. The process is equivalent to casting rays in the posterior-anterior, left-right or inferior-superior directions respectively: if a ray encounters one or more voxels of the mask, a '1' is recorded, and otherwise '0' is recorded. Projections in a given plane were summed for all hearts analyzed and the result was divided by the number of hearts, producing a 2D probability distribution for dose greater than or equal to a set level (Gy) occurring at any point on the projection within the structure of interest. The resulting images were convolved with a Gaussian kernel of 3mm standard deviation (shown to scale in the inset of Figure 5b) to avoid the identification of features smaller than the typical registration error. In order to produce the individual substructure images, the high-dose mask was first restricted to the appropriate substructure using a Boolean AND operation. The process was otherwise identical.

Appendix 6. Univariable Cox regression analysis of all cause death rate in IDEAL-6 patients: Oesophageal principal components

Co-variate	p-value	HR (95% CI)
Oesophageal PC1	0.27	1.21 (0.86-1.68)
Oesophageal PC2	0.38	1.18 (0.81-1.73)
Oesophageal PC3	0.93	1.02 (0.70-1.48)
Oesophageal PC4	0.33	1.19 (0.84-1.70)
Oesophageal PC5	0.61	0.88 (0.54-1.45)
Oesophageal PC6	0.67	0.70 (0.54-1.48)
Oesophageal PC7	0.41	1.15 (0.82-1.61)
Oesophageal PC8	0.63	1.09 (0.76-1.57)
Oesophageal PC9	0.34	1.19 (0.83-1.71)
Oesophageal PC10	0.52	1.23 (0.65-2.32)
Oesophageal PC11	0.41	1.20 (0.78-1.83)
Oesophageal PC12	0.72	0.92 (0.58-1.45)
Oesophageal PC13	0.98	1.01 (0.69-1.48)
Oesophageal PC14	0.70	0.91 (0.55-1.49)
Oesophageal PC15	0.69	0.92 (0.60-1.40)
Oesophageal PC16	0.39	0.84 (0.57-1.24)
Oesophageal PC17	0.68	1.08 (0.76-1.51)
Oesophageal PC18	0.59	1.11 (0.76-1.63)
Oesophageal PC19	0.60	1.13 (0.72-1.77)

Appendix 7. Diagnostics of multivariable model consisting of PTV, Any ECG change and $V_{L\text{Awall63-69}}$

Figure 1. Index plot to visualize the dfbeta values for Cox regression of time to death on covariates (Any ECG change, PTV and $V_{L\text{Awall63-69}}$) with most residuals symmetrically distributed around 0 and have very small values. Case 42 (furthest away from 0) is circled in red.

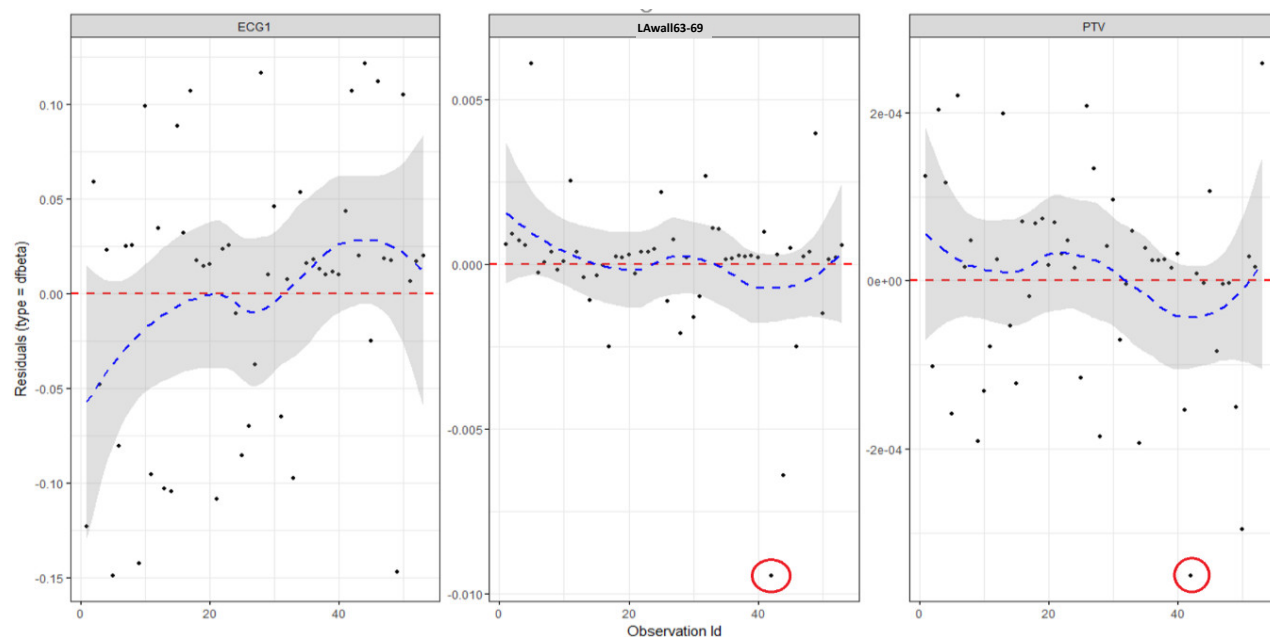
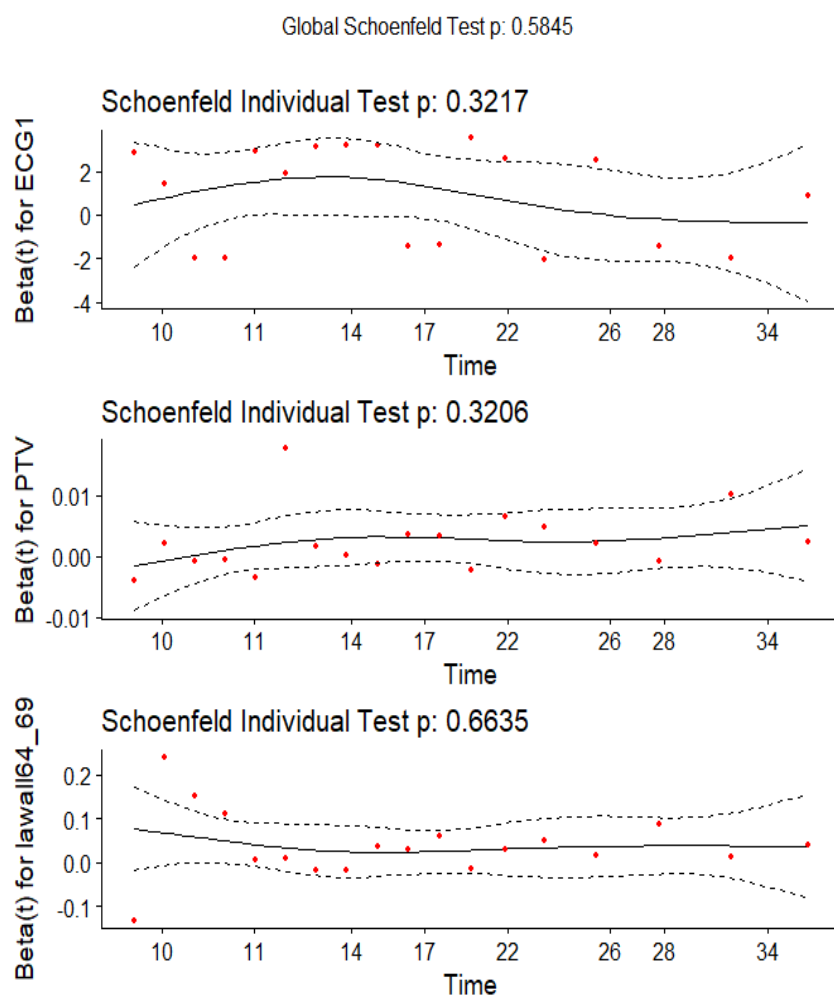


Table 1. Beta values and Standard errors (SE) of MV models for 53 patient cohort and 52 patient cohort (potential removed outlier 42)

Variables	Comparison of Betas for model with and without potential outliers	
	53 patient cohort Beta (SE)	51 patient cohort (exclude 2 outliers) Beta (SE)
Any ECG change at 6 months	.89 (.51)	.80 (.52)
PTV size (cm^3)	.002 (.001)	.003 (.001)
$V_{L\text{Awall63-69}}$ (%)	.04 (.02)	.05 (.02)

Figure 2. Plot of scaled Schoenfeld residuals against time for each co-variate in MV model containing PTV, Any ECG change, LA Wall 63-69 showing a random pattern. Also there was no significant correlation between the corresponding set of scaled Schoenfeld residuals with time



Appendix 8. Subcarinal node (SC) status impact on DR

SC status was suggested by a more recent study to be a confounder, so this analysis was carried out after the initial modelling was conducted in chapter 3 to assess if SC status is a confounder for high dose to LA wall.

Existence of SC has been suggested to be a bad prognostic factor though not significant in my study UVA. As SC could impact DR directly, and also impact dose delivered to LA wall due to its proximity, and therefore increase $V_{LAwall63-69}$. So SC status could be a confounder and was checked this effect. On entering SC status with the PTV, Any ECG change and $V_{LAwall63-69}$ together, the p-value for both Any ECG change and $V_{LAwall63-69}$ increase but $V_{LAwall63-69}$ remain significant at 0.04 and the HRs remain similar. When stratified according to SC status, the HR and p-value for $V_{LAwall63-69}$ remain similar to the MV model not containing SC status suggesting SC status is not a confounding effect for $V_{LAwall63-69}$. For Any ECG change, the p-value improves a little and HR increases when stratified according to SC status, suggesting SC status may not be a confounder for the Any ECG change effect. HR for PTV when stratified according to SC status remains similar but the p-value was no longer significant. As presence of SC could result in a larger PTV, it may be a confounder for PTV effect on DR.

Table shows MV model with SC added and also MV model stratified according to SC status

	UVA		MV model containing PTV, Any ECG change, $V_{LAwall63-69}$, and SC		MV model containing PTV, Any ECG change, SC		M MV model containing PTV, Any ECG change $V_{LAwall63-69}$	
Variables	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
PTV size (cm ³)	.04	1.00 (1.00-1.00)	.08	1.00 (1.00-1.00)	.04	1.00 (1.00-1.00)	.08	1.00 (1.00-1.01)
Any ECG change	.03	2.94 (1.12-7.76)	.12	2.25 (.82-6.16)	.06	2.59 (.97-6.96)	.08	2.43 (.90-6.55)
$V_{LAwall63-69}$	.01	1.04 (1.01-1.06)	.04	1.04 (1.00-1.07)			.02	1.04 (1.01-1.07)
SC	.12	1.92 (.84-4.37)	.09	2.42 (.88-6.65)	.06	2.55 (.95-6.86)		

Appendix 9. Table comparing IDEAL-6 and Oxford cohorts

Characteristic	IDEAL 6 (n=78)		Oxford (n=64)		Mann Whitney/T-test/ChiSq (p-value)
Age (years; median (range))	66	(43-84)	71	(44-89)	.002
WHO performance status No. (%)					.025
0	32	(41.0)	17	(26.6)	
1	46	(59.0)	34	(53.1)	
2	-		5	(7.8)	
3	-		1	(1.6)	
Missing	-		7	(10.9)	
Gender No. (%)					.087
Female	20	(25.6)	25	(39.1)	
Male	58	(74.4)	39	(60.9)	
Nodal status No. (%)					<.001
N 2 or 3	65	(83.3)	32	(50.0)	
N 0 or 1	13	(16.7)	29	(45.3)	
Missing	-		3	(4.7)	
Histology No. (%)					.470
Squamous	42	(53.8)	36	(56.3)	
Non-squamous	36	(46.2)	24	(37.5)	
Missing	-		4	(6.3)	
Planning target volume (PTV) (cm ³ ; median (range))	400.6	(138.7-1262.1)	319	(82 – 1120)	.004
4D CT used for planning No (%)	34	(44)	56	(88)	
Prescribed dose (no of patients)					
	63-65 in 30# (22)		66Gy in 33# (56)		-
	65.1-67 in 30# (15)		64Gy in 32# (3)		-
	67.1-69 in 30# (10)		62Gy in 31# (2)		-
	69.1-71 in 30# (11)		60Gy in 30# (2)		-
	71.1-73 in 30# (20)		58Gy in 29# (1)		-
Prescribed tumour EQD2 α/β 10 (no of pts)					
≤ 66 Gy	22		64		-
> 66 Gy	56		0		-
Mean prescribed tumour dose (EQD2)	69.3Gy		65.5Gy		<.001
Concurrent Chemotherapy					<.001
Yes	78		17	(26.6)	
No (sequential; no chemotherapy)	0		45	(70.3) (16;29)	
Missing	0		2	(3.1)	
Mean EQD2 Gy; median (range)					
Heart	8.0	(0.4-29.2)	7.6	(0.5-32.2)	.676
Left atrium wall	17.1	(0.5-64.2)	12.5	(0.5-56.2)	.090

Appendix 10. Oxford cohort 10 varimax rotated Heart Principal components

The mean heart dDVH (top) of 64 patients, plotted together with the 10 varimax-rotated principal components (PCs) (bottom) describing >95% of heart dosimetric variance in Oxford cohort.

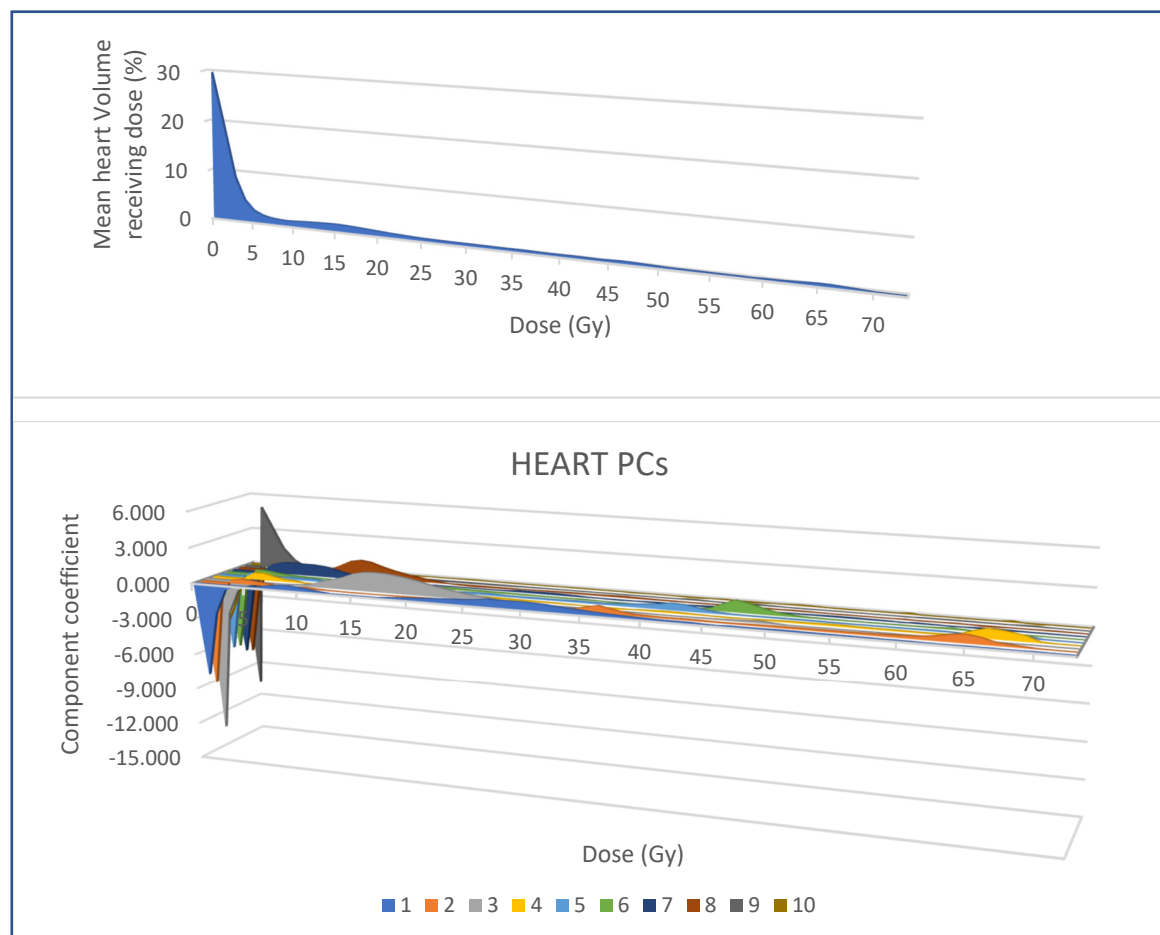
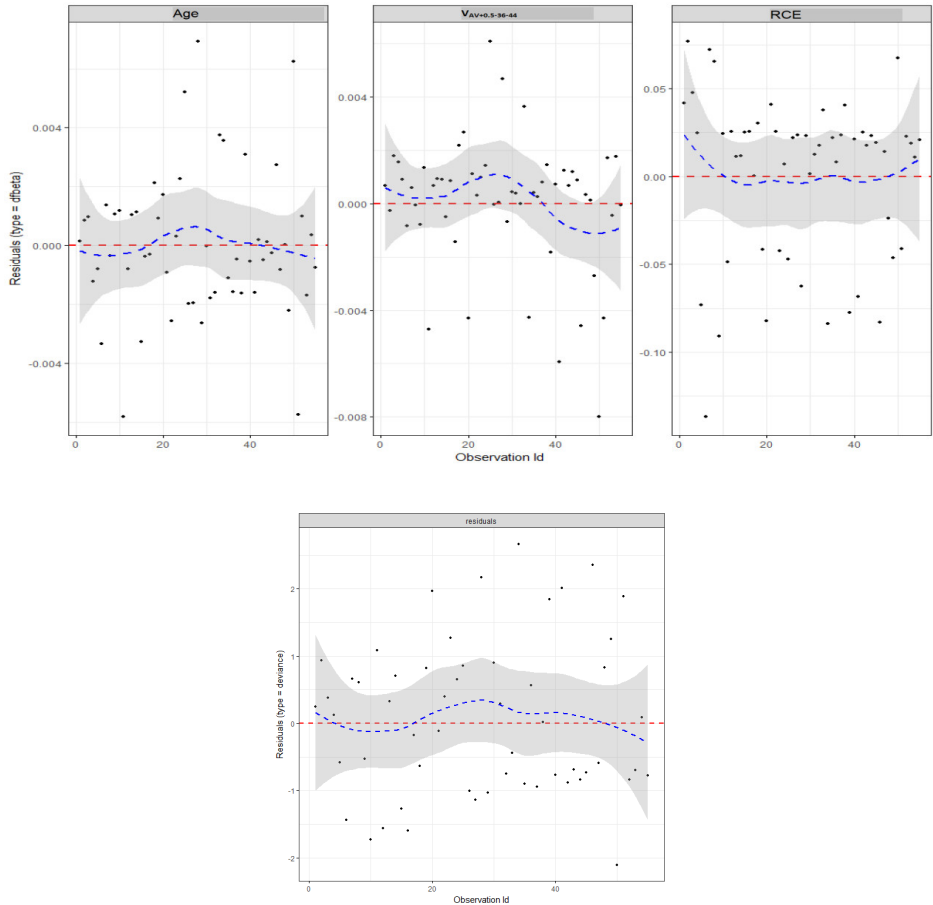


Table of variance explained by the PCs

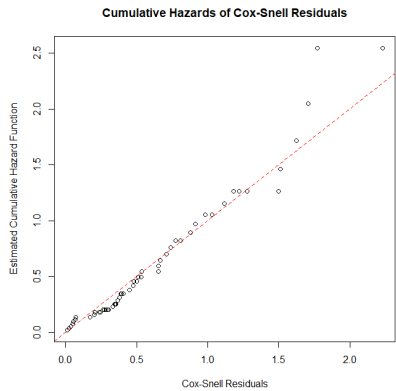
Heart Principal Component	% of Variance	Cumulative %
1	9.380	9.380
2	10.740	20.120
3	25.800	45.920
4	3.649	49.569
5	5.610	55.180
6	6.010	61.189
7	7.820	69.009
8	8.528	77.537
9	20.221	97.758
10	1.945	99.704

Appendix 11. Diagnostics of MV model 5 in Oxford cohort containing Age, cardiac-morbidity and $V_{AV+0.5-36-44}$

Index plots to visualise dfbeta values for the Cox regression of time to death on covariates in MV model 5 Table 8 (top three) and deviance residuals (bottom) to test for influential observations.



Plot of estimated cumulative hazard function against Cox-Snell residuals for MV 2 model containing Age, cardiac-morbidity and $V_{AV+0.5-36-44}$



Appendix 12. Smoking and Cardiac comorbidity are not confounders for heart substructure and cardiac event impact on DR based on Oxford analysis

MV cox regression model containing Age, cardiac-morbidity, and $V_{AV+0.5-36-44}$ in Oxford cohort

Co-variate	p-value	HR (95% CI)
Age	.02	.96 (.92-.99)
Cardiac-morbidity	.02	2.77 (1.18-6.49)
$V_{AV+0.5-36-44}$	<.01	1.06 (1.02-1.10)

MV cox regression model containing Age, cardiac-morbidity, $V_{AV+0.5-36-44}$ and smoking status in Oxford cohort

Co-variate	p-value	HR (95% CI)
Age	<.01	.95 (.91-.99)
Cardiac-morbidity	.02	2.75 (1.16-6.54)
$V_{AV+0.5-36-44}$	.03	1.05 (1.01-1.10)
Smoker/Ex-smoker V Non-smoker	.39	2.46 (.31-19.19)

MV cox regression model containing Age, cardiac-morbidity, $V_{AV+0.5-36-44}$ and baseline cardiac comorbidity in Oxford cohort

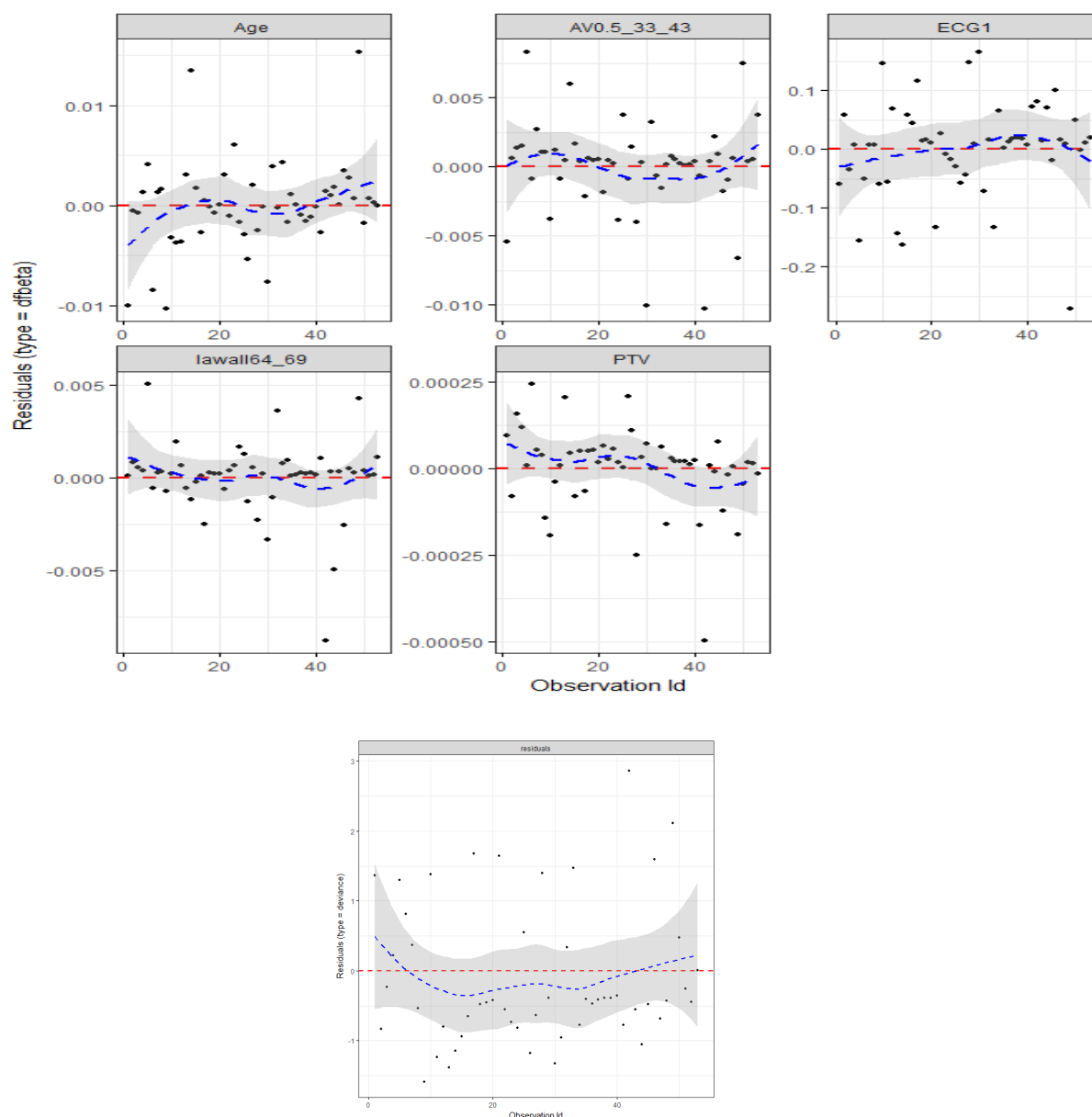
Co-variate	p-value	HR (95% CI)
Age	.02	.95 (.91-.99)
Cardiac-morbidity	.02	2.79 (1.15-6.72)
$V_{AV+0.5-36-44}$	.02	1.05 (1.01-1.10)
Baseline Cardiac comorbidity	.85	1.08 (.58-2.45)

p-values remain significant for Age, Cardiac-morbidity and $V_{AV+0.5-36-44}$ and HRs remain similar after the addition of smoking status and baseline cardiac comorbidity suggesting these are not confounders for the findings in the MV model of Age, Cardiac-morbidity and $V_{AV+0.5-36-44}$.

Appendix 13. Diagnostics of MV model in IDEAL-6 including Age, PTV, Any ECG

change, $V_{\text{LAWall63-69}}$ and $V_{\text{AV+0.5-36-44}}$

Index plots to visualise dfbeta values for the Cox regression of time to death on covariates in the MV model (top five) and deviance residuals (bottom) to test for influential observations. Case 42 and 49 were furthest from 0 and may be potential outliers.

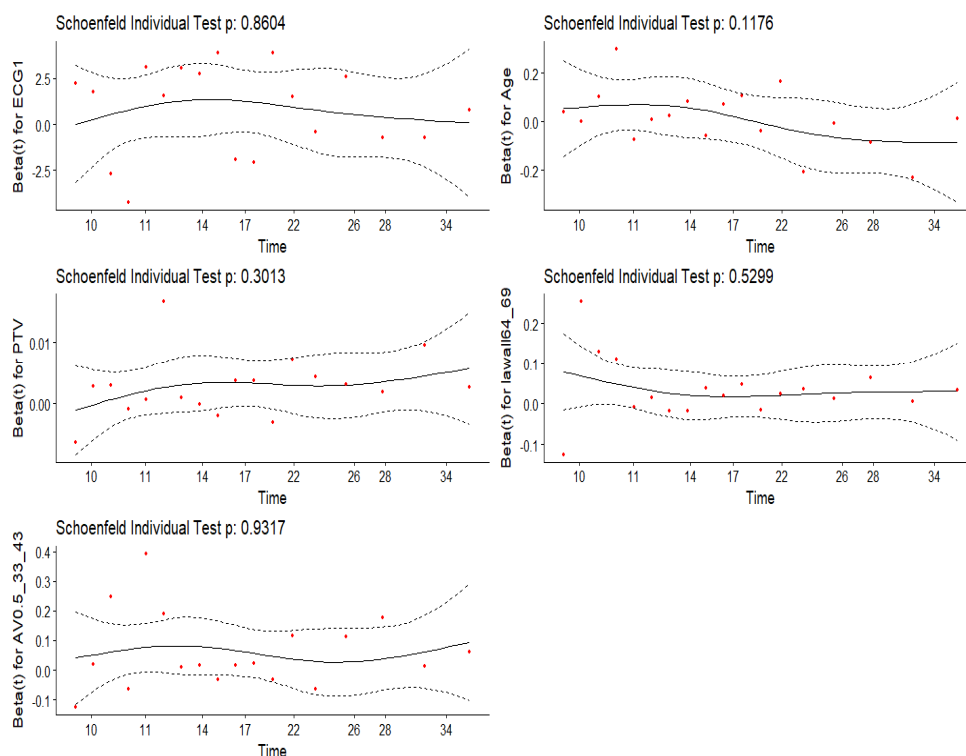


So, case 42 and 49 were omitted and reanalysed and there were large differences in HRs and p-values as shown in Section 4.3.8 Table 10.

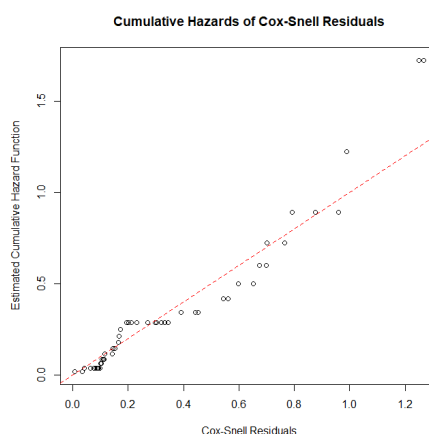
Plots of Schoenfeld residuals (Beta(t)) against time for each co-variate in MV model showing random pattern around the horizontal line. The p-values for Chi square test for covariates

and the whole model for proportional-hazards are also shown. This supports proportional-hazards assumption was met.

Global Schoenfeld Test p: 0.4399



A good model fit was good as seen as assessed by Cox-Snell residual plot below.



GND test when censored at 12, 24 and 36 months, showed there was good model calibration with chi square p- values of $> .05$. Though the test was conducted after splitting the data into halves not deciles as 5 or more events are ideally required in each group and the groups had to be collapsed until this was met.

Appendix 14. MV models with GTV, Cohort, $V_{LAWall64-73}$, $V_{Heart33-44}$, $V_{Heart3-12}$ in the combined cohort

Covariate	MV model 5 $V_{Heart3-12}$ replacing Heart PCs		MV model 6 $V_{Heart33-44}$ replacing Heart PCs		MV model 7 $V_{LAWall64-73}$ replacing Heart PCs	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
GTV	<.01	1.00 (1.00-1.01)	.04	1.00 (1.00-1.00)	<.01	1.00 (1.00-1.01)
COHORT (IDEAL-5)	.89	.95 (.48-1.90)	.85	.94 (.47-1.87)	.86	.94 (.47-1.87)
COHORT (IDEAL-6)	.02	.52 (.31-.89)	.04	.58 (.34-.98)	<.01	.44 (.25-.77)
$V_{Heart3-12}$	.03	1.02 (1.00-1.04)				
$V_{Heart33-44}$			<.01	1.06 (1.02-1.11)		
$V_{LAWall64-73}$					<.01	1.04 (1.02-1.06)

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