Cardiac toxicity from radical radiotherapy for lung cancer

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The candidate confirms that the work submitted is his own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below, in each individual chapter. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

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Abstract

Introduction

Lung cancer is the leading cause of cancer mortality worldwide. Radical radiotherapy is the standard non-surgical management of non-metastatic lung cancer. Cardiac toxicity has been associated with worse survival outcomes following lung cancer radiotherapy. This research project aims to discover clinical and radiotherapy dosimetric factors associated with radiotherapy-induced cardiac damage in lung cancer.

Methods

The research project consist of two phases. Phase one involves retrospective analysis of clinical, tumour and radiotherapy dosimetric data in a cohort of patients treated with radical radiotherapy at the Leeds Cancer Centre from 2010 to 2016. Additional national data was requested from Public Health England. Cause of death from cardiac causes and cancer causes were analysed, and compared in patients who died at home and at the hospital. Medical comorbidities, including pre-existing cardiac disease, diabetes, COPD and kidney failure are analysed for their association with overall survival and post radiotherapy cardiac events. Phase two is a prospective cohort study. This involves testing cardiac biomarkers in 100 patients who are undergoing radical lung cancer radiotherapy at the Leeds Cancer Centre, and correlating the results with clinical and dosimetric variables. These form part of a multi-centre study funded by Yorkshire Cancer Research.

Results

Pre-existing cardiovascular conditions comprise in excess of 30% of this study population. Dosimetric analysis of radiotherapy plans reveal different dose regions associated with cardiovascular death, in patients with or

without pre-existing heart disease. Cardiac death is likely to be under reported, particularly in the community. Medical comorbidities, in particular COPD and chronic kidney disease, affect post radiotherapy survival and can influence onset of post radiotherapy cardiac events.

The prospective biomarker study has been set up in Manchester and Leeds, and is currently recruiting.

Conclusion

Cardiac toxicity from lung cancer radiotherapy occurs due to complex interactions between demographic, medical and radiotherapy factors. Further work involving prospective studies, cardiac biomarkers and novel imaging techniques will help to further elucidate the mechanisms of cardiac damage, and strategies to minimise it.

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Chapter 1
Introduction

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1.1 Lung cancer

Lung cancer is the most commonly diagnosed malignancy worldwide, affecting more than 14 million people annually[1]. Every year, lung cancer causes more than 1.6 million deaths, which is greater than breast, colon and prostate cancers combined[2]. Similarly, in the UK, lung cancer is diagnosed in excess of 46,000 people each year and is the leading cause of cancer related death[3]. Smoking is known to be the primary cause of lung cancer in more than 80% of patients[4]. The incidence of lung cancer has fallen in the UK in the last 10 years, owing primarily to the reduction in male smoking, yet the incidence of female lung cancer has risen. An increasing proportion, although still a minority, of lung cancer patients are never or non-smokers[5].

More than 85% of lung cancers in the UK are now diagnosed as Non-Small Cell Lung Cancer (NSCLC)[6]. This is a histological sub classification of lung cancer, and encompasses adenocarcinoma, squamous cell carcinoma, large cell carcinoma and undifferentiated carcinomas. Over 40% of patients with NSCLC have metastatic disease at diagnosis, often due to lack of specific early cancer symptoms[6]. For these patients, management is primarily palliative using systemic therapy and prognosis is generally poor. Progress in targeted therapies, however, including tyrosine kinase inhibitors and immune checkpoint inhibitors, is benefiting a significant proportion of these patients. Patients with non-metastatic disease have early or locally advanced disease and can potentially receive curative-intent treatment, which primarily consists of surgery or radical radiotherapy.

1.1.1 Early and locally advanced NSCLC

Lung cancer staging is shown in figure 1[7]. Early NSCLC refers to stage I and stage II disease whereas locally advanced NSCLC refers to stage III disease. In recent years, there has been increasing numbers of patients diagnosed with early lung cancer, compared to advanced disease. This is

likely to be due to improved public awareness[8] and implementation of lung cancer screening[9]. Traditionally, surgery has been the standard treatment of early and a proportion of locally advanced NSCLC in suitable individuals. A large percentage of lung cancer, however, is diagnosed in elderly patients with multiple comorbidities and poor lung function[10]. Improvements in radiotherapy technology and delivery has led to increasing numbers of these patients, who are medically unfit for surgery, receiving radical radiotherapy or chemoradiotherapy.

1.1.2 Radiotherapy in early and locally advanced NSCLC

Radiotherapy was first used to treat lung cancer patients in the early 20th century. Over the past few decades, CT scanning has allowed accurate recognition of tumour location and anatomy, which has enabled higher doses of radiation to be delivered safely, thus giving the potential for cure in localised disease[11]. Improvements in computing power has given rise to more complex radiotherapy planning and Intensity Modulated Radiotherapy (IMRT) is increasingly used in many cancer sites. IMRT is an advanced form of 3D conformal radiotherapy characterised by non-uniform radiation beam intensities and computerised inverse planning.[12] IMRT combined with 4D CT (4 dimensional computerised tomography, recording multiple images over time), which follows organ/tumour motion further reduces radiation dose to surrounding structures, permits higher doses to be delivered. In the case of early stage lung cancer, Stereotactic Body Radiotherapy (SBRT) (also known as Stereotactic Ablative Radiotherapy SABR) has become established as an effective non-surgical management option. SBRT is defined as ‘a form of external beam radiotherapy that accurately delivers a high dose of irradiation in one or few treatment fractions to an extracranial target’.[13] Using short fractionations (3-8) and high Biological Equivalent Doses (BED), SBRT delivers ablative doses of radiation to an accurately defined area. Evidence points to possible equivalence to surgery in terms of outcomes with excellent local control of disease[14]. In the UK, as in the rest of the world, SBRT has therefore become the standard of care for patients with inoperable early-stage peripheral lung cancer[15, 16]. Previously in the UK, SBRT was not routinely used for more central lesions due to safety concerns

and is therefore unsuitable for patients with locally advanced disease, when there is disease near the main airways. A central lesion is defined as a lesion within 2cm of the proximal bronchial tree.[17]

Clinical trials in the early 1980s demonstrated that it was safe to deliver 60-66 Gy in 30 to 33 fractions to patients with locally advanced NSCLC and this has remained the standard of care over the last 20-30 years[18]. Concurrent treatment with platinum containing chemotherapy has also been shown to improve survival outcomes[19, 20] Despite this, the 5 year survival of treated patients remains poor, with a considerable number of patients suffering from local relapse[21]. Efforts have been made to improve this by intensifying the dose of radiotherapy in the hope that this would lead to enhanced local control and ultimately survival. Early phase trials established that dose escalation to 74Gy with concurrent chemotherapy was safe and was associated with better survival[22-24].

In light of these, a major phase 3, multi-centre randomised controlled trial (RTOG 0617) was carried out, comparing 74Gy/37 fractions of radiotherapy to 60Gy/30 fractions with concurrent chemotherapy[25]. The RTOG 0617 trial showed inferior survival for patients assigned to the higher dose group (HR 1·38, 95% CI 1·09–1·76; p=0·004). In addition, local disease control was worse in the high dose group, which has led to much debate in the Oncology community. Many hypotheses were put forward for the trial findings and closer analysis of the data showed that radiotherapy-associated cardiac toxicity may have contributed to mortality[26]. Secondary analysis of the trial data demonstrated the significance of cardiac dose volume histogram(DVHs), with cardiac V5 (volume of heart that receives >5Gy) and V30 (volume of heart that receives >30Gy) associated with early mortality; in particular, mortality within the first 2 years of treatment.

1.2 Cardiac toxicity from radiotherapy

1.2.1 Heart as an Organ at risk

The heart is a recognised Organ At Risk (OAR) for lung cancer radiotherapy and is routinely contoured for radical radiotherapy though whether the heart, or sub-structures of the heart, should be a dose-limiting OAR remains unknown. Existing guidelines have mostly used the whole heart or pericardium as the OAR[27, 28]. Several heart contouring atlases have been developed[29-31]with the aim of consistent dose reporting in clinical practice and research trials. Key differences exist between these atlases and attention is given to different structures in different atlases.

Duane et al published an atlas which subdivides the left ventricle into five sections, as well as highlighting the anatomy of 10 coronary arteries. Feng et al's atlas[30] describes 4 cardiac chambers, as well as the heart valves and the AV node. Both atlases have been developed in breast cancer patients undergoing breast cancer radiotherapy and, therefore, in a cohort of patient with different demographics and comorbidities.

Kong et al[31] published a heart atlas as part of a group of OARs for thoracic radiotherapy. Other than the detailing the method to outline the standard 4 cardiac chambers, there are no additional cardiac structures detailed. Cancer centres adopting different contouring atlases will therefore produce dissimilar contours, which will impact dose reporting and comparison of outcomes. In addition to these atlases, many UK centres contour the pericardium rather than the heart. This is detailed in the RTOG 0236 trial and adopted in the UK SABR consortium guidelines[32, 33].

Establishing the dose and volume effects of radiotherapy to the heart is challenging. A QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) organ specific paper[34] studied relationships between dose to the

heart and cardiac events, including pericarditis, myocardial infarction, heart failure and valvular disease. Clinical trials included in the analysis were mostly performed in lymphoma and breast cancer patients. The paper acknowledges difficulties in contouring heart substructures and competing patient and treatment risk factors, such as use of chemotherapy, when evaluating factors contributing to cardiac mortality. There is evidence which associates adjuvant breast radiotherapy with ischaemic heart disease. Compared to patients who received no radiotherapy, those who received radiotherapy had increased risk of cardiac death (RR 1.27)[34]. There was also increased risk of cardiac death in patients who received left sided and internal mammary nodal radiotherapy in the post mastectomy setting. Data for incidence of heart failure and valvular disease is conflicting. The paper recommended that for breast cancer, adjuvant radiotherapy should involve the heart as little as possible. For partial radiation of the heart in breast cancer, NTCP (normal tissue complication probabilities) model suggests V25<10%(Less than 10% of lung volume receiving more than 25Gy, in 2Gy per fraction) is associated with <1% probability of cardiac mortality 15 years after treatment. If the whole heart were to be irradiated, doses of <15 Gy appear safe.

1.2.2 Radiotherapy and cardiac toxicity

It is widely acknowledged that thoracic radiotherapy can affect the heart. Long term follow up studies in the setting of breast cancer[35, 36] and lymphoma[37, 38] have demonstrated cardiac events associated with radiotherapy that involves the heart. A variety of cardiac events have been described, including ischaemic events, pericardial effusion, heart failure and cardiomyopathies. However, the exact mechanism of radiotherapy-induced cardiac damage is not completely understood. There are suggestions of increased oxidative distress and radiotherapy induced endothelial damage. Animal models have demonstrated that radiation to myocardium is associated with short term inflammatory response, and long term decrease in density of microvasculature. In many breast and lymphoma patients, cardiac toxicities have emerged 10-20 years after radiotherapy treatment, which can make the diagnosis of radiation-induced heart disease

challenging. It has been observed that lower doses of radiotherapy are associated with longer latent periods, and that younger age at radiotherapy and pre-existing heart disease increase the risk of cardiac events[34].

Little has been published regarding the cardiac effects of radical radiotherapy for lung cancer. There has been a historical lack of significant focus in this area probably because of the previous poor outcomes in this setting: prior to the year 2000, radiotherapy for early lung cancer yielded a median survival of around 2 years[39]. Another reason for the lack of focus in this area is the presence of obvious confounding factors such as smoking. Retrospective analysis of patients treated 20-40 years ago with post-operative thoracic radiotherapy has demonstrated a potential association between radiotherapy and cardiac death[40]. This could potentially explain the detrimental effect of post-operative radiotherapy in patients with N0 or N1 NSCLC shown in the Cochrane Post-Operative Radiotherapy meta-analysis[41]. The meta-analysis demonstrated benefit of post-operative radiotherapy for margin positive lung cancer after resection. It is possible that any potential benefit from radiotherapy in N1 patient particularly is outweighed by the likely cardiac toxicity. In N2 disease there was a potential benefit and hence the LUNGART study was performed. Dosimetric associations and thresholds for cardiac damage remain controversial and no prospective studies have been performed to address these issues. It appears that the mechanism of cardiac injury in this setting is different to that in breast and lymphoma patients: a major disparity is the timing of onset of cardiac events and cardiac related death, which appear to manifest much earlier in lung cancer patients treated with radical radiotherapy[40].

In the wake of RTOG 0617 trial, there has been more interest in radiotherapy-induced cardiac disease in patients treated with radical radiotherapy for LA-NSCLC. The following review aims to examine the key studies in this area.

1.2.3 Cardiac dose constraints

In the last 10 years, there have been increasing interest in the effect of radiotherapy on the heart in the setting of lung cancer. In the RTOG 0617 trial[25], cardiac V5 and V30 were demonstrated to be associated with worse overall survival in initial analysis. A secondary analysis[21] comparing outcomes from IMRT (intensity modulated radiotherapy) to 3D-CRT (3-dimensional computerised radiotherapy) showed that IMRT significantly reduced heart doses compared to 3D-CRT, and resulted in similar survival outcomes to 3D-CRT, despite IMRT being used for larger tumours. In this analysis, cardiac V40 was found to significantly correlate with survival. Long term follow-up results[42] from the study confirmed cardiac V5 as a factor which affected survival, while V30 and V40 lost significance.

Analyses focusing on cardiac toxicity have also been performed using results from published trials. For example, Wang et al[43] performed a pooled analysis on 112 patients, from six dose escalation trials in lung cancer. Mean heart dose (MHD) correlated with the occurrence of cardiac events, especially with MHD of >20Gy, versus MHD of <10Gy (HR 5.47, $p<0.01$). Heart doses, however, did not correlate with survival.

Dess et a[43] conducted a summary analysis on 125 patients from 4 radiotherapy trials. MHD, cardiac V5 and V30 were associated with cardiac events, but not with overall survival.

Zhang et al[47] performed a systematic review of 22 published studies. Most evaluated studies were retrospective, from single institutions and had different test populations as well as differing endpoints. The authors concluded that although some studies found associations between heart dose and cardiac events or survival, the findings were inconsistent, and no firm conclusion could be drawn. The analysis therefore could not derive reliable dose constraints for the heart.

A key issue for existing literature investigating cardiotoxicity associated with lung cancer radiotherapy is that most published work consist of retrospective studies, which were mostly single centre, included low numbers of patients and assessed different endpoints. Large variations in pre-existing cardiac disease, comorbidities, radiotherapy technique and use of chemotherapy in

test populations also contribute to different outcomes/conclusions. Thus, there is a need for prospective, randomised and sufficiently powered studies with an agreed cardiac atlas and with robust quality assurance to address this question.

1.2.4 Literature review

An online search was carried out on Medline and Embase databases. Key words used were ‘Non-Small Cell Lung Cancer’, ‘Radical Radiotherapy’, ‘Radiotherapy Dosimetry’, ‘Heart toxicity’ and ‘Cardiac toxicity’. Original studies from 01/01/1993 to 31/12/2019 were included. Conference abstracts and abstract only submissions were excluded.

Fourteen relevant individual studies were identified, all of which were retrospective analyses and eight of which were single institution studies. Two studies examined patients who were treated with SBRT, and the remainder focused on patients treated with radical dose, conventionally fractionated radiotherapy. A variety of dose and fractionations have been used. Some studies contained patients who received radiotherapy only, while others contained a proportion of patients who had induction, concurrent or adjuvant chemotherapy. A systematic review was also identified, which is discussed later.

A summary of the studies with key findings can be found in table 1.

Wong et al[44] performed a single institution, retrospective analysis in patients who received SABR for early stage NSCLC. In addition to basic demographics, baseline cardiac conditions and Charlson’s comorbidity score were obtained for all patients. Heart DVHs were calculated for all radiotherapy plans, including heart substructures consisting of bilateral ventricles, LA (left atrium), RA (right atrium), LV (left ventricle), SA (Sino-atrial) node and AV (atrial-ventricular) node, which were contoured

separately according to RTOG guidelines. Outcomes were cancer or non-cancer related death. Multivariate analysis in a logistic regression model demonstrated that the maximum dose to the bilateral ventricles was associated with non-cancer related death.

Chan et al[45] performed a retrospective, single institution study on 153 patients who received SBRT for early stage NSCLC. Whole heart DVH, and 15 cardiac substructures, as set out in RTOG 1106 'Atlases for Organs at Risk in Thoracic Radiation Therapy', were contoured for each patient. The outcome was overall survival. A >grade 1 cardiac toxicity was identified in 17% of patients. The most common cardiac toxicity was arrhythmia. On multivariate analysis, RV V10Gy was associated with worse overall survival. A RV V10Gy of < 4% had significantly longer overall survival than V10Gy of >4% (HR 0.46, 95% CI 0.18-1.11, p=0.03).

Stam et al[48] and Amode et al[49] both reported cardiac toxicity in patients who received SBRT treatments for early NSCLC. Stam et al conducted a multi-centre study which involved 803 patients. The end point was either cancer death (taken from the medical notes if patients had progressive or metastatic disease before death) or non-cancer death. Amode et al conducted a single centre study involving 118 patients. The end point was either cardiac event or cardiac or non-cardiac related death (information taken from medical notes). Stam et al used computer-based software to calculate average anatomy and define cardiac substructures as well as deform planned doses accordingly. Amode et al calculated cardiac DVH parameters. Stam et al concluded that maximum dose to the left atrium (HR 1.005, p=0.03) and dose to 90% of the superior vena cava (HR 1.03, p=0.01) were associated with non-cancer death in multivariate analysis. Importantly, non-cancer death is not necessarily cardiac death. In contrast, Amode et al did not find any association between cardiac dose and survival.

Tucker et al[50] performed a single institution, retrospective analysis in patients who received chemoradiotherapy for stage III NSCLC. Radiotherapy techniques consisted of 3D CT planned radiotherapy, IMRT and proton treatments. Heart and lung DVHs were analysed and the outcome was overall survival. On multivariate analysis, no heart dose contraints were

associated with survival. Higher mean lung dose, however, was found to be detriment to overall survival.

Vivekanandan et al[51] performed a post-hoc analysis of prospective data from the IDEAL-CRT trial, a trial of dose escalation in concurrent chemoradiotherapy for stage IIb-III NSCLC. Heart DVH and dose to 5 substructures were calculated. Patients also underwent an ECG at baseline and at 6 months after radiotherapy. The authors found an association between ECG changes after radiotherapy, maximum dose to the LA and overall survival.

McWilliam et al[52] studied a large population of 1101 UK patients in a single institution. Patients received radical radiotherapy, including some who received induction chemotherapy. All patients were treated with 55Gy in 20 fractions. Using deformable image registration, mean dose distributions were created for surviving patients and compared with those for patients who did not survive. The team identified a significant region across the base of heart, where higher mean doses were associated with inferior survival. Cardiac DVHs, in particular cardiac V5 and V30 showed no significant association with survival, on multivariate analysis.

Speirs et al[53] studied 416 patients from a single institution. Patients were treated with radical radiotherapy, 79% of whom also received concurrent chemotherapy and 18% of whom received induction chemotherapy. Overall, 40% of treatments were planned with IMRT and the remainder with 3D planning. Cardiac DVHs were calculated for all patients. Cardiac events were defined as cardiac toxicity of grade 1 or above in the Common Terminology Criteria for Adverse Events (CTCAE)[54]. The team recorded cardiac events in 24% of the population post radiotherapy. The authors concluded that there were associations between Cardiac V50, heart volume and survival. Cardiac V50 was also associated with cardiac events post radiotherapy. The authors suggested that IMRT decreased most heart dosimetric parameters.

Wang et al[43] studied 112 patients from a single institution. Patients received radical radiotherapy. All patients received induction chemotherapy and 90%

received concurrent chemotherapy. Cardiac substructures were contoured to allow dosimetric evaluation. Outcomes were cardiac events, which were divided into pericardial, ischaemic and arrhythmias. The team concluded that cardiac events were heterogenous. Pericardial events were associated with whole heart, right atrium(RA) and left atrium(LA) doses. Ischaemic events were associated with left ventricle(LV) and whole heart doses. Arrhythmic events were associated with RA, LA and whole heart doses. Median time to pericardial, ischaemic and arrhythmic events was 14 months, 26 months and 23 months respectively.

Dess et al[46] studied 125 patients from a single institution. Patients received radical radiotherapy, of whom 84% of patients had concurrent chemotherapy and 27% of whom had a diagnosis of cardiac disease prior to treatment. Cardiac DVHs were calculated. Cardiac events were defined as a grade 3 or above cardiac toxicity from CTCAE. The authors found a 15% cardiac event rate post treatment, and this was associated with mean heart dose. Most cardiac events were coronary artery syndromes or newly diagnosed heart failures. Cardiac events were also associated with inferior survival. Median time to a cardiac event was 11 months.

Schytte et al[55] studied 250 patients at from single institution. Patients received radical radiotherapy. Three cardiac substructures were delineated and included LV, both ventricles and whole heart. High mean doses (MHD) were calculated as the mean dose level that exceeded the dose received by 75% of the patients. In total,15% cardiac events were recorded post treatment. The authors found no association between MHD and cardiac events. MHD was also not associated with survival.

Ning et al[56] studied 201 patients from a single institution. Patients received radical radiotherapy, 99% of whom received concurrent chemotherapy, 33% received induction chemotherapy and 36% received adjuvant chemotherapy. All patients were planned using IMRT and 37% of treatments were delivered using proton beam radiotherapy. The primary endpoint was Grade 2+ (symptomatic) pericardial effusion. Cardiac DVHs were calculated. Overall, 45% of the study population had baseline cardiac disease. The authors identified an association between cardiac V35 and pericardial effusion. The median time to pericardial effusion development was 8.9 months.

Belliere et al[57] studied 50 patients from a single institution. This was a feasibility study of high dose 3D conformal radiotherapy for the treatment of localised NSCLC. Overall, 70% of patients received 74Gy in 37 fractions and 78% of patients received induction chemotherapy and 28% received concurrent chemotherapy. All treatments were 3D planned. Heart DVHs were calculated. In total, 66% of patients had baseline cardiac disease. The authors found a 6% of cardiac event rate post treatment. There was no association between cardiac dose and cardiac events or survival.

Lee et al[58] performed a retrospective analysis on 43 patients across two hospitals, who were treated with post-operative radiotherapy for stage I-III NSCLC. Most patients also received adjuvant chemotherapy with platinum doublet. Cardiac DVHs were calculated for each patient. Outcomes included post radiotherapy myocardial infarction and overall survival. There were no myocardial infarctions during follow up, and the authors found no association between cardiac dose parameters and overall survival.

1.2.5 Literature search discussion

Radiotherapy dose related cardiac toxicity is a relatively new area of research in lung radiotherapy. Therefore, it is unsurprising that only a limited number of studies have been performed and published to date. It is difficult to draw firm conclusions from the studies, as different outcome measures were adopted, and different studies focused on different aspect of treatment. Several important issues are, however highlighted by the existing evidence.

- Firstly, all studies are retrospective analyses and mostly from single institutions. Furthermore, most studies contained relatively small patient numbers.

- Secondly, a variety of radiotherapy dose/fractionations have been used. In some studies, chemotherapy was delivered either

concurrently, as induction or in the adjuvant setting. Radiotherapy planning techniques also varied between studies. Some studies also contained a mixture of patients planned with 3D planning and IMRT. Not all studies compared outcomes between 3D planning and IMRT.

- Thirdly, not all studies established background cardiac co-morbidity in patients. For those that did, there are large discrepancies in the proportion of patients with cardiac disease at baseline. Not all studies recorded cardiac events. Only two studies evaluated cause of death (cancer or non-cancer, cardiac vs non-cardiac). Most studies used CTCAE grading to assess cardiac events but few differentiated between different forms of cardiac events, such as ischaemic events, arrhythmias and pericardial effusions.

- Fourthly, all studies used cardiac DVHs for dosimetry. Some, but not all studies calculated dose to different substructures of the heart. McWilliam et al used a new technique involving computer deformable registration, as mentioned above.

Some conclusions can, however, be drawn from the existing data despite the above heterogeneity. More than half of the studies reported an association between cardiac dose and cardiac events, and post treatment cardiac events mostly occurred within the first two years. Four studies concluded that radiotherapy dose to a particular region of the heart was associated with survival. Two studies mentioned better outcomes for patients who were planned with IMRT.

The systematic review by Zhang et al[47] reached similar conclusions. This review used a different literature search strategy compared to the one detailed above. The reviewers included studies listed on Medline and Embase, from their inception to 31/01/2018. All studies reported the incidence of cardiac events post radiotherapy, cardiac mortality and post treatment survival. The aim was to pool data to investigate the relationship between heart doses and cardiac specific and survival outcomes. Most of the included studies were retrospective, from single institutions and had different test populations as well as differing endpoint definitions. The

authors concluded that although some studies have found associations between heart dose and cardiac events or survival, the findings were inconsistent, and no firm conclusion could be drawn. The analysis therefore could not derive reliable dose constraints for the heart.

Given the expanding use of radiotherapy in lung cancer, research into radiotherapy induced cardiac damage is of paramount importance. SBRT is now routinely used for early stage NSCLC and has shown superior outcomes compared to conventional fractionated radiotherapy[59]. There is increasing adoption of concurrent chemoradiotherapy for locally advanced disease and the use of immunotherapy for a large subset of patients can significantly improve their survival[60] (median OS not reached in immunotherapy patients versus 29 months in the control group) For patients with metastatic disease, the emergence of mono, or combination immunotherapy/chemotherapy treatments over the last 5 years has significantly altered the thoracic oncology landscape. A proportion of patients with advanced disease can now expect survival of more than 2 years[61]. Newer generations of Tyrosine Kinase Inhibitors targeting the GFR and ALK pathways have also led to improved outcomes with better tolerability and tumour control[62]. There are ongoing trials testing combinations of immunotherapy with radical radiotherapy in early and locally advanced NSCLC[63]. At a time of improving cure rates for patients with non-metastatic disease, treatment toxicity management is becoming more important as more patients who have been cured may experience significant, life limiting treatment related cardiac events. This is also becoming relevant for patients whose cancers relapse late, as with improving systemic treatment, some patients can potentially experience prolonged survival. Future research into radiotherapy dose intensification or combination with other novel agents will greatly benefit from the knowledge regarding the areas of the heart which are more susceptible to radiation damage.

Going forward, a number of key questions remain and need to be addressed in future studies.

Firstly, what is the optimal method of dosimetric evaluation of the heart? Most studies have used cardiac DVHs but many have not reproduced the same findings as RTOG 0617. Some studies contoured cardiac

substructures. McWilliam et al used an innovative method of computer assisted deformable registration of the heart. This made no assumptions regarding pre-defined heart structures or constraints. Manual contouring is also not required for this method. To analyse dosimetric data for large groups (hundreds to thousands) of patients, it is likely that validated computer-based solutions will be essential to allow efficient estimation and analysis.

Secondly, how should cardiac events be documented? Some studies documented baseline cardiac events, but this may not capture all those with a baseline risk. Some studies used Framingham score (clinical algorithm used to estimate 10-year cardiovascular risk of an individual) at baseline to stratify those who were at increased risk. A variety of cardiac events may occur after radiotherapy and so it may be necessary to divide the toxicities into different subcategories such as pericardial, ischaemia and arrhythmia.

Thirdly, how reliable is cause of death information and how can this be assessed? Studies have shown that death certificates are often inaccurate in revealing the true cause of death[64]. Post-mortem is the ideal way, however, it is not possible to perform this in every situation. There is the need therefore, to review combined clinical information from all disciplines prior to a patient's death to ascertain the most likely causes contributing to death.

Finally, there needs to be further work in characterising microscopic mechanisms of radiation-induced heart damage. One possible explanation is that radiotherapy results in acceleration of atherosclerosis of coronary arteries, leading to ischaemic events. Darby et al suggested that higher doses of radiation led to reduced microvasculature[33] density and questioned if this could lead to cardiomyopathies. However, the research was conducted in breast cancer patients, and for lung cancer patients the mechanism may be different. This is because lung cancer patients, with their advanced age at presentation and high prevalence of smoking related comorbidities, are significantly different to breast and lymphoma patients. Lung cancer radiotherapy also employ higher doses, and often treat structures much closer to the heart than radiotherapy for breast cancer and lymphoma. Alternatively, radiation could directly damage the conduction pathways in the heart. It is likely that different mechanisms are present when different

structures of the heart are affected, such as the pericardium. Other than reducing radiation dose to the heart, there may also be a role for heart-protecting agents, which could potentially reduce radiation-induced heart damage.

This leads onto the question of how best to detect and characterise cardiac damage from radiotherapy. So far, most institutions have a passive approach. When cardiac events occur patients are usually seen and managed by cardiology or internal medicine teams, with little input from oncology. There have been efforts to investigate the use of imaging and biomarkers for the detection of cardiac changes after radiotherapy, and not only in lung cancer. Cardiac CT and cardiac MRI[65] have been used to evaluate radiotherapy induced cardiac damage, with MRI changes occurring as soon as 6 months after radiotherapy[66], corresponding to heart regions which received high radiation doses. Key issues are that many patients also received chemotherapy and most studies have been done in patients with breast cancer. Similarly, biomarkers such as Troponin I[67] and BNP (Brain Naturietic Peptide)[68] have been tested in patients who received breast cancer radiotherapy. Authors have noticed rises in BNP as early as 1 month after radiotherapy, however this did not correlate with cardiac dosimetry, in particular cardiac V20/V25/V30/V45 or mean heart dose. There is scope to explore the usefulness of imaging and biomarker techniques, to allow for early detection and management of cardiac damage, which could lead to improved outcomes for patients.

1.3 Project structure

The research project so far consist of two parts.

- Part one is a retrospective analysis of clinical and dosimetric data from patients who have been treated with radical radiotherapy for lung cancer with the aim of investigating correlations between radiotherapy dose to sub regions of the heart and survival outcomes.

- Part two is a prospective clinical study utilising cardiac specific biomarkers. These biomarkers will be tested before and after radiotherapy to ascertain their use for the detection of cardiac damage. They will also be tested for potential associations with clinical and dosimetry parameters for the patient.

The research project is part of a large, multicentre study funded by Yorkshire Cancer Research (grant reference M401). Two UK cancer centres (Leeds cancer centre and Christie hospital, Manchester) are participating. The study is divided into 7 work packages (WP).

- WP1 and WP2 involve data mining, analysis of radiotherapy plans in Leeds, and identification of risk factors to improve knowledge of cardiac specific death.
- WP3 utilises prospective blood sampling following radiotherapy to assess cardiac biomarker change.
- WP4 tests prospective cardiac imaging to assess post radiotherapy cardiac damage.
- WP5 aims to establish cardiac dose constraints by linking findings from prospective cohorts with findings from retrospective series, taking correlations of different variables into account.
- WP6 is a RT planning study that investigates the feasibility of sparing identified sub-structures of the heart.
- WP7 is a prospective cohort study which integrates cardiac follow-up and risk factor interventions for a defined high-risk group of patients.

This thesis details the candidate’s involvement in primarily WP1 to 3. The overall research project is still ongoing. Interim results are presented in subsequent chapters.

Chapter 2
Methodology

Main author of this chapter: Dr Fei Sun

ACCOLADE trial protocol: Dr Kathryn Banfill

Contributors: Dr Louise Murray and Dr Franks, review and editing.

2.1 Retrospective data analyses

WP1+2 involves data mining to:

1. Identify and extract clinical data for eligible patients
2. Retrieval of extra clinical data from national databases from PHE
3. Analysis of radiotherapy plans
4. Perform statistical analyses to assess associations

The aim is to define a high-risk region in the heart, refined by clinical factors, which is associated with worse outcomes when exposed to a certain dose of radiotherapy.

2.1.1 Collection of clinical data

The inclusion and exclusion criteria for the retrospective analysis, presented across chapters 3 to 4, are:

- All patients diagnosed with lung cancer and who received radical radiotherapy at the Leeds Cancer Centre, UK, from 01/01/2010 to 31/12/2016 were included.
- Radical radiotherapy is defined as radiotherapy given with intention of cure and consists of stereotactic body radiotherapy (SBRT), conventionally fractionated radical radiotherapy (CFRT) or chemoradiotherapy (given either concurrently or sequentially).
- Patients who received prior radiotherapy to the chest, including those for breast and oesophageal cancers, were excluded.

Electronic health records containing primary care and secondary care information for each patient were reviewed. Patient demographics, tumour

diagnosis and treatment information were collected. Patient demographics included sex, age, ECOG performance status, Charlson co-morbidity index, prior diagnosis of CVD, diabetes, COPD and kidney function at the time of diagnosis. For patients under the age of 80 with no previous history of CVD, QRISK2 score was calculated. QRISK2[69] is a clinically validated tool which estimates 10-year risk of cardiovascular disease. Information regarding CVD related medications at diagnosis of lung cancer was also collected. These included statins, antiplatelet agents (aspirin, ticagrelor, clopidogrel and dipyridamole), angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ACE-I) and beta receptor blockers (BB). Hospitalisation episodes with cardiac events were collected by reviewing local secondary care records and discharge summaries. Tumour related data included date of diagnosis (either tissue or radiological diagnosis), histology, cancer stage (TNM version 8) at diagnosis, date and type of disease relapse (thoracic or distant or both).Treatment information included radiotherapy starting date, total radiotherapy dose (in Gray), number of fractions and duration of treatment (in days). Chemotherapy information (where given) was also included. This included date of treatment start, type of chemotherapy and number of cycles given.

Outcome data included date of death, date of disease relapse and type of disease relapse(thoracic, extra-thoracic or both). For patients who had not died at the time of analysis, last hospital follow up was recorded. The cut off for data collection was 01/12/2018.

2.1.2 Data from Public Health England

Additional data was obtained from national databases. This includes NCRAS (National Cancer Registry and Analysis Service) and HES (Hospital Episodes Statistics) databases controlled by Public Health England (PHE). From the NCRAS database, tumour and death data were requested. Tumour data includes date, site and histology of diagnosis, as well as staging information. Death data includes date and place of death, causes of death and post-mortem information. Details of this are illustrated in detail in table 2. From the HES database, hospital admissions with diagnosed cardiac conditions were requested. For each admission, there is a primary diagnosis

(cardiac related), followed by a series of secondary diagnoses. Details of this, including corresponding ICD 10 codes, are presented in table 3.

Eligible patients were identified locally using Patient Pathway Manager, an electronic healthcare record software, and MOSAIQ, electronic radiotherapy booking system. Database query software was used, with assistance of data scientists, to identify and extract relevant patient details and radiotherapy treatment information locally. Patients who expressed a National Op Out preference were excluded. Patient identifiers including NHS number, date of birth and project ID were sent to PHE via encrypted file transfer. Data received from PHE was encrypted in separate spreadsheet files, with passwords sent separately. All clinical data received were coded in ICD 10 codes under ICD classification, version 10. PHE data was then checked against local data, collected under criteria detailed in Chapter 2.1.1, for inconsistencies.

2.1.3 Dosimetric analysis of radiotherapy plans

Radiotherapy specific data is held within Leeds Cancer Centre systems. A look up table has been used to identify patients from MOSAIC (Elekta Inc, Crawley, UK), which is the radiotherapy record and verifying system. This look up table provides a pseudo-anonymisation mechanism. When radiotherapy DICOM (Digital Imaging and COmmunications in Medicine) data is exported, only the anonymisation codes will be associated with each patient's data. A data sharing agreement with the Christie hospital in Manchester was established prior to the analysis. This allowed the Manchester team to access radiotherapy planning CT scans and radiation dosimetry information, as well as patient outcome data in an anonymised or de-identified fashion. The output from the analysis does not contain patient radiological images but just dosimetric data and generic cardiac risk factors. This information cannot be linked back to the patient without access to the

original look-up table held with the robust information governance structure of the Leeds Cancer Centre.

The details of the data sharing agreement are summarised in figure 2

Patient images were deformably registered to a reference patient (in Manchester) using the Nifty Registration package[75]. Nifty Registration is a research software developed by University College London, with the ability to perform rigid, non-linear registration of medical images. To avoid potential sliding imaging effects between ribs and lungs, bone was excluded from the registration process. The deformable registration is based on a B-spline parameterisation approach. The planned dose distribution was normalised to the reference by directly applying the derived deformable vector field. A visual validation of the registration was performed to ensure that all patients were successfully normalised into the same spatial reference. The process allows large number of patients to be analysed without the need to perform additional radiotherapy contouring. Further details of the methodology can be found in the publication by A. McWilliam[49].

2.1.4 Research ethics and approvals

The research proposal (reference 18/YH/0058) was presented to NHS regional ethics committee on 06/03/2018. Members of the committee gave a favourable ethical opinion.

On 01/11/2018, the research proposal (application number 18/CAG/0071) was granted HRA (Health Research Authority) approval. Research review was conducted by CAG (Confidentiality Advisory Group) subcommittee, who initially gave conditional approval pending feedback from PPI (Patient and

Public Involvement) meetings. Successful PPI meetings were subsequently held in Manchester and Leeds, where the project received unanimous positive opinions from those present. CAG accepted the PPI activity with no further queries.

2.1.5 Statistical analysis

SPSS statistics version 25 (IBM, New York, USA) was used for statistical analysis. Descriptive statistics were performed. Categorical data was analysed using Chi squared tests. Unpaired T test was used for continuous data. Statistical significance was defined as $P<0.05$.

Further details of specific statistical analyses are detailed separately in individual chapters.

2.2 Prospective cardiac biomarker study (ACCOLADE)

Radiotherapy is the standard non-surgical radical treatment for non-metastatic lung cancer. Existing evidence points to an area of interest at the base of the heart, which could be more prone to radiation damage leading to worse survival outcomes. The precise mechanism of damage is not currently known. This study aims to explore the relationship between radiotherapy dose to the heart and its biological effect. This involves testing biomarkers specific to the heart in patients undergoing radical radiotherapy for lung cancer.

2.2.1 Prospective study design

The full name of the study is ‘A study investigating how to avoid CardiaC tOxicity in Lung cancer pAtients treateD with curative-intent radiotherapy to improvE survival, funded by Yorkshire Cancer Research’. The abbreviated title is ‘ACCOLADE’.

This is a multicentre prospective cohort study, aiming to recruit 200 participants,100 from Manchester and 100 from Leeds. In addition, 50 participants from Manchester will undergo heart imaging at two time points.

The objectives are to:

- Collect blood samples in a cohort of patients from centres in Manchester and Leeds
- Correlate blood sample results with patient outcome data
- Define heart dose constraints and implement modern radiotherapy planning methods to minimize dose to critical structures of the heart.

The eligibility criteria is as follows:

1. Histological or clinical diagnosis of lung cancer (stage I to III NSCLC and SCLC)
2. Suitable for curative-intent radiotherapy (minimum 15 fractions for conventional fractionation and 3-8 fractions for SABR)
3. Life expectancy of more than 4 months
4. Age more than 18 years
5. Patient has read and understood the participant information sheet and been able to give informed consent

Patients are excluded if they received prior thoracic radiotherapy, which includes radiotherapy for breast, lung and upper gastrointestinal cancers.

This is no restriction on concurrent medication, which can include chemotherapy agents.

The study is funded by Yorkshire Cancer Research (grant reference M401) and National Institute for Health Research (NIHR) Manchester Biomedical Research Centre. The study sponsor is University of Manchester.

In Leeds, the study opened early 2020 after local R&I(Research and Innovation) approval. Prior to this, the study proposal was extensively discussed, and approved by pathology research, R&I finance and oncology research. Recruitment of patients began after a successful site induction presentation.

Eligible patients are identified prior to clinic. They are then approached by a member of the local research team in the clinic at a pre-treatment appointment. The study is discussed with the patient and the patient is given a detailed participation information sheet (PIS, see appendix). Patients who decide to take part in the study return to the cancer centre and sign the trial consent form (see appendix). This is then countersigned by the person taking consent. The patient is then given a copy of the information sheet and signed consent form.

Acquired patient medical data consists of height, weight, blood pressure, history of cardiac disease, relevant cardiac medications and calculated Q-risk score. Data is entered on case report forms (see appendix).

Blood samples are collected at 3 time points: within 14 days before starting radiotherapy, within 7 days after completion of radiotherapy; and 4 months post radiotherapy (+/- 14 days).

The following blood samples will be collected: full blood count (FBC), lipid profile, total cholesterol, high sensitivity troponin, C-reactive protein (CRP) and brain natriuretic peptide (BNP).

Further detail about the ACCOLADE study and the candidate’s contribution to this is provided in appendix B.

Chapter 3
Is Cardiovascular death under-reported in lung cancer patients following radical radiotherapy?

Main author: Dr Fei Sun (study design, data extraction and preparation, statistical analysis, drafting of content)

Contributors:

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Data preparation – B Wheller

Critical revision – Dr K Franks, Dr L Murray, Dr K Banfill, Dr A. McWilliam, Dr A Abravan, Prof M Van-Herk, Prof C Faivre-Finn

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3.1. Cancer and death certificates

As previously discussed lung cancer is the leading cause of cancer mortality in the UK and worldwide. If cardiac toxicity has a significant effect on post radiotherapy survival in lung cancer, it is important that research into this area differentiates cancer mortality from non-cancer ones, especially death from cardiac disease. As discussed in the literature review, many published studies have not made this distinction. This negatively affects the strength of those studies, and adds to the difficulty of discovering true associations between radiotherapy and radiation-induced heart damage.

Obtaining accurate cause of death can be challenging. Most deaths in patients who received cancer treatment are not subjected to coroner's review, and very few undergo autopsies. More than half of all deaths occur in the community[66], and are certified by community general practitioners who may have little knowledge of the patient's disease control and treatment. In many situations, primary cause of death is believed to be cancer without adequate review of clinical information. This issue has been ongoing for a considerable length of time, and dates back to the 1960s[70]. This is also not exclusive to lung cancer, as a similar situation can be found in patients with breast[71] and bowel cancers[72].

Death from cardiac disease come in many forms. Coronary artery disease and arrhythmias account for the majority of sudden cardiac death[73]. The lack of prior symptoms and investigations compounds the complexity of death certification, especially in patients known to have cancer. This study has been performed to investigate the possibility of underdiagnosis of cardiac death, in lung cancer patients who received radical radiotherapy.

3.2. Methods

Inclusion criteria for eligible patients are detailed in chapter 2. Electronic health records containing primary care and secondary care information for each patient were reviewed. Patient demographics, tumour diagnosis and treatment information were collected. Hospitalisation episodes with cardiac events were collected by reviewing local secondary care records and discharge summaries. Information regarding cardiovascular disease (CVD) related medications at diagnosis of lung cancer was also collected. These included statins, antiplatelet agents (aspirin, ticagrelor, clopidogrel and dipyridamole), angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ACE-I) and beta receptor blockers (BB). For patients under the age of 80 with no previous history of CVD, QRISK2 score was calculated[74]. QRISK2 is a clinically validated tool which estimates 10-year risk of cardiovascular disease. This is based on patient demographic information as well as comorbidities (hypertension, atrial fibrillation) and certain medications, such as long-term use of corticosteroids and antihypertensives.

Official mortality and morbidity data were acquired from Public Health England, in particular to define the causes of death (from the Office of National Statistics database) and details of hospital admissions (from Hospital Episodes Statistics). Chapter 2 provides further details and cause of death data includes the primary cause of death and place of death according to the certifying physician. Hospital admissions data include primary and secondary diagnosis for each hospital admission episode, coded according to ICD-10 (International statistical classification of diseases and related health problems – version 10) criteria. The primary diagnosis was used to define the main diagnosis of each hospital admission episode. Cardiac hospitalisation and cardiac death are defined by ICD 10 codes for myocardial infarction/angina/ischaemic heart disease (I20-I25), heart failure (I50), arrhythmias (I47-I49), non-rheumatic valve disease(I34-I37) and atypical chest pain (R07).

A cardiac death is defined by primary cause of death (part 1a) on death certificates, which includes myocardial infarction/angina/ischaemic heart disease (I20-I25), heart failure (I50), arrhythmias (I47-I49), non-rheumatic valve disease (I34-I37). A lung cancer death is defined by ICD 10 code C34. A respiratory related death is defined by ICD 10 codes for pneumonia (J09-J18), COPD (J44) and lower respiratory tract infection (J20-22).

Death from other cancers is defined by ICD10 codes for cancers other than lung cancer.

Statistics:

IBM SPSS statistics version 25 was used for statistical analysis. Descriptive statistics were performed. Categorical data was analysed using Chi squared tests. Unpaired T tests were used for continuous data. Statistical significance was defined as $P<0.05$.

3.2. Results

1224 patients were included, with a median follow-up period of 34 months. 378 (31.8%) patients were diagnosed with cardiovascular disease at baseline, of whom 140 had previous myocardial infarction (MI), 124 had prior angina or ischaemic heart disease, 45 patients had heart failure, 91 had arrhythmias and 15 had valvular disease. Cancer and radiotherapy treatment demographics are summarised in table 4. Of patients with no previous CVD, 53.5% had QRISK2 of more than 20, which predicts a 20% or more risk of cardiovascular events in 10 years. Patients with CVD at baseline were significantly older, had earlier stage disease and more radiologically diagnosed tumours than patients without CVD.

There were 215 hospitalisation events due to cardiac cause following radiotherapy in 179 patients (14.6%). More than one cardiac hospitalisation occurred in 26 patients. Of all cardiac hospitalisation events, there were 68 (31.6%) related to myocardial infarction, 15 (7.0%) to angina, 14 (6.5%) to ischaemic heart disease, 5 (2.3%) to valve disease (all aortic stenosis), 65 (29.8%) to heart failure, 26 (12.1%) to arrhythmias, 2 (1.0%) to myocarditis and 20 (9.3%) to atypical chest pain. Demographics of patients who had a cardiac event are summarised in table 5, compared to patients who did not have cardiac hospitalisations. A significantly greater proportion of patients who experienced cardiac hospitalisations, had CVD at baseline (58%), as well as radiologically diagnosed (54%) tumours. There were also more males and early stage disease in this group. Of patients who had CVD at baseline, 70% were on a statin, 66% were on antiplatelet therapy, 53% were on ACE-I and 51% were on BB.

830 patients had died at the time of the study, of whom 622 had cause of death available. Only 33 patients had death certification based on post-mortem examination, of which 10 were death from cardiac causes. 260 patients died at homeand 322 patients died in hospitalFor 40 patients, the location of death was unknown. Documented cause of death data is summarised in table 6, for patients who died at home or in hospital. Whilst 71% of patients who died at home were documented as cancer related, only 40% of patients who died in hospital were recorded as having cancer-related death (p=0.02). 34% of deaths in the hospital death group were attributed to respiratory related death, although only 11% in the home death group has a documented respiratory related death (p=0.01). Of these patients, those who died at home had a higher rate of post radiotherapy cardiac hospitalisations and lower rate of documented disease relapse, including relapsed disease outside the chest. For patients who died at home and certified as cancer death, 29% did not have documented disease relapse, and only 39% had community palliative care input prior to death, suggesting in the majority, death was unexpected and sudden.

Use of statins, and its effect on cancer survival has also been explored. A ‘High Risk Cohort’ was identified in the study population, which consists of patients with a history of cardiac disease or Qrisk^3 score >40. In the high risk cohort, patients on statins had improved Overall Survival and PFS (p=0.016

and p=0.031 respectively). Further details of this can be found in Appendix A.

3.3. Discussion

The study population is typical of the patient group diagnosed with non metastatic, NSCLC in the UK, with respect to age, sex, smoking habits and performance status[76]. Over 30% of patients in this study had prior diagnosis of CVD, and over 10% had a prior MI. This is greater than the prevalence of CVD in the general population, which is around 6%[77]. However, in comparison to patient groups with a known diagnosis of COPD and of similar age, similar rates of ischaemic heart disease are observed[16]. It is likely that this still represents an underestimate of the real burden of CVD in the population, especially amongst females.[77] Indeed, patients without a history of CVD exhibited high predicted risk of developing CVD in the future, as more than half had a predicted 10-year event rate >20% according to QRISK2. Together, these demonstrate that the study population is one with high (known or unknown) existing CVD burden and would be expected to be prone to future cardiac events.

Our analysis revealed a high number of cardiac hospitalisations following radiotherapy treatment. Most cardiac hospitalisations occurred within the first two years of radiotherapy, and this is consistent with reports from recent literature[44]. Cardiac hospitalisations mainly occurred in patients with pre-existing CVD, however over 40% (75 out of 179) occurred in patients without pre-existing CVD. This group of patients had a median Qrisk score of 26%. This further highlights the increased risk of cardiac events after thoracic radiotherapy in this undiagnosed population.

Only 5.3% of deaths in the study cohort were certified as primarily cardiac, which is substantially lower than the 25% of deaths in the general population that are believed to be caused by cardiovascular disease[79]. In addition, 10 out of 33 patients who received post-mortem were certified as cardiac deaths. Unsurprisingly, most deaths are classified as cancer related,

especially for patients who died at home. In this group of patients, 26% had no diagnosed disease relapse following radiotherapy and very few received community palliative care input prior to death. This raises the suspicion that many who died at home could have died from causes other than cancer. Just 3.9% of deaths in the cohort were assessed with post-mortem examination and defining the likely cause of death in cancer patients can be complex. However, studies have shown that up to a third of death certificates could be incorrect and half of post-mortems produce findings unsuspected before death[80]. Lung cancer and its treatments predispose patients to CVD[81]. Interaction between radiotherapy and the heart in lung cancer is an area of current research and there are ongoing studies investigating potential mechanisms. A recently published study[82] found an association between mean cardiac radiotherapy dose and cardiac events as well as all-cause mortality in patients without pre-existing CVD. Future work in this area should take into account baseline CVD, cardiac specific hospitalisation and cardiac specific death.

Our data suggest the need for increased awareness of CVD in lung cancer patients. In the cohort presented here, even established CVD was not well managed with evidence-based preventative medications at the time of lung cancer diagnosis, as evident by the number of patients with pre-existing CVD, but not found to be taking statins or ACE-I. Furthermore, many people without known CVD had high predicted-cardiovascular risk, and so may benefit from consideration of CVD prevention strategies. Our results from above shows, in at risk populations, statins can lead to improved outcomes following radiotherapy. Given than lung cancer radiotherapy may increase the risk of cardiovascular death, it is imperative that cardiovascular health is considered prior, during and after starting radiotherapy treatment. Although evidence is lacking, this could take the form of a physician led assessment of CVD risk at time of lung cancer diagnosis. Our data should also prompt increased suspicion of cardiac related death in people dying without evidence of recent cancer progression, particularly if the death was sudden and unexpected. Given the role of certification data in guiding future strategies to improve survival in people with cancer, it can be suggested that certifying physicians consider:

- Post-mortem examination for patients where the cause of death is not clear

- Recording non-cancer causes of death in these circumstances

Major limitations of this study include the retrospective nature of data collection and patients from a single cancer centre. Our conclusion is speculative, based on available information. A prospective cohort study with review of medical notes +/- autopsy after death, could further analyse accuracy of death certificates. A major strength of this study is the inclusion of data from national database which complement local datasets. The data is strengthened by the fact that the study population had a long follow up period close to 3 years.

Chapter 4
Impact of social deprivation and comorbidities on cardiac events and survival in lung cancer patients following radical radiotherapy

Main author: Dr Fei Sun (study design, data extraction and preparation, statistical analysis, drafting of content)

Contributors:

Study design – Dr R Cubbon, Dr K Spencer

Data preparation – B Wheller

Statistical analysis – Dr K Spencer

Critical revision – Dr K Franks, Dr L Murray, Dr K Spencer, Dr R Cubbon

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4.1 Comorbidities and cardiac events

CVD comprises of many illnesses related to dysfunction of the heart and blood vessels. The ones that most commonly result in death or hospitalisation are coronary artery disease, arrhythmia and heart failure[83]. There are many social, lifestyle and medical risk factors associated with CVD, some of which (e.g. social deprivation and smoking) are also associated with lung cancer. Notable medical factors associated with CVD include diabetes[84], chronic kidney disease[85] and COPD[86]. These diagnoses tend to be prevalent in patients with lung cancer due to their advanced age at diagnosis and smoking habits. Analysis of post radiotherapy cardiac events to date have tended to focus on radiotherapy dosimetry, rather than risk factors and comorbidities. This project analyses the impact of social deprivation and medical comorbidities on post radiotherapy survival and cardiac events.

4.2 Methods

Patient inclusion criteria are outlined in chapter 2. Only exception is that patients with NSCLC are included in this study. This is because of the poor overall survival of patients with SCLC and their death predominantly due to cancer. Local data extraction and integration of ONS/NCRAS data is detailed in chapter 2. Comorbidity data were collected for each patient. This includes documented diagnoses of COPD, CVD at baseline, diabetes and kidney failure at the time of cancer diagnosis. CVD is defined as established diagnoses of ischaemic heart disease, arrhythmia or heart failure. Kidney failure is further divided into 3 categories based on estimated glomerular filtration rate (eGFR, see below).

Deprivation index(DI) for each patient was also acquired from Public Health England. This is a 5-point score measuring degree of deprivation based on average income in an area, compared to the national average. A score of 1 indicates least deprivation, whilst a score of 5 indicates most deprivation

Statistics:

The baseline characteristics of the cohort were assessed. Differences in the baseline characteristics of the different treatment groups were assessed using chi-squared test for categorical data and unpaired t-tests for continuous data. Statistical significance was defined as $P<0.05$.

Overall survival was measured from the date of diagnosis to date of death. Censoring was at the point of last hospital contact for overall survival. The factors associated with overall survival were considered using univariable Cox proportional hazards models. COPD, CVD at baseline, diabetes and kidney failure, alongside age and PS were included in multivariate analyses.

Competing risks regression analysis (Fine and Gray method) was used to model the cumulative incidence function of cardiac events, accounting for the competing risk of death. Separate analysis was done for SBRT and

ChemoRT cohorts. Univariable and multivariable analyses were used to test comorbidity variables. Analysis was performed using SAS (SAS Institute, NC, version 9.4).

Statistical significance was defined as $p<0.05$,

4.3 Results

1149 patients were included in the analysis. Median follow-up was 34 months. Patient demographics are summarised in table 7. The largest cohort of patients (47.5%) received SABR, followed by those who received CFRT (30.1%) and ChemoRT (22.4%). 361 patients had CVD at baseline; 170 had diabetes (all type 2); 456 had COPD. 417 patients had EGFR of over 90ml/min. Patients who received SABR were significantly older with poorer PS, had earlier stage cancer most of which were radiologically diagnosed, compared with patients who received ChemoRT. SABR patients also had significantly higher rates of baseline CVD, diabetes, COPD and worse kidney function compared to ChemoRT patients.

Median overall survival for the whole cohort was 22 months. Male sex, increasing age, poor PS, higher cancer stage and non-adenocarcinomas were significantly associated with worse survival in both univariate and multivariate analyses. SABR treatment was associated with better survival than CFRT in univariate and multivariate analyses (HR 1.58 CFRT vs SABR, $p=0.01$). Diagnosis of COPD was associated with worse outcome in multivariate analysis (HR 1.23, $p=0.02$). (Table 8). For patients who received SABR, male sex, increasing age and poor PS were significantly associated with worse survival in both univariate and multivariate analyses (Table 9). Patients with an EGFR of 45-59 ml/min had worse survival than patients with an EGFR of >60ml/min on univariate analysis. Over 30% of the cohort had a DI of 5. DI had no significant impact on survival for all patients and patients were received SABR, in multivariate or univariate analyses.

There were 176 cardiac events following radiotherapy, which occurred in 156 patients. Median time from end of radiotherapy to time of cardiac event was 12 months. Of all cardiac hospitalisation events, there were 65 related to myocardial infarction, 19 to angina, 16 to ischaemic heart disease, 2 to valve disease (all aortic stenosis), 42 to heart failure, 14 to arrhythmias, and 20 to atypical chest pain. 106 events occurred in SABR patients (19.4% of all SABR), 53 in CFRT patients (15% of all CFRT) and 17 in ChemoRT patients (6.8%).

Cumulative incidence of cardiac events rises quickly for SABR patients, particularly during months 20-40 after radiotherapy. For ChemoRT patients, this occurs mostly after 40 months (figure 3). For both groups of patients, risk of death (from all causes) overtakes risk of cardiac events. For SABR patients, pre-existing CVD is associated with cardiac events in both univariate and multivariate analyses (HR 3.73, $p<0.01$). Male sex, COPD and diabetes are associated with cardiac events in univariate analyses only (Table 10). For ChemoRT patients, increasing age is associated with cardiac events in both univariate and multivariate analyses (HR 2.07, $p=0.01$). Pre-existing CVD is associated with cardiac events in univariate analysis.

4.4 Discussion

The cohort of patients included in this study is typical for NSCLC cancer patients, with high prevalence of background COPD and CVD[87]. Patients who received SABR are considerably older and had greater number of comorbidities compared to patients who received chemoRT. SABR treatment is primarily given for early lung cancer, the large proportion of radiological diagnoses in the SABR group reflect medical comorbidity(such as emphysema) and frailty which often preclude interventions to establish a histological diagnosis. There is evidence that SABR patients are more likely to die from non-cancer causes compared to patients who undergo surgery for early lung cancer[88].

This study demonstrates that in addition to patient demographic and tumour factors, comorbidities such as COPD can influence survival outcomes. A large proportion of lung cancer patients have COPD at time of diagnosis, and patients with severe COPD have significantly reduced life expectancy even in the absence of lung cancer[89]. In the SABR group, reduced kidney function was associated with worse survival. Chronic kidney disease is known to have an impact on life expectancy[90]. Patients with poor creatinine clearance are also at risk of developing other comorbidities, including heart failure[91], which carries a poor prognosis.

This study highlights the different in survival outcomes, and risk of cardiac events for patients receiving different radiotherapy treatments. SABR is a treatment for early lung cancer, most patients have long term tumour control. However, they are older and have more comorbidities. These combined with longer survival are likely to explain the increased likelihood of cardiac events. There was increased likelihood of early cardiac events (less than 40 months after radiotherapy), which could be explained by these factors. Unlike patients who received ChemoRT, which is indicated for locally advanced lung cancer. Cardiac events can only occur to patients who live long enough to experience them and this may explain the difference between SABR and chemoRT which is used for more advanced disease (i.e. stage III disease) where historical median overall survival ranges from 21 to 28 months. In this setting risk of death is significantly higher due to higher risk of tumour relapse. This combined with younger age and low comorbidities, are likely to explain the reduced incidence of cardiac events in the first 40 months post radiotherapy. The finding that pre-existing cardiac disease infers the largest risk for development of subsequent cardiac event is not surprising. It has long been known that survivors of myocardial infarctions are at greater risk of experiencing a second event[92]. The mechanism associated with cardiac injury from radiotherapy is likely different for patients with established CVD than for those with undiagnosed CVD. This does not take into account of patients with undiagnosed CVD, which is likely to be highly prevalent in patients with COPD[93]. The association of SABR treatment with cardiac events is likely due to demographics of the group, with older patients and higher numbers of comorbidities, such as much higher rates of pre-existing CVD.

This study suggests that in addition to optimising anti-cancer treatment, attention must be paid to other medical illnesses which could have a significant impact on survival and cardiac events post treatment. As cancer therapies improve and patients live for longer, other medical conditions will have a major impact on patient survival, particularly for those with early lung cancer who received radical treatment. A similar theme is observed in patients who received lobectomy for early lung cancer: for patients over the age of 65, the incidence of death due to non-cancer causes is greater than that of cancer[94].

Social deprivation has not been shown to have had an impact on overall survival or cardiac events post radiotherapy in this analysis. This is despite almost a third of patients falling into the most deprived (DI 5) group. This can perhaps be explained by the universal healthcare provided the by the free at the point of delivery NHS, which ensures access to all irrespective of wealth and health insurance. Yorkshire is also a region in the UK with less wealth divide, compared to areas such as London or southeast, measured by the difference in income between those who are wealthiest and poorest[95].

This study has several limitations. It was carried out in a single cancer centre using retrospectively collected data. We also did not include all comorbidities related to cardiac events, of which there are many. Medical comorbidities analysed in this study were chosen as they are often the ones most reliably documented. Comorbidities which we could not investigate in the study include obesity, hypertension, autoimmune inflammatory disorders and hyperlipidaemia. These comorbidities were not reliably found in electronic patients records and could not be used in the study key strengths of this study are its relatively large patient population, long follow up duration and integration of data from national databases.

Chapter 5
Dosimetric correlation outcomes

Main author: Dr Fei Sun (Data extraction and preparation, ACCOLADE set up and recruitment, drafting of content)

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ACCOLADE study set up and recruitment – Dr K Franks, L Loughman, P Shuttleworth

Critical revision – Dr K Franks, Dr L Murray

5.1 Comparison of Leeds radiotherapy data with Manchester

.

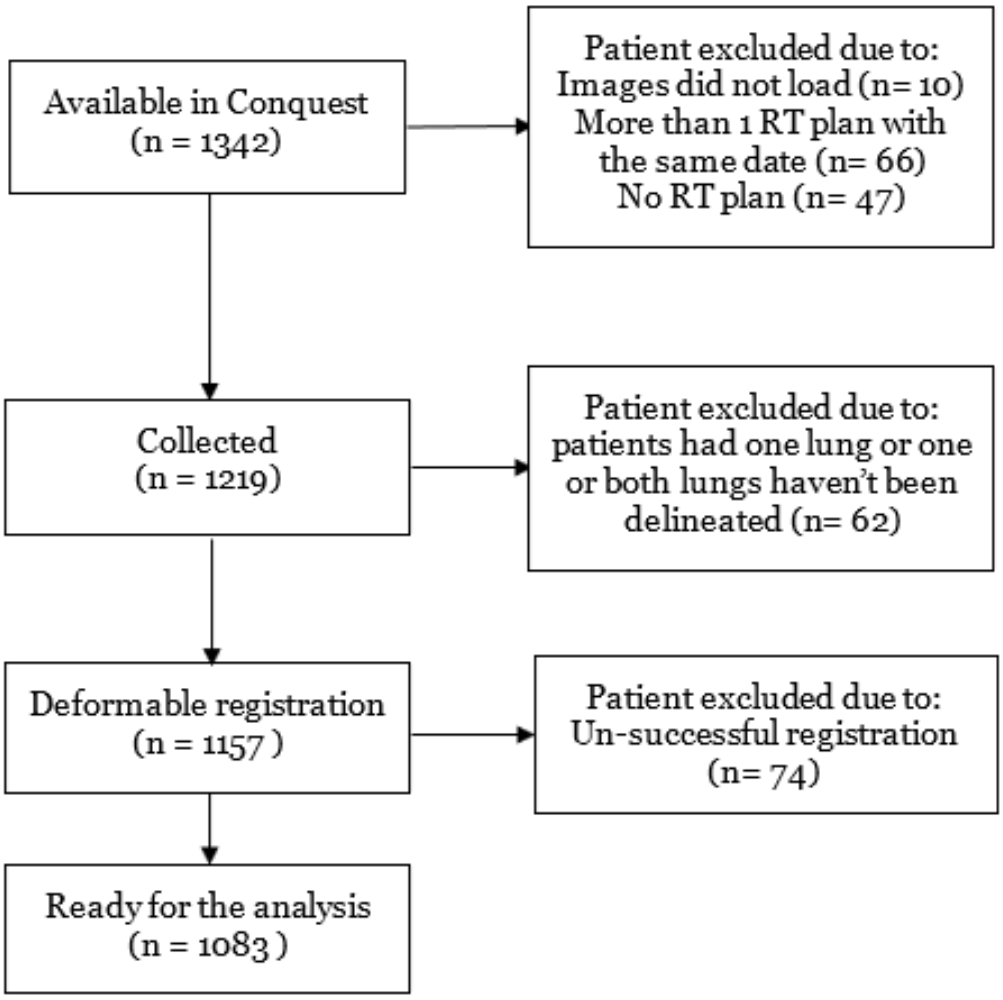
The aim of WP 1+2 is to analyse existing radiotherapy data (stored in DICOM format in local servers), combine with relevant clinical information, and discover potential association between heart regions and worse clinical outcomes. As discussed in chapter 4, pre-existing cardiac disease is a major factor associated with post radiotherapy cardiac events, and has been included in this analysis. This allows stratification of patients into groups based on baseline cardiac diseases, expanding on the work done by McWilliam et al[50].

This chapter also presents a comparison between treatment schedules and radiotherapy volumes between Leeds and the Manchester.

Data has been successfully obtained from clinical databases, and combined with national data retrieved from PHE. The candidate collected local clinical data, communicated with PHE regarding data transfer, and combined national data with local data for form one registry. Physicists (Dr A Abravan and Dr A McWilliam) from Manchester remotely accessed radiotherapy data and clinical data of eligible patients, and performed deformable registration of radiotherapy plans and statistical analyses. The preliminary results are presented here.

5.1.1 Methods

Radiotherapy data for Leeds patients, who were selected using methods detailed in chapter 2.1, is stored in DICOM format in local data servers. The radiotherapy data consist of simulation CT scan, radiation dosimetry, dose and fractionation of treatment. This data, alongside relevant clinical data, has been accessed by the physicists at the Christie hospital remotely. Flow chart of data acquisition is below:



The clinical and dosimetric data has been compared with radiotherapy data from Manchester patients. Manchester patients are selected using the same criteria, detailed in chapter 2.1, from the Christie hospital radiotherapy database. This includes radiotherapy regimes, tumour volumes and mean heart doses. Patient demographics are similar for patients in Leeds and Manchester, as demonstrated in the national lung cancer audit[76]; with similar rates of surgical resection for early disease and use of chemotherapy for late disease.

Statistical analysis was performed using clinical data (pre-existing cardiac disease - PCD) and cardiac dosimetry to determine factors linked to cardiac

death (CD). This was done for patients from both institutions. CD is defined as death from ICD-10 coded cardiac disease (see chapter 2). PCD data was obtained from hospital admissions ONS data (see chapter 2).

The difference in mean cardiac dose distributions for patients who survived versus those who did not was calculated, with patients censored for follow-up. To test if the dose difference between the two groups was statistically significant, permutation testing was used, with 1000 permutations performed. The maximum t-value was used over the average dose distribution to test for significance. The test statistic, maximum t-value, is calculated from the difference in mean dose between the two groups. Permutations then generate random samples to determine the distribution of maximum t-values, this tests the null hypothesis that there is no difference between the two groups. This approach indicates areas of interest where the observed dose difference is related to difference in survival.

The area of highest statistical significance was used to define a small region, defined at 90% of the maximum t-value. The mean of the individual doses received to this region was calculated for every patient. Parameters significantly associated with patient survival, using univariate analysis were determined (significance at $p < 0.05$). Factors that remained significant were included in a Cox-regression multivariate survival model. Heart V5 and V30 were collected. Hazard ratios (HR) were calculated for all variables with 95% confidence intervals (CIs). Kaplan–Meier curves were plotted as quartiles of dose received to the identified anatomical region, allowing an appropriate dose to be selected with which to group patients. Log-rank tests were performed to show any significance in overall survival. All statistical analysis was performed using the Statistical Package for Social Sciences, version 22 (SPSS, Chicago, IL).

Radiotherapy scan data is deformably registered against a reference patient (see chapter 2).

5.1.2 Results

1083 patients from Leeds and 2599 patients from Manchester are included in the analysis. Median follow up was 34 months in Leeds and 40 months in Manchester. The 1083 patients from Leeds is less than the number patients included in the analyses in chapter 3 and 4 (n = 1224). This is because for a number of patients, there were technical difficulties retrieving full radiotherapy plans with appropriate contours. In addition, some patients' radiotherapy plan could not be processed through deformable registration.

The number patients treated with different radiotherapy regimes, at each hospital, is shown in the table 11. The Christie hospital analysis contained more patients overall. 74.6% of the Christie patients were treated with 55Gy in 20 fractions whereas in Leeds 43.1% patients received SABR. The 5 fraction SABR treatment was the most commonly used regime for both hospitals.

A breakdown of different radiotherapy regimes and their relevant treatment volume as measured by Planning Target Volume) is shown in figure 4.

A breakdown of mean heart dose is shown in figure 5. Radical radiotherapy with 55Gy in 20 fractions, and chemoradiotherapy in 30-33 fractions were associated with the highest doses to the heart in both hospitals.

At both hospitals, a total of 1653 deaths occurred. 1243 patients had documented cause of death and past medical history. PCD was present in 419 patients. 175 patients were documented to have died from cardiac causes.

There was an increased risk of CD in patients with pre-existing CVD (HR 4.24, $p<0.01$). For patients without PCD, mean dose to a defined heart region (figure 6) of >10 Gray was associated with a higher risk of CD

(HR=2.8, P<0.01). For patients with PCD, higher mean dose to a lung region (figure 6) was associated with a higher risk of CD (HR 1.02, p=0.02). The analysis has adjusted for performance status, tumour stage and treatment modality.

5.1.3 Discussion

Leeds and Manchester regions are thought to contain lung cancer patients with similar demographics. It is unsurprising that the tumour volumes, and heart doses across different radiotherapy regimes at the two hospitals are very similar. Conventionally fractionated radiotherapy and chemoradiotherapy are primarily used to treat locally advanced disease, which is defined by either large tumour size or mediastinal lymphadenopathy. These treatments are therefore associated with higher heart doses compared to SABR, which is used to treatment peripheral lesions. Leeds did initiate SABR treatment at an earlier date than Manchester, therefore the Leeds cohort contains a higher percentage of SABR patients.

It is likely that the lung region shown in figure 5 corresponds to the entry dose region for radiotherapy treatments. In the study, most patients received radiotherapy 3D planned with fixed beam treatment delivery. IMRT/VMAT therapy was not routinely used at either hospital during this time. The region of heart considered high risk is located near the base of the heart, corresponding to the area identified by McWilliam et al[49]. This is an area which encompass the sinoatrial node This reinforces the concept that there may be a region at the base of the heart, containing the sinoatrial node and origin of coronary arteries, which may be more prone to radiation damage, leading to worse survival outcomes.

In view of different regions of significance identified in patients with and without PCD, the analysis suggest that thoracic radiotherapy in patients with PCD may have different mechanisms of cardiac toxicity induction compared to patients without PCD. Patients with PCD can have existing widespread

large and small vessel change, which could be more prone to further damage from radiation, leading to cardiac events. The heart region identified corresponds to the coronary arteries. This can explain its significance in CD, as critical stenosis or damage in this region can lead to fatal consequences. The sinoatrial node, which is also proximal to this region, is a key structure in electrical signal transduction in the heart. Damage to this area could also lead to arrhythmias, such as atrial fibrillation, which could lead to stroke or sudden death. It is difficult to interpret the clinical significance of the lung region. This could represent entry point of anterior radiotherapy beams, and may relate to global irradiation of the heart. In patients without PCD, radiation may induce changes slowly, potentially affecting many areas of the heart, rather than just one region. This may explain the non-specific nature of the lung region. With longer follow up in prospective studies, we may identify different pattern of cardiac events, potentially at different time intervals, in those without PCD, compared those with PCD.

The analysis did not take into account the type of PCD or other medical comorbidities. Calculations using death certificates, as demonstrated in chapter 3, are at risk of under estimating the true scale of cardiac death, particularly in the community. As demonstrated in chapter 3 and 4, a significant proportion of patients do hot have diagnosed PCD, but possess high risk of developing cardiac events due to medical/social risk factors. Results presented here so far represent preliminary research, which will set the scene and provide background information for further studies. Future studies can analyse this group separately, as they may behave similar, or potentially worse than patients with PCD, as their risk factors may not have been addressed prior to a cardiac event.

Chapter 6
Conclusion and future prospects

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Cardiotoxicity after lung cancer radiotherapy is an area of research that is now attracting increasing attention from researchers worldwide. There is increasing recognition that the heart is an important OAR in lung cancer radiotherapy, and can be associated with long term survival in lung cancer patients. At a time of increasing use of radical radiotherapy to treat lung cancer, alongside better technology and novel systemic therapies, reducing normal tissue complications from radiotherapy is of increasing importance.

This research so far has demonstrated that this is a complex research topic, with conflicting findings from published studies. Retrospective studies performed in chapters 3 and 4 indicate potential under reporting of cardiac death on death certificates, and that medical comorbidities contribute to post radiotherapy survival and cardiac events. Dosimetric analyses point to an area of the heart which may be associated with worse survival after radiotherapy, and prospective studies utilising biomarkers and cardiac imaging are underway.

Research in this field is challenging in many ways. A few examples include:

1. Lung cancer is primarily diagnosed in the elderly, many of whom have heavy smoking history, multiple medical comorbidities which translate to high risk of developing cardiac events. It is difficult to separate the risks added by radiotherapy and existing cardiovascular risk.
2. Many elderly patients have undiagnosed and untreated cardiac conditions which lead to poor cardiac outcomes.
3. Many radiotherapy regimes exist for lung cancer and there are increasingly more combinations with chemotherapy and immunotherapy. This makes it more difficult to define cardiac doses and attribute outcomes to radiotherapy only.
4. Death from cancer and other causes is a significant competing event for cardiac events (Chapter 4).
5. Registration of death in cancer patients , especially in the community, can be inaccurate (Chapter 3).

Many questions remain unanswered. As mentioned in chapter 1, published research in this area has mostly been small scale and retrospective. There has been no consensus over key issues in this field, which include:

1. What is the mechanism of cardiac injury from radiotherapy, and is this different in lung cancer compared to other cancers? Radiotherapy induced changes at the cellular and tissue level may be different in lung cancer patients, many of whom have pre-existing cardiac disease. There may also be additional changes associated with concurrent platinum based chemotherapy.

2. Is there a dose threshold or a region of the heart that is associated with greater risk of cardiotoxicity? The base of the heart region identified by McWilliam et al[50] is yet to be replicated in other centres, and for other radiotherapy regimes such as SBRT or ChemoRT. Patients with pre-existing heart disease may have different dose threshold or sensitive regions, as demonstrated in chapter 5.

3. What are the ideal methods of detecting cardiotoxicity, and identifying patients at risk? As identified in chapter 4, patients with pre-existing cardiac conditions are most likely to develop cardiac events post radiotherapy. These patients, and those with undiagnosed cardiac disease are likely to be most at risk of cardiac events. They too are most likely to benefit from therapies which optimise their cardiovascular health.

4. What practical preventative measure can be taken to reduce risk of cardiotoxicity following radiotherapy? WP 6 of the YCR funded project will test the feasibility of sparing identified sub-structures of the heart. WP7 integrates cardiac follow-up and risk factor interventions for a defined high-risk group of patients.

Potential answers to these questions would involve concerted efforts from multiple disciplines, and may take the forms of:

1. Tissue/animal model research investigating mechanism of radiotherapy induced cardiac damage, potentially in the setting of existing ischaemic heart disease or heart failure. This is because of the prevalence of cardiac disease in lung cancer patients. The studies should use a range of radiotherapy doses and fractionations, as many radiotherapy regimes exist for lung cancer. If possible, different regions of the heart should be exposed to radiotherapy to ascertain the effect on different regions of the heart.

2. Large scale prospective, randomised studies to investigate the effect of different radiotherapy doses to various regions of the heart. If WP6 succeeds in proving the feasibility of sparing specific cardiac substructures, large scale studies are needed to prove the reproducibility of the methods and its effect on a larger population. Many radiotherapy regimes exist for lung cancer, and tumour locations are highly variable. Potential studies may involve a certain regime of radiotherapy (such as CFRT) only, or specify a tumour location or mean heart dose as inclusion criteria.

3. Biomarker and imaging studies to study the possibility of early detection of radiotherapy induced cardiac injury. These are currently being studied in the ACCOLADE study (Appendix B). In the future, new cardiac biomarker and imaging modalities can also be studied in this context.

4. Involvement of cardiology/internal medicine in the assessment of radiotherapy patients and management of comorbidities and cardiovascular risks. Many patients have undiagnosed cardiac disease or have a high risk of developing one. Optimising medical care for those patients will improve their cardiovascular health and could lead to better long term outcomes. In addition, if lung cancer

radiotherapy contributes to cardiac injury, then it too, like medical comorbidities, should be considered in risk calculations of cardiovascular morbidity and mortality.

Management of lung cancer is constantly evolving and the speed of change has been rapid. The shifting landscape, with evolving standard of care and integration of more systemic therapies, add complexity to research. Future research would likely involve teams from different disciplines, and collaboration is key. Large scale, multi-centre collaboration is necessary, to generate large datasets and perform studies which could overcome challenges listed above. Over the last few decades, control of cancer has been the focus of oncology practise. There is now increasing recognition, that reducing non-cancer related morbidity and mortality will become equally as important as reducing cancer related ones.

Chapter 7
Tables and Figures

7.1 Tables

Table 1 - Chapter 1, Radiotherapy and cardiac toxicity, search of literature. DVH - Dose volume Histogram. IMRT - Intensity modulated radiotherapy. 3DP - 3D planned radiotherapy.

	RT	Chemo	N	Heart measure	CVD history	Cardiac Event post RT	Outcome measure	Dosimetric association	RT technique
Wong et al [44]	SBRT	N/A	189	Heart DVH 7 sub-structures	64%		Either cancer or non-cancer from notes	Bilateral ventricle max dose with non cancer death	All IMRT
Chan et al[45]	SBRT	N/A	153	Heart DVH 15 sub-structures		17% >G1	Overall survival	RV V10 with worse survival	
Stam B et al[48]	SBRT	N/A	803	Average anatomy/deformable register,7 sub-structures		-	Either cancer or non-cancer from notes	LA & SVC with Non cancer death	
Amode R et al[49]	SBRT	N/A	118	Heart DVH		11% >G3	Cardiac or non-cardiac from notes	None	38% 3DP 62% IMRT
Tucker et al[50]	60-70 Gy/ in 30-35#	All conc chemo	468	Heart DVH			Any death	None	41% 3DP 49% IMRT 10% Proton
Vivekanandan et al[51]	63-73Gy in 30#	All conc chemo	78	Heat DVH 5 sub-structure ECG			Any death	ECG changes and LA dose with OS	
McWilliam A et al[52]	100%55Gy/20#	24% Induc	1101	Deformable register, Heart DVH		-	Any death	Base of heart with OS	
	RT	Chemo	N	Heart measure	CVD history	Cardiac Event post RT	Outcome measure	Dosimetric association	RT technique

Speirs C et all[53]	60% 66Gy/33# Rest 50-85Gy/24-40#	18% Induc 79% Conc	416	Heart DVH		24% >G3	Any death	Heart V50/Volume with OS and Cardiac Event	40%IMRT 60%3DP Less heart dose with IMRT
Wang K et al[53]	72% 74Gy/37#	100% Induc 90% Conc	112	Manual contour 7sub-structures Heart DVH	14%	8% pericardial effusion 6% ischaemic 11% arrhythmia	Any death	Separate substructures correlated with effusion/ischaemic/arrhythmia events	100% 3DP
Dess R et a[46]	Med dose 70Gy	84% Conc	125	Heart DVH	27%	15% > G3	Any death	Mean heart dose with cardiac event and OS	97% 3DP 3% IMRT
Schytte T et al[55]			250	Manual contour 3sub-structure		15% cardiac disease	Any death	None	100% 3DP
Ning M et al[56]	Mostly 60-66Gy/30-33#	33% Induc 99% Conc 36% Adj	201	Heart DVH	45%	43% effusion 2% > G3 effusion		Heart V35 with pericardial effusion	100% IMRT 37% Proton
Bellier e A et al[57]	70% 74Gy/37#	78% Induc 28% Conc	50	Heart DVH	66%	6%	Any death	None	100% 3DP
Lee et al[58]	Post op 60Gy	60% with adj chemo	43	Heart DVH		0% infarction	Any death	None	70% 3DP 30%IMRT

Table 2 – Chapter 2, Data from PHE/NCRAS database

Cause of death data	Death date
	Death Cause Code 1A
	Death Cause Code 1B
	Death Cause Code 1C
	Death Cause Code 2
	Death Cause Code Underlying
	Death location code
	Site code of death
Tumour data	Date of diagnosis
	Site coded
	Coding system
	Morphology
	Histology
	Tumour Size
	Nodes excised
	Laterality
	Multifocal
	Radiological TNM
	Radiological staging
	Radiological staging system
	Pathological TNM
	Pathological staging
	Pathological staging system

Table 3, chapter 2, Data from PHE/HES database

ICD code	Description
I11	Hypertensive heart disease
I130	Hypertensive heart disease with heart failure
I139	Hypertensive heart disease with renal disease
I20	Angina pectoris
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Central current complication follow acute myocardial infarct
I24	Other acute ischaemic heart diseases
I25	Chronic ischaemic heart disease
I26	Pulmonary embolism
I27	Other pulmonary heart diseases
I28	Other disease of pulmonary vessels
I30	Acute pericarditis
I31	Other diseases of pericardium
I32	Pericarditis in diseases classified elsewhere
I33	Acute and subacute endocarditis
I34	Nonrheumatic mitral valve disorders
I35	Nonrheumatic aortic valve disorders
I36	Nonrheumatic tricuspid valve disorders
ICD code	Description
I37	Pulmonary valve disorders

I38	Endocarditis, valve unspecified
I39	Endocarditis and heart valve disorders in diseases EC
I40	Acute myocarditis
I41	Myocarditis in diseases classified elsewhere
I42	Cardiomyopathy
I43	Cardiomyopathy in diseases classified elsewhere
I44	Atrioventricular and left bundle-branch block
I45	Other conduction disorders
I46	Cardiac arrest
I47	Paroxysmal tachycardia
I48	Atrial fibrillation and flutter
I49	Other cardiac arrhythmias
I50	Heart failure
I51	Complications and ill-defined descriptions of heart disease
I52	Other heart disorders in diseases classified elsewhere

Table 4 – Chapter 2, Demographics of all patients

		Total patients N = 1224	Patients with CVD N = 378	Patient without CVD N = 846	P value
Sex	Male	623 (51%)	232 (61%)	391 (46%)	
	Female	601 (49%)	146 (39%)	455 (54%)	0.06
Age	Median	73 years	77 years	70 years	
	Range	39 – 97 years	49 - 97 years	39-97 years	0.035
Smoking status	Never smoker	54 (5%)	15 (4%)	39 (4%)	
	Ex-smoker	760 (62%)	265 (70%)	495 (59%)	
	Current smoker	410 (33%)	98 (26%)	312 (37%)	0.232
Performance status	0	95 (8%)	16 (4%)	79 (9%)	
	1	584 (48%)	159 (42%)	425 (50%)	
	2	466 (38%)	174 (46%)	292 (35%)	
	3	79 (6%)	29 (8%)	50 (6%)	0.209
Charlson co-morbidity score	<3	73 (6%)	4 (1%)	69 (8%)	
	4-6	758 (62%)	155 (41%)	603 (71%)	
	7-9	377 (31%)	208 (55%)	169 (20%)	
	>10	12 (1%)	11 (3%)	1 (1%)	0.354
Cancer stage	1	662 (54%)	246 (65%)	416 (49%)	
	2	180 (15%)	54 (14%)	126 (15%)	
	3	382 (31%)	78 (21%)	304 (36%)	0.001
Cancer pathology	Adenocarcinoma	274 (22%)	65 (17%)	209 (25%)	
	Squamous Cell	371 (30%)	91 (24%)	280 (33%)	

	Mixed adenosquamous	13 (1%)	5 (1%)	8 (1%)	
	Undiferrentiated carcinoma	58 (5%)	21 (6%)	37 (4%)	
	Large cell carcinoma	16 (1%)	2 (1%)	14 (2%)	0.003
	Radiologically diagnosed	492 (41%)	193 (51%)	299 (35%)	
Radiotherapy modality	SBRT	546 (45%)	207 (55%0	339 (40%)	
	Fractionated radical radiotherapy	423 (35%)	128 (34%)	295 (35%)	
	Chemoradiotherapy	255 (20%)	43 (11%)	212 (25%)	0.068
Medication at diagnosis	Statins	577 (47%)	266 (70%)	311 (37%)	
	Antiplatelets	442 (36%)	249 (66%)	193 (23%)	
	ACE-I	420 (34%)	200 (53%)	220 (26%)	
	BB	270 (22%)	192 (51%)	78 (9%)	0.04

Table 5 – Chapter 3, Patients who had a cardiac event after radiotherapy versus patients who have not

		Patients who had cardiac hospitalisation N = 179	Patients who had no cardiac hospitalisation N=1045	P value
Sex	Male	104 (58%)	519 (50%)	
	Female	81 (42%)	520 (50%)	0.033
Age	Median	76 years	73 years	0.202
Smoking status	Never smoker	8 (4%)	46 (4%)	
	Ex-smoker	121 (68%)	639 (61%)	
	Current smoker	50 (28%)	360 (35%)	0.309
Performance status	0	6 (3%)	89 (9%)	
	1	68 (38%)	516 (49%)	
	2	85 (47%)	381 (36%)	
	3	19 (12%)	60 (6%)	0.680
Charlson co-morbidity score	<3	4 (2%)	69 (7%)	
	4-6	83 (46%)	675 (65%)	
	7-9	90 (50%)	287 (27%)	
	>10	2 (2%)	10 (1%)	0.700
Pre-existing cardiac condition	Total	104 (58%)	274 (26%)	
	Myocardial infarction	33 (18%)	107 (10%)	
	Angina/ischaemic heart disease	28 (16%)	117 (11%)	
	Heart failure	11 (6%)	34 (3%)	
	Arrhythmia	28 (16%)	63 (6%)	
	Valvular disease	3 (2%)	12 (1%)	0.001
Cancer stage	1	130 (73%)	532 (51%)	
	2	22 (12%)	158 (15%)	

	3	27 (15%)	355 (34%)	0.001
Cancer pathology	Adenocarcinoma	30 (17%)	244 (23%)	
	Squamous Cell	40 (22%)	331 (32%)	
	Mixed adenosquamous	1 (1%)	12 (1%)	
	Undiferrentiated carcinoma	8 (4%)	50 (5%)	
	Large cell carcinoma	3 (2%)	13 (1%)	0.195
	Radiologically diagnosed	96 (54%)	396 (38%)	
Radiotherapy modality	SBRT	103 (58%)	443 (43%)	
	Fractionated radical radiotherapy	60 (34%)	363 (35%)	
	Chemoradiotherapy	16 (8%)	239 (22%)	0.049

Table 6 – Chapter 3, Primary cause of death data for all patients, patients who died at home or nursing home and patients who died in hospital or hospice.

	All patients N=622	Patients who died at home/nursing home N=260	Patients who died in hospital/hospice N=322	P value
Lung cancer or related secondary cancer	343 (55%)	184 (71%)	129 (40%)	0.02
Cardiac related death	33 (5%)	13 (5%)	19 (6%)	0.25
Respiratory related death	139 (22%)	29 (11%)	108 (34%)	0.01
Stroke and vascular events	15 (2%)	3 (1%)	12 (4%)	0.32
Other cancers	39 (7%)	21 (8%)	13 (4%)	0.15
Other	54 (9%)	11 (4%)	41 (12%)	0.07

Table 7 – Chapter 4, patient demographics. P value reflect comparison between SABR and CFRT groups.

		SABR	ChemoRT	CFRT	P value
Age (Years)	Median	76	67	75	<0.01
	Range	50 - 97	42 - 85	39 - 93	
Sex	Male	268 (49.1%)	131 (52.4%)	177 (50.1%)	

	Female	278 (50.9%)	119 (47.6%)	176 (49.9%)	0.08
Performance score	0	30 (5.5%)	42 (16.8%)	16 (4.5%)	<0.01
	1	208 (38.1%)	169 (67.6%)	156 (44.2%)	
	2	251 (46.0%)	39 (15.6%)	162 (45.9%)	
	3	57 (10.4%)	0	19 (5.4%)	
Cancer stage	1	521 (95.4%)	0 (2.0%)	125 (35.4%)	<0.01
	2	25 (4.6%)	30 (20.0%)	133 (37.7%)	
	3	0	220 (88.0%)	95 (26.9%)	
Number of deaths		257	171	267	
CVD		207 (37.9%)	43 (17.2%)	111 (31.4%)	<0.01
Diabetes		88 (16%)	21 (8%)	61 (17%)	<0.01
COPD		268 (49.1%)	66 (26.4%)	122 (34.6%)	<0.01
eGFR (ml/min)	≥90	121 (22.1%)	124 (49.6%)	97 (27.5%)	<0.01
	60-89	194 (35.5%)	93 (37.2%)	130 (36.8%)	
	45-59	77 (14.1%)	18 (7.2%)	43 (12.2%)	
	31-44	21 (3.8%)	6 (2.4%)	14 (4.0%)	
	≤30	14 (2.6%)	0	9 (2.5%)	
	Unknown	119 (21.8%)	9 (3.6%)	60 (17.0%)	

Pathology	Squamous	63 (11.5%)	123 (49.2%)	147 (41.6%)	
	Adeno	88 (16.1%)	84 (33.6%)	74 (21.0%)	
	Radiologically diagnosed	380 (69.6%)	0	102 (28.9%)	<0.01
	Other	15 (2.8%)	43 (17.2%)	30 (8.5%)	
Deprivation index	1	70 (12.8%)	44 (17.6%)	50 (14.2%)	
	2	101 (18.5%)	56 (22.4%)	67 (19.0%)	
	3	92 (16.8%)	41 (16.4%)	56 (15.9%)	0.17
	4	106 (19.4%)	41 (16.4%)	68 (19.4%)	
	5	177 (32.4%)	68 (27.2%)	112 (31.7%)	
Total		546	250	353	

Table 8 – Chapter 4, Univariable and multivariable Cox regression analysis of variables on OS in all patients.

		Univariate analysis				Multivariate analysis			
		HR	Sig.	95% CI lower	95% CI upper	HR	Sig.	95% CI lower	95% CI upper
Sex (female)		**1.35**	**<0.01**	**1.18**	**1.56**	**0.75**	**<0.01**	**0.64**	**0.88**
Age		1.01	0.06	1.00	1.02	**1.1**	**0.01**	**1.003**	**1.022**
Performance status	0-1	1				1			
	2 vs 0-1	**0.65**	**<0.01**	**0.49**	**0.86**	**1.23**	**0.02**	**1.02**	**1.466**
	3 vs 0-1	0.80	0.13	0.60	1.07	**1.75**	**<0.01**	**1.25**	**2.44**

CVD		0.98	0.83	0.85	1.14	0.98	0.80	0.82	1.17
Diabetes		1.07	0.50	0.88	1.30	1.03	0.83	0.82	1.28
COPD		0.95	0.46	0.82	1.09	**1.22**	**0.02**	**1.03**	**1.45**
Estimated Glomerular Filtration Rate	EGFR>60	1				1			
	EGFR45-59	1.17	0.14	0.95	1.45	1.18	0.15	0.95	1.47
	EGFR<44	1.11	0.52	0.81	1.51	1.14	0.44	0.82	1.57
TNN stage	**1**	**1**	**<0.01**			**1**			
	2	**1.41**	**<0.01**	1.54	1.72	1.17	0.27	0.88	1.56
	3	**1.35**	**<0.01**	**1.15**	**1.59**	**1.57**	**<0.01**	**1.14**	**2.16**
		Univariate analysis				Multivariate analysis			
Treatment technique	SABR	1				1			
	ChemoRT (vs SABR)	**1.24**	**0.02**	1.03	1.49	1.08	0.67	0.76	1.55
	CFRT (vs SABR)	**1.58**	**<0.01**	1.34	1.86	**1.32**	**0.02**	**1.05**	**1.67**
Histology	Adeno	1				1			
	Squamous	**1.48**	**<0.01**	**1.21**	**1.81**	**1.28**	**0.03**	**1.03**	**1.61**
	Other	1.41	0.02	1.06	1.88	1.33	0.07	0.98	1.82
	Rad. Diagnosed	1.09	0.39	0.90	1.32	1.12	0.33	0.89	1.43
Deprivation index(DI)	DI 1	1				1			
	DI 2 (vs D1)	0.91	0.46	0.71	1.17	1.06	0.68	0.80	1.40
	DI 3 (vs D1)	0.79	0.08	0.61	1.03	0.77	0.09	0.57	1.04
	DI 4 (vs D1)	0.98	0.90	0.77	1.26	1.12	0.43	0.85	1.47
	DI 5 (vs D1)	0.98	0.84	0.78	1.22	1.07	0.63	0.83	1.38

Table 9 – Chapter 4, Cox regression analysis of variables on OS in SABR patients. Multivariate and Univariate analysis done for each variable.

		Multivariate analysis				Univariate analysis			
		HR	Sig.	95% CI lower	95% CI upper	HR	Sig.	95% CI lower	95% CI upper
Sex (female vs male)		**0.61**	**<0.01**	**0.47**	**0.80**	**0.68**	**<0.01**	**0.55**	**0.85**
Age		1.02	0.03	1.00	1.04	1.01	0.10	0.99	1.03
Performance status	**0-1**	**1**				**1**			
	2 vs 0-1	**1.51**	**<0.01**	**1.14**	**1.99**	**1.57**	**<0.01**	**1.24**	**1.99**
	3 vs 0-1	**1.93**	**<0.01**	**1.26**	**2.9**	**2.13**	**<0.01**	**1.50**	**3.03**
CVD		0.78	0.83	0.59	1.03	0.97	0.79	0.78	1.21
Diabetes		1.05	0.78	0.74	1.47	1.11	0.48	0.83	1.47
COPD		1.18	0.23	0.90	1.54	1.07	0.52	0.87	1.33
Estimated Glomerular Filtration Rate	EGFR>60	1				1			
	EGFR45-59	1.38	0.49	1.00	1.89	**1.45**	**0.01**	**1.08**	**1.95**
	EGFR<44	0.95	0.84	0.58	1.54	1.05	0.83	0.66	1.67
TNM stage	1	1				1			
	2 vs 1	**1.38**	**0.05**	**1.00**	**1.89**	1.02	0.94	0.56	1.87
Histology	Adenocarcinoma	1	0.47			1	0.18		
	Squamous	1.06	0.83	0.65	1.72	1.22	0.35	0.80	1.86
	Other	1.75	0.14	0.83	3.68	1.90	0.08	0.93	3.87
	Rad. Diagnosed	1.18	0.36	0.83	1.68	1.33	0.07	0.98	1.81

Deprivation Index	DI 1	1				1			
	DI 2 (vs D1)	0.90	0.63	0.57	1.40	0.83	0.37	0.56	1.24
	DI 3 (vs D1)	0.80	0.35	0.49	1.29	0.84	0.93	0.56	1.25
	DI 4 (vs D1)	1.20	0.41	0.77	1.88	1.03	0.88	0.69	1.52
	DI 5 (vs D1)	1.02	0.91	0.68	1.54	0.96	0.83	0.67	1.37

Table 10 – Chapter 4, competing risks analysis for cardiac events, with death as competing event. Univariate and multivariate analyses of variables for 10.1 SBRT cohort, 10.2 ChemoRT cohort.

10.1

	Univariate analysis		Multivariate analysis	
	HR	Sig.	HR	Sig.
Sex (male)	**4.90**	**0.03**	1.2	0.30
Age	1.03	0.06	1.00	0.73
PS 0-1	1		1	
PS2	1.32	0.58	1.22	0.28
PS3	1.43	0.42	1.35	0.80
CVD	**4.33**	**<0.01**	**3.73**	**<0.01**
Diabetes	**1.70**	**0.02**	1.02	0.7
COPD	**1.65**	**0.01**	1.32	0.10
EGFR>60	1		1	
EGFR45-59	1.14	0.05	1.11	0.23
EGFR<44	2.57	0.76	1.39	0.81

10.2

	Univariate analysis		Multivariate analysis	
	HR	Sig.	HR	Sig.
Sex (male)	1.28	0.62	1.43	0.23
Age	**1.08**	**0.01**	**2.07**	**0.01**
PS 0-1	1		1	
PS2	1.38	0.66	1.01	0.99
CVD	**2.78**	**0.04**	1.96	0.39
Diabetes	0.17	2.33	1.17	0.54
COPD	1.17	0.76	2.01	0.57
EGFR>60	1		1	
EGFR45-59	1.55	0.97	3.83	0.47
EGFR<44	2.43	0.60	5.04	0.22

Table 11, Chapter 5, comparison of radiotherapy regimes used in Leeds and Manchester

	The Christie hospital	Leeds Cancer Centre
SABR 3 fractions	21	63
SABR 5 fractions	236	308
SABR 8 fractions	53	81
CFRT 50 Gray in 20 fractions	1939	283
CFRT 45 Gray in 20 fractions	11	2
Chemoradiotherapy 45 Gray in 15 fractions	0	175
Chemoradiotherapy 45 Gray in 30 fractions	71	1
Chemoradiotherapy 60-66 Gray in 30-33 fractions	268	136
Other	0	34
Total	2599	1083

7.2 Figures

TNM 8th - Primary tumor characteristics	
T_x	Tumor in sputum/bronchial washings but not be assessed in imaging or bronchoscopy
T_0	No evidence of tumor
T_{is}	Carcinoma in situ
T_1	≤ 3 cm surrounded by lung/visceral pleura, not involving main bronchus
$T_{1a(mi)}$	Minimally invasive carcinoma
T_{1a}	≤ 1 cm
T_{1b}	> 1 to ≤ 2 cm
T_{1c}	> 2 to ≤ 3 cm
T_2	> 3 to ≤ 5 cm *or* involvement of main bronchus without carina, regardless of distance from carina or invasion visceral pleural *or* atelectasis or post obstructive pneumonitis extending to hilum
T_{2a}	>3 to ≤4cm
T_{2b}	>4 to ≤5cm
T_3	>5 to ≤7cm in greatest dimension *or* tumor of any size that involves chest wall, pericardium, phrenic nerve *or* satellite nodules in the same lobe
T_4	> 7cm in greatest dimension *or* any tumor with invasion of mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, spine *or* separate tumor in different lobe of ipsilateral lung
N_1	Ipsilateral peribronchial and/or hilar nodes and intrapulmonary nodes
2	Ipsilateral mediastinal and/or subcarinal nodes
3	Contralateral mediastinal or hilar; ipsilateral/contralateral scalene/ supraclavicular
M_1	Distant metastasis
M_{1a}	Tumor in contralateral lung or pleural/pericardial nodule/malignant effusion
M_{1b}	Single extrathoracic metastasis, including single non-regional lymphnode
M_{1c}	Multiple extrathoracic metastases in one or more organs

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB

Figure 2 – Chapter 2, data sharing schematic

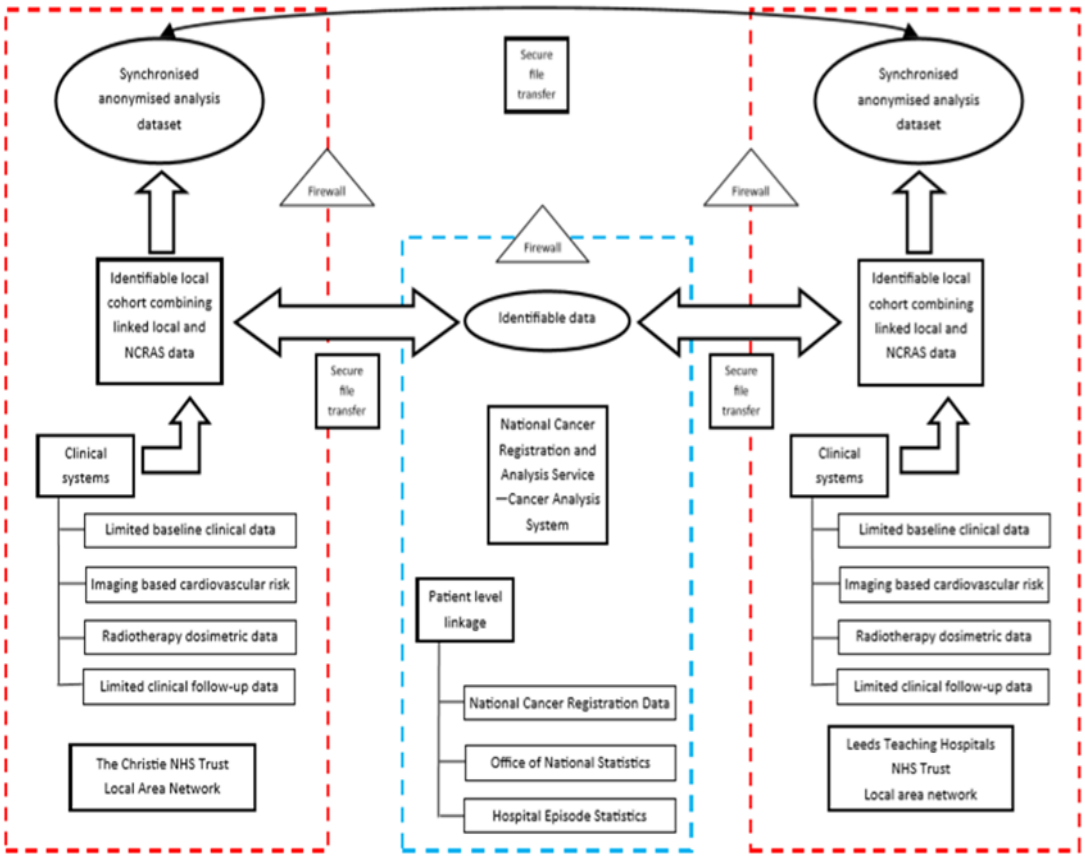
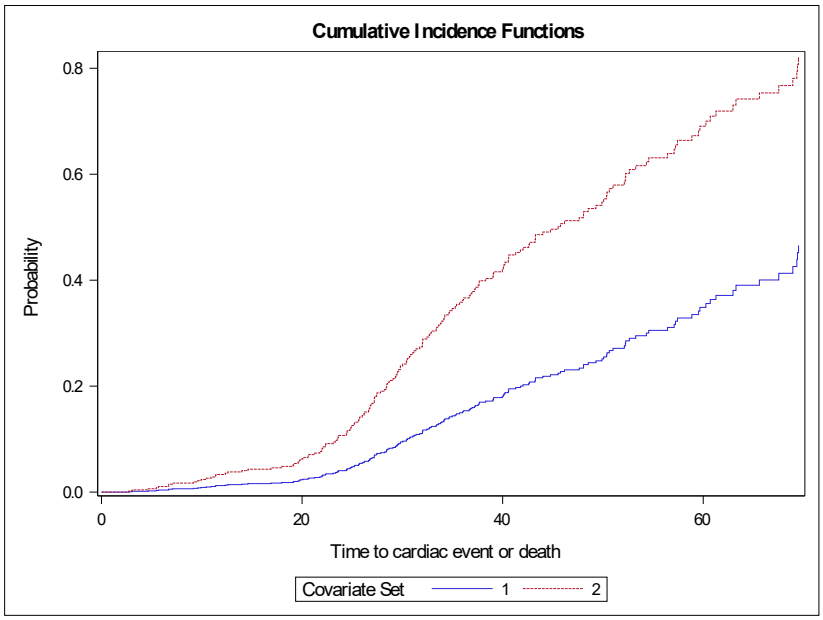


Figure 3 Chapter 4 - Cumulative incidence plots of cardiac event and death in SABR (upper graph) and ChemoRT (lower graph) cohorts. 1 (blue line) = cardiac event, 2 (red dotted line) = death. X axis: time in months, Y axis: probability



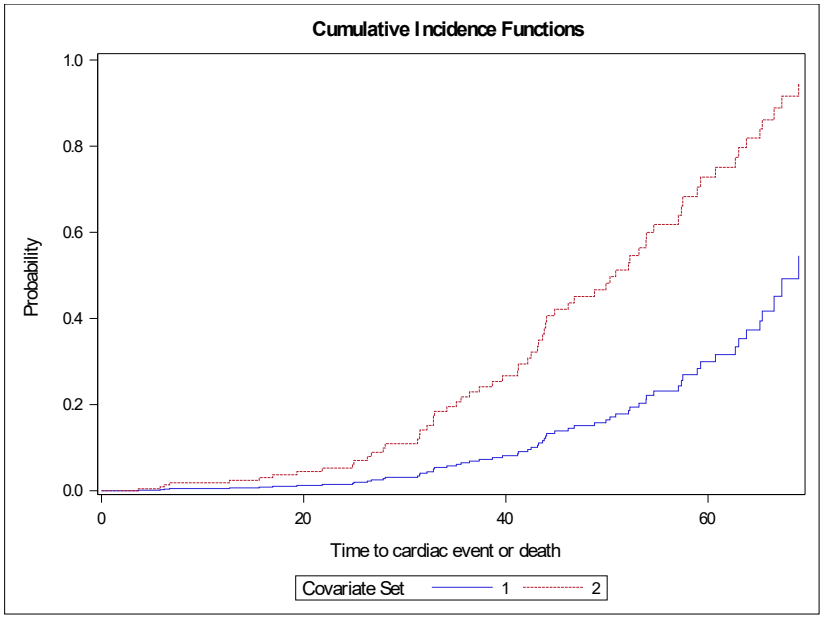
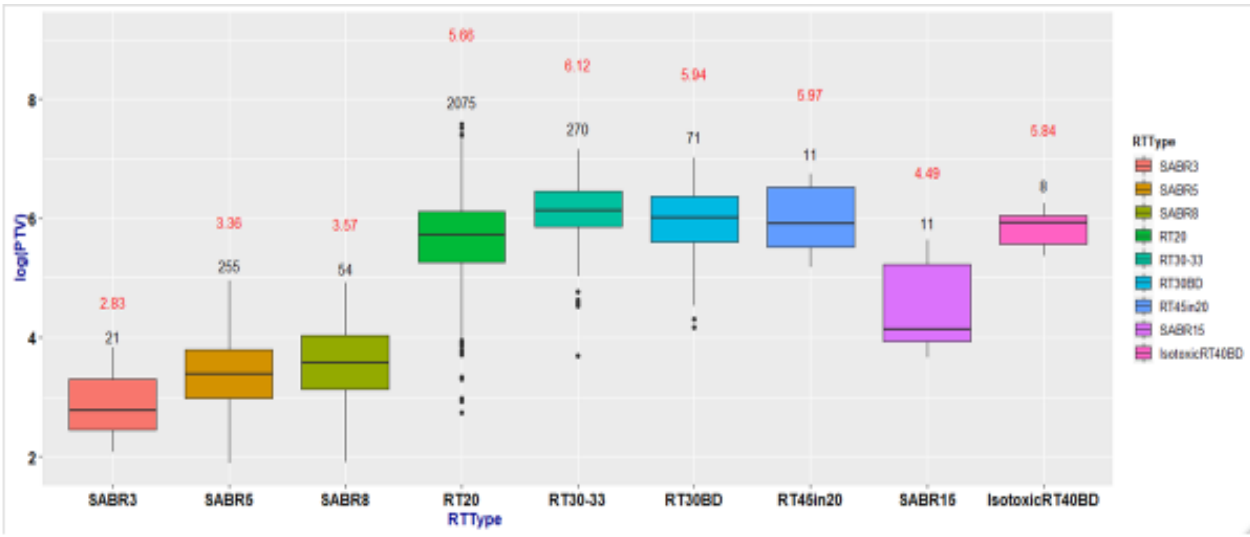


Figure 4, chapter 5, comparison of tumour PTV volume between Leeds and Manchester. Box and whisker plots of tumour volumes for each radiotherapy regime. Median, first quartile, third quartile, minimum, maximum log PTV values are displayed with outliers. Upper and lower graphs illustrate data from Manchester and Leeds respectively.


log(PTV)
RTType
SABR3
SABR5
SABR8
RT20
RT30-33
RT30BD
RT45in20
SABR15
IsotoxicRT40BD
2.83
3.36
3.57
5.66
6.12
5.94
5.97
4.49
5.84
21
255
54
2075
270
71
11
11
8

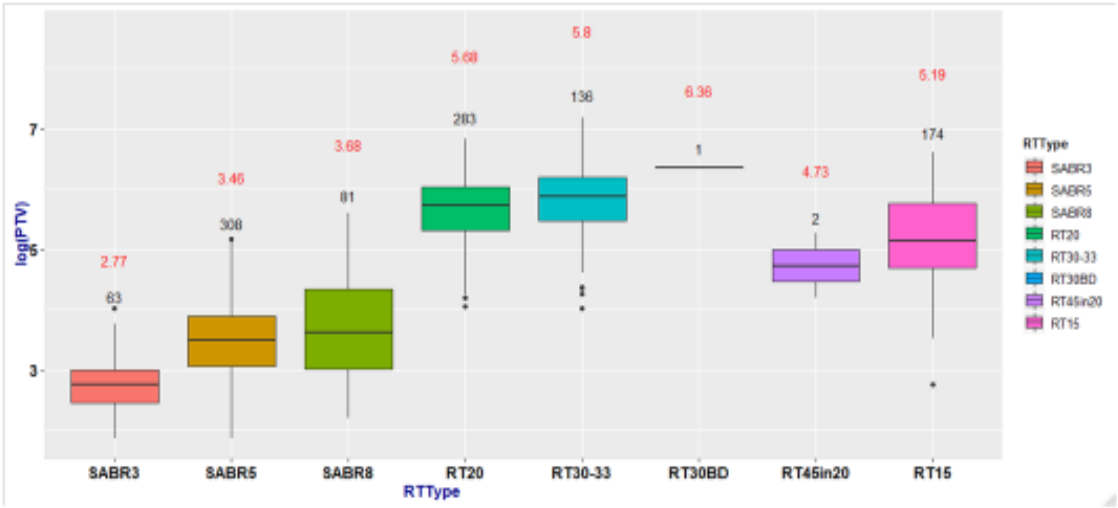

log(PTV)
RTType
SABR3
SABR5
SABR8
RT20
RT30-33
RT30BD
RT45in20
RT15
2.77
3.46
3.68
5.68
5.8
6.36
4.73
5.19
63
308
81
283
136
1
2
174

Figure 5, chapter 5, comparison of mean heart doses between Leeds and Manchester. Box and whisker plots of mean heart dose (Gy) for each radiotherapy regime. Median, first quartile, third quartile, minimum, maximum mean heart doses are displayed with outliers. Upper and lower graphs illustrate data from Manchester and Leeds respectively.

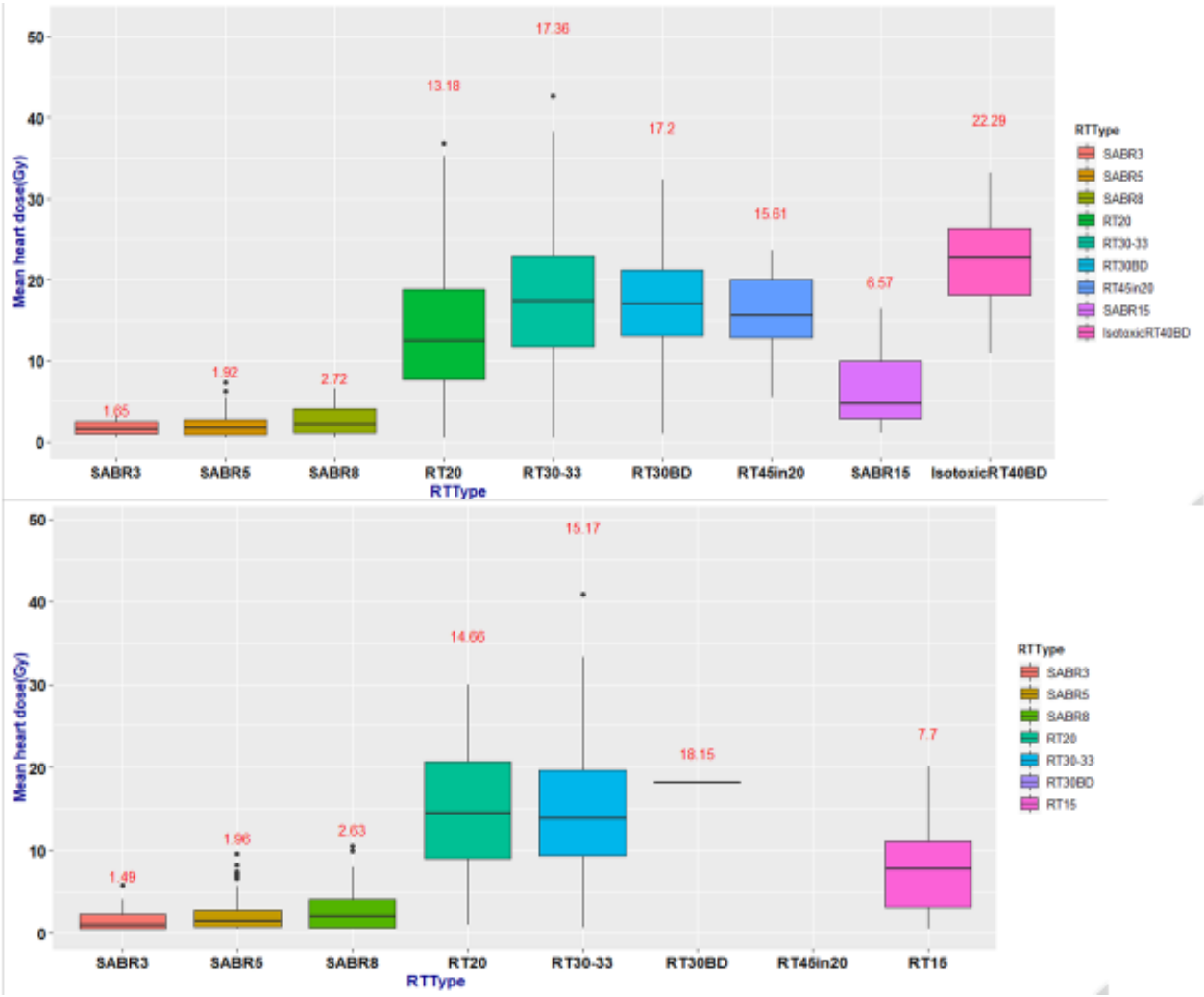
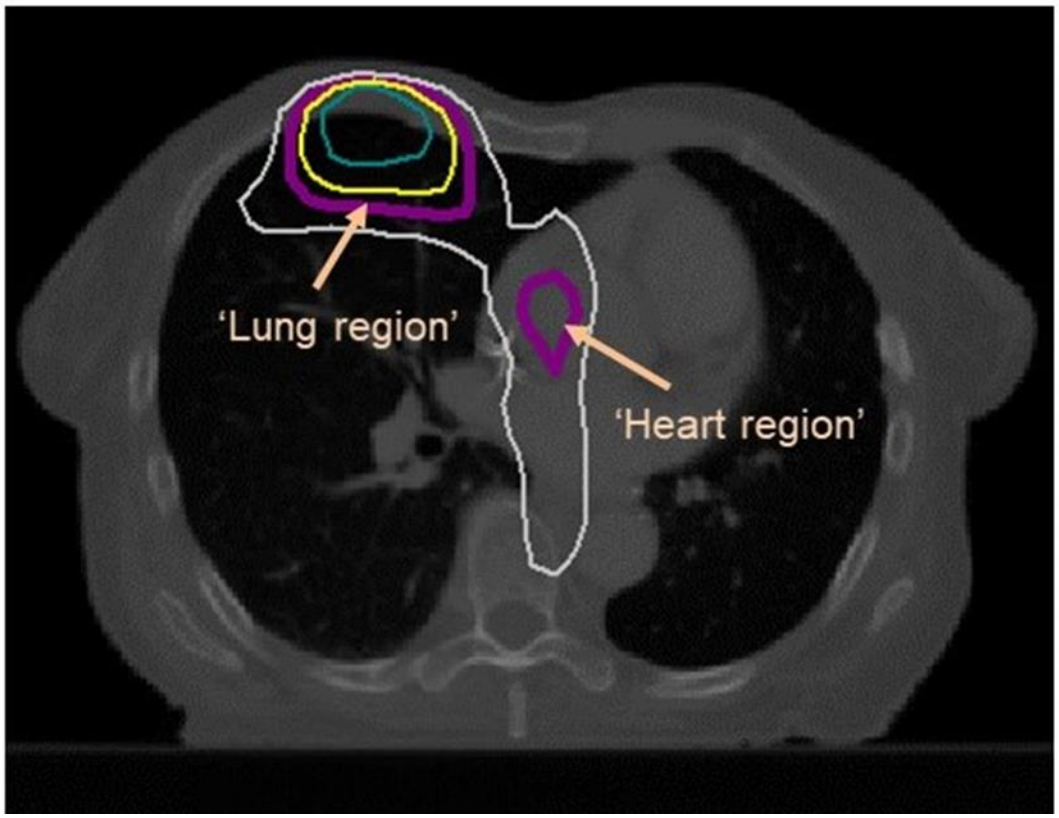


Figure 6 – Chapter 5, ‘lung region’ and ‘heart region’ associated with increased risk of CD.



List of References

1.http://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer/incidence#heading-One

2.http://wclc2017.iaslc.org/wp-content/uploads/2017/09/2017-WCLC-Fact-Sheet-Lung-Cancer-Final.pdf

3.http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#ref-5

4. http://www.who.int/mediacentre/factsheets/fs339/en/

5. Wakelee HA, Chang ET, Gomez SL, Keegan TH, Feskanich D, Clarke CA, et al. Lung cancer incidence in never smokers. J Clin Oncol. 2007;25:4728. 10.1200/JCO.2006.07.2983

6.http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-Three

7. Lim W, Ridge CA, Nicholson AG, Mirsadraee S. The 8th lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. *Quant Imaging Med Surg*. 2018;8(7):709–718. doi:10.21037/qims.2018.08.02

8. Kennedy MPT, Cheyne L, Darby M, et al. Lung cancer stage-shift following a symptom awareness campaign. *Thorax*. 2018;73(12):1128. doi:10.1136/thoraxjnl-2018-211842

9. Bansal S, Okoli S, Cole C, Jeannerat D. Beneficial lung cancer stage-shift: implementation of large scale lung cancer screening program in a

community health care system. *Chest*. 2019;155(4):191A. doi:10.1016/j.chest.2019.02.187

10. Froesch P, Martucci F, Györik S, Dutly AE, Cafarotti S. Management of non-small cell lung cancer in the elderly. Eur J Intern Med. 2014 Dec;25(10):888-94. doi: 10.1016/j.ejim.2014.10.024. Epub 2014 Oct 31. Review.

11. Spiro SG, Silvestri GA. One hundred years of lung cancer. Am J Respir Crit Care Med. 2005 Sep 1;172(5):523-9. Epub 2005 Jun 16. Review.

12. Taylor A, Powell MEB. Intensity-modulated radiotherapy—what is it? . *Cancer Imaging*. 2004;4(2):68-73. doi:10.1102/1470-7330.2004.0003.

13. Kirkbride P, Cooper T. Stereotactic body radiotherapy. Guidelines for commissioners, providers and clinicians: a national report. Clin Oncol (R Coll Radiol). 2011 Apr;23(3):163-4. doi: 10.1016/j.clon.2011.01.155.

14. Senthi S, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol. 2012 Aug;13(8):802-9. doi: 10.1016/S1470-2045(12)70242-5. Epub 2012 Jun 22.

15. https://www.nice.org.uk/guidance/cg121/chapter/1-guidance

16.https://www.astro.org/News-and-Publications/News-and-Media-Center/News-Releases/2017/ASTRO-issues-guideline-for-use-of-stereotactic-radiation-in-early-stage-lung-cancer/

17. Timmerman R, Mcgarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy in medically inoperable early stage lung cancer. J Clin Oncol. 2006;24:4833–9.

18. Perez CA, Stanley K, Seydel HG. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. Cancer. 1980 Jun 1;45(11):2744-53.

19. O'Rourke N, Roqué, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev. 2010 Jun 16;(6):CD002140. doi: 10.1002/14651858.CD002140.pub3.

20. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer. *JCO*. 2010;28(13):2181-2190. doi:10.1200/JCO.2009.26.2543

21. Chun SG, Hu C, Choy H, et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. *J Clin Oncol*. 2017;35(1):56-62. doi:10.1200/JCO.2016.69.1378

22. JD Bradley, J Moughan, MV Graham, *et al.*A phase I/II radiation dose escalation study with concurrent chemotherapy for patients with inoperable stages I to III non-small-cell lung cancer: phase I results of RTOG 0117 Int J Radiat Oncol Biol Phys, 77 (2010), pp. 367-372

23. SE Schild, WL McGinnis, D Graham, *et al.*Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer Int J Radiat Oncol Biol Phys, 65 (2006), pp. 1106-1111

24. MA Socinski, AW Blackstock, JA Bogart, *et al.*Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105 J Clin Oncol, 26 (2008), pp. 2457-2463

25. Bradley JD, Paulus R, Choy H. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015 Feb;16(2):187-99. doi:10.1016/S1470-2045(14)71207-0.

26. Simone CB 2nd. New Era in Radiation Oncology for Lung Cancer: Recognizing the Importance of Cardiac Irradiation. J Clin Oncol. 2017 May 1;35(13):1381-1383.
doi: 10.1200/JCO.2016.71.5581.

27. Nestle, Ursula et al, ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer, Radiotherapy and Oncology, Volume 127, Issue 1, 1 – 5

28. Bezjak A, Temin S, Franklin G. Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical

29. Duane F, Aznar MC, Bartlett F, et al. A cardiac contouring atlas for radiotherapy. *Radiother Oncol*. 2017;122(3):416–422. doi:10.1016/j.radonc.2017.01.008

30. Feng M, Moran JM, Koelling T, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. *Int J Radiat Oncol Biol Phys*. 2011;79(1):10–18. doi:10.1016/j.ijrobp.2009.10.058

31.Kong FM, Ritter T, Quint DJ, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. *Int J Radiat Oncol Biol Phys*. 2011;81(5):1442–1457. doi:10.1016/j.ijrobp.2010.07.1977

32. Timmerman RD, Hu C, Michalski JM, Bradley JC, Galvin J, Johnstone DW, Choy H.

Long-term Results of Stereotactic Body Radiation Therapy in Medically Inoperable

Stage I Non-Small Cell Lung Cancer. JAMA Oncol. 2018 Sep 1;4(9):1287-1288

33. https://www.sabr.org.uk/wp-content/uploads/2019/04/SABRconsortium-guidelines-2019-v6.1.0.pdf

34.Gagliardi G, Constine LS, Moiseenko V. Radiation dose-volume effects in the heart. Int J Radiat Oncol Biol Phys.2010 Mar 1;76(3 Suppl):S77-85. doi: 10.1016/j.ijrobp.2009.04.093.

35. Darby SC, Ewertz M, Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013 Mar 14;368(11):987-98.

36.Darby SC, McGale P, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort
study of about 300,000 women in US SEER cancer registries. Lancet Oncol. 2005
Aug;6(8):557-65.

37. Aleman BM, van den Belt-Dusebout AW, van Leeuwen FE. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood. 2007 Mar 1;109(5):1878-86.

38. Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of
Hodgkin's disease in children and adolescents. J Clin Oncol. 1993 Jul;11(7):1208-15.

39. Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): a systematic review. *Thorax*. 2001;56(8):628. doi:10.1136/thorax.56.8.628

40. Darby SC, Cutter DJ, Shore RE. Radiation-related heart disease: current knowledge and future prospects. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3):656-65. doi: 10.1016/j.ijrobp.2009.09.064.

41. Burdett S, Rydzewska L, Tierney J, et al. Postoperative radiotherapy for non-small cell lung cancer. *Cochrane Database of Systematic Reviews*. 2016;(10). doi:10.1002/14651858.CD002142.pub4

42.J.D. Bradley, C. Hu, R.U. Komaki. Long-Term Results of RTOG 0617: A Randomized Phase 3 Comparison of Standard Dose Versus High Dose Conformal Chemoradiation Therapy +/- Cetuximab for Stage III NSCLC, International Journal of Radiation Oncology*Biology*Physics, Volume 99, Issue 2, Supplement, 2017,Page S105, ISSN 0360-3016

43. Wang K, Eblan MJ, Deal AM, et al. Cardiac Toxicity After Radiotherapy for Stage III Non-Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy. *J Clin Oncol*. 2017;35(13):1387–1394. doi:10.1200/JCO.2016.70.0229

44. O.Y. Wong, V. Yau, J. Kang, *et al.*Survival impact of cardiac dose following lung stereotactic body radiotherapy Clin Lung Cancer, 19 (2018), pp. e241-e246

45. Chan ST, Ruan D, Shaverdian N, Raghavan G, Cao M, Lee P. Effect of Radiation Doses to the Heart on Survival for Stereotactic Ablative Radiotherapy for Early-stage Non–Small-cell Lung Cancer: An Artificial Neural Network Approach. *Clinical Lung Cancer*. October 2019. doi:10.1016/j.cllc.2019.10.010

46.Dess RT, Sun Y, Matuszak MM, et al. Cardiac Events After Radiation Therapy: Combined Analysis of Prospective Multicenter Trials for Locally Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2017;35(13):1395–1402. doi:10.1200/JCO.2016.71.6142

47.Zhang, Tina Wanting et al. Is the Importance of Heart Dose Overstated in the Treatment of Non-Small Cell Lung Cancer? A Systematic Review of the Literature. International Journal of Radiation Oncology • Biology • Physics, Volume 104, Issue 3, 582 – 589

48. Stam B, van der Bijl E, van Diessen Heart dose associated with overall survival in locally advanced NSCLC patients treated with hypofractionated chemoradiotherapy. Radiother Oncol. 2017 Oct;125(1):62-65. doi: 10.1016/j.radonc.2017.09.004.

49.Tembhekar AR, Wright CL, Daly ME. Cardiac Dose and Survival After Stereotactic Body Radiotherapy for Early-stage Non-Small-cell Lung Cancer. *Clin Lung Cancer*. 2017;18(3):293–298. doi:10.1016/j.cllc.2016.12.007

50. S.L. Tucker, A. Liu, D. Gomez, *et al.*Impact of heart and lung dose on early survival in patients with non-small cell lung cancer treated with chemoradiation Radiother Oncol, 119 (2016), pp. 495-500

51. S. Vivekanandan, D.B. Landau, N. Counsell, *et al.*The impact of cardiac radiation dosimetry on survival after radiation therapy for non-small cell lung cancer, Int J Radiat Oncol Biol Phys, 99 (2017), pp. 51-60

52.McWilliam A, Kennedy J, van Herk M. Radiation dose to heart base linked with poorer survival in lung cancer patients. Eur J Cancer. 2017 Nov;85:106-113. doi: 10.1016/j.ejca.2017.07.053.

53.Speirs CK, DeWees TA, Robinson CG. Heart Dose Is an Independent Dosimetric Predictor of Overall Survival in Locally Advanced Non-Small Cell Lung Cancer. J Thorac Oncol. 2017 Feb;12(2):293-301. doi: 10.1016/j.jtho.2016.09.134.

54.https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

55.Schytte T, Hansen O, Brink C. Cardiac toxicity and radiation dose to the heart in definitive treated non-small cell lung cancer. Acta Oncol. 2010 Oct;49(7):1058-60. doi: 10.3109/0284186X.2010.504736.

56.Ning MS, Tang L, Liao Z. Incidence and Predictors of Pericardial Effusion After Chemoradiation Therapy for Locally Advanced Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2017 Sep 1;99(1):70-79. doi: 10.1016/j.ijrobp.2017.05.022.

57. Bellière A, Girard N, Mornex F. Feasibility of high-dose three-dimensional radiation therapy in the treatment of localised non-small-cell lung cancer. Cancer Radiother. 2009 Jul;13(4):298-304. doi: 10.1016/j.canrad.2009.04.004.

58. Lee CC, Chua GWY, Zheng H, et al. Are heart doses associated with survival in patients with non-small cell lung cancer who received post-operative thoracic radiotherapy?: A national population-based study. *Medicine (Baltimore)*. 2019;98(35):e17020. doi:10.1097/MD.0000000000017020

59. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. *The Lancet Oncology*. 2019;20(4):494-503. doi:10.1016/S1470-2045(18)30896-9

60. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-2350. doi:10.1056/NEJMoa1809697

61. Somasundaram A, Burns TF. The next generation of immunotherapy: keeping lung cancer in check. J Hematol Oncol. 2017 Apr 24;10(1):87. doi: 10.1186/s13045-017-0456-5.

62. Le AD, Alzghari SK, La-Beck NM. Update on targeted therapies for advanced non-small cell lung cancer: nivolumab in context. Therapeutics and Clinical Risk Management. 2017;13:223-236. doi:10.2147/TCRM.S104343.

63. Taunk NK, Rimner A, Chaft J. Immunotherapy and radiation therapy for operable early stage and locally advanced non-small cell lung cancer. *Translational Lung Cancer Research*. 2017;6(2):178-185. doi:10.21037/tlcr.2017.03.05.

64. Johnson CJ, Hahn CG, German RR. Variability in cancer deathcertificate accuracy by characteristics of death certifiers. Am J Forensic Med Pathol. 2012 Jun;33(2):137-42. doi: 10.1097/PAF.0b013e318219877e.

65. de Roos A. Onco-Cardiology: Value of Cardiac Imaging by Using CT and MRI after Radiation Therapy. *Radiology*. 2018;289(2):355-356. doi:10.1148/radiol.2018181039

66. Takagi H, Ota H, Umezawa R et al. Left ventricular T1 mapping during chemotherapy-radiation therapy: serial assessment of participants with esophageal cancer. Radiology 2018;289:347–354.

67. Nellessen U, Zingel M, Hecker H, Bahnsen J, Borschke D. Effects of Radiation Therapy on Myocardial Cell Integrity and Pump Function: Which Role for Cardiac Biomarkers? *Chemotherapy*. 2010;56(2):147-152. doi:10.1159/000313528

68.Palumbo I, Palumbo B, Fravolini ML, et al. Brain natriuretic peptide as a cardiac marker of transient radiotherapy-related damage in left-sided breast cancer patients: A prospective study. *The Breast*. 2016;25:45-50. doi:10.1016/j.breast.2015.10.004

69. https://www.gov.uk/government/publications/end-of-life-care-profiles-february-2018-update/statistical-commentary-end-of-life-care-profiles-february-2018-update

70. BARCLAY TH, PHILLIPS AJ. The accuracy of cancer diagnosis on death certificates. Cancer. 1962 Jan-Feb;15:5-9

71. Brinkley D, Haybittle JL, Alderson MR. Death certification in cancer of the breast. *Br Med J(ClinResEd)*.1984;289(6443):465467.doi:10.1136/bmj.289.6443.465

72. Vellacott KD, Ferro MA. Cause of death and accuracy of certification of colorectal cancer. *J R Soc Med*. 1984;77(1):22–25.

73. Yow AG, Rajasurya V, Sharma S. Sudden Cardiac Death. [Updated 2019 Jul 30]. In: StatPearls [Internet]. StatPearls Publishing; 2020 Jan-.

74. https://qrisk.org/2017/index.php

75. https://sourceforge.net/projects/niftyreg

76. https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2018

77. https://www.bhf.org.uk/what-we-do/our-research/heart-statistics/heart-statistics-publications/cardiovascular-disease-statistics-2018

78. Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice?. *Ther Adv Respir Dis*. 2018;12:1753465817750524. doi:10.1177/1753465817750524

79. Keteepe-Arachi T, Sharma S. Cardiovascular Disease in Women: Understanding Symptoms and Risk Factors. *Eur Cardiol*. 2017;12(1):10–13. doi:10.15420/ecr.2016:32:1

80. Smith Sehdev AE, Hutchins GM. Problems with proper completion and accuracy of the cause-of-death statement. Arch Intern Med. 2001 Jan 22;161(2):277-84

81. Yuan, Min et al. Lung Cancer and Risk of Cardiovascular Disease: A Meta-analysis of Cohort Studies. Journal of Cardiothoracic and Vascular Anesthesia, Volume 32, Issue 1, e25 - e27

82. Atkins KM, Rawal B, Chaunzwa T. Cardiac Radiation Dose, Cardiac Disease, and Mortality in Patients With Lung Cancer. J Am Coll Cardiol. 2019 Jun 18;73(23):2976-2987. doi:10.1016/j.jacc.2019.03.500.

83. https://www.bhf.org.uk/what-we-do/our-research/heart-statistics/heart-statistics-publications/cardiovascular-disease-statistics-2019

84. Strain WD, Paldánius PM. Diabetes, cardiovascular disease and the microcirculation. *Cardiovasc Diabetol*. 2018;17(1):57. Published 2018 Apr 18. doi:10.1186/s12933-018-0703-2

85. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *The Lancet*. 2013;382(9889):339-352. doi:10.1016/S0140-6736(13)60595-4

86. Durham AL, Adcock IM. The relationship between COPD and lung cancer. *Lung Cancer*. 2015;90(2):121–127. doi:10.1016/j.lungcan.2015.08.017

87. https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2018

88. Spencer KL, Kennedy MPT, Lummis KL, et al. Surgery or radiotherapy for stage I lung cancer? An intention to treat analysis. *Eur Respir J*. January 2019:1801568. doi:10.1183/13993003.01568-2018

89. Shavelle, Robert M et al. “Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study.” *International journal of chronic obstructive pulmonary disease* vol. 4 (2009): 137-48. doi:10.2147/copd.s5237

90. Neild, Guy H. “Life expectancy with chronic kidney disease: an educational review.” *Pediatric nephrology (Berlin, Germany)* vol. 32,2 (2017): 243-248. doi:10.1007/s00467-016-3383-8

91. Tuegel C, Bansal N. Heart failure in patients with kidney disease. *Heart*. 2017;103(23):1848. doi:10.1136/heartjnl-2016-310794

92.https://www.who.int/cardiovascular_diseases/priorities/secondary_prevention/country/en/index1.html

93. Alter P, Mayerhofer BA, Kahnert K, et al. Prevalence of cardiac comorbidities, and their underdetection and contribution to exertional symptoms in COPD: results from the COSYCONET cohort. *Int J Chron Obstruct Pulmon Dis*. 2019;14:2163–2172. Published 2019 Sep 20. doi:10.2147/COPD.S209343

94. Eguchi T, Bains S, Lee M-C, et al. Impact of Increasing Age on Cause-Specific Mortality and Morbidity in Patients With Stage I Non–Small-Cell

Lung Cancer: A Competing Risks Analysis. *JCO*. 2016;35(3):281-290. doi:10.1200/JCO.2016.69.0834

95.https://www.ons.gov.uk/peoplepopulationandcommunity/personalandhouseholdfinances/incomeandwealth/bulletins/wealthingreatbritainwave5/2014to2016

List of Abbreviations

3D-CRT	3-dimentional computerised radiotherapy
ACCOLADE	A study investigating how to avoid CardiaC tOxicity in Lung cancer pAtients treateD with curative-intent radiotherapy to improvE survival, funded by Yorkshire Cancer Research
ACE-I	Angiotensin converting enzyme inhibitor
ALK	Anaplastic lymphoma kinase
BB	Beta blocker
BNP	Brain nautrietic peptide
CAG	Confidentiality advisory group
CD	Cardiac death
CFRT	Conventionally fractionated radiotherapy
ChemoRT	Chemoradiotherapy
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
CVD	Cardiovascular disease
DI	Deprivation index
DICOM	Digital imaging and communications in medicine
DVH	Dose volume histogram
ECOG	Eastern cooperative oncology group
EGFR	Estimated glomerular filtration rate
GFR	Growth fator receptor
HES	Hospital episodes statistics
HH	Death at hospital or hospice
HN	Death at home or nursing home
HRA	Health research authority
ICD 10	10th revision of international statistical classification of diseases and related health problems
IMRT	Intensity modulated radiotherapy
LA	Left atrium
LV	Left ventricle
MHD	Mean heart dose
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NCRAS	National cancer registry and analysis service
NCTP	Normal tissue complication probability
NIHR	National institute for health research
NSCLC	Non-small cell lung cancer

OAR	Organ at risk
PCD	Pre-existing cardiac disease
PHE	Public health England
PIS	Patient information sheet
PPI	Patient and public involvement
QUANTEC	Quantitative analyses of normal tissue effects in the clinic
RA	Right atrium
RTOG	Radiation therapy oncology group
SABR	Stereotactic body radiotherapy
V30	Volume of tissue that receives >30Gy
V40	Volume of tissue that receives >40 Gy
V5	Volume of tissue that receives >5Gy
WP	Work package

Appendix A
List of conference abstracts

Multi-centre analysis of cardiac events following radical radiotherapy for lung cancer

F Sun, K Banfill, J Lilley, B Wheller, L Murray, A McWilliam, M Van Herk, A Abravan, C Faivre-Finn, K Franks

Oral presentation presented at European Lung Cancer Congress 2019

Background: Radical radiotherapy (RRT) plays an essential role in the management of early and locally advanced lung cancer. Recent studies suggest cardiac events post radiotherapy worsen survival outcome for patients. This study aims to identify risk factors which predispose patients to cardiac events post radiotherapy.

Methods: All patients who received RRT (including Stereotactic Body Radiotherapy (SBRT), radical fractionated radiotherapy and chemoradiotherapy) for lung cancer between 01/01/2010 to 30/12/2016 at 2 UK institutions have been included. Patients were excluded if they had multiple courses of radiotherapy to the chest. Individual patient clinical information has been retrieved from hospital electronic database. Patient and cancer demographics have been collected. Pre-existing cardiac conditions, Charlsons' Co-morbidity index and Qrisk 3 scores were calculated. Post radiotherapy cardiac events were identified rom electronic patient records and time to cardiac events were calculated.

Results: 600 patients have been identified so far and processed. Median follow up is 31 months. Of all patients, 29% had pre-existing cardiac conditions. 52 patients experienced cardiac events following radiotherapy, of which 37% were ischaemic events. Of patients who experienced an ischaemic event, 58% did not have a known pre-existing cardiac condition. 71% of cardiac events post RRT occurred in the first 2 years following RT. Proportionally, patients who underwent radical fractionated radiotherapy and concurrent chemoradiotherapy had the highest incidence of cardiac events. Patient characteristics of those who experienced cardiac toxicity are summarized in the table below.

Conclusions: A clinically significant proportion of patients developed cardiac toxicity following radical radiotherapy for lung cancer. Cardiac events occur much sooner after lung cancer radiotherapy than radiotherapy for breast cancer or lymphoma. Work is ongoing to identify greater number of patients and combine local data with data from national registry to aid analysis.

Cardiac toxicity after radical dose radiotherapy for lung cancer - initial results from a multi-centre study

Fei Sun, Kathryn Banfill, Sally Falk, Alan McWilliam, John Lilley, Robert Wheller, Azadeh Abravan , Matthias Schmitt, Marcel Van Herk, Corinne Faivre-Finn, Kevin Franks

Poster presentation at European society of radiation and oncology 2019

Introduction. Lung cancer is the leading cause of cancer mortality worldwide. Radical radiotherapy plays a pivotal role in the management of early and locally advanced disease. Recent studies suggest adverse cardiac events post treatment may worsen survival outcome for patients. This study aims to identify risk factors which predispose patients to cardiac events post radiotherapy and we present the initial results from the initial 107 patients.

Methods. All patients who received radical radiotherapy for lung cancer between 01/01/2010 to 30/12/2016 in Leeds and Manchester are to be included. 1709 patients have been identified. From these cohorts patients were excluded if they had multiple courses of radiotherapy to the chest. Individual patient clinical information was retrieved from the hospitals electronic patient record (EPR). Patient and cancer demographics have been collected. Pre-existing cardiac conditions, Charlsons' Co-mobidity index and Qrisk 3 scores were calculated. Post radiotherapy cardiac events were recorded, survival times were calculated.

Results. 107 patients have been analysed so far. Median follow up is 26 months. Patient, tumour and radiotherapy characteristics are summarised in table 1. In the patients studied 30% had pre-existing cardiac conditions and 13% of patients experienced a cardiac events following radiotherapy (83% of these patients had pre-existing cardiac conditions. The median time from

treatment to cardiac event was 13 months post radiotherapy. Patient characteristics of those who experienced cardiac toxicity are summarized in charts 2.

Conclusion. A substantial proportion of patients had a cardiac event following radical radiotherapy for lung cancer. A large proportion of these patients had pre-existing cardiac conditions. Cardiac events occur much sooner after lung cancer radiotherapy than post-radiotherapy for breast cancer or lymphoma. Further work is on-going to expand the patient numbers, examine risk factors and correlate cardiac events/survival with radiotherapy dosimetry.

Avoiding cardiac toxicity in patients undergoing curative intent radiotherapy for lung cancer

Kathryn Banfill, Fei Sun, Sally Faulk, Alan McWilliam, Azaday Abrahams, Matthias Schmitt, Kevin Franks, Corinne Faivre-Finn

Poster presentations at British thoracic oncology group meeting 2019

Introduction.Lung cancer and ischaemic heart disease (IHD) are two of the five main cases of death in the United Kingdom [1] and about a quarter of lung cancer patients have concomitant IHD [2]. In the last 3 years evidence has emerged that increased heart dose is associated with poorer survival in lung cancer patients treated with curative radiotherapy(RT) [3]. Dose to the base of the heart appears to be particularly important, however cardiac dose volume constraints are not well defined [4]. This study aims to validate the correlation between heart dose and mortality in lung cancer patients treated with radical radiotherapy. In addition, a prospective trial of cardiac biomarkers and imaging will be conducted.

Methods. Deformable registration methodology will be applied to >1000 lung cancer patients treated in Leeds. The patients will have a diagnosis of non-metastatic lung cancer and received radical doses of radiotherapy. We will analyse the planning CT data from the Leeds and Manchester cohorts (>2000 patients) to quantify coronary artery calcification using the Agatston score. We will obtain data on cardiac risk factors, hospital admissions and cause of death for these patients to conduct a multivariate survival analysis.

The prospective trial aims to recruit 200 patients with a histological or clinical diagnosis of stage I-III lung cancer suitable for curative intent radiotherapy. Patients will have blood collected before, on completion of and four months after RT. Samples will be taken for: full blood count; lipids; cholesterol; high sensitivity troponin levels; C-reactive protein and brain natriuretic peptide. Fifty participants will undergo cardiac CT, echocardiogram and 12 lead electrocardiogram at baseline and 4 months after RT. The biomarker and imaging data will be linked to heart dose and survival.

Conclusions. This study aims to assess the utility of blood biomarkers and cardiac imaging in the management of lung cancer patients. We will also use both retrospective and prospective data to derive dose cardiac dose constraints. This will lead to improved treatment of lung cancers patients both in terms of managing cardiac co-morbidities and limiting dose to the heart.

Do statins improve outcomes after radical radiotherapy for lung cancer? An in-depth analysis of over 1100 patients.

Fei Sun, Kathryn Banfill, Sally Falk, Alan McWilliam, John Lilley, Robert Wheller, Azadeh Abravan , Matthias Schmitt, Marcel Van Herk, Corinne Faivre-Finn, Kevin Franks

Poster presentation at IASLC world lung cancer congress 2019

Background. Statins exhibit anti-cancer activity in vitro in addition to cardiovascular protection effects. Trials using statins in lung cancer have shown mixed results. This study investigates statins' impact on patients treated with curative radiotherapy for lung cancer

Methods. All patients who received radical radiotherapy for lung cancer from 01/01/2010-31/12/2016 at a large cancer centre were included. Individual patient information, including drug history at diagnosis, has been retrieved from hospital electronic database. Pre-existing cardiac conditions, Charlson Co-mobidity index and Qrisk^3 scores were calculated.

Results. 1181 patients were identified. Patient and treatment demographics are summarised in table 1. Patients in the statin group were older, had more co-morbidities and higher Qrisk^3 scores. A 'High Risk Cohort'(HRC) was identified, which consists of patients with a history of cardiac disease or

Qrisk^3 score >40. In HRC, statins significantly improved Overall Survival and PFS (p=0.016 and p=0.031 respectively), Graph 1.

Conclusion. In this retrospective analysis, patients who were on statins in the HRC had better survival outcomes. Mechanism of action of statins in lung cancer remains unclear and may be different in the post radiotherapy setting. Prospective studies would be useful to evaluate statins in this setting.

Trial in Progress: Cardiac Toxicity in Patients Undergoing Curative Intent Radiotherapy for Lung Cancer

Banfill, K, Mcwilliam, A, Abravan, A, Wheller, B, Schmitt, M, fei, S, Franks, K, Van Herk, M & Faivre-Finn, C

Poster presentation at IASLC world lung cancer congress 2019

Background: The cardiotoxic effects of radiotherapy (RT) in long term survivors of breast cancer or lymphoma are well documented. Post-mortem studies and animal models have shown that RT causes fibrosis of cardiac structures leading to a wide variety of cardiac pathology. RTOG 0617 has highlighted a link between survival and cardiac dose and has led to a number of studies of cardiac toxicity in lung cancer patients. It is difficult to draw conclusions on cardiac dose constraints from available studies due to their retrospective nature and heterogeneity. We present an ongoing multicentre retrospective data mining study and prospective trial of cardiac biomarkers and imaging in patients undergoing radical lung RT, the aim of which is to define cardiac dose contraints leading to cardiac sparing treatment strategies.

Method(s): Retrospective Validation Image based data mining results for heart substructures will be validated using a larger cohort. We will obtain data from Public Health England on cardiac risk factors, hospital admissions and cause of death for these patients to conduct a multivariate survival analysis. Clinical Trial (NCT03645317) A prospective study will collect cardiac risk factors (Qrisk 3), detailed cardiac imaging (CT and echocardiogram), ECG and cardiac blood biomarkers to evaluate effect of the radiotherapy on the heart. [Figure presented] Result: Over 4000 patients treated with curative intent RT from 1/1/2010 to 30/12/206 have been

identified. Details on 600 patients have been obtained and will be presented at WCLC 2019. Fifty-two patients (9%) had cardiac events following RT. The prospective trial is due to open in May 2019

Conclusion(s): Studies of cardiac toxicity in lung RT have so far mainly been heterogeneous and retrospective. We describe a package of work incorporating large retrospective datasets with prospective imaging and blood biomarker collection to define cardiac dose parameters. This will improve the outcomes of lung cancer patients treated with radical radiotherapy by limiting heart dose and reducing cardiac events.

Poor Diffusing Capacity for Carbon Monoxide (DLCO) is associated with worse overall survival post SABR

F. Sun, P. Murray, P. Dickinson, M. Teo, A. Saha, P. Jain, K. Clarke, K. Franks

To be presented as a poster at European society of oncology and radiotherapy 2020

Introduction.Stereotactic ablative radiotherapy (SABR) is the standard non-surgical management for peripheral early lung cancers. Existing literature suggest SABR is safe in patients with poor lung function. This study evaluates the effect of lung function on survival outcomes for patients treated with SABR.

Methods. All patients who received SABR at a large cancer centre in the UK from 01/01/2010 to 31/12/2016 were reviewed. Patients were included if they had pre-SABR full pulmonary function tests (PFTS) which include forced expiratory volume in one second (FEV1), FEV1 as a percentage of predicted (%FEV1), forced vital capacity (FVC) and DLCO as a percentage of predicted (%DLCO). Patient and tumour demographics were obtained for each patient from electronic health records. Survival times were calculated and analysed using SPSS statistics.

Results. 410 patients with complete medical records and pre-SABR PFTs were included in the study. Median follow up was 26.1 months. Patient and cancer demographics are summarised in table 1. Median overall survival for the whole cohort was 29.7 months. %DLCO was found to be associated with worse overall survival (cox regression, p=0.001). Performance status and

age were also found to be associated with worse survival (p=0.035 and p<0.001 respectively). Overall survival of patients with a DLCO>50% of predicted was 31.9 month, versus 25 months (log rank p=0.011) for patients with %DLCO <50% of predicted.

Conclusion. Poor %DLCO was found to be associated with poor overall survival in this study. Further studies using radiation dosimetry and additional co-morbidity factors are needed to clarify true correlation and post SABR survival.

Appendix B
ACCOLADE set up in Leeds

Study methods

Potential participants are identified and approached by a member of the local research team in the clinic at a pre-treatment appointment. The study is discussed with the patient and the patient is given a detailed participation information sheet (PIS, see appendix). Patients have time to read the PIS, discuss it with relatives and their GP as they feel appropriate, before deciding on whether or not to participate. Patients are free to ask questions about the study.

Patients who decide to take part in the study return to the cancer centre and sign the trial consent form (see appendix). This is then countersigned by the person taking consent. The patient is then given a copy of the information sheet and signed consent form.

Once the participant consents to participate, they are registered and given sequential ID numbers. These numbers will be used to identify all collected samples anonymised patient data.

Acquired patient medical data consists of height, weight, blood pressure, history of cardiac disease, relevant cardiac medications and calculated Q-risk score. Data is entered on case report forms (see appendix).

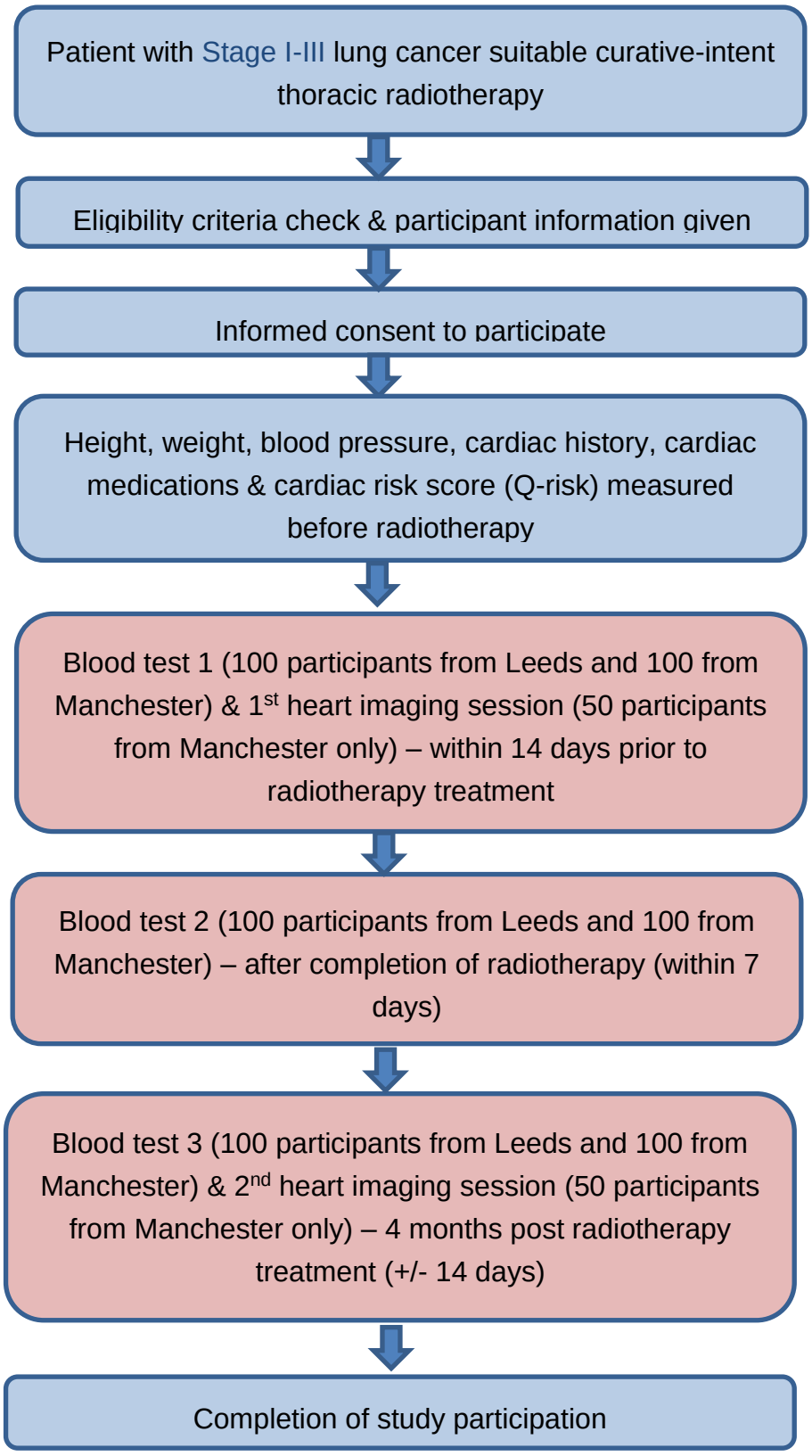
Blood samples are collected at 3 time points: within 14 days before starting radiotherapy, within 7 days after completion of radiotherapy; and 4 months post radiotherapy (+/- 14 days).

The following blood samples will be collected: full blood count (FBC), lipid profile, total cholesterol, high sensitivity troponin, C-reactive protein (CRP) and brain natriuretic peptide (BNP).

Blood tests will be analysed as a function of dose received to the heart. Dose to the heart will be extracted from the patients plan, including mean heart dose and volume based dose statistics. Details are contained in end of treatment case report form (see appendix). Additionally, blood markers and dosimetric parameters will be included in a multivariate analysis including patient demographics and clinical information.

The study does not involve any experimental therapy. Patient will be treated as per standard of care. Therefore no adverse or serious adverse events directly relating to blood sampling is expected.

Study flow diagram



Research ethics and approvals

The research proposal was presented to the NHS regional ethics committee on 25/10/2018 (reference 18/NW/0706). The committee gave favourable ethical opinion of the research, subject to minor changes on participant information sheet and informed consent form. These conditions were since met and full approval was granted on 01/11/2018.

The research proposal applied for Health Research Authority (HRA) approval on 10/10/2018 (reference 230736). Full HRA approval was granted on 01/11/2018.

At the Leeds Cancer Centre, the research study capacity and capability assessment was completed on 15/01/2019 and the study was granted approval from the Oncology Department. Approval from the Pathology Department was granted on 30/04/2019. Approval from the Medical Physics Department, was granted on 07/08/2019. Final approval from Trust Finance and research and innovation departments was granted on 22/11/2019.

Set up

After gaining necessary departmental approvals, a site initiation visit took place at the lung oncology research group meeting. This briefing introduced trial concept, recruitment criteria, research staff an follow up protocol to the oncology team. ACCOLADE formally opened at the Leeds cancer centre in January 2020 and the first patient was recruited at the end of January.

The local ACCOLADE research team consist of a principle investigator, co-investigators (research fellow and clinical oncologists treating lung cancer) and research support staff (research therapy radiographers). The research team holds regular meetings, either in person or via email, to discuss recruitment and follow up. Regular telephone meetings take place with the Manchester team to discuss trial recruitment and issues relating to the study.

Potentially eligible patients are identified before lung oncology clinics. In clinic, they are approached by an investigator, who explains the trial to the patient and provides the patient with a patient information sheet (appendix B). Patient is then given time to consider the trial proposal. At the time of simulation CT scan, prior to radiotherapy, the trial team approach the patient again. If the patient has decided to go into the study, the trial team sign the trial consent form (appendix B) with the patient. This consist of two copies, one to be kept by the trial team and the other by the patient. Just before the patient starts radiotherapy the first trial blood test is performed. Alongside the blood test the main case report form (appendix B) is filled in. At the end of radiotherapy, the second trial blood test is performed. The end of treatment case report form (appendix B) is filled in, by reviewing the radiotherapy plan and performing dosimetry calculations. 4 months after radiotherapy, the trial team synchronises a study follow up with patient's post radiotherapy clinic. At this point the third blood test is performed.

The candidate introduced the study to the local clinical team, consisting of oncologists, specialist nurses and research staff. The candidate communicated with pathology, local research and innovation, research finance and research physics departments and arranged necessary approvals to commence the research study. The candidate identified patients prior to clinic, approached eligible patients, consented patients before radiotherapy and completed necessary study proformas.

At time of writing, 14 patients have been recruited into the study. Recruitment is ongoing and the aim is to recruit 100 patients in Leeds.

The study tests a number of biomarkers which may be elevated at baseline in the population, particularly in patient with lung cancer due to their advance age and comorbidities. After extensive consultation with the Manchester team, cardiologists and reviewing NICE (national institute of clinical excellence) guidelines, a standard operating procedures for blood results was created. This is based on national guidelines and ensures results are act upon, with relevant investigations and referral made.

Troponin

If troponin elevated patients will need to be clinically assessed. If they are asymptomatic, they should have an ECG and repeat troponin in 3-6hours (or as early as possible) via JONA. If patient's repeat troponin remains raised, then discussion with on call cardiology SPR needed.

If patient has chest pain or ECG changes consistent with a myocardial infarction/ischaemia, then the standard pathway for NSTEMI/STEMI applies.

Lipids/Qrisk Score

Q risk score is not validated for use in patients over the age of 84 or who have known cardiovascular disease (such as MI/angina or stroke).

Patients with dyslipidaemia should be investigated for secondary causes such as: alcohol excess; uncontrolled diabetes; hypothyroidism; liver disease and nephrotic syndrome. This is defined as cholesterol > 9.0 mmol/litre or non-HDL cholesterol > 7.5 mmol/litre

If Q-risk2 estimated 10yr risk of CVD > 10% or raised lipids, and not on a statin, a non-urgent letter to GP to inform finding and give lifestyle advice/start statins in the community which will be done by the trial team.

NT-proBNP

If patient is **not known** to have heart failure and found to have a raised NT-proBNP, they should have history, examination and ECG. **If symptom/signs suggestive of heart failure**, then:

According to NICE guidelines if NT-proBNP > 2,000 ng/litre (236 pmol/litre) patient should be referred for transthoracic echo and cardiology review within 2 weeks. If NT-proBNP 400-2,000 ng/litre (47 to 236 pmol/litre) patient should be referred for transthoracic echo and cardiology review within 6 weeks. Letter to be sent to GP advising the need for referral as appropriate.

If patient is **known** to have heart failure, BNP is not valid as a tool to assess severity or guide management. Medical management of symptomatic heart failure should be as per NICE guidelines.

Appendix C
ACCOLADE documents

ACCOLADE patient information sheet

Leeds Participant Information Sheet

Version 3.1, 20th October 2019

A study investigating how to avoid cardiac toxicity in lung cancer patients treated with curative-intent radiotherapy to improve survival, funded by Yorkshire Cancer Research.

You are being invited to take part in a research study for patients with lung cancer undergoing radiotherapy, which will involve having extra blood samples taken.

- Before you decide whether to take part, it is important to understand why the research is being done and what is involved.
- Please take time to read this information carefully and discuss it with others if you wish.
- Please ask if there is anything that is not clear or if you would like more information.
- Take time to decide whether or not you wish to take part.
- Thank you for taking the time to read this.

Who will conduct the study?

This study is being organised by researchers at the University of Manchester (who is the Research Governance Sponsor), The Christie NHS Foundation Trust and Leeds Cancer Centre. The study is being funded by a grant from Yorkshire Cancer Research (grant reference number M401) and supported by the Manchester Biomedical Research Centre.

What is the purpose of the research & why have I been chosen?

- Do I have to take part in the study? – No.
- You have been diagnosed with lung cancer and will be receiving radiotherapy either alone or with chemotherapy (chemo-radiotherapy) as part of your treatment.
- The purpose of the study is to improve our understanding of how radiotherapy to the chest area affects the heart and how we can improve heart health and survival in patients with lung cancer.
- Research has shown that when radiotherapy is delivered to the heart it can cause side effects. However it is not known which parts of the heart are the most sensitive to radiotherapy.
- When giving radiotherapy we take great care in limiting the radiation dose delivered to the surrounding healthy tissue, including the heart. However as most lung tumours are close to the heart this cannot be avoided completely. We would like to investigate whether certain parts of the heart are more sensitive to radiotherapy than others. We hope that this information will help to improve the delivery of radiotherapy by avoiding the sensitive part of the heart and ultimately improve survival rates for lung cancer patients.
- Two hundred participants with lung cancer will be included in this study (100 from The Christie in Manchester & 100 from Leeds Cancer Centre).

In this study, we will investigate:

- whether we can monitor changes caused by radiotherapy to the heart with imaging and blood tests

- whether we can identify the part(s) of the heart that are the most sensitive to radiotherapy

What would I be asked to do if I took part?

- If you agree to take part in the study you will first be asked to sign a consent form.
- All 200 participants will be asked to have extra blood samples taken at 3 time points (before your radiotherapy starts, straight after you have finished your course of radiotherapy and then at 4 months after radiotherapy has finished).
- We will arrange for the blood samples to be taken on days that you are already at the hospital for another appointment, so you will not have to make any extra visits.
- We will also collect information relating to your medical history, treatment for lung cancer, and any medications you are currently taking.
- Some of the blood tests will be done as part of your standard care but others are for research only. The blood samples will be destroyed once they have been analysed.
- Once the blood samples have been taken your participation in the study will be finished.

What does having blood tests involve?

- Collecting blood only takes 5 minutes. Up to 4 tubes (approximately 15mls) of blood will be taken on each occasion.
- The tests we will be carrying out on your blood are called full blood count (routine test), Creactive protein (extra test), lipids/cholesterol (extra test), troponin levels (extra test), and brain natriuretic peptide (extra test).

You should not experience any adverse effects from having blood samples taken although you may feel a slight sensitivity or develop a bruise in the area where the blood has been taken.

What are the possible benefits of taking part?

The blood tests may pick up problems with your heart. If this happens, the doctors in charge of your treatment will decide on the appropriate care that may be needed. If anything abnormal is found on the blood tests the study doctors may discuss the results with your GP or a heart specialist.
The treatment for your lung cancer will not be affected by taking part in the study. The information we get from this study will hopefully benefit patients receiving radiotherapy treatment for lung cancer in the future.

What are the possible disadvantages and risks of taking part?

You should not experience any adverse effects from having blood samples taken although you may feel a slight sensitivity or develop a bruise in the area where the blood has been taken. Your visit to the hospital may be slightly longer as you will be having blood tests taken, we will try to minimise any delays wherever possible.

What will happen to my personal information?

In order to undertake the research project the study team will need to collect the following personal information about you:

- your name
- your contact details (address and telephone number)
- your hospital number and NHS number

This is so that we can contact you during the study to discuss study visits or afterwards if you would like to receive a copy of the results of the study. Only the research team will have access to this information. However, your consent form (which has your name on) will be kept for 15 years. This will be held securely in the study files. We are collecting and storing this personal information in accordance with the General Data Protection Regulation (GDPR) and Data Protection Act 2018 which legislate to protect your personal information. The legal basis upon which we are using your personal information is “public interest task” and “for research purposes” if sensitive information is collected. For more information about the way we process your personal information and comply with data protection law

please see the University of Manchester's Privacy Notice for Research Participants: http://documents.manchester.ac.uk/display.aspx?DocID=37095.

The University of Manchester (as data controller for this study) take responsibility for the protection of the personal information that this study is collecting about you. In order to comply with the legal obligations to protect your personal data the university has safeguards in place such as policies and procedures. All researchers are appropriately trained and your data will be looked after in the following way:

The study team will have access to your personal identifiable information, that is data which could identify you, but they will anonymise it as soon as it is practical. After the study has finished, all the data collected as part of the study will be kept and stored according to research regulations and the University of Manchester's standard procedures. All study data will be kept for a period of at least 15 years, in case it is needed for audit or inspection. All the data will be kept securely and access will be restricted to authorised personnel. The blood sample results collected as part of this study may be used in future research with appropriate approvals. At the end of the 15 year period all research data will be destroyed.

You have a number of rights under data protection law regarding your personal information. For example you can request a copy of the information we hold about you. This is known as a Subject Access Request. If you would like to know more about your different rights, please consult the University of Manchester's privacy notice for research and if you wish to contact us about your data protection rights, please email dataprotection@manchester.ac.uk or write to The Information Governance Office, Christie Building, University of Manchester, Oxford Road, M13 9PL. at the University and we will guide you through the process of exercising your rights.

You also have a right to complain to the Information Commissioner's Office (https://ico.org.uk/make-a-complaint/), Tel 0303 123 1113.

Will my information be kept confidential?

Your participation in the study will be kept confidential to the study team and those with access to your personal information. Your name will not appear in any publications. Your medical records (which contain personal information) will be reviewed by the direct care team to assess if you are

able to enter the study and by authorised members of the research team at your local hospital so that they can collect information needed for the study.

To ensure confidentiality, once you have joined the study you will be assigned a unique reference number that will be used to label the blood samples we collect. All data we collect about you will be linked through this participant ID number and will only be known by the research team (this is called pseudonymised or coded data). By collecting and reporting data in this way we can ensure that individuals cannot be identified outside the research team. The research team will also look at any routine scans that you have had during your treatment. All study data will be kept secure with restricted access.

Individuals from the University of Manchester (study sponsor) and Leeds Cancer Centre or regulatory authorities may need to look at your medical records and the data collected for this study to make sure the project is being carried out as planned. This may involve looking at identifiable data but all individuals involved in auditing and monitoring the study, will have a strict duty of confidentiality to you as a research participant.

We will also inform your GP of your participation in the study with your permission.

What happens if I don't want to take part or if I change my mind?

It is up to you to decide whether or not to take part. If you decide not to take part in the study then your care will not be affected. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason and without detriment to yourself. This will not affect your care. However, it will not be possible to remove your data from the project once it has been anonymised and forms part of the dataset as we will not be able to identify your specific data. This does not affect your data protection rights.

In the unlikely event that, during the study, you are unable to give your consent to continue (for example, due to an accident, another major illness or if you require surgery) the research team will keep the data, blood samples results and scans already collected and continue to use them confidentially in connection with the study. This may include further ethically approved research after the current project has ended.

Will my data be used for future research?

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies. The future research should not be incompatible with this research project and will concern lung cancer. The researchers who would be provided with information from this study include: universities; NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you regarding any other matter or to affect your care. It will not be used to make decisions about future services available to you.

Will I be paid for participating in the research?

No you will not be paid for participating in the research.

What is the duration of the research?

The length of time that each patient will spend on the study will differ depending on how long each person's radiotherapy treatment lasts (this could be anything from 1 week to 6½ weeks). The final blood tests will be taken 4 months after your course of radiotherapy finishes. Overall, we expect the study to last for 18 months.

Where will the research be conducted?

The research will be conducted at Leeds Cancer Centre.

Will the outcomes of the research be published?

The results of this study will be analysed and written up jointly by the study teams at the participating centres (in Manchester and Leeds) in order to be published in a scientific journal.

We will communicate the results of this study to the participants through publications. We expect the results to be available 12 months after the last patient has finished participating in the study. Your name will not appear in any of these reports. The research team will ask if you would like us to send you a copy of the publications or a summary of the research when the study has finished. Your name and hospital number will be kept on record securely (on a password protected hospital database) to enable us to check your records for up-to-date contact details in order to contact you. Alternatively, you may contact your local study team (details below) for a copy of the results.

Who has reviewed the study?

All research in the NHS involving patients is reviewed and approved by an independent group of people called a Research Ethics Committee to protect your safety, rights, wellbeing, and dignity. The local research and development department at Leeds Teaching Hospital NHS Trust has also given approval. This study has also been independently reviewed by a group of scientific experts.

What if I want to make a complaint?

Thousands of blood samples are carried out daily worldwide with no reports of any harm. In the event that something does go wrong and you are harmed during the research you may have grounds for a legal action for

compensation against the University of Manchester or Leeds Teaching Hospital NHS Trust but you may have to pay your legal costs.

The normal National Health Service complaints mechanisms will still be available to you. If you wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service on:
Tel: 0113 2066261 - Available during normal working hours only (9:00am to 4:30pm Monday to Friday) or 0113 2067168 - For queries outside of normal working hours, please leave a voicemail.
Email: patientexperience.leedsth@nhs.net

By taking part in the study you do not waive any of your legal rights.

Minor Complaints - If you have a minor complaint then please contact your research team (details below) in the first instance who will do their best to answer your questions.

Fei Sun f.sun@nhs.net 07765 048960 (Clinical Research Fellow)

(Research Nurses)

Formal complaints – If you wish to make a formal complaint or if you are not satisfied with the response you have gained from the researchers in the first instance the please contact the Research Governance and Integrity Manager, Research Office, Christie Building, University of Manchester, Oxford Road, Manchester, M13 9PL, by emailing: research.complaints@manchester.ac.uk or by telephoning 0161 275 2674 or 275 2046.

What is the next step?

If you have any queries about the study or if you are interested in taking part then please contact researchers (details as shown below).

Fei Sun f.sun@nhs.net 07765 048960 (Clinical Research Fellow)

ACCOLADE informed consent form

Informed Consent Form (Leeds)

A study investigating how to avoid cardiac toxicity in lung cancer patients treated with curative intent radiotherapy to improve survival, funded by Yorkshire Cancer Research.

Hospital Number:_____

If you are happy to participate please complete and sign the consent form below.

		Initials
1	I confirm that I have read the attached information sheet (Version 3.0, dated 05/09/2019) for the above study and have had the opportunity to consider the information and ask questions and had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. I understand that it will not be possible to remove my data from the project once it has been anonymised and forms part of the data set. I agree to take part on this basis.	
3	I agree to my GP being informed of my participation in this study.	
4	I agree to gift blood samples for the research purpose as explained to me.	
5	I understand that if I withdraw from the study, or lose the capacity to give consent to continue on the study, the research team will keep the anonymised data and blood samples already collected and continue to use them confidentially in connection with the study.	

6	I understand that data collected during the study may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.	
7	I agree that any data collected may be published in anonymous form in academic books, reports or journals.	
8	**Optional:** I agree that the researchers / researchers at other institutions may contact me in future about other research projects.	
9	**Optional:** I agree that the researchers may retain my contact details in order to provide me with a summary of the findings for this study.	

10	I agree to take part in this study.	

Data Protection

The personal information we collect and use to conduct this research will be processed in accordance with data protection law as explained in the Participant Information Sheet and the Privacy Notice for Research Participants: http://documents.manchester.ac.uk/display.aspx?DocID=37095.

_____	_____	_____
Name of Participant	Signature	Date
_____	_____	_____
Name of the person taking consent	Signature	Date

Copies of the consent form – 1 copy for the participant, 1 copy for the research team (original), 1 copy for the medical notes.

ACCOLADE case report form

ACCOLADE
CARDIAC TOXICITY IN LUNG CANCER STUDY

A study investigating how to avoid cardiac toxicity in lung cancer patients treated with curative-intent radiotherapy to improve survival, funded by Yorkshire Cancer Research.

Sponsor number: NHS001442
REC number: 18/NW/0706
IRAS ID: 230736

Case Report Form

Version 4.0, 27 January 2020

Participant ID: | | | | | | |

Participant Initials: | | | |

Cardiac Toxicity in Lung Cancer Study CRF Completion Guidelines

The CRF booklet for the study is provided as a single file. The patient questionnaires are separate files and can be printed as required.

CRF pages can be posted (with the exception of SAEs) to the address below or emailed to the ACCOLADE Project Manager using the study mailbox (ACCOLADE@manchester.ac.uk). If posting CRFs, please ensure a copy is retained at site for your records.

ACCOLADE Project Manager
Department of Radiotherapy Related Research (Dept 58)
The Christie NHS Foundation Trust
Withington
Manchester
M20 4BX

General points about CRF completion

All CRF data should be completed in line with Good Clinical Practice requirements, and must be consistent with the source data in the patient notes.

1. Only complete CRF pages if you are authorised to do so. You must be listed on the site delegation log with 'CRF completion' as one of your authorised tasks.
2. Only use a BLACK ballpoint pen.
3. Write as neatly as possible, ensuring your entries are legible.
4. Use specific medical terminology.
5. Avoid abbreviations and acronyms, unless they are standard medical abbreviations. If in doubt, please write out in full.
6. Enter a true response in each field and a not cross reference to other completed fields. For example, "see above" or ditto marks.
7. Ensure that you complete the header information on each page fully and consistently.
8. When completing numeric data, completely fill in each box using leading and trailing zeroes if needed. e.g. 021.30
9. All dates should be in the format DD/MM/YYYY e.g. 1st March 2017 is 01/03/2017.
10. Make any corrections to errors in the data recorded as follows:
    - Draw a single line to cross through the incorrect data, ensuring it remains legible.
    - Record the correct data alongside.
    - Date and initial any corrections, clarifications and changes.
    - Do not use correction fluid or any other method of erasure, or scribble through the data so that it becomes illegible.
11. Please fill in EVERY field on each CRF page unless indicated otherwise.
    e.g. where the response to Sample collected = No and no further data would be logically expected, the remaining fields should be left blank.
    If an expected procedure/assessment was not done or not applicable, cross through the fields for that assessment and record as ND or NA.
    If expected information is not available, cross through the field and note an explanation.

ACCOLADE - Cardiac Toxicity in Lung Cancer Study **Patient ID** ☐☐☐☐☐☐

Sponsor Ref: NHS001442 **Screening** **Patient Initials** ☐☐☐

Screening

Patient information

Visit date ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

Gender ☐ Male ☐ Female

Date of birth ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

Histology ☐ SCLC ☐ Squamous ☐ Adenocarcinoma ☐ Large cell

☐ Clinical Diagnosis (No histology) ☐ Other, please specify……

Site of primary ☐ LUL ☐ LLL ☐ RUL ☐ RML ☐ RLL

Stage at screening T☐ N☐ M☐

Stage based on (tick all that apply) ☐ CT ☐ PET CT ☐ MRI ☐ Other, please specify .....

ECOG performance status ☐

Smoking status ☐ Current Pack Years ☐☐☐

☐ Never

☐ Ex-smoker

Current Medications

Please record any **cardiac medications** the patient is currently taking on the Concomitant Medications log.

Screening – *continued.*

Eligibility Assessment

Date of consent ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

Optional Consents	NO	YES
A. Has patient consented to being contacted about future projects?	☐	☐
B. Has patient consented to being contacted with a summary of findings?	☐	☐

Inclusion Criteria – *Answers must be yes for patient to be eligible*	NO	YES
1. Stage I-III lung cancer (NSCLC and SCLC)	☐	☐
2. Suitable for curative-intent radiotherapy	☐	☐
3. Life expectancy of >4 months	☐	☐
4. Male or female aged 18 years or above	☐	☐

Exclusion Criteria – *Answers must be no for patient to be eligible*	NO	YES
1. Metastatic disease	☐	☐
2. Previous radiotherapy to the chest	☐	☐

Cardiac Imaging patients only			N/A
3. Atrial fibrillation or any other contraindications to cardiac CT	☐	☐	☐

Investigator initials ……

To register the patient on study, please submit your completed 'Patient Registration form' to the study mailbox: **ACCOLADE@manchester.ac.uk**

Date of registration ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

Please submit completed screening CRFs

Before Radiotherapy Visit

within 14 days prior to radiotherapy

Visit date DD/MM/YYYY

Height cms

Weight kgs

Heart rate BPM

Blood pressure /

Cardiac history

Hypertension	No	Yes	If yes, start date MM/YYYY
Previous MI / CABG	No	Yes	If yes, start date MM/YYYY
Congestive heart failure	No	Yes	If yes, start date MM/YYYY
Angina	No	Yes	If yes, start date MM/YYYY
Atrial fibrillation	No	Yes	If yes, start date MM/YYYY
Other cardiac arrhythmia	No	Yes	If yes, start date MM/YYYY
Heart block	No	Yes	If yes, start date MM/YYYY
Stroke/TIA	No	Yes	If yes, start date MM/YYYY
Diabetes	No	Yes	If yes, start date MM/YYYY

If yes, Type 1 or Type 2

Has a 1st degree relative of the patient experienced angina or a heart attack under the age of 60? No Yes

Before Radiotherapy Visit – *cont.*

Blood Sampling

Sample date ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

Test	Result
WCC	☐☐.☐ (x 10^9/L)
Neutrophils	☐☐.☐ (x 10^9/L)
Lymphocytes	☐☐.☐ (x 10^9/L)
Hb	☐☐☐ g/L
Platelets	☐☐☐ (x 10^9/L)
Creatinine	☐☐☐ µmol/L
Urea	☐☐.☐ mmol/L
Total cholesterol	☐.☐ mmol/L
HDL	☐☐.☐ mmol/L
LDL	☐☐.☐ mmol/L
Triglycerides	☐☐.☐ mmol/L
Troponin	☐☐ ng/L
NT-proBNP	☐☐☐ ng/L
CRP	☐☐ mg/L

Cardiac risk score

QRISK®3 Score should be calculated using the online calculator: https://qrisk.org/three/

QRISK®3 Score ☐☐.☐ %

Please tick if QRISK®3 Score not applicable ☐ Reason not applicable ……

After Radiotherapy Visit

within 7 days post completion of radiotherapy

Blood Sampling

Visit date ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

Test	Result
WCC	☐☐.☐ (x 10^9/L)
Neutrophils	☐☐.☐ (x 10^9/L)
Lymphocytes	☐☐.☐ (x 10^9/L)
Hb	☐☐☐ g/L
Platelets	☐☐☐ (x 10^9/L)
Creatinine	☐☐☐ µmol/L
Urea	☐☐.☐ mmol/L
Total cholesterol	☐.☐ mmol/L
HDL	☐☐.☐ mmol/L
LDL	☐☐.☐ mmol/L
Triglycerides	☐☐.☐ mmol/L
Troponin	☐☐ ng/L
NT-proBNP	☐☐☐ ng/L
CRP	☐☐ mg/L

Please complete End of Treatment form

4 Months Post Radiotherapy Visit

+/- 14 days

Blood Sampling

Visit date DD / MM / YYYY

Heart rate BPM

Blood pressure /

Test	Result
WCC	. (x 10^9/L)
Neutrophils	. (x 10^9/L)
Lymphocytes	. (x 10^9/L)
Hb	g/L
Platelets	(x 10^9/L)
Creatinine	µmol/L
Urea	. mmol/L
Total cholesterol	. mmol/L
HDL	. mmol/L
LDL	. mmol/L
Triglycerides	. mmol/L
Troponin	ng/L
NT-proBNP	ng/L
CRP	mg/L

Have there been any changes to the patient's cardiac medications?

Yes ☐ *If yes, please record on the medications sheet*

No ☐

Has the patient been referred to cardiology?

Yes ☐

No ☐

If yes, please record the reason for referral and subsequent action taken:

_____

_____

_____

_____

_____

Please complete Further Treatment form

End of Study

Complete if patient ends participation at any time throughout the study or at study completion
Please submit study visits, concomitant medications, AE log, and end of study CRF when ALL fields are completed.

Date completed/discontinued ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

Reason for discontinuation *(please tick main reason only)*

- Completed participation ☐
- Patient decision to discontinue (withdrawal of consent) - reason related to study ☐ *Specify:*.....
- Patient decision to discontinue (withdrawal of consent) - reason unrelated to study ☐ *Specify:*.....
- Investigator / medical decision ☐ *Specify:*.....
- Death ☐ *Cause of death:*.....
- Other reason ☐ *Specify:*.....

If patient has an AE related to the study procedure please complete AE log.
If radiotherapy treatment ended, please ensure End of Treatment form has been completed.

If consent withdrawn, please confirm if patient has withdrawn from optional consents:

A: being contacted about future projects? ☐ Yes ☐ No ☐ N/A

B: being contacted with a summary of findings? ☐ Yes ☐ No ☐ N/A

Survival status at end of study

Date of last contact/ Status confirmed: ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

Survival status: ☐ Alive ☐ Dead

If patient has died, please complete below:

Date of death: ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

Cause of death: .....

ADVERSE EVENTS

Patient

Patient Initials

Adverse Events

Only record AE if related to study procedure. If event fulfills seriousness criteria, complete and submit SAE report. If no events, score through page and submit.

Adverse Event	Grade (CTCAE v5.0)	Start date DD-MM-YYYY	Stop date DD-MM-YYYY		Serious No	Serious Yes	Inv'r initials
		__/__/____	__/__/____	ongoing ☐	☐	☐	
		__/__/____	__/__/____	ongoing ☐	☐	☐	
		__/__/____	__/__/____	ongoing ☐	☐	☐	
		__/__/____	__/__/____	ongoing ☐	☐	☐	
		__/__/____	__/__/____	ongoing ☐	☐	☐	
		__/__/____	__/__/____	ongoing ☐	☐	☐	
		__/__/____	__/__/____	ongoing ☐	☐	☐	
		__/__/____	__/__/____	ongoing ☐	☐	☐	
		__/__/____	__/__/____	ongoing ☐	☐	☐	
		__/__/____	__/__/____	ongoing ☐	☐	☐	

Last Page ☐

Concomitant Medications

Only record concomitant cardiac medications.

Medication	Dose & Units / Route	Start date DD-MM-YYYY	Stop date DD-MM-YYYY		Indication	Inv'r initials
		/ /	/ /	ongoing ☐		
		/ /	/ /	ongoing ☐		
		/ /	/ /	ongoing ☐		
		/ /	/ /	ongoing ☐		
		/ /	/ /	ongoing ☐		
		/ /	/ /	ongoing ☐		
		/ /	/ /	ongoing ☐		
		/ /	/ /	ongoing ☐		
		/ /	/ /	ongoing ☐		
		/ /	/ /	ongoing ☐		

Last Page ☐

ACCOLADE end of treatment form

ACCOLADE – Cardiac Toxicity in Lung Cancer Study **Patient ID** ☐☐☐☐☐☐

Sponsor Ref: NHS001442 **End of Treatment Form** **Patient Initials** ☐☐☐

End of Treatment Form

To be completed at After Radiotherapy visit or at End of Study, whichever occurs first

Radiotherapy

Start date of radiotherapy ☐☐ / ☐☐ / ☐☐☐☐ (DD / MM / YYYY)

End date of radiotherapy ☐☐ / ☐☐ / ☐☐☐☐ (DD / MM / YYYY)

Radiotherapy completed as planned ☐ Yes ☐ No

If No, reason _____

Radiotherapy technique
- ☐ 3D CRT
- ☐ ARC therapy (e.g. VMAT, RapidARC)
- ☐ IMRT

Radiotherapy planning & delivery

Dose per fraction (Gy) ☐☐.☐☐

Fractions per week ☐☐

Total dose (Gy) ☐☐.☐☐

Total no. of fractions ☐☐

Motion-adapted ☐ Yes ☐ No

Mean Lung Dose (Lung-ITV) (Gy) ☐☐.☐☐

GTV (tumour & nodes if applicable (cm^3)) ☐☐☐.☐

CTV (tumour & nodes if applicable (cm^3)) ☐☐☐.☐

V5 Lung – PTV (%) ☐☐.☐

PTV (tumour & nodes if applicable (cm^3)) ☐☐☐.☐

V20 Lung – PTV (%) ☐☐.☐

V5 (%) Heart ☐☐.☐

V30 (%) Heart ☐☐.☐

V40 (%) Heart ☐☐.☐

V50 (%) Heart ☐☐.☐

Max dose to 1cc of Heart (Gy) ☐☐.☐☐

Mean Heart Dose (Gy) ☐☐.☐

Heart Delineation as Per protocol ☐ Yes ☐ No

ACCOLADE – Cardiac Toxicity in Lung Cancer Study **Patient ID** ☐☐☐☐☐☐

Sponsor Ref: NHS001442 **End of Treatment Form** **Patient Initials** ☐☐☐

End of Treatment Form - *continued*

Chemotherapy

Has patient received chemotherapy for lung cancer?

☐ No
☐ Yes

If yes, start date:

☐☐ / ☐☐ / ☐☐☐☐
DD MM YYYY

Date of last dose:

☐☐ / ☐☐ / ☐☐☐☐

No. of cycles:

☐☐

Schedule:

☐ Prior to radiotherapy
☐ Concurrent with radiotherapy
☐ Induction + concurrent
☐ Not known

Chemotherapy drugs given:

1: ----------

2: ----------