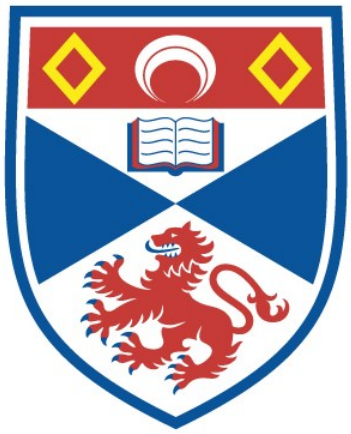
Nutritional, inflammatory and functional biomarkers in lung cancer: identifying patients at risk of adverse outcomes through two retrospective cohort studies

Joanna Catherine Scott Bowden

A thesis submitted for the degree of MD
at the
University of St Andrews



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Presentations and publications

Published paper

Bowden et al, Prediction of 90 Day and Overall Survival after Chemoradiotherapy for Lung Cancer: Role of Performance Status and Body Composition. *Clinical Oncology* 2017; 1-9.

Poster presentation

Cachexia-related risk factors for premature death following chemoradiotherapy for lung cancer: the potential to inform cancer treatment decision making and to identify candidates for proactive cachexia management. The 15th Congress of the European Association for Palliative Care. Madrid, 2017.

Oral presentations

Cachexia-related biomarkers in patients undergoing treatment for lung cancer in South East Scotland. Professor Ken Fearon Memorial Symposium. Edinburgh, 2018.

Cachexia-related biomarkers in patients undergoing treatment for lung cancer in South East Scotland. Lung Oncology Away Day. Edinburgh, 2019.

Abstract accepted for poster presentation

Cachexia-related biomarkers predict a range of adverse outcomes in people receiving palliative chemotherapy for lung cancer. National Cancer Research Institute Conference. Glasgow, November 2019

Abstract

Nutritional, inflammatory and functional biomarkers in lung cancer: identifying patients at risk of adverse outcomes through two retrospective cohort studies

Background

Lung cancer is the commonest cause of cancer death worldwide. A range of biomarkers are associated with adverse outcomes in lung cancer, but these have not been assimilated into routine clinical practice. The aim of the two studies was to identify predictive variables within existing healthcare data for adverse outcomes following lung cancer treatment, with a view to informing optimal treatment selection for future patients.

Methods

Two retrospective cohort studies of lung cancer patients in South East Scotland were undertaken using demographic and clinical data from healthcare records. A range of explanatory variables were explored using descriptive statistics, logistic regression and survival analysis for treatment-related outcomes. These included overall survival (OS), early mortality and treatment completion.

Results

194 patients were included the chemoradiotherapy study, median OS 19 months. Low skeletal muscle attenuation (MA), (odds ratio [OR] 1.61 [95% CI 1.16, 2.23, *p*=0.004) independently predicted reduced OS. Independent predictors of death within 90 days of treatment completion were Eastern Cooperative Oncology Group Performance Status ≥2 (OR 3.97 [1.20, 13.08], *p*=0.024) and body mass index (BMI) ≤20 (OR 3.91 [1.24, 12.38], *p*=0.020).

397 patients were included in the palliative chemotherapy study, median OS 6.9 months. Independent predictors of reduced OS were: neutrophil-to-lymphocyte ratio ≥4, albumin <35, MA and low skeletal muscle mass. Patients who did not receive guideline-recommended treatment (GRT) had a median OS of 3.3 months. Independent predictors of non-GRT receipt

were: non-small cell lung cancer, BMI ≤20, neutrophil count ≥7, lymphocyte count <1 and MA <31.55.

Discussion

A range of routinely available biomarkers can identify patients with lung cancer at increased risk of adverse outcomes. Optimal treatment selection for each patient could be improved by routine utilising these biomarkers. Biomarkers may also be useful to identify patients for integrated supportive care during their cancer treatment. Further research is needed.

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The work presented in this thesis is dedicated to the enduring memory of Professor Ken Fearon. He was a world leader in cancer cachexia research, and I had the very great privilege of beginning my research apprenticeship under his expert guidance. Ken was an exemplary mentor and he remains a source of great inspiration to me, with his impeccable academic standards and constant questioning of accepted truths. I am committed to continuing my studies in cancer cachexia, building on all that we have learned in the quest to improve the reality of this desperate condition.

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Abbreviations

Alb	Albumin
ALC	Absolute Lymphocyte Count
AMC	Absolute Monocyte Count
ANC	Absolute Neutrophil Count
BMI	Body Mass Index
BSC	Best Supportive Care
CAP	Cyclophosphamide, Adriamycin and Cisplatin
CC	Cancer Cachexia
CCI	Charlson Comorbidity Index
CCNU	Chloroethyl-Cyclohexyl-Nitrosurea
CFS	Cancer-Free Survival
CHI	Community Health Index number
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
CRT	Chemoradiotherapy
CRUK	Cancer Research UK
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DEXA	Dual-energy X-ray absorptiometry
ECC	Edinburgh Cancer Centre
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FACT-L	Functional Assessment of Cancer Therapy-Lung
GPS	Glasgow Prognostic Score
GRT	Guideline Recommended Treatment
GTV	Gross Tumour Volume
HR	Hazard Ratio
HU	Hounsfield Units
IQR	Inter-Quartile Range
ISD	Information Services Division

L3	Third Lumbar Vertebral Level
LCSS	Lung Cancer Symptom Scale
MA	Muscle Attenuation
MDT	Multidisciplinary Team
MDTM	Multidisciplinary Team Meeting
mGPS	Modified Glasgow Prognostic Score
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MV	Multivariable
NHS	National Health Service
NLR	Neutrophil to Lymphocyte Ratio
NoSCAN	North of Scotland Cancer Network
NSCLC	Non-Small Cell Lung Cancer
ONS	Office for National Statistics
OS	Overall Survival
PACS	Picture Archiving and Communication System
PFS	Progression Free Survival
PLR	Platelet to Lymphocyte Ratio
Plt	Platelet Count
QoL	Quality of Life
QPI	Quality Performance Indicator
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
REE	Resting Energy Expenditure
RTOG	Radiation Therapy Oncology Group
SACT	Systemic Anti-Cancer Treatment
SCAN	South East Scotland Cancer Network
SCLC	Small Cell Lung Cancer
SCS	Simplified Comorbidity Score
SCSS	Scottish Comorbidity Scoring System
SDM	Shared Decision Making
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation

SIR	Systemic Inflammatory Response
SMI	Skeletal Muscle Index
SMR	Standardised Mortality Ratio
SPSS	Statistical Package for the Social Sciences
T4	Fourth Thoracic Vertebral Level
TRM	Treatment-Related Mortality
UV	Univariate
VP	Vindesine and Cisplatin
WCC	White Cell Count
WoSCAN	West of Scotland Cancer Network

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Chapter 1

Introduction

1.1 Background

Lung cancer is the most common cause of cancer-related death worldwide (1). 46,388 people were diagnosed with lung cancer in the UK in 2015 (2) and a 10 year survival rate in the UK of 4.9% remains disappointingly low (3). In South East (SE) Scotland, around half of people with lung cancer have the most advanced (stage IV) disease at diagnosis, with their survival typically measured in months (4).

1.1.1 Decision making around lung cancer treatment

Cancer stage is the major determinant of lung cancer treatment options (5), alongside the patient's apparent fitness for treatment. In the UK, the Eastern Cooperative Group Performance Status (ECOG PS), a measure of patients' functional status, routinely informs clinical decisions about suitability for treatment. However, ECOG PS is known to be imperfect and subjective, with considerable inter-observer variability (6) (7) (8). Furthermore, there is acknowledgement that some patients with an apparently poor ECOG PS can benefit from cancer treatments (9) (10), although identifying these particular patients may not be straightforward.

For patients with inoperable lung cancer, there is robust evidence that oncological treatments can offer significant benefits, in terms of both extended survival and/or improved quality of life (QoL) (11-14) (15). However, it is also acknowledged that some patients come to harm as a result of lung cancer treatment, and that treatment may even shorten life (16).

The evidence base surrounding lung cancer treatments is derived almost exclusively from randomised-controlled trials (RCTs), and clinical trials have been criticised for being too narrow in their focus, with outcome measures that are said to be more tumour-centred than patient-centred (17). Furthermore, RCTs are typically based on younger and fitter patients than those presenting in clinical practice, and this has called some to question the relevance of the evidence they generate and the guidelines they inform to real-world populations (18).

The decision to proceed with lung cancer treatment is straightforward for some patients and more complicated for others (19). Patients' attitudes towards lung cancer treatment vary greatly, with some individuals keen to proceed with treatment, whatever the burden, for a small chance of extended survival; and others only willing to accept treatment if it is likely to

have a positive impact on their symptoms and QoL (20) (21). Clinicians cannot assume what a patient's preference around treatment might be, and it is accepted that an exploration of preferences is an important part of the oncology consultation (22). Shared decision making (SDM), where patients are empowered to be active partners in treatment choices along with their clinicians, is a cornerstone of the Scottish Chief Medical Officer's report Realistic Medicine (23). However, whilst SDM is an appealing concept, it is not necessarily an easy option; requiring patients to assimilate detailed information about the likely risks and benefits of treatment options, before weighing these up in the context of their personal values and priorities, in light of their diagnosis. It is well-recognised that patients may struggle to grasp detailed information around cancer treatments, and that they may proceed with treatment without a clear understanding of its likely outcomes (20).

1.1.2 Best supportive care

If SDM is to be realised, based on informed discussion about the risks and benefits of different treatment approaches, the option not to undergo cancer treatment must be presented. In clinical practice in the UK, if cancer treatment is not the agreed management plan (either because patients are too unwell or because they choose not to receive treatment) patients are recorded as being 'for best supportive care' (BSC).

One barrier to discussing the option of BSC with patients can be the strong societal narratives around battling or fighting cancer that exist in the UK and globally (24). Tessa Richards, a senior editor at the British Medical Journal, highlighted the inadequacy of discussions about her own cancer treatment, and the refusal by her treating clinicians to talk about the option of BSC (25). And yet, research has shown that when presented with hypothetical scenarios about a variety of cancer treatments, many oncologists would choose, for themselves, the option of BSC (26).

BSC is known to be ill-defined and poorly and inconsistently described in clinical trials (27) (28) (29). This is critically important as it threatens both the internal and external validity of RCT findings where BSC is one arm of the study (28). In addition to these scientific concerns, Cherny et al highlight major ethical issues with the lack of standardised approach to BSC in clinical trials. They remind their readers that the welfare of all trial participants should be paramount, and that this should translate to acceptable levels of supportive care in line with

standards of practice and, where available, best evidence. In more recent years, the clear value that palliative care can add to cancer care has been demonstrated, most famously with a study reported in The New England Journal of Medicine by Temel and colleagues in 2010 (30); in which specialist palliative care intervention alongside oncological therapy for a population with advanced NSCLC was associated with significant improvements in QoL, symptom control and survival. These improvements were associated with lower levels of so-called 'aggressive care', including chemotherapy, towards the end of life. A subsequent secondary analysis, published by the same research team in 2012, revealed that although overall cancer treatment receipt was comparable between the integrated palliative care and standard care groups, those in the palliative care group were half as likely to receive chemotherapy in their last two months of life (31). One important unknown is the extent to which improvements in QoL and other outcomes resulted simply from lower levels of chemotherapy receipt as patients deteriorated, or whether the palliative care intervention was therapeutic in itself.

In light of the stated scientific and ethical concerns of BSC being poorly defined in clinical trials, as well as a growing evidence base for the value of supportive and palliative care, consensus-based standards of BSC within clinical trials in advanced cancer have been published (29). Zafar et al recommend that the specifics of BSC within clinical trials should be described in detail, just as medical interventions such as chemotherapy are described in trial protocols.

In the same vein, but in the clinical practice context rather than the trial setting, a working model of BSC for people with advanced lung cancer has been developed in NHS Fife (32). The trigger for this development was the recognition that, for many patients, BSC simply meant 'no anti-cancer treatment'. Given the high proportion of people with stage IV disease at diagnosis, a heavy symptom burden and a typically short prognosis, the case for BSC to mean more than 'no anti-cancer treatment' was clear. The new model of care was positively evaluated, with improved reliability of palliative care for people with advanced lung cancer and those close to them, as well as a reduction in time spent in the acute hospital.

The two studies presented within this thesis both investigate predictive factors for adverse outcomes in people with lung cancer. Ultimately it is intended that the findings of these studies, and other research in this area, will enable improved patient selection for lung cancer treatment in the future. A more individualised approach to patient selection, based on the presence of key indices at diagnosis, may lead to more patients being offered BSC in place of

systemic anti-cancer treatment (SACT). It is only right that such patients have should be a meaningful management plan for their BSC, rather than it being an empty label.

The majority of patients who are for BSC (i.e. they do not receive lung cancer treatment) have been deemed too frail or unwell for treatment to be clinically appropriate. In Scotland, this is captured by cancer audit data in non-specific terms, typically referring to 'poor ECOG PS'(32). At present, there is no systematic approach to the clinical assessment and/or recording of data for patients who are unfit for cancer treatment. However, it is widely accepted that individual patients may have any number of contributing factors, including advanced cancer and associated frailty itself, comorbid conditions and/or cancer cachexia. It is cancer cachexia, with its strong associations with systemic inflammation, nutrition and functional status, that is the focus of the studies within this thesis.

1.2 Cancer cachexia

1.2.1 Epidemiology and impact

Cancer cachexia is a highly debilitating syndrome affecting up to 60% of people with lung cancer (33). It is characterised by severe muscle wasting, weight loss and weakness. Its aetiology is complex, but includes reduced appetite, altered metabolism and systemic inflammation (34). Cachexia is estimated to be a direct contributor to death in 20-40% of patients with cancer (35) (36) (37). It reduces tolerance to chemotherapy (38) (39) (40), necessitating dose reduction and early treatment discontinuation (41) (42). It causes loss of function and independence, social withdrawal and significant psychological distress for patients and families (34) (43) (44) (45).

Despite an understanding that cancer cachexia is both common and debilitating, weight loss is not assessed or managed actively in routine cancer care in the UK. There are many potential reasons for this, including a lack of established, effective treatment approaches (46) and an acceptance by many that weight loss in cancer is simply to be expected (47).

1.2.2 Skeletal muscle wasting beyond cancer

Cancer cachexia commonly co-exists alongside other chronic non-malignant conditions such as chronic obstructive pulmonary disease (COPD), which itself can cause cachexia (34) (48) (49). Frailty is now recognised to be a distinct clinical syndrome, and is similarly associated with muscle wasting, disability and death (50) (51) (52). Age is a major risk factor for muscle loss, with healthy individuals losing 1-2% of their muscle mass each year after the age of 50 (53). Lung cancer is typically a disease of older age, with 90% of patients diagnosed in SE Scotland in 2012 over 60 years of age (4). Whilst not exclusive to older patients, comorbidity and frailty are both more common with advancing age.

1.2.3 International consensus definition and classification system for cancer cachexia

In 2011, Fearon et al published a landmark paper in The Lancet Oncology, providing a consensus definition of cancer cachexia as follows: '*Cancer cachexia is defined as a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or*

without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.'(46)

The definition, developed by a panel of international cancer cachexia experts, was accompanied by a detailed description of cachexia as a continuum, comprising three stages:

- **Pre-cachexia**: weight loss of ≤5%, anorexia and metabolic change
- **Cachexia:** weight loss of >5% over past 6 months, or BMI <20 and weight loss ≥2%, or appendicular skeletal muscle index consistent with sarcopenia (definitions contained within the published paper)
- **Refractory cachexia:** variable degree of cachexia, cancer disease pro-catabolic and not responsive to anticancer treatment, low performance score, <3 months expected survival.

The three cachexia stages have great clinical relevance, with the broad management strategies proposed by Fearon et al tailored to each stage and the likely outcomes. Recognition of the three stages is important both for clinical practice, but also for research, including the development and evaluation of definitive cachexia management strategies

1.2.4 Assessment of skeletal muscle mass

Fearon et propose a comprehensive, structured approach to assessing cancer cachexia, in order that any contributing factors (such as nausea and associated reduced oral intake) can be identified, and a personalised management can plan be developed (46). Evaluation of muscle mass and strength is an important component of cancer cachexia assessment, although the panel of experts acknowledge that a variety of methods are available. Cross-sectional imaging using computerised tomography (CT) or magnetic resonance imaging (MRI) was their preferred choice. Upper limb hand-grip dynamometry was proposed as preferable to lower limb strength testing.

The opportunistic use of CT scans was described by Prado et al in 2009 as a means of accurately assessing body composition in patients with cancer. The availability of images from both diagnostic and follow-up CT scans was reported to be a great enabler of both one-off and longitudinal assessment of skeletal muscle mass and other indices, without the need for additional imaging. In 2010, Baracos et al published the results of CT-based body composition analysis for a cohort of 441 patients with NSCLC (54). Images from the third lumbar vertebral

level (L3) were used in the study, on the understanding that muscle measurements from this level had been shown in non-cancer populations to correspond to whole body muscle mass. Baracos et al demonstrated that there was significant variability in body composition indices between patients, and even between patients within the same BMI category (54). Patients with low muscle mass (below sex-specific thresholds derived using an optimal stratification approach) were identified in all BMI categories. Since these two reported early studies using CT-based body composition analysis, this method has been used extensively in cancer cachexia research (55) (56) (42) (57) (58) (59) (60).

1.2.5 Systemic inflammation in cancer cachexia

The host's systemic immune response to cancer is believed to play a significant role in the development and evolution of cachexia (34). The production of pro-inflammatory cytokines as part of the systemic immune response to cancer is well recognised, and there is ever-increasing understanding of the complex cascade of interactions between key inflammatory mediators which include Tumour Necrosis Factor Alpha (TNF-α), interleukins 1 and 6 (IL-1 and IL-6) (61) (34).

Systemic inflammation may be both acute and chronic, and the chronic inflammatory state has been described as often the root cause of cachexia (62). A chronic immune response leads to muscle catabolism, a hallmark of cancer cachexia, through a complex web of processes including gene activations involved in muscle homeostasis (upregulation of the ubiquitin proteasome complex) and a reduction in sensitivity to anabolic stimuli (such as testosterone and insulin) (62).

Systemic inflammation has been shown to be closely correlated with an array of physical manifestations of cancer cachexia, including fatigue, poor sleep, low mood and anorexia (63) (64). A study of 2,520 patients with advanced cancer revealed a strong association between the magnitude of systemic inflammation and poor QoL, including specific symptoms such as fatigue, nausea, dyspnoea, pain and appetite (65).

A large systematic review of systemic inflammation-related biomarkers in cancer studies was published in 2017 by Dolan et al (66). Data from 198 articles were analysed, incorporating a wide range of indices including C-reactive protein (CRP), albumin (Alb), white cell count (WCC) and neutrophil count (ANC). Several composite measures including the Glasgow Prognostic

Score (GPS/mGPS) and the neutrophil to lymphocyte ration (NLR) were also examined. The review concluded that there was extensive evidence for a range of biomarkers of systemic inflammation to predict survival, across a large number of tumour types and geographical locations (66). The thresholds for indices utilised within individual studies varied greatly. The focus of the study was not cancer cachexia per se, but the findings provide solid evidence that systemic inflammation is implicated in poor survival in cancer, albeit with the mechanisms poorly understood.

Currently, markers of the systemic inflammatory response do not feature in the diagnostic criteria for cancer cachexia. However, there are clear links between inflammation, cachexia and poor outcomes, and research is needed to establish the nature of the relationship. It is noteworthy that Macdonald does not describe chronic inflammation as the root of *all* cachexia, rather as 'commonly a route cause' (62). It is not yet known the extent to which cancer cachexia can occur in the absence of systemic inflammation, and conversely, whether chronic inflammation can exist in cancer without evidence of cachexia.

1.3 The thesis

1.3.1 Personalised cancer care and the evidence base that is needed

A key assumption underpinning this thesis is that there are patient- and/or cancer-related factors, identifiable at diagnosis, which are predictive of adverse outcomes during or following lung cancer treatment; and that knowledge of these factors could usefully inform clinical decision making around lung cancer treatment.

The clinical context for this assumption is that in cancer care we are striving to offer ever more personalised approaches to treatment (67) (6); in theory offering a greater likelihood of benefit to each patient, whilst at the same time making the best possible use of healthcare resources. For many cancer types, this aspiration is being realised at genetic and molecular levels; with a rapidly growing evidence base of the factors (present in the host and/or the tumour at diagnosis) which identify some patients as better or worse candidates for particular treatments (68). In other words, enabling optimal patient selection for specific cancer treatments.

Where progress has been less forthcoming is in our understanding of the patient-related, biopsychosocial factors that might inform optimal patient selection for cancer treatment (6). It could be argued that we know a lot about risk factors for adverse outcomes in cancer, and on one level this is true. For instance, we have a wealth of evidence which tells us that people who are functionally frail often do not live long with their cancer (69) (70) (41) (71) (72) (73). Similarly, we have known for decades that people with cancer who are losing weight typically live less long than their non-weight-losing counterparts (33) (41). Yet, there are a number of fundamental questions around both functional status and weight loss which remain unanswered, and which limit our ability to robustly identify the best cancer treatment approach for the person in front of us. Furthermore, there are many other known factors which are associated with adverse outcomes in cancer, such as the presence of comorbid conditions, but which we do not currently assess in any systematic way in practice.

The two studies described in this thesis were planned in order to begin to address the important gap between what we know about risk factors for adverse outcomes in people with lung cancer and how individual patient-level data informs decision making around proposed treatment.

1.3.2 Introducing the studies

Two retrospective cohort studies were undertaken. These were based around two distinct cohorts with lung cancer in South East Scotland who received different treatment modalities. The first study focused on a cohort who received chemoradiotherapy during 2008-2010 (presented in Chapter 2) and the second study examined a cohort who received palliative chemotherapy during 2013-2015 (presented in Chapter 3).

The overarching aim of two studies was to utilise routine healthcare data to identify predictive factors for a range of adverse outcomes during or following lung cancer treatment, with a view to:

- Developing a real-world evidence base which could inform the discussions that oncology teams have with people with lung cancer and those close to them about the likely benefits and risks of treatment.
- Supplementing the current evidence base around the prevalence and impact of cancer cachexia and how it might be evaluated in clinical practice; in order that it can be used to inform clinical decision making around the best treatment approach for individuals.

Both studies were designed around explanatory variable data that is available to clinicians caring for people with lung cancer; rather than data that could be extracted electronically from administrative and/or clinical databases retrospectively via data linkage research. The reasons for this were two-fold:

- The availability and accuracy of clinical data for the lung cancer population were not known and required investigation;
- The long-term aim was to generate findings that would be transferrable to the lung cancer clinic, necessitating findings which were derived from data that clinicians use in real-time in their practice.

Chapters 2 and 3 describe the two distinct studies in detail. Each chapter begins with a comprehensive review of the research literature relating to the cohort under study, including the evidence base surrounding the relevant treatment modality. Research questions specific to each study are presented, following by detailed Materials and Methods sections. Results are first presented and then explored in Discussions sections, in

the context of others' relevant published research. Strengths and limitations of the studies are discussed.

Chapter 4 summarises and compares the key findings from both studies. The implications of these for both clinical practice and future research are considered. Finally, reflections on the two studies are shared and conclusions drawn.

1.3.3 Hypotheses underpinning both studies

Three core hypotheses underpinned and informed both studies:

1. Routine NHS healthcare data can be utilised in order to describe a range of real-world outcomes for two patient cohorts receiving lung cancer treatment.
2. Cachexia can be identified and described using routine NHS clinical data in two patient cohorts undergoing systemic treatment for lung cancer.
3. Cachexia-related biomarkers are predictive of adverse outcomes in two patient cohorts receiving lung cancer treatment.

1.3.4 Terminology around prognostic and predictive variables

The terms predictive and prognostic are frequently used in cancer research to describe variables (typically clinical or biological characteristics of the host and/or the tumour) that are associated with a particular outcome or set of outcomes. However, there is a lack of consistency in how these terms are applied (74) (75). The purist approach is that *'prognostic factors define the effects of patient or tumor characteristics on the patient outcome, whereas predictive factors define the effect of treatment on the tumor.'* (74). And one step further, that '*the term predictive marker should, according to the most rigorous criteria, be reserved for markers fully validated prospectively in randomised clinical trial.'* (75).

One of the key areas of investigation described in this thesis is the range of outcome measures, beyond overall survival (OS), that are available within routine clinical data. The term prognostic has strong connotations of survival in the clinical cancer and palliative care world, and applying this term to outcomes that do not relate directly to survival risks causing confusion. Therefore, for the purposes of this thesis, and in the interests of clarity, the term predictive will be used to refer to any variable that is found to be associated with a particular outcome of interest. This simplistic approach may be criticised on a theoretical level, but the priority for this thesis is of clarity for the reader.

Chapter 2

Predictive factors for adverse outcomes for a cohort who received chemoradiotherapy for lung cancer in South East Scotland.

Chapter outline

Chapter 2 describes a retrospective cohort study undertaken during 2015-2016, of 197 patients who received chemoradiotherapy for lung cancer in SE Scotland between 2008 and 2010.

- The clinical context is described first, with an examination of chemoradiotherapy as a treatment modality for lung cancer, including the evidence base for its use and known potential risks and complications.
- Research questions specific to this study are outlined, relating to the cohort under study and their outcomes, as well as a wider exploration of routine data relating to cancer cachexia and the clinical implications of the findings.
- Detailed methods are described, including a comprehensive summary of the data sources and the practical aspects of conducting the study. The rationale for the approach taken to CT-based body composition analysis is presented and the statistical analysis is outlined.
- Findings are first presented in objective terms and are then discussed in relation to the wider literature, with a particular focus on the limitations of the present study and of others' work to date. These aspects are considered in practical terms in light of the second study (described in Chapter 3) that was conducted following the present study, and which was heavily informed by both the findings and the limitations of this first piece of work.
- Chapter 2 concludes with a summary of the key findings of the present study and consideration of the implications for clinical practice and further study.

A paper based on this study was published in 2017:

Bowden et al, Prediction of 90 Day and Overall Survival after Chemoradiotherapy for Lung Cancer: Role of Performance Status and Body Composition. *Clinical Oncology* 2017; 1-9.

See Appendix A

2.1 Background

2.1.1 Chemoradiotherapy as a treatment for lung cancer

High dose, radical radiotherapy has been recognised for several decades as the treatment most likely to offer long term survival or cure for people with stage III (stage IIIA and certain patients with stage IIIB) lung cancer who are of good performance status (76) (77) (78). More recently, it has been demonstrated that combining radiotherapy and chemotherapy (so-called chemoradiotherapy) provides additional survival benefit (13). The rationale for this approach is that it offers the best chance of both local disease control (via radiotherapy) and systemic control (via chemotherapy). Furthermore, chemotherapy given concurrently with radiotherapy can enhance its effect, a phenomenon known as radiosensitisation. There is convincing evidence that the survival benefits of chemoradiotherapy are greatest when chemotherapy is administered alongside radiotherapy (so-called concurrent chemoradiotherapy) as opposed to chemotherapy being given either in advance of or following radiotherapy (sequential chemoradiotherapy) (13) (79) (80). Despite being less effective, sequential chemoradiotherapy is an option for people who are not fit for concurrent treatment at the point of diagnosis and who respond to chemotherapy (81) (80).

In the UK, concurrent chemoradiotherapy is the guideline recommended treatment (GRT) for patients with stage II-III Non-small cell lung cancer (NSCLC) who are not suitable for surgery but who are of good performance status; and for patients who have limited stage SCLC, whose disease cannot be encompassed in a radiotherapy field, and who are of good performance status (81) (4).

Around 1200 people are diagnosed with lung cancer in SE Scotland each year (4). Approximately 60% of patients received anti-cancer treatment, the majority of which is for advanced disease and aims to extend life and/or improve quality of life. Approximately 60-70 patients with intermediate stage disease receive combination treatment with chemoradiotherapy at the Edinburgh Cancer Centre (4). Concurrent chemoradiotherapy typically entails around 6-8 weeks of intensive treatment, with significant side-effects for many (82); these usually get progressively worse over the course of treatment subsiding over the weeks following treatment completion for most.

2.1.2 The potential benefits and burdens of chemoradiotherapy treatment for lung cancer.

Evidence relating to early mortality and longer-term survival

Concurrent chemoradiotherapy is a 'curative-intent' strategy for defined populations with lung cancer (83) and results in long term survival for a minority (13) (79) (80). Retrospective analysis of a large, multicentre dataset, relating to 1245 patients who received concurrent chemoradiotherapy for NSCLC, revealed 1 year, 2 year and 5-year survival rates of 71%, 45% and 22% respectively (82). Median survival for this population was 20.9 months. Thus, for the majority of patients, chemoradiotherapy may offer extended, but not long term, survival. The same study by Warner et al examined predictive factors for early mortality (defined as death within 180 days of initiating radiotherapy); univariate analysis revealed several predictive factors for 180- day deaths including poor performance status, total radiation dose and gross tumour volume (GTV). On multivariable analysis, GTV and pulmonary function were both significantly predictive of death within 180 days of initiating radiotherapy (p=0.029 and p=0.047 respectively). A two-class risk stratification score based on these variables was developed, which was able to identify a three-fold increase in 180-day deaths for the high-risk patients (21%) versus low-risk patients (7%). Interestingly, patients with large tumours (high GTV) but good lung function had comparable 180-day death rates, 3- and 5-year survival rates to patients with small (low GTV) tumours; although their 1-and 2-year survival was reduced. Patients with large tumours and poor lung function fared worse on all (early and late mortality) outcomes. One possible explanation for this observation, proposed by the study's authors, is that patients with good lung function may be able to tolerate radiotherapy better and therefore be at lower risk of radiotherapy toxicity and early mortality. This study did not incorporate data relating to cachexia by way of weight loss, BMI, systemic inflammatory biomarkers or body composition. Furthermore, beyond lung function, there were no measures included which reflected comorbidity or frailty. The authors appreciated these limitations, using the term 'unmeasurable confounders'. Whilst this is accurate on one level, on another level we can say that some of the variables that they did not examine *are* technically measurable, but perhaps just not routinely measured.

Cancer treatment-related morbidity and mortality is increasingly well recognised, with significant recent attention focused on early mortality (death within 30 days) of systemic anti-cancer treatment (SACT) (16). The premise for this early mortality outcome is that patients

dying within 30 days of treatment have clearly not benefitted from the treatment as intended (with improved survival, symptoms or quality of life) but in addition may well have come to harm from (even died as a result of) the treatment itself.

It is argued that clinical trials data will never yield accurate estimates of serious complications arising from systemic cancer treatment; given that their data is typically based on populations that are younger, less comorbid and with better functional status than patients presenting in the real world through the cancer clinics (18). The case for population-based research based on clinical data and examining real-world outcomes following cancer treatment has been made by some researchers (16) (18).

An interesting observation was noted in a study by Wallington et al which examined 30-day mortality in breast cancer and lung cancer populations (16). This study included 9,634 patients with NSCLC, for whom rising age was associated with higher rates of early deaths where treatment was given with curative intent; whereas rising age was associated with lower rates of early death for patients who received treatment with palliative intent. Poorer tolerance of radical cancer treatment by older people was proposed as an explanation of their higher early mortality. The lower rates of early mortality in older people receiving palliative treatment could be explained by fewer treatment cycles being received, although this was not reported or evidenced; or by younger patients having more aggressive disease, although this was also not examined or evidenced. As would be expected, poor ECOG PS was a predictive factor for early death in both curative and palliative treatment populations. Early mortality was lower in women than men, a finding that was anticipated by the authors given published evidence of women presenting with earlier stage disease and at a younger age (84), although no hypotheses were described as to why this might be the case in early mortality scenarios. Although non-significant, there was a trend towards patients who were underweight being at higher risk of early mortality, and those who were overweight or obese at lower risk (both compared to patients in the 'normal' BMI category). Dose-limitation practices, where heavier patients may receive lower doses of SACT in relation to their weight, and thus be at reduced risk of treatment toxicity, was suggested as one explanation for this finding. Unhelpfully, cause of death was recorded as 'lung cancer' for almost all patients who died within 30 days of treatment in this study, which the authors propose as justification for death certification data not being a useful indicator of the aetiology of early deaths; however death certificates were not actually examined to explore whether this was the case. Neither a history of weight loss

nor quantified weight loss was examined in the study. Patients receiving SACT as part of chemoradiotherapy treatment for lung cancer were included, but were not specifically identified, as a result of poor recording of this information within the national SACT dataset, which is held and managed by Public Health England. Patients with small cell lung cancer (SCLC) were excluded from the study on the basis of inadequate numbers for analysis.

Evidence relating to treatment toxicity

Toxicity from chemoradiotherapy for lung cancer is common and can result in significant burden to patients, as well as additional healthcare system costs (13) (83) (82) (85) (79). In the acute phase of treatment, oesophageal, pulmonary and haematological toxicities are monitored weekly by clinical teams and these are usually graded according to validated criteria (typically the Common terminology Criteria for Adverse Events, CTCAE, or Radiation Therapy Oncology Group, RTOG, scales) (82) (86) (87). Acute oesophagitis, typically manifesting as difficult swallowing (dysphagia), develops during radiotherapy and gets worse over the course of treatment (85).

Within clinical trials, chemoradiotherapy toxicity is variably reported, with some early toxicities and many late effects such as pulmonary fibrosis often not captured (13) (82) (80). This in turn precludes meta-analysis of data in this area, limiting the extent to which the incidence of these complications is understood. However, is it consistently reported that rates of oesophageal toxicity (oesophagitis) are higher in people receiving concurrent chemoradiotherapy compared to those receiving sequential treatment (13) (79) (80) (88). Rates of acute pulmonary toxicity have been found to be comparable between people receiving concurrent and sequential treatment (13) (80) (88).

The retrospective cohort study published by Warner et al which investigated predictors of 180-day deaths following chemoradiotherapy did not examine predictors for pulmonary toxicity, despite reporting the incidence of this complication where it had been recorded by the individual cancer centres (82). Thirteen patients (out of 736 with available data, 1.8%) were recorded as having grade 5 toxicity, indicating that they died of this complication; 327/736 (44.4%) had no evidence of pulmonary toxicity, 341/736 (46%) had grade 1 or 2 (mild to moderate) toxicity and 55/736 (7.5%) had severe or life threatening (grade 3 or 4) toxicity. The headline finding of the study that tumour size (GTV) and lung function were significant

independent predictors of 180-day deaths suggest that acute pulmonary toxicity may have been implicated in more of the early deaths than the 13 that were reported with grade 5 pulmonary toxicity. 127/1245 patients included in the study died within 180 days of starting radiotherapy treatment.

Decision-making around chemoradiotherapy for lung cancer

Given that chemoradiotherapy is a comparatively lengthy and potentially burdensome treatment (82), balancing the intended benefits with the potential and/or likely burdens of treatment is important. The published reviews and studies presented in this chapter present evidence of significantly extended survival for many patients undergoing chemoradiotherapy for lung cancer (13) (79) (80) (81) (82) (83). However, the studies also highlight the need to understand and be able to quantify the potential harms of cancer treatment (84). Where patients are either at risk of dying during or soon after treatment, it is clear that they will not have benefitted in the way that was intended, and may even have died as a result of treatment. Thus, there is a clear need to identify people who are at greatest risk of adverse outcomes during or following treatment. In the first instance this necessitates identifying predictive factors for adverse outcomes, but it must also follow that this knowledge is assimilated into clinical consultations and decision-making, whether informally, or potentially using formal risk-stratification approaches as described by Warner et al (82).

The studies presented in this chapter section highlight the importance of examining both early and late mortality in patients undergoing chemoradiotherapy for lung cancer; since the timeframes of each are likely to be distinct given the anticipated extended survival for most. The studies also reveal some specific risk factors for adverse outcomes in this patient population, including larger tumours, reduced lung function, older age, male gender and poor functional status. However, it is important to acknowledge that none of the reported studies incorporate basic data relating to cancer cachexia; such as weight loss, body mass index or systemic inflammatory profile. Nor do they incorporate measures of comorbid conditions. In planning the present study, variables relating to cancer cachexia were a priority, to be examined in conjunction with wider demographic and clinical variables. In addition, it was of interest to examine the availability of data relating to comorbidity. Where it is decided that chemoradiotherapy is not the appropriate treatment for a patient, whatever the reasoning might be, alternative modes of oncology treatment can be considered. In the setting of stage

III NSCLC or limited stage SCLC these might include chemotherapy or radiotherapy alone, given with palliative intent (i.e. with the intention of extending life and/or improve QoL). A minority of patients with technically treatable lung cancer and who deemed fit to receive treatment choose not to have any cancer treatment at all, the so-called BSC group (4).

2.1.3 Rationale for the cohort under study

Patients who had received chemoradiotherapy for lung cancer treatment were of interest for a number of reasons:

- Chemoradiotherapy is an intensive and often burdensome treatment, given with the goal of significantly extending survival for many and offering cure to some. Therefore, identifying people who do not do well with treatment in that they either do not live long enough to benefit or they come to harm from treatment, is clinically important.
- Weight loss is prevalent in people undergoing chemoradiotherapy, both as a result of the treatment and its complications (particularly oesophagitis) but also apparently independently of this, suggesting metabolic imbalance (73) (85).
- Median survival following chemoradiotherapy for lung cancer is in the order of 20 months (82) and therefore it should be possibly to identify distinct predictive factors for both early mortality and overall survival (OS). This may be more difficult for populations with more advanced lung cancer, for whom early mortality and OS may be less distinct.
- Ultimately, it is intended that greater understanding of predictive factors for adverse outcomes may enable patient selection for lung cancer treatment to be optimised. Furthermore, it is hoped that patients with overt cachexia, or with indicators that suggest that they are at risk of cachexia, may be identified for proactive cachexia management; either alongside or in advance of their cancer treatment. An important retrospective cohort study which included 242 patients with lung cancer (51% stage IIIB, 49% stage IV) undertook body composition analysis at multiple time points between diagnosis and death utilising routine CT scan data (89). Whilst two-thirds of patients lost muscle over time, one third did not. Perhaps unsurprisingly, patients who gained the most muscle were those whose cancer was either said to be responding well to cancer therapy, often with accompanying symptomatic response, or those with stable disease. No anabolic potential was demonstrated in patients who were in their last 90 days of life. Thus, a significant proportion of the population undergoing chemoradiotherapy for lung cancer, with an expected survival of almost two years, could have real anabolic potential; this being another important reason to try and identify individuals within this population who are either not in that category (for whom a more palliative treatment approach may be best)

and those who are, for whom proactive nutritional support and cachexia management may be beneficial.

2.1.4 Study aim and research questions

The aim of the present study was to identify predictive factors for early mortality following chemoradiotherapy completion, and for OS.

Research questions:

1. What are the demographic and clinical characteristics of the cohort who received chemoradiotherapy for lung cancer in SE Scotland between 2008 and 2010?
2. Which cachexia-related biomarkers are feasible to collect from routine NHS clinical data for this cohort?
3. Which variables, identifiable at diagnosis and based on routine healthcare data for this cohort, are predictive of early mortality and OS?
4. What might the clinical significance of identified predictive variables for early mortality and OS be?
5. What are the limitations around routine healthcare data research for this cohort and how might these inform future research?

2.2 Materials and Methods

2.2.1 Study approvals

Ethical approval was not required for this study. However National Caldicott approval was granted for the collation of existing routine patient data from two neighbouring health boards in SE Scotland (NHS Lothian and NHS Fife). Caldicott Guardian approval was granted in 2014 (Appendix B).

2.2.2 Study logistics including information governance

This retrospective cohort study was undertaken during 2015-2016.

JB has been Good Clinical Practice trained since 2013, with two-yearly updates since then (Appendix C). JB completed a Medical Research Council (MRC) online module in Research Data and Confidentiality in 2014 (Appendix D) and an NHS Learnpro online training module in Information Governance in 2015, updated in 2017 (Appendix E).

The foundation of the present study was the clinical review and manual collation of routinely collected lung cancer audit data with clinical and administrative data from several wider sources. These wider data sources included electronic health records and patients' paper clinical records (case notes). At the time that the study was planned, electronic linkage of data from these sources was not possible, thus the data collection process required JB to identify and extract individual patient-level data manually. This was done over the course of twelve months between 2015 and 2016. The datasets were selected in order to provide broad, but also detailed, individual patient-level data.

The first stage of the study, following Caldicott approval being granted, involved the SE Scotland Cancer Network (SCAN) data manager extracting basic demographic and clinical information for the patient cohort of interest. This data was transferred to an Excel spreadsheet which was emailed via secure NHS email to JB. JB stored the spreadsheet within a password protected drive within the NHS Lothian secure network.

JB expanded the Excel spreadsheet with the data fields required from each of the wider data sources. Over a one-year period, JB systematically examined multiple data sources for each patient, extracting relevant data and updating the Excel spreadsheet with it. Basic details of

this process, including the different data sources and the data fields from each, are described in the sections that follow.

Robust identification and collation of data from a variety of sources was made possible by the existence of the unique health record identifier, the Community Health Index (CHI) number. This Scotland-wide identifier is made up of ten digits, including each person's date of birth (first six digits, DD.MM.YY), followed by two further digits, a ninth digit which is always an even number for females and an odd number for males, and a tenth digit which acts as an arithmetical check digit (90).

When data collection was complete, JB allocated a unique, anonymised, study number to each patient and a further spreadsheet was created with all patient identifiers (including CHI number, first name, surname and postcode) removed. This anonymised spreadsheet contained the entire dataset for statistical analysis, and it was shared with the single statistician for the study (Dr Linda Williams) via secure NHS email. A document containing the linked anonymised study numbers and patient CHI numbers was stored securely in the password protected drive within the NHS Lothian network, in case data queries necessitated further checks to be made or additional data to be collected.

2.2.3 Outcomes and exploratory variables

The main outcome of interest for the present study was OS, which was calculated from the date of diagnosis (date of diagnostic CT scan) until the date of death. A censor date of April 16th, 2015 was applied for patients who were still alive at the time of data collection.

Other outcome measures of interest related to early mortality following treatment, cancer progression and chemotherapy completion rates.

Early mortality encompassed death within 30 or 90 days of chemoradiotherapy completion. The assumption underlying the early mortality outcomes was that deaths in the immediate period after treatment completion could represent direct treatment-related mortality and/or may identify patients whose cancer was so rapidly progressive that undergoing chemoradiotherapy may not have been in their best interests.

CT-scan evidence of progression was examined for all patients with follow-up CT scans, and was of particular interest for the patients who died shortly after treatment in order to examine

whether they had evidence of disease progression, despite recent treatment, which might explain their early death.

Chemotherapy completion (number of cycles of chemotherapy received) was examined as it was of interest to identify whether patients had received their treatment as intended.

The intention was to collect data for a range of explanatory variables, which were to be examined in relation to the outcome measures described. These were informed by the research literature on known predictive factors for adverse outcomes in lung cancer and cancer more broadly, but also what was likely to be available within routine NHS clinical data. The included variables were:

- Demographics: age, gender
- Cancer subtype and stage: NSCLC (stage I-IV), SCLC (limited or extensive)
- Details of comorbid conditions
- Chemoradiation schedule: concurrent or sequential
- Functional status: ECOG PS
- Patient-reported weight loss at diagnosis
- CT-based body composition variables: skeletal muscle index (SMI) and muscle attenuation (MA)

Description of where the variable data was sourced from and relevant definitions are discussed in the sections that follow.

2.2.4 The index dataset and identifying the study cohort

The cohort for study was identified within routine cancer audit data held by SCAN - the index dataset. All patients with lung cancer who completed at least one cycle of chemotherapy as well as radiotherapy (recorded as either concurrent or sequential chemoradiotherapy) in SE Scotland with a date of first treatment between January 1st 2008 and December 31st 2010 were included in the study.

Scotland has three regional cancer networks (SE Scotland, SCAN; North of Scotland NoSCAN; West of Scotland WoSCAN), covering the entire Scottish population of around 5.4 million. Cancer audit data is collected prospectively by local cancer audit facilitators in twelve-month cohorts of patients newly diagnosed with one of nine different tumour types, including lung

cancer. Beyond basic demographic and cancer diagnosis details, the data collected closely corresponds to nationally quality performance indicators (QPIs), most of which relate to cancer diagnostic and treatment pathways. QPI data is presented annually to regional network groups, but in addition there is also comparison of data at a national level for each tumour group in order to identify any variations in practice or outcomes that might warrant investigation. Each year, tumour-specific audit reports are published which relate to the previous year's QPIs

Beyond the data submission date for the purposes of annual reports, data that becomes available at a later date for patients described within the reports is not collected. For example, audit data is not revised to include additional follow-up information such as further cancer treatments received or whether the person has died. Thus, cancer audit data contains useful information about diagnostic pathways and initial treatment plans, but in itself does not contain complete treatment pathway information or dates of death unless patients have died within the timeframe of prospective data collection for the given year's report.

For the purposes of the present study, the following basic demographic and clinical data was extracted by the SCAN data manager for each patient:

- CHI number
- Patient name
- Cancer histology and stage
- ECOG PS recorded at multidisciplinary team (MDT) meeting
- Date of MDT meeting discussion
- Cancer treatment start and completion dates
- Total number of chemotherapy cycles received
- Date of death

For the present study, the 2008-2010 timeframe was chosen to enable access to follow-up data for a minimum period of three years for all patients, following the completion of their cancer treatment.

Case ascertainment is the term used by the regional cancer networks to describe the completeness of data capture for patients with a new diagnosis of each specified cancer type. It is calculated retrospectively through comparison with national cancer registry data. For the

three-year period that data was provided by SCAN for the present study (2008-2010) data capture was consistently greater than 99%. Given that this SCAN lung cancer dataset was to form the basis of what would become the much wider dataset, confidence in this case ascertainment level was important.

2.2.5 Data extraction and collation

Table 2.1 outlines the range of data sources from which data was extracted, patient by patient, by JB for the population identified through the cancer audit dataset. Further detail around where the data was held within each data source, and the nature of the data, is described thereafter.

All patients who received chemoradiotherapy had Lothian-held electronic and paper records, since all patients in SE Scotland requiring radiotherapy receive this in the Edinburgh Cancer Centre (ECC). However, patients living in Fife also had Fife-held records.

Table 2.1 Summary of data sources and data fields of interest within each source

Data source	Data fields
TrakCare (electronic patient record in NHS Lothian)	• Comorbid health conditions • Patient-reported weight loss • Height and weight • Date of death
Clinical Portal (electronic patient record in NHS Fife)	• Patient-reported weight loss • Height and weight • Date of death
Online radiology system (Picture Archiving and Communication System, PACS)	• Diagnostic CT scan date ○ Single slice image of CT from this scan, for body composition analysis • Follow-up CT scan date
Hard copies of clinical case records	• Height and weight
National Records of Scotland (NRS) Death Registration	• Cause of death

TrakCare (electronic patient record in NHS Lothian) and Clinical Portal (electronic patient record in NHS Fife)

Data extracted from within TrakCare (NHS Lothian) and the Clinical Portal (NHS Fife) was found in a variety of locations, including referral letters, clinic letters and hospital discharge letters. A basic search function within TrakCare enabled height and weight to be searched for across all correspondence and records. Height and weight recorded close to diagnosis were important for body mass index (BMI) calculation, but heights were also required as part of the body composition analysis in order to correct individuals' muscle mass for stature.

Patient-reported weight loss around the time of diagnosis, where described in clinic letters or patient assessments, was recorded as a yes/no, with no attempt to quantify the amount or over what time period. Where patients had described not being sure whether they had lost weight, this was recorded as 'no'.

The intention at the outset of the present study was to collect detailed information about individuals' comorbid health conditions from their case records. However, it was immediately apparent that the reliability of this data was highly questionable, with contradicting information for individual patients between data sources. This likely reflected inconsistent practice with regards to the assessment of patients' comorbidity, (e.g. divergent practice in the questions that clinicians ask patients in their history taking, as well as the wider sources of clinical information that were utilised by individual clinicians). In addition, these contradictions likely reflected the fact that there was, and still is, no standardised approach to recording details of comorbid conditions within clinical records.

At the outset of the present study when it became apparent that individual patient records contained inconsistent data relating to their comorbid conditions, consideration was given to whether this data might instead be extracted from Information Services Division (ISD) administratively-held datasets. However, the decision was made not to access and utilise this data for the present study for two main reasons:

- **The feasibility of utilising the data:** JB did not have the expertise to manage coded data herself, and whilst this was a skill that she could acquire with training, the decision was made with her MD supervisors that she should instead focus on mastering CT-based skeletal muscle analysis. As an alternative, JB explored whether the ISD analytical team would de-code the comorbidity data into a usable format to be included in the study.

However, the cost of this was prohibitive at several thousand pounds, as there was no formal funding for the MD studies other than for JB's time.

- **The focus of the study:** As has already been described, one of the aims of the present study was to describe the availability of routine healthcare data which could be utilised in decision making about treatments for individual patients by lung cancer teams in secondary care; rather than using derived coded data from large administratively held datasets. This was not a data linkage study based on coded data, rather it was based on individual case record reviews to extract and collate detailed clinically held data.

Therefore, whilst comorbid conditions and their contribution to adverse outcomes for the study population were of interest, the decision was taken by JB and her MD supervisors that comorbidity data would not be included in the present study. Consideration to how this limitation could be overcome in future research is discussed towards the end of this chapter and again in Chapter 4.Dates of death were extracted for all patients who had died by the study censor date of April 16th 2015. Patients who had died by the time of cancer audit data collection already had their date of death recorded, but anyone who had died following cancer audit data submission but before the censor date required this to be extracted from TrakCare or Clinical Portal.

Online radiology system (Picture Archiving and Communication System, PACS)

Two CT scan dates were identified within PACS and were recorded for each patient. The first date was for the nearest CT scan to the date of the lung cancer MDT meeting where the diagnosis was made. The second date was for the subsequent CT scan following the completion of their chemoradiotherapy treatment. Diagnostic CT scans were viewed within PACS and a single image of a single slice at the level of the fourth thoracic vertebra (T4) was downloaded for each patient. This was later utilised for body composition analysis, see section 2.2.6 for details of this process. Images from follow-up CT scans for were examined at a later date in 2016 by a specialist thoracic radiologist, Dr Alan Simms, in order to assess disease response to treatment and/or recurrence. Given the recognised challenges of accurately assessing disease after high-dose thoracic radiotherapy (91) (92), no attempt was made to quantify disease. Instead, a pragmatic expert radiological assessment was made, with patients

classified as having progressive disease (local, and/or distant) or not. The radiologist was blind to patient outcomes during the review.

Hard copies of clinical case records

The majority of patients did not have their height and weight at diagnosis recorded in their electronic records, which included their clinical letters. Nor was there any routine electronic capture of this information during 2008-2010, when the cohort under study was diagnosed with lung cancer. Therefore, paper case records for around 140 patients were requested from the ECC in order to find this data where possible. During 2008-2010, all patients who came through the ECC had a height and weight one-page document. Requesting, receiving and searching the paper case records took around 3 months. It also cost several hundred pounds which funded the retrieval of records from an off-site store and courier costs to bring them to the ECC.

National Records of Scotland (NRS) Death Registration

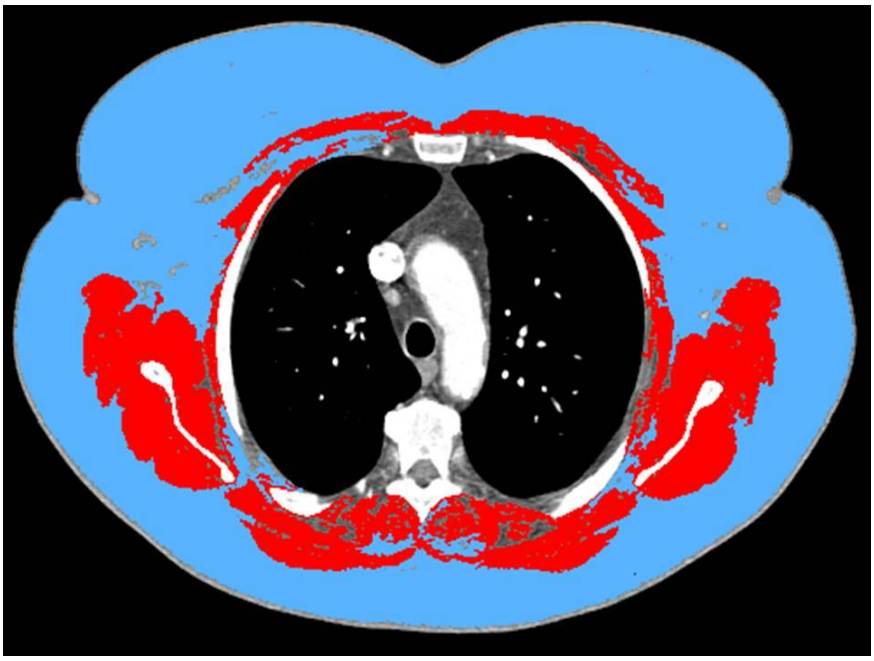
National death registry information of the recorded cause of death for each patient was accessed and extracted.

2.2.6 Body composition analysis

Skeletal muscle analysis using cross-sectional CT or MRI imaging is described within the Lancet consensus framework as the preferred method for muscle mass evaluation (46). The overwhelming majority of CT-based body composition research in cancer cachexia has utilised images from the third lumbar vertebral level, L3 (93) (55) (54) (94) (95) (96) (97)**.** Cross-sectional muscle measurement at L3 has been shown to correlate with whole body muscle mass (98) (93) (99). Sex-specific cut-offs for low muscle mass (sarcopenia), derived from L3 images, have been reported for a variety of cancer populations (93) (55) (54) (94) (95) (96) (97). However, it is also recognised that CT imaging in many cancer centres does not routinely extend as far as L3 for patients with lung cancer; and thus for pragmatic reasons the fourth thoracic vertebral level, T4, has been proposed as an alternative (100). The T4 vertebral level contains pectoralis muscles, external intercostal, serratus anterior, teres major, subscapularis, infraspinatus, rhomboid major, erector spinae and trapezius muscles (100). The decision to utilise muscle data from the T4 level in the present study was made by expert consensus, led by Professor Fearon (MD supervisor) in discussion with Professor Vicki Baracos, an international expert in skeletal muscle evaluation utilising CT scan imaging. It was deemed preferable to have images from a consistent T4 level for the entire study cohort rather than to expect missing data for an estimated one-third of patients whose diagnostic CT scans did not extend to the L3 level.

A single transverse image at the T4 vertebral level from each patient's diagnostic CT scan was downloaded from PACS and anonymised. Images were uploaded into specialist *Slice-O-Matic* V4.3 software (Tomovision, Montreal), which is used internationally by cachexia researchers for CT scan-based body composition analysis (54) (55) (93). The software semi-automatically demarcates different tissues including skeletal muscle (the focus of study here), visceral and subcutaneous adipose tissue (not included in this study), based on their relative densities, as measured by Hounsfield Units (HU). Standard HU thresholds for skeletal muscle of -29 to 150 were used (58). Skeletal muscle tissue was coloured in red, see Figure 2.1. Boundaries between different tissues within each CT image were checked by JB, who undertook minor corrections manually as needed.

Figure 2.1 Cross-sectional CT image at T4 vertebral level showing skeletal muscle in red and subcutaneous fat in blue.



Once each image had been manually checked, and corrected where needed, skeletal muscle area (cm^2) and muscle attenuation (measured in HU) were calculated by the *Slice-O-Matic* software. Whole body muscularity was then extrapolated by normalising skeletal muscle area (cm^2) for stature (m^2) and this was reported as the skeletal muscle index (SMI). Muscle density was quantified on the basis of skeletal muscle density (measured in HU) and this was reported as muscle attenuation (MA).

Thresholds for sarcopenia derived from T4 level images have been published (42) (57) but they have not been validated, and none has been specific to a lung cancer cohort receiving chemoradiotherapy. Therefore, optimal stratification (93) (101) was used to determine population and gender-specific high/low thresholds for both SMI and MA (continuous covariates) in relation to OS. Optimal stratification was conducted using SAS software, V9.4 of the SAS system for Windows.

2.2.7 Derived data - variables and outcome measures

As has been described, data was collected for every patient from a range of sources, relating to a variety of variables and outcomes of interest. Some variable and outcome data was already in its requisite format, but other measures were derived from the raw data. Examples of these included age at diagnosis, BMI and OS.

2.2.8 Statistical analysis

Statistical analysis was undertaken by Dr Linda Williams (LW), Senior Statistician at the University of Edinburgh. JB and LW worked closely for the duration of the MD.

Data were analysed using SPSS v19 (IBM SPSS Statistics, Ontario, Canada) and Version 9.4 of the SAS System for Windows. Copyright © 2002-2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Descriptive statistics of the demographic and cancer-related data are presented in simple tables, both overall and by gender or cancer type.

Simple bivariate associations of categorical variables were analysed using the chi-squared test. The relationship between a continuous and a categorical variable was analysed with Student's *t*-test or the Mann-Whitney U for non-parametric data. Agreement between two continuous variables was assessed by Pearson's correlation coefficient, and illustrated with simple scatterplots.

Logistic regression was used to analyse binary outcomes, such as death within 90 days, or treatment completed as intended, as both continuous and categorical variables can be included as explanatory variables. Cox proportional hazards regression and Kaplan-Meier estimates were used to examine the relationship between the explanatory variables and survival. Results for both methods are presented as univariate and multivariable analyses, to explore the potential effect of confounding.

Where appropriate, odds ratios (OR) for logistic regression and hazard ratios (HR) for survival are reported. All tests are two-sided, and a significance level of 5% has been assumed.

Validated reference ranges and normal values for variables were used where available, for example BMI and ECOG PS.

Optimal stratification (93) (101) was used to identify discriminatory cut-points for SMI and MA variables, based on the log-rank statistics (that is, survival data).

The creation of simple composite scores was explored, in order to identify patients at increased risk of adverse outcomes, by combining the statistically significant results from the multivariable analyses. By comparison of the parameter estimates, relative scores were assigned based on the size of the effect generated by each parameter.

2.3 Results

2.3.1 The study cohort

194 patients with newly diagnosed lung cancer who completed a course of chemoradiotherapy treatment at the Edinburgh Cancer Centre between January 1st 2008 and December 31st 2010 were included in the present study.

204 patients had been identified through the SCAN database, but following examination of their records, ten patients were excluded as they either had been inaccurately coded and were not in fact the intended study population; for instance they had either not received combined chemoradiotherapy (e.g. receiving palliative chemotherapy followed by radiotherapy for bone pain) or did not have lung cancer (one patient had lymphoma).

Basic demographic and clinical characteristics of the population at baseline are presented in Table 2.2.

Table 2.2 Demographic and clinical characteristics at diagnosis of 194 patients with lung cancer who received chemoradiotherapy

	Overall (n=194)	**Female** (n=103)	**Male** (n=91)	***p*-value** (F vs M)
Age				
Median (IQR)	64 (58-70)	63 (58-69)	65 (58-70)	0.602
	No. (%)	**No. (%)**	**No. (%)**	
NSCLC	113 (58.2)	58 (56.3)	55 (60.4)	
SCLC	81 (41.8)	45 (43.7)	36 (39.6)	0.561
NSCLC				
Stage I	0 (0)	0 (0)	0 (0)	
Stage II	5 (4.4)	3 (5.2)	2 (3.6)	0.677
Stage III	107 (94.7)	54 (93.1)	53 (96.4)	
Stage IV	1 (0.9)	1 (1.7)	0 (0)	
SCLC				
Limited	70 (86.4)	38 (84.4)	32 (88.9)	0.562
Extensive	11 (13.6)	7 (15.6)	4 (11.1)	
Chemoradiation				
Concurrent	151 (77.4)	74 (71.8)	77 (84.6)	0.033
Sequential	43 (22.2)	29 (28.2)	14 (15.4)	
ECOG PS				
0	29 (14.9)	14 (13.6)	15 (16.5)	
1	147 (75.8)	80 (77.7)	67 (73.6)	0.801[a]
2	16 (8.2)	8 (7.8)	8 (8.8)	
3	2 (1.0)	1 (1.0)	1 (1.1)	
4	0 (0)	0 (0)	0 (0)	

[a]ECOG PS 2 and 3 were combined due to small numbers

The majority of patients had stage III NSCLC or limited stage SCLC and received concurrent chemoradiotherapy. A minority (n= 43, 22.2%) received sequential treatment, with radiotherapy following their course of chemotherapy. 90% of patients (176/194) were categorised as ECOG PS 0/1 at diagnosis.

Data relating to body composition and weight loss variables are presented in Table 2.3.

Table 2.3. Body composition and weight loss characteristics at diagnosis of 194 patients with lung cancer who received chemoradiotherapy, by gender.

	Overall (n=194) No. (%)	**Female** (n=103) No. (%)	**Male** (n=91) No. (%)	***p*-value** (F vs M)
BMI (kg/m^2)[a]				
Mean (SD)	26.2 (5.2)	25.8 (5.7)	26.6 (4.7)	0.135
BMI category[a]				
Underweight (<20)	19 (10.0)	13 (12.9)	6 (6.7)	
Normal (20-24.9)	61 (32.1)	35 (34.7)	26 (29.2)	0.287
Overweight (25-29.9)	72 (37.9)	33 (32.7)	39 (43.8)	
Obese (>30)	38 (20.0)	20 (19.8)	18 (20.2)	
Weight-losing status[b]				
Weight-losing	109 (57.1)	57 (57.0)	52 (57.1)	0.984
Non-weight-losing	82 (42.9)	43 (43.0)	39 (42.9)	
CT-derived skeletal muscle area (cm^2)[c]				
Median	161.7	138.1	207.1	<0.001
IQR	135.5-202.7	122.8-153.9	182.5-226.9	
Skeletal muscle index (SMI) (cm^2/m^2)[c]				
Median	60.0	55.9	70.8	<0.001
IQR	53.1-69.7	49.0-61.3	59.2-76.3	
Stratified SMI[d]				
Above threshold	121 (69.5)	77 (81.1)	44 (55.7)	<0.001
Below threshold	53 (30.5)	18 (18.9)	35 (44.3)	
Skeletal muscle attenuation (MA) (HU)[c]				
Median	43.5	42.5	45.3	0.03
IQR	38.6-50.2	36.6-48.8	40.5-50.4	
Stratified MA[e]				
Above threshold	95 (53.7)	51 (52.6)	44 (55.0)	0.748
Below threshold	82 (46.3)	46 (47.4)	36 (45.0)	

[a]BMI and BMI category data available for 190/194 patients (missing data for 2 male and 2 female patients)

[b]Weight-losing status available for 191/194 patients (missing data for 3 female patients)

[c]CT-derived muscle area, muscle attenuation (MA) skeletal muscle index (SMI) for 177/194 patients (17 diagnostic CT scans unavailable/poor quality image)

[d]Stratified SMI threshold for females=46.2720, for males=67.2859.

[e]Mann Whitney U test

[f]Stratified MA threshold for females=40.45, for males=44.06

The mean BMI for both females and males was in the overweight category (BMI >25), with over half of women and nearly two-thirds of men either overweight or obese according to their BMI. Over half of patients reported weight loss to their Respiratory Medicine or Oncology team at diagnosis, as recorded in their outpatient consultation letters. Weight loss was

reported by 90% (17/19 patients) of patients in the underweight BMI group, 69% (42/61) in the normal BMI group and 44% (48/108) in the combined overweight and obese BMI groups.

Males were significantly more muscular (as measured by SMI which is corrected for stature) than females, although there were significantly more men with an SMI below the gender-specific optimal stratification threshold. Muscle attenuation (MA) was also significantly higher in males than females, although there was a comparable proportion of males and females below the optimal stratification threshold. Optimal stratification-derived thresholds, as presented in Table 2.3, were utilised for the analyses that follow.

2.3.2 Chemotherapy completion rates

All patients received some chemotherapy but 62/194 patients (32%) received only one, two or three cycles, where the intention was four or more. Patients who were booked to receive chemotherapy as part of chemoradiotherapy but who did not receive this (e.g because of deterioration in their health) were not captured by the study; since the index cancer audit dataset only included patients who had completed one or more cycles of chemotherapy and radiotherapy.

Patients who completed fewer than four cycles of chemotherapy were likely to be older (66 years versus 61 years), p=0.002. ECOG PS, BMI, weight-losing status, SMI and MA did not differ significantly between the groups. There was no significant difference in OS for patients who completed <4 or ≥4 cycles of chemotherapy (p=0.778).

2.3.3 Predictive variables for early mortality

Deaths within 30 days of treatment completion

4/194 patients died within 30 days of completing their chemoradiotherapy. This very low number did not allow for any meaningful statistical analysis.

Deaths within 90 days of treatment completion

22/194 patients died within 90 days of completing their chemoradiotherapy. Of these, ten patients had follow-up CT scans that were available for specialist radiology evaluation. 2/10 CT scans for this population demonstrated evidence of disease progression.

On univariate analysis, ECOG PS ≥2, BMI <20 and patient-reported weight loss were all associated with death within 90 days of treatment completion. On multivariable analysis, only ECOG PS ≥2 and BMI <20 remained independently associated with death within 90 days of treatment completion (see Table 2.4, below).

Table 2.4: Univariate (UV) and multivariable (MV) analysis of predictors of death within 90 days of chemoradiotherapy completion.

	Died within 90 days of treatment completion¥		**UV analysis Odds ratio of death within 90 days (95% CI)**	**MV analysis Joint odds ratio of death within 90 days (95% CI)**
	Yes (n=22) N (%)	**No (n=172) N (%)**		
Age (continuous, per year increase)	n/a	n/a	1.02 (0.97, 1.07) *p*=0.41	-
Gender (F vs M)				
F	8 (7.8)	95 (92.2)	0.46 (0.19, 1.16)	-
M	14 (15.4)	77 (84.6)	*p*=0.10	
Cancer type (NSCLC vs SCLC)				-
NSCLC	14 (12.4)	99 (87.6)	1.29 (0.51, 3.24)	
SCLC	8 (9.9)	73 (90.1)	*p*=0.59	
NSCLC stage (III versus II)			Unable to calculate OR. Fishers Exact test, *p*=1.0	-
III	13 (12.1)	94 (87.9)		
II	0 (0)	5 (100)		
SCLC Stage (Ext versus Lim)				-
Extensive	1 (9.1)	10 (90.9)	0.90 (0.10, 8.11)	
Limited	7 (10.0)	63 (90.0)	*p*=0.93	
ECOGPS (≥2vs0 /1)	6 (33.3)	12 (66.7)	**5.00 (1.65, 15.12)**	**3.97 (1.20, 13.08)**
≥2	16 (9.1)	160 (90.9)	***p*=0.004**	***p*=0.024**
0 or 1				
BMI (<20 vs ≥20)				
<20	7 (36.8)	12 (63.2)	**6.07 (2.08, 17.73)**	**3.91 (1.24, 12.38)**
≥20	15 (8.8)	156 (91.2)	***p*=0.001**	***p*=0.020**
Reported weight loss (yes vs no)				
Yes	18 (16.5)	91 (83.5)	**3.85 (1.25, 11.88)**	2.89 (0.89, 9.37)
No	4 (4.9)	78 (95.1)	***p*=0.019**	*p*=0.08
SMI at diagnosis (low versus high)[a]				
Low	10 (18.9)	43 (81.1)	2.33 (0.92, 5.87)	-
High	11 (9.1)	110 (90.9)	*p*=0.07	
CT scan-derived MA at diagnosis (low versus high)[b]				-
Low	8 (9.8)	74 (90.2)	0.68 (0.27, 1.74)	
High	13 (13.7)	82 (86.3)	*p*=0.42	

[a] Optimal stratification SMI cut-offs for males = 67.3 (n=44 above and 35 below) and for females = 46.3 (n=77 above and 18 below)

[b] Optimal stratification MA cut-offs for males = 44.1 (n=44 above and 36 below) and for females =40.5 (n=51 above and 46 below)

2.3.4 Predictive variables for overall survival

Median OS for the population of 194 patients was 19.0 months (95% CI 16.3, 21.7) from the date of diagnosis. There was no significant difference in OS between patients with NSCLC and those with SCLC. Nor was there a significant difference in survival between those with different disease stages, accepting that the vast majority of patients had either stage III NSCLC (107/113 of people with NSCLC had stage III disease, 94.6%), or limited stage SCLC (70/81 patients with SCLC had limited stage disease, 86.4%).

On univariate analysis, ECOG PS, patient-reported weight loss and muscle density (Muscle Attenuation, MA) were associated with reduced OS (see Table 2.5). On multivariable analysis, only MA remained independently associated with OS.

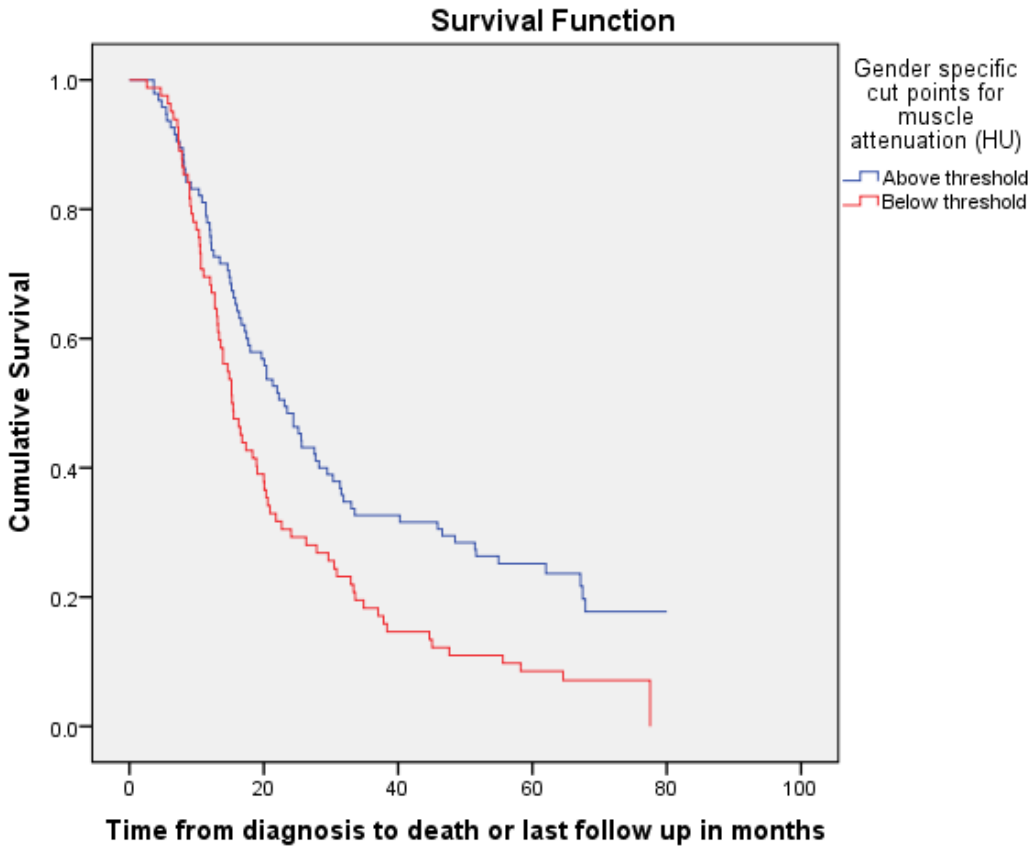
Table 2.5: Univariate and multivariable analysis evaluating the prognostic significance of a range of demographic and clinical variables (in relation to OS).

The second category is the reference category

	Alive at last record	**Died**	**Univariate analysis Hazard ratio of death (95% CI)**	**Multivariable analysis Joint hazard ratio of death (95% CI)**
Age (continuous, per year increase)	-	-	1.00 (0.99, 1.02) *p*=0.68	-
Gender (F vs M)				
F	18 (17.5)	85 (82.5)	0.84 (0.62, 1.14)	-
M	10 (11.0)	81 (89.0)	*p*=0.26	
Cancer type (NSCLC vs SCLC)				
NSCLC	17 (15.0)	96 (85.0)	1.21 (0.88, 1.64)	-
SCLC	11 (13.6)	70 (86.4)	*p*=0.24	
Cancer stage (NSCLC stage III vs II)				-
III	14 (13.1)	93 (86.9)	3.64 (0.89, 14.80)	
II	3 (60.0)	2 (40.0)	*p*=0.07	
Cancer stage (SCLC extensive vs limited)				-
Ex	1 (9.1)	10 (90.9)	1.68 (0.85, 3.31)	
Lim	10 (14.3)	60 (85.7)	*p*=0.13	
ECOG PS (≥2 vs 0 or 1)				
≥2	1 (5.6)	17 (94.4)	**1.78 (1.04, 2.84)**	1.36 (0.80, 2.30)
0 or 1	27 (15.3%)	149 (84.7)	***p*=0.035**	*p*=0.25
BMI (<20 vs ≥20)				
<20	2 (10.5)	17 (89.5)	1.27 (0.76, 2.10)	-
≥20	26 (15.2)	145 (84.8)	*p*=0.36	
Reported weight loss (yes vs no)				
Yes	10 (9.2)	99 (90.8)	**1.43 (1.05, 1.95)**	1.32 (0.95, 1.83)
No	16 (19.5)	66 (80.5)	***p*=0.025**	*p*=0.10
CT scan-derived SMI at diagnosis (low vs high)				-
Low	6 (11.3)	47 (88.7)	1.23 (0.87, 1.74)	
High	19 (15.7)	102 (84.3)	*p*=0.24	
CT scan-derived MA at diagnosis (low vs high)				
Low	5 (6.1)	77 (93.9)	**1.62 (1.17, 2.23)**	**1.61 (1.16, 2.23)**
High	20 (21.1)	75 (78.9)	***p*=0.003**	***p*=0.004**

Median OS for patients with low MA was 15.2 months (95% CI 12.7, 17.7) compared with a median survival of 23.0 months for people with high MA (95% CI 18.3, 27.8), hazard ratio 1.62 (95% CI 1.18, 2.23), *p*=0.003. See Figure 2.2.

Figure 2.2 Kaplan Meier curve demonstrating predictive value of muscle attenuation (MA) for OS.

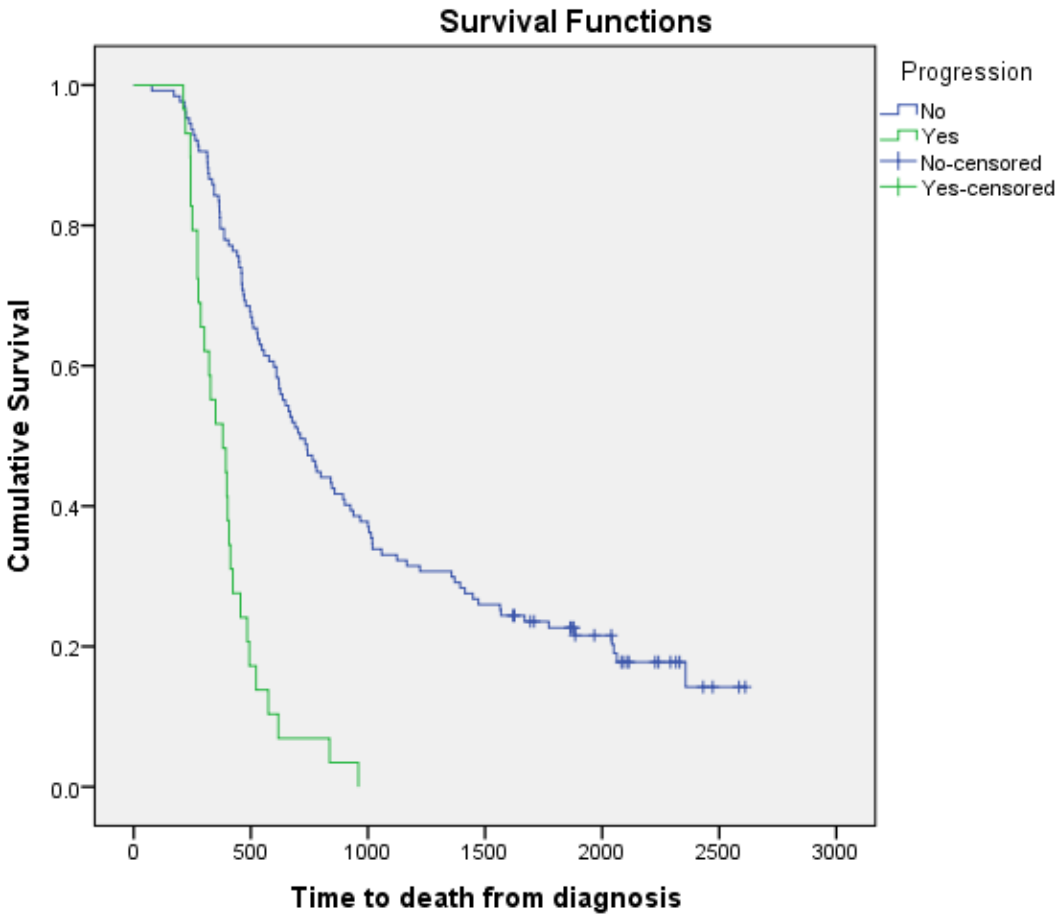


2.3.5 Disease progression evidence on follow-up CT scans

176/194 patients (88.6%) had follow-up CT scans after the completion of their cancer treatment. The median time from the last day of treatment to the CT scan was 90 days (IQR 55–110). 156/176 CT scans which encompassed the required fields were available for radiologist review. Of these, 29 (18.6%) had clear evidence of disease progression, either locally (*n* =5) or at a distant site (*n* =17) or both (*n* =7).

There was no correlation between MA (the only variable that was independently predictive of OS) and disease progression as evidenced by patients' follow-up CT scans. Median OS of patients with no evidence of disease progression on their first follow-up CT was 712 days from diagnosis (95% CI 590, 834) compared to 380 days for those with evidence of disease progression (95% CI 264, 496). See Figure 2.3.

Figure 2.3 Kaplan Meier curve demonstrating significantly reduced survival for patients with CT evidence of disease progression compared to those without disease progression on CT.



Patients with CT-evidence of disease progression were no more likely to have low MA than those who did not have progressive disease (Chi-squared test *p*=0.61).

2.3.6 Cause of death

At the outset of the present study, the intention had been to record cause of death, as per death registry data, for every patient who had died before the censor date. However, on examination of death registry data for the cohort of patients who died within 90 days of completion of their chemoradiotherapy, it became clear that it was not reliably accurate. Indeed, for the ten patients who died within 90 days of treatment completion *and* who had follow-up CT scans available for analysis, all were recorded as having a primary cause of death of 'lung cancer'. This is despite specialist radiological review demonstrating no disease progression. Therefore, cause of death was not examined for the remainder of the population as it was felt not to provide an accurate reflection of the actual cause of death.

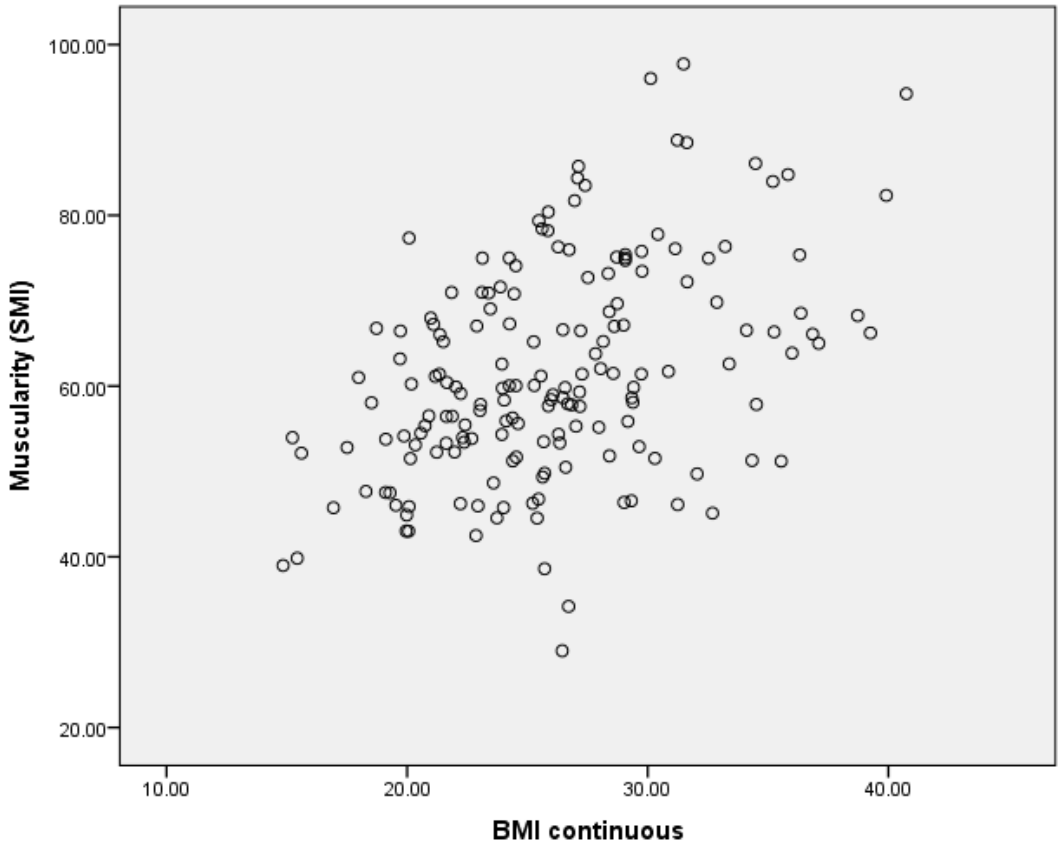
2.3.7 Associations between BMI, body composition and weight loss

Further to the planned analysis already described and given the findings presented, additional exploratory analysis was undertaken to examine the associations between BMI, skeletal muscle measurements and weight loss.

Patients reporting weight loss at diagnosis (109/191, with missing data for 3 patients) had a significantly lower BMI compared to those who did not report weight loss (BMI 25.0 in weight-losing patients versus 27.7 in non-weight-losing patients, (95% CI of difference 1.23, 4.17; p <0.001).

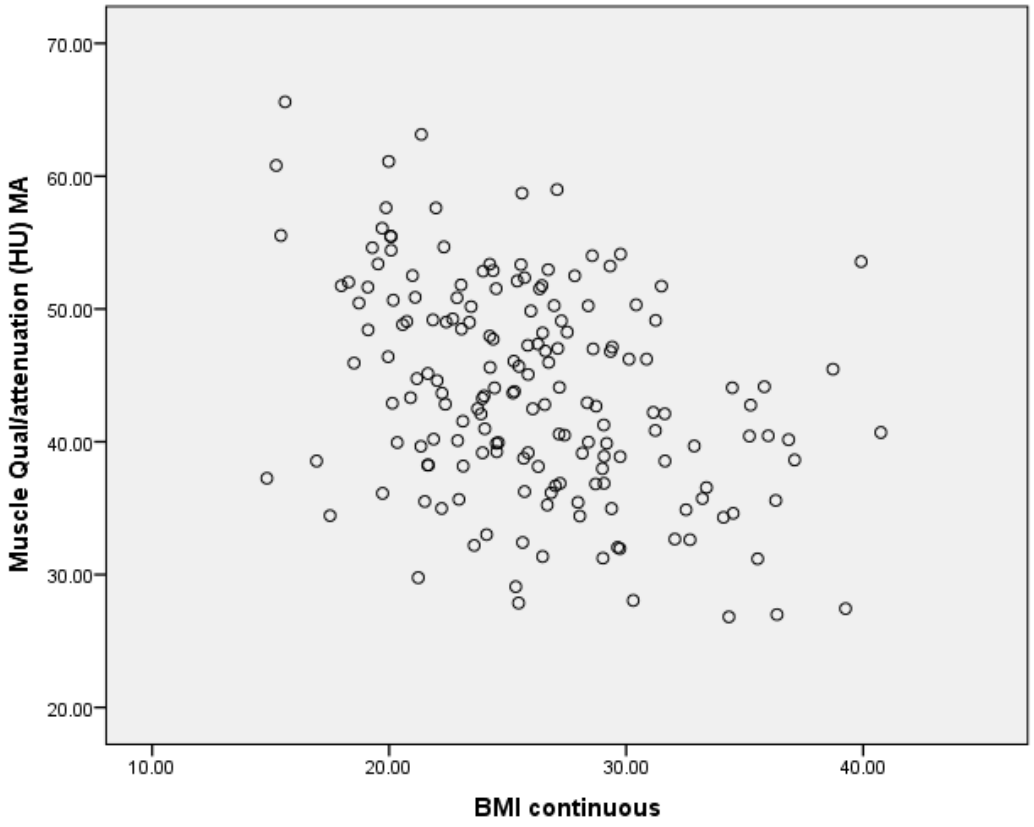
As patients' BMI increased, so did their SMI, r=0.44 (p<0.001), see Figure 2.4.

Figure 2.4 A scatter plot of BMI by muscularity (SMI)



As patients' BMI increased, their muscle density (Muscle Attenuation, MA) fell (r = -0.39, p<0.001). See Figure 2.5.

Figure 2.5 A scatter plot of BMI and muscle attenuation (MA)



2.4 Discussion

Chemoradiotherapy is a lengthy and potentially burdensome treatment. The intention of lung oncologists and the expectation of their patients is that this treatment should offer significantly extended survival.

Current criteria for starting systemic cancer treatment such as chemoradiotherapy include disease stage and ECOG PS, both of which are firmly embedded in clinical decision making. In the present study, 98% of patients survived beyond 30 days after completing treatment and 89% of patients survived beyond 90 days after completing treatment; these figures suggest that, for most, these criteria are fit for purpose.

The present study cohort was selectively well in that all were deemed fit enough to undergo chemoradiotherapy treatment for their lung cancer; indeed, >90% patients we studied were said to be 'fit', with an ECOG PS of 0/1 recorded at diagnosis.

2.4.1 Low BMI and poor ECOG PS predict death within 90 days of treatment completion

BMI <20 and ECOG PS ≥2 were independent predictors of death for the 22/194 patients (11.3%) who died within 90 days of treatment completion. 18/194 patients who had an ECOG ≥2 at diagnosis had an odds ratio of death with 90 days of treatment completion of 3.97 (adjusted OR), compared with those patients who had an ECOG PS of 0/1. A poor ECOG PS has been shown repeatedly to be associated with reduced survival in lung cancer (69) (70) (41) (71) (72) (73). In a landmark study by Dewys et al published in 1980, poor performance status surpassed weight loss as the major predictor of reduced survival (33).

10% of patients were underweight as measured by BMI (BMI <20) at diagnosis. This figure is comparable with data from other cancer cachexia studies (54) (55) (102). Patients with a low BMI were at increased risk of death within 90 days of chemoradiotherapy completion. It is known that cancer treatment itself can cause weight loss (103) and it is possible that weight loss during chemoradiotherapy in people with an already low BMI leads to a critical level of malnutrition that contributes to early death. Pre-existing nutritional reserve, measured by low BMI, has been shown to be independently prognostic in a large study of people with advanced cancer (102). Low BMI had previously been shown by the same researchers to be a key

determinant of survival in people with cancer (55). Martin et al (102) described the concept of 'metabolic bankruptcy'; to describe patients with cancer with the lowest BMI, and the poor prognosis they often face.

In addition to the hypothesis relating to energy reserve (or lack of) in patients with a low BMI, it is also possible that these patients experienced higher rates of treatment toxicity and that they may have deteriorated, or even died, as a result. Patients with low muscle mass are known to be at increased risk of severe toxicity from chemotherapy, and/or not completing their treatment as intended (40) (41) (93) (97). In the present study, low muscle mass (as measured by the Skeletal Muscle Index, SMI) was not predictive of death within 90 days of treatment completion. However, it is known that BMI and SMI are commonly correlated, with low BMI patients typically having low muscle mass (55). The additional exploratory analysis described in section 2.3.7 (and depicted in Figure 2.4) confirmed moderate positive correlation between BMI and SMI. Thus, it is likely that in the present study, BMI and SMI are confounders.

In the present study, there were two patients who had both low BMI and poor ECOG PS who received chemoradiotherapy as planned and lived for a considerable amount of time following treatment. Thus, and as we might expect clinically, these risk factors do not equate to certainty of early death. However, explaining these risk factors to individuals who are at increased risk of early death following chemoradiotherapy could help to inform the decision about whether chemoradiotherapy is the right treatment for them; it is increasingly understood that decisions around cancer treatment are individual, and should be personalised, with risks and benefits as they apply to/matter to the person considered. For some people, a significant risk of death in the weeks or short months following cancer treatment would make them question the value of the treatment in the first place, whilst others might feel very differently about risk and be keen to proceed. Furthermore, we must appreciate that some people with cancer do not want to hear detailed information about risks and benefits of treatment. This can pose challenges when it comes to informed consent for treatment as we currently understand it, but such preferences must be respected if decision making is to be both person-centred and personalised. It is an important role of expert oncologists to gauge how detailed discussions with patients and those close to them need to be, based on what they understand about the people in front of them. It is possible that where oncologists are already feeling uncertain about whether the intended benefits of chemoradiotherapy outweigh the benefits for the

individual in front of them, knowledge of risk factors for early adverse outcomes from research such as this might help them to decide that they should not be offering treatment with radical intent. The evidence from studies such as this one may be useful to describe to patients why a particular form of cancer treatment is not appropriate for them. In this patient population, there may be other cancer treatment options with palliative intent such as systemic treatment with chemotherapy, targeted or immunotherapy, or radiotherapy, which would be lower risk and may still offer significant benefit. Thus, particularly in this population, with either stage 3 NSCLC or limited stage SCLC, the question may not be 'treatment or no treatment?', rather 'treatment with what intent?'

2.4.2 Low muscle density (muscle attenuation, MA) is associated with significantly reduced overall survival

Low skeletal muscle density, as measured by muscle attenuation (MA) using patients' routine diagnostic CT scans, was independently predictive of reduced OS in the present study. Using a single threshold for high/low MA, individuals with low muscle density (MA below the derived threshold) had a median OS of 15.2 months (95% CI 12.7, 17.7), compared with a median OS of 23.0 months (95% CI 18.3, 27.8) for those with high muscle density, p =0.003.

Low density muscle is understood to be one manifestation of skeletal muscle wasting as part of the cancer cachexia syndrome; reflecting muscle that has been infiltrated by fat, known as myosteatosis (104). However, it may also reflect ageing, obesity and non-cancer illnesses including type two diabetes (105, 106). Systemic inflammation is known to be predictive of reduced OS in a range of cancer types, with several studies of people with lung cancer have shown reduced survival in people with high levels of systemic inflammation (70) (42) (107) (108) (109). One study examined the relationship between host inflammatory response and body composition in a cohort who underwent surgery for colorectal cancer, and discovered that a high neutrophil to lymphocyte ratio (NLR) was predictive of both low muscle density (low muscle attenuation, MA) and low muscle mass (low skeletal muscle index, SMI) (105). Another study in a different cancer population (with incurable pancreatic cancer), also demonstrated an association between low MA and systemic inflammation, as measured by the NLR, white cell count and C-reactive protein (96); in the cohort with pancreatic cancer described by Lobo et al, low MA was independently associated with significantly reduced OS (88 days versus 237 days, p=0.0008). This is consistent with the present study's findings of

significantly reduced OS for people with low MA. A small study of 52 people with SCLC, treated with chemoradiotherapy, revealed that pre-treatment NLR was the only independently predictive variable of reduced OS (110); median survival for patients with an NLR of ≥ 5 was 6.6 months, versus 21.5 months for those with an NLR of less than 5 (p=0.03). We did not collect data relating to systemic inflammatory status for the present study cohort, and so we do not know the extent to which muscle density and systemic inflammation were correlated. It possible that a number of processes, including cancer cachexia-related inflammation and comorbidity, were implicated in the muscle density of the patients included in this study. The non-inclusion of data relating to systemic inflammation and comorbidity in the present study meant that we were not able to explore these important areas. A further fundamental unknown is whether myosteatosis is a driver of shortened survival in itself, or whether it is simply reflective of underlying systemic inflammation, or indeed some other process, which itself may be the cause of poor survival (96). It is interesting to note that whilst low MA was associated with reduced OS, it was not associated with evidence of disease progression in patients' CT scans. This suggests that muscle density may be related to factors beyond the cancer itself which impact on survival. Further investigation of this key area is needed.

A median OS of 15.2 months for the population with low muscle density may still represent significantly extended survival as a result of chemoradiotherapy treatment. However, the discrepancy in median survival of almost 8 months between the populations with high and low muscle density is striking. Thus, an important question for the future is whether it may be possible to improve OS for the population with low muscle density in any way. However, on the basis of this study's findings we are unable to make suggestions about the kind of interventions that could improve survival for this population as we do not understand the extent to which systemic inflammation or other unmeasured variables such as comorbidity may be implicated.

2.4.3 Weight loss

Even low-grade weight loss (as low as 2.4%) has been shown to be predictive of reduced survival in cancer (102). Such apparently minor weight loss may reflect early or 'pre-cachexia', as part of what is now understood to be a continuum ranging from clinically undetectable cachexia to refractory cachexia (46). In one study of people receiving chemoradiotherapy for lung cancer, weight loss during the first three weeks of treatment (before the onset of

radiation-induced oesophagitis) was shown to be predictive of OS (73). Helpfully, it has been demonstrated that weight loss during chemoradiotherapy for lung cancer takes place independently of both nutritional intake and oesophagitis (85). Therefore, we now understand that weight loss associated with cancer cachexia manifests both in advance of and during cancer treatment (46).

A history of weight loss has been shown repeatedly to be predictive of reduced OS lung cancer (111) (55) (102) (41) (72). Fewer than 10% of patients in the present study were underweight by BMI, despite more than half of patients reporting weight loss. Weight loss was reported by patients in all BMI categories but it was far more common in underweight patients. The mean BMI for both females and males was in the overweight category. Therefore, it is clear that clinicians must look beyond an apparently well-nourished exterior if they are to identify people who are at risk of, or who already have, cancer cachexia. Furthermore, we have to be mindful that patients who were in the higher weight categories may not have noticed their weight loss, or felt that it was not important enough to mention if they remained overweight.

A large study of patients with lung or gastrointestinal cancers revealed that weight loss was independently predictive of reduced survival in patients in all BMI categories, along with low MA and low SMI (55). Obese patients had the longest survival, with patients who were obese with no adverse variables (no weight loss, high MA and high SMI) having a median survival of 36 months. Obese patients with all three adverse variables, including weight loss, had a median survival of just 8.5 months. Thus, weight loss can be important prognostically even in patients who are obese. Weight loss, where reported, was not quantified within the present study, due to this data not being captured routinely. Ultimately, this meant that we could not formally classify patients as cachectic, in line with the consensus definition of cancer cachexia, published in The Lancet in 2011 by Fearon et al, which requires percentage weight loss to be known (46).

In our study, patient-reported weight loss was predictive of OS on univariate analysis but not multivariable analysis. On multivariable analysis it was only muscle density (MA) that remained independently predictive of reduced OS. One hypothesis informed by this finding is that patient-reported weight loss reflected cachexia, but that cachexia was more sensitively detected by CT-based body composition analysis of muscle density. One further hypothesis is that weight loss reflects active (potentially cancer-related) cachexia, and that myosteatosis (as indicated by low MA) may reflect chronic inflammation which may be cancer-related and/or

reflective of other factors such as comorbid illness. However, we do not understand the natural history of myosteatosis, including how long it takes to develop. For the present study, we do not have reliable data on cause of death, which might have helped us to understand whether the reduced survival for people with low MA was associated with a death from cancer or other comorbid conditions. The recorded cause of death for ten patients who had died within 90 days of chemoradiotherapy completion and who had follow-up CT scans available for examination was lung cancer; despite the fact that only 2/10 of these patients had evidence of disease recurrence or progression on CT. Due to a lack of confidence in the validity of death certification data, cause of death using these records was not examined for the wider cohort.

2.4.4 Strengths and limitations of the present study and relevant learning to inform future study.

There were a number of strengths and limitations associated with this study which are important to reflect upon . A second study was planned immediately following the present study, and so understanding the limitations in particular was of interest in case any were likely to be surmountable in the future work.

The study cohort

The study cohort was selected in that all had been deemed to be fit to undergo chemoradiotherapy and all had completed sufficient treatment (i.e. one or more cycles of chemotherapy plus radiotherapy) that they were recorded within the cancer audit database as having undergone chemoradiotherapy. Patients with lung cancer of the appropriate stage, but who were not deemed fit for treatment, were not included in the study. Similarly, patients who were booked to receive chemoradiotherapy, but who did not receive either chemotherapy or radiotherapy for whatever reason were not included. Therefore, we have to accept that we do not know how representative of all patients starting chemoradiotherapy for lung cancer the final cohort is. Furthermore, we do not know whether it might have been possible to identify predictive biomarkers for the adverse outcome of deteriorating in advance of receiving treatment; and if so, whether these might have been identical or different to the variables that predicted adverse outcomes for those who did receive treatment This is of clinical importance because the decision of whether to offer intensive cancer treatment is

often not straightforward, and identifying predictive variables for poor outcomes in the wider population (with technically treatable disease) could ultimately lead to more informed approaches to patient selection. This limitation would not have been possible to overcome for the present study cohort because data about patients who did not receive treatment, or who received incomplete treatment, was not collected by the cancer audit team during 2008-2010; thus these individuals were not identifiable. However, it should be possible to avoid this in future studies by identifying the cohort for study by other means, e.g. selecting patients within a treatment database rather than a cancer audit database. During 2008-2010, no such electronic treatment database existed. t.

The present study examined data for 194 patients who underwent chemoradiotherapy in a single centre, commencing over a three-year period. Chemoradiotherapy is a treatment that is only received by a minority of people with lung cancer and this naturally limited the size of the population that was available for study. One consequence of this was that there were sometimes very small groups with variables or outcomes of interest. This limitation would be possible to overcome by studying a cohort who undergo a more common treatment modality and/or over a longer time period. It is also fair to say that a strength of the present study is that data was sourced from a single treatment centre; it is well-recognised that variation in data definitions between different institutions (e.g. whether 'date of diagnosis' is calculated from the date of diagnostic imaging or the onset of symptoms) can be problematic when data is pooled (112) (113). Certainly, including data from multiple treatment centres has been recognised as a threat to data quality in others' studies in this field of research (82).

The study methods

Retrospective cohort studies offer great potential for learning from existing data, and unlike prospective clinical research, new knowledge can be generated relatively quickly, cheaply and with no patient burden (114). Clinical records typically contain patient data from multiple timepoints, enabling longitudinal follow-up and examination of exposures and outcomes (115). Evidence from population-based data has great potential to inform and influence policy and practice; not least because the patients studied are 'real-world', rather than selectively well for clinical trial participation (116, 117).

However, many limitations are inherent research using routine clinical data, often related to the fact that the data under study was not originally collected for research purposes. Routine healthcare data is observational data, and as such it can reveal associations between variables and outcomes, but it cannot typically infer causation (113). Associations are of great potential interest, and these can be validated with further retrospective, but also prospective, studies.

Electronic health records have been conceptualised as 'an indirect reflection of the true patient state due to the recording process' (113). Data is generated as a result of dynamic interactions and processes between the patient who presents to healthcare services, their clinicians, administrators and data coders. Therefore, understanding healthcare associated administrative processes is fundamentally important in research using routine health data. One strength of the present study is that JB has worked as a clinician in palliative care and oncology, and has a working knowledge of the clinical pathways that patients move through, as well as the data that is generated by each encounter or intervention. This was crucial when data of interest was not obviously available from the intended source, as alternative sources could be examined.

Another major limitation of research using healthcare records is the availability of data of interest; which is a product of not only what data is collected routinely (and its completeness and accuracy) but also where it is recorded. In SE Scotland, electronic cancer treatment records did not exist before the end of 2012. Significant data of interest was available for individuals, but with a great degree of variability; often recorded and stored in a range of different locations, including paper notes. This made automated electronic data extraction within the present study impossible, and manual data extraction patient by patient extremely onerous. The need to examine hard copies of patients' notes, which had to be retrieved from a storage facility and brought to the hospital (with significant time and cost), is one example of a consequence of this. In itself, this did not impact on the quality of the data that was extracted. However, it was not always possible to find the correct piece of paper on which patients' heights and weights are recorded at their first cancer clinic appointment, leading to missing data for some. In practice, 4/194 patients had missing height and/or weight data which meant that their BMI could not be calculated. Given this, an alternative source was considered, in oncology pharmacy, but their records from this time period were not available.

The present study was not a data linkage study; rather a review of individual patient records and extraction and collation of detailed clinical data. The 'patient by patient' approach to data

extraction in the present study, as opposed to the auto-extraction of large-scale data that has become commonplace in research using electronic health records, may have improved the both the completeness and accuracy of the data; where missing data (such as height or weight) was identified, alternative sources within routine records could be sought; where data appeared contradictory in two different sources (e.g. a description of 'no weight loss' in one letter and 'significant weight loss' in another), a pragmatic judgement could be made about which source was most likely to be accurate, and where possible, a third data source could be identified; where data appeared clinically implausible (e.g. a height or weight that was highly atypical, suggesting erroneous recording), alternative data sources could be sought. We do not know how accurately patients' reports of weight loss were and the decision to include this measure at all was pragmatic, given that no objective measure of whether patients were weight losing at diagnosis existed. Several published studies have shown that patient-reported weight loss is associated with adverse outcomes in people with lung cancer (111) (55) (41) (72) (55). It is interesting to note that patients who were underweight by BMI were much more likely to report weight loss than those who were overweight or obese (90% with BMI<20 versus 44% with BMI ≥25). It is possible that overweight patients were less able to detect weight loss, or indeed that their weight loss carried less predictive significance given their remaining nutritional reserves.

The level of missing data in the present study was relatively low. However, data completeness is a concern in research using existing healthcare data, given that (for all sorts of reasons) routine clinical data is often less complete than data collected for primary research purposes (118). A key question for researchers is whether data is 'missing at random' or 'missing not at random' (119). This is important because where data is missing for a systematic reason, observed and missing data is not likely to be similarly distributed, potentially leading to erroneous research findings (120). In the present study, it was very likely that some missing data, such as patient heights and weights, were missing at random. Since all patients were receiving chemoradiotherapy treatment, and would have required heights and weights for the calculation of chemotherapy doses, these would have been available for all at some time. It was the fact that for many patients this was only recorded on paper, and that this piece of paper was not always still in the patients' notes, that led to some missing data. On the other hand, it was clearly the case that follow-up data such as patients' CT scans after chemoradiotherapy completion, relied upon patients being both alive and well enough to attend for a scan. Thus, the 18 patients who did not have follow-up CT scans were not likely to

be representative of the wider population (a 'missing not at random' situation). This was borne out when the follow-up CT scans of patients who died within 90 days of chemoradiotherapy completion were examined; of the 22 patients who died within this timeframe, only ten had CT scans available for examination. The intention of the present study was to undertake a complete analysis of patient data; and exploring methods of imputation for missing data were beyond the scope of the MD. Had there been significant levels of missing data, it would have been necessary to review this decision.

The lack of height and weight data captured within routine electronic records for the patients in the present study led to discussion with the TRAKCare team and an agreement that it should be recorded within TRAKCare going forward. Such data is clearly of interest for a variety reasons, relating both to individual patients and whole populations. Practice has since changed and there is a dedicated location within TRAKCare where height and weight are recorded now as standard. In addition, since the end of 2012, height and weight data has been recorded routinely within the online cancer treatment database ChemoCare for all patients who receive systemic cancer treatment. Thus, this very specific data issue will not be relevant for future study.

CT-based body composition analysis and potential confounders not included in the study

As has already been described (in Methods, section 2.2.6), CT-based body composition in the present study was based on images from the T4 vertebral level. There are very few published studies of body composition analysis utilising T4 images and this limits the extent to which our findings can be related to others'. We did not assume a relationship between muscularity (SMI) derived from T4 images and whole-body muscle mass. Rather, we were interested in the possible significance of SMI and MA (derived from T4 images) in relation to 90 day and OS. We developed our own thresholds for low muscularity (low SMI) and low muscle density (low MA) using an optimal stratification approach. Whilst there are no known reported thresholds for MA derived from T4, Neefjes et al have reported sex-specific thresholds based on a median (IQR) SMI in males of 67 (59-73) and in females of 55 (51-62) (57); reassuringly, these are very similar to the present study's optimal stratification-derived thresholds of 71 (IQR 59-76) in males and 56 (49-61) in females. In the study by Neefjes et al, which examined muscle measures from different cohorts with either T4 or L3 data, L3 muscle mass and cancer-related fatigue was significantly correlated in males (with low SMI being strongly associated with higher levels of fatigue), but this was not the case for females; in fact, the relationship in females was inverse, with a non-significant trend towards higher L3-derived SMI associated with more fatigue. The study's authors hypothesised that hormone-related treatments (for men with prostate cancer and women with breast cancer) may have influenced these findings. Interestingly, in the same study by Neefjes et al, T4 SMI levels were not correlated with cancer-related fatigue in either males or females.

Se-II-Go et al studied 117 males with SCLC and identified a clinically significant threshold for sarcopenia (low SMI) based on a lowest quartile measurement from the T4 CT images of 44 (42). The study examined the significance of both sarcopenia and systemic inflammation in relation to progression-free survival (PFS) and OS. Patients with *both* sarcopenia *and* high NLR had significantly earlier evidence of disease progression and significantly worse OS, with a median OS for this group of only 3.2 months. Interestingly, patients who were sarcopenic with a *low* NLR had comparable PFS and OS to their non-sarcopenia counterparts. The findings reported by Se-II Go et al are consistent with a recent study based on a very different cohort with a significantly longer OS, namely patients undergoing resection of liver metastases with colorectal cancer (56). No patients in the study by van Dijk et al met the criteria for myosteatosis. However, a combination of systemic inflammation (measured by CRP) in

combination with *either* sarcopenia (low SMI) *or* low visceral fat was associated with significantly reduced OS (median 79 months compared to 110 months for patients with none of the three identified adverse factors), whist patients with all three adverse factors had a median OS of 43 months. Thus, as with the study reported by Se-II-Go et al, the combination of adverse body composition and systemic inflammation appears to be key. In the present study, fat levels (either visceral and/or subcutaneous) were not evaluated. This decision, led by JB's MD supervisors, reflected where the research literature and interest were at the time of the study conception in 2013. The Lancet definition of cancer cachexia, published in 2011 by Fearon et al did not include fat measures (46). More recent research, such as the study described above by van Dijk et al has demonstrated that fat may be important in cancer cachexia and its impact (56). Therefore, future studies would ideally incorporate both muscle and fat measures.

We did not capture patients' NLR or other direct measures of systemic inflammation within the present study. Had this data been available, it may have helped to explain the significance of low muscle density (low MA) in relation to OS for our population. It is also possible that the combination of systemic inflammation and sarcopenia (low SMI) would have been associated with adverse outcomes. It will be a priority for future studies to incorporate both body composition analysis and direct measures of systemic inflammation. Cohorts treated at the Edinburgh Cancer Centre after 2012, when electronic cancer treatment records became available, should all have blood measures of systemic inflammation available as standard.

Comorbidity – an unmeasured, albeit not unmeasurable, potential confounder in the present study

Data held within clinical case notes relating to patients' comorbid health conditions was found to be inconsistent and unreliable and were therefore not included in the present study. Every patient who had received chemoradiotherapy had a clinic letter (available electronically) detailing their initial oncology consultation. Within this, comorbid conditions were always commented upon. Typically, this involved conditions (such as heart disease, chronic lung disease) being listed. However, on examining data from triangulating sources for individuals (such as referral letters into oncology or hospital discharge letters following previous admissions) it became clear that there were often major discrepancies between what was recorded by different clinicians. One question which comes up repeatedly in research using

routine clinical data is whether the absence of mention of a condition of interest (e.g. diabetes) can be assumed to mean that the person does not have that condition. In reality, it may in fact mean that the person does have the condition, but does not know it; or that they knew it but did not mention it; or maybe even that the condition was deemed not severe enough to be recorded or perhaps not relevant to the current (here, cancer) diagnosis. Within oncology practice there are no standard approaches for recording comorbid conditions, and insufficient evidence of which conditions might be most relevant to populations with different cancers and the treatments that they may be offered. Furthermore, where they do exist (e.g. in heart failure), grading systems of comorbidity severity are also not used consistently; and we know that they do not exist for many conditions (121). Thus, it is recognised that examining patients' comorbid health status in any systematic way is difficult, even prospectively, and therefore it is not a surprise that examination of routine clinical data in this area is a major challenge. The present study did not ultimately include data relating to comorbidity because of the inconsistencies identified and the impact of this on data quality. Other researchers in this area have mad this same decision (82). For future study this could be overcome by utilising data that has already been coded and extracted (e.g. health conditions recorded within primary and/or secondary care held by ISD), although this would not include disease severity and, as always, it would rely upon the data sources used to inform coding having been accurate and complete. It also requires researcher expertise to handle coded data. These are important areas for consideration in any future study.

Other unmeasured variables

Warner et al identified gross tumour volume and respiratory function as the two independent predictors of mortality within 180 days of chemoradiotherapy treatment for lung cancer (82). Neither of these variables was examined in the present study, highlighting that caution is needed in the interpretation of our findings. For the same reasons, the findings reported by Warner et al should be interpreted with caution given that no data relating to BMI, weight loss, body composition or systemic inflammation was included in their analysis. Ideally studies should include examination of all potential variables of interest.

Outcome data

Data relating to chemoradiotherapy treatment toxicity and side-effects was not recorded electronically for this population. There was variable recording within paper records for individuals, but this was not extractable in any consistent way and for many patients it was missing entirely. Thus, toxicity and side-effect data were not included in the present study. This would have been of particular interest for the patients who died within 30 or 90 days of treatment completion, since is possible that their cancer treatment contributed to their deterioration and death. Death certification records often did not provide details beyond the diagnosis of lung cancer which could have enlightened about the precise aetiology of each patient's deterioration and death and highlighted where treatment-related mortality was possible. Wallington et al described this scenario in their large study of patients who died within 30 days of receiving chemotherapy, but concluded that deaths within this timeframe were evidence enough of non-benefit of treatment, potentially including harm as a result of treatment (16).

In the study of 117 men with SCLC reported by Se-II-Go et al, it was the combination of sarcopenia and a high NLR that was most strongly associated with reduced survival; these same variables were associated with significantly higher rates of early discontinuation of chemotherapy treatment and also a 50% treatment-related mortality rate (42). This compared to a treatment-related mortality rate of 8% in the other patient groups (p<0.001). A broader approach to outcome measure examination is of great interest for two main reasons. Firstly, it provides a more holistic evidence base about what patients might expect of their treatment, including the risks of treatment-related mortality; enabling the value or benefit of cancer treatments to be questioned where they are discontinued early. Secondly, it raises important questions about the mechanisms involved in the adverse outcomes experienced by patients who have unfavourable body composition and/or inflammatory status. For future studies examining ECC cohorts after 2012, electronic recording of cancer treatment toxicity and side-effects should enable a broader range of outcome measures (than simply survival) to be to be examined.

The decision was made to examine mortality within 30 and 90 days of treatment completion, based on the assumption that patients dying within this timeframe were unlikely to have benefited from chemoradiotherapy and/or may have died as a result of treatment toxicity or complications (16). However, one limitation of the 30 and 90-day measures is that they do not account for treatment length; patients who have a very protracted treatment course, perhaps because of significant toxicity, may appear to have lived longer than others who die following an 'on schedule' treatment regime. Warner et al, in their analysis of predictive factors for early mortality in a large population undergoing chemoradiotherapy for lung cancer, used an alternative approach of examining deaths within 180 days of treatment *commencement* (82). This avoids the potential for bias by treatment length, although it does not necessarily give an indication of whether patients died during or following treatment. Thus, both approaches have their limitations. This area requires consideration in relation to further study, and the best approach may depend on population-specific (and treatment-specific) factors.

Limitations summary

Transparency about the present study's limitations was essential to ensure that the findings were interpreted with appropriate caution. However, they were also critical to the planning of the second study that followed. Key learning to take forward to the second study was basic; including the need for optimum data capture, both around variables of interest and outcome measures (including measures beyond survival). An awareness that there may always be some unmeasured (and perhaps even unmeasurable) confounders was also important.

2.4.5 Conclusions

The aim of the present study was to identify predictive factors for early mortality following chemoradiotherapy completion, and for OS. Research questions addressed by this study were:

1. What are the demographic and clinical characteristics of the cohort who received chemoradiotherapy for lung cancer in SE Scotland between 2008 and 2010?
2. Which cachexia-related biomarkers are feasible to collect from routine clinical data for this cohort?

3. Which variables, identifiable at diagnosis and based on routine healthcare data for this cohort, are predictive of early mortality and OS?
4. What might the clinical significance of identified predictive variables for early mortality and OS be?
5. What are the limitations around routine healthcare data for this population how might these inform future research?

The present study cohort was selectively well, with >90% of patients having an ECOG PS of 0/1. This was also reflected in the fact that all had been deemed fit to undergo intensive chemoradiotherapy treatment. Despite this relative homogeneity, there were key factors, present at the point of diagnosis, which translated to significantly poorer outcomes for some patients. These included low BMI and ECOG ≥2 (strongly associated with early mortality after treatment completion) and low muscle attenuation (MA, associated with significantly reduced OS). Arguably all three adverse factors may reflect cancer cachexia, although we were not able to classify patients formally as cachectic or non-cachectic because percentage weight loss data is not routinely collected in cancer care in SE Scotland. Furthermore, a lack of reliably available clinical data relating to systemic inflammation, comorbid illness and potentially a wider range of variables too, meant that we were not able to draw clear conclusions about the aetiology of the key adverse variables or the precise mechanisms involved in the adverse outcomes. However, interpreting the present study's findings in the context of others' research in this area has enabled some gaps in knowledge to be better understood, whilst also informing the second study that followed.

One critically important finding to acknowledge, with great relevance to clinical practice and supported by others' findings, is that patients with cachexia-related adverse factors may not appear cachectic to their clinicians (34) (55). The mean BMI for the present study's population was in the overweight category, and only one in ten patients was underweight according to their BMI. And yet 57% of patients were weight-losing. This finding alone suggests that we should question our current practice. Undertaking CT-based body composition analysis may not be obviously feasible, or even desirable, but there is a clear need to explore broader approaches to identifying 'at risk' patients. The concept of 'hidden cachexia' has been described previously (34) and if we are to identify patients with cachexia that may still be at a treatable stage, a more intelligent approach to clinical assessment is likely to be needed.

We know that true long-term survival is rare in lung cancer, but also that some treatments (including chemoradiotherapy) can offer some patients significantly extended survival. Ultimately, the intention is that research of this kind should inform clinical decision making about the most appropriate treatment choices for patients; supporting better identification of those who are at greatest risk of not benefitting from treatment, and perhaps even coming to harm from treatment; and also identifying patients who are most likely to benefit. It may also be the case that some patients undergoing chemoradiotherapy could benefit from proactive cachexia management in advance or alongside their cancer treatment. However, despite low MA clearly being a predictive factor for reduced OS in the present study, we do not know enough about what low MA signified to be able to recommend that this would be an appropriate means of stratifying patients for cachexia management. Further research is needed.

Chapter 3

Predictive factors for adverse outcomes for a cohort who received palliative chemotherapy for lung cancer in South East Scotland.

Chapter outline

Chapter 3 describes a retrospective cohort study undertaken during 2017-2019, of 397 patients with advanced lung cancer who were booked to receive palliative chemotherapy in SE Scotland between 2013 and 2015.

- The clinical context is described first, with a detailed review of the evidence base for palliative chemotherapy for both NSCLC and SCLC. A discussion of key issues surrounding outcome measures in lung cancer studies is presented, followed by a review of known predictive factors for adverse outcomes in lung cancer.
- Research questions specific to the present study are outlined, relating to the availability and limitations of routine electronic healthcare data for the study cohort; characteristics of the study cohort; predictive factors for outcomes of interest and the clinical implications of the findings.
- Detailed Methods are described, including a comprehensive summary of the data sources and the practical aspects of conducting the study.
- Detailed findings relating to key research questions are presented first. These are followed by an exploratory examination of data for a small sample of patients in order to provide additional context for the observed main findings. A discussion of the present study's findings in relation to the wider literature is provided, followed by a summary of the main strengths and limitations of the study.
- Chapter 3 concludes with a review of the key findings of the present study and consideration of the implications for clinical practice and further study.

3.1 Background

Most lung cancer is already at an advanced stage by the time of diagnosis; almost 50% of UK patients with a new diagnosis of lung cancer during 2012-2014 had stage IV disease (122). In the UK, around 15% of men and 19% of women with stage IV disease are alive one year from diagnosis, compared with 81% of men and 85% of women with stage I disease. (122) Thus, late presentation is a major factor in poor survival.

NSCLC accounts for around 85% of new lung cancer (123) (124) and includes adenocarcinomas, squamous cell and large cell carcinomas. SCLC is much less common, accounting for around 15% of new lung cancer cases in males and 17% in females (125). SCLC is categorised as 'limited disease' or 'extensive disease' on the basis of its stage at diagnosis, and around two-thirds of patients have extensive disease at presentation, with metastatic disease in one or often multiple sites (126). SCLC has a particularly poor survival rate when untreated, with median survival for patients without treatment of 8-12 weeks (127).
The section that follows provides a critical review of the evidence base for systemic chemotherapy for advanced lung cancer. The intention was to provide relevant context for the present study in the following ways: to evidence the rationale for current clinical practice; to highlight the limitations of current evidence including what is understood by 'benefit' in cancer treatment and to make the case for observational research examining real-world outcomes. The evidence base for palliative chemotherapy for advanced NSCLC and extensive SCLC are reviewed in turn.

3.1.1 Palliative chemotherapy as a treatment for advanced lung cancer

Over the last decade, new systemic treatment options have become available to some patients with NSCLC. The development of these drugs, referred to generically as 'targeted therapies', has been made possible by a greater understanding of the genetic and molecular profiles of some NSCLC subtypes (128) (129). The National Institute for Care and Health Excellence (NICE) published an updated Lung Cancer Guideline in 2019, containing clear algorithms for the detailed pathological molecular testing for both squamous and non-squamous lung cancers (81). Whilst these targeted treatments have resulted in significant survival benefits for some patients with NSCLC, palliative chemotherapy remains the mainstay of first-line cancer treatment for stage IV NSCLC and extensive stage SCLC (14) (13). The goal of palliative

chemotherapy in both NSCLC and SCLC is to extend life and/or improve quality of life and symptoms.

3.1.1.1 Palliative chemotherapy for advanced NSCLC

Where targeted treatments are not suitable, current UK cancer guidelines recommend combination chemotherapy for first-line treatment of NSCLC for patients who are of good performance status (130) (81, 130) A Cochrane review of the evidence for palliative chemotherapy for advanced NSCLC, compared to supportive care alone, was published in 2010 (12) The systematic review updated a previous Cochrane review published in 1995 (131) and was based on 16 randomised controlled trials (RCTs) comprising a total of 2714 patients; including seven new trials which had been published since 1995. Key features of the review and findings were as follows:

- All included trials were said to be of good methodological quality.
- 12/16 RCTs were based on platinum-containing chemotherapy (cisplatin in 11/12 and carboplatin in one) and four RCTS were based on single-agent, non-platinum chemotherapy (etoposide, vinorelbine, gemcitabine and paclitaxel).
- A highly statistically significant survival benefit was demonstrated for patients receiving chemotherapy (HR=0.77; 95% CI 0.71 to 0.83, p<0.0001), which equated to an increased survival rate of 9% (29% of people receiving chemotherapy were alive at 12 months compared to 20% of those who did not receive chemotherapy). Median survival increased from 4.5 months to 6 months.
- There was no significant difference in the effect of chemotherapy based on age, gender, disease stage or histological subtype and ECOG PS.
- When compared with the pre-1995 studies, the demographic profile of patients in the post-1995 studies was somewhat different, with a higher median age (66 years post-1995 compared to 61 years pre-1995) and more females (28% compared to 19%).
- QoL-related outcome data was not collected formally. However, 6/7 post-1995 included studies reported on QoL, with the conclusion that QoL was either no worse or was improved for patients who received chemotherapy.

- There was no difference in survival by chemotherapy type, including single-agent versus combination treatment (p=0.40) although the authors caution that this review did not include any direct comparative studies.

A previous meta-analysis published in 1998 compared single-agent chemotherapy with combination treatment and reported a two-fold increase in response rate with combination treatment, although this did not translate to a significant survival benefit (132). There was significantly more toxicity reported with combination chemotherapy and a 3.6 fold increase in treatment-related mortality.

The 2010 Cochrane review of palliative chemotherapy for advanced NSCLC concludes by recommending: *'Therefore, all patients who are fit enough and wish to receive it should be offered chemotherapy.'* The authors go on to propose that no further trials comparing chemotherapy with supportive care alone are needed, and that future research should focus on identifying optimal regimens and treatment duration, and should capture treatment toxicity and side-effects. However, it is important to acknowledge that the two studies informing these conclusions each included one ill-defined treatment arm ('supportive care alone'), and this in itself may warrant further study. This issue is discussed in more detail in the sections that follow.

Optimal duration of palliative chemotherapy for NSCLC

There has long been uncertainty in lung oncology about the value of extended courses of chemotherapy, and a suspicion that this approach may result in additional toxicity with no additional survival or symptomatic benefit (133) (134) (135) (136) (137). A systemic review published in 2009 focused on the optimal duration of first-line chemotherapy for advanced NSCLC and included seven clinical trials comprising a total of 1559 participants (137). All studies tested platinum-containing combination chemotherapy except one. In three studies, the shorter treatment arm was 3 cycles, and in four studies it was 4 cycles. The headline finding from the meta-analysis was that extension of chemotherapy beyond 3 or 4 cycles did not improve OS. Furthermore, haematological toxicities were significantly more frequent with extended treatment. Given the predominance of platinum-containing chemotherapies and the known risk of neuropathy with these agents, the authors had hoped to examine this outcome along with febrile neutropenia. However, a lack of consistency in how these toxicities were assessed between studies meant that data relating to these two outcomes could not be

amalgamated. The authors of this meta-analysis conclude: '*Four cycles of treatment with third-generation doublets can be considered the optimum duration of first-line treatment for advanced NSCLC.'* This has become standard practice in Scotland, as recommended by the Scottish Intercollegiate Guidelines Network in their Lung Cancer Guideline (130).

QoL following palliative chemotherapy in NSCLC

A review of the use of QoL-related outcome measures in clinical trials of NSCLC populations was published in 2014 (15). Fifty-five studies of palliative chemotherapy in advanced NSCLC included QoL as an endpoint. The majority of these studies had been published since 2000, which was said to reflect growing acknowledgement of the importance of QoL for people with advanced lung cancer. A range of validated questionnaires was employed by researchers, often in combination. The most frequently used questionnaire was the EORTC-QLQ (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire), supplemented with validated lung cancer-specific questions (used in 29 studies). Other frequently employed tools included the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and the Lung Cancer Symptom Scale (LCSS). The impact of palliative chemotherapy on quality of life for people with advanced NSCLC was of interest to the study's authors, but there was no description of how this evidence was examined or analysed. Descriptive summaries of the studies' findings suggest that palliative chemotherapy offered improvements in quality of life and/or cancer-related symptoms when compared to best supportive care alone. Mixed results were described for studies comparing platinum-based combination chemotherapy with various combinations of single and combination chemotherapies, most of which also included platinum-based agents. The authors of this review, Mannion et al, concluded that the quality of life measures should be incorporated as a primary endpoint in studies and proposed that this may be helpful in defining meaningful response to treatment. The study described by Mannion et al has some methodological issues of its own, predominantly related to a lack of consistency between its stated aims, methods and the results that are presented. However, the authors have succeeded in bringing this important subject into the spotlight.

Cost-effectiveness of treatment for NSCLC

A cost-effectiveness analysis of palliative chemotherapy for advanced NSCLC versus best supportive care (BSC) was published in 1990 by Jaakkimainen et al (138). The headline of this publication was that BSC was more costly than chemotherapy, and was accompanied by the suggestion that cost should not be seen as a barrier to the recommendation of palliative chemotherapy for advanced NSCLC. This study, whilst now almost 30 years old, continues to be cited in the lung oncology literature, despite multiple areas of methodological concern. The study involved retrospective economic evaluation of data from a Canadian, multi-centre RCT, the results of which had been published two years previously (139). The original RCT included three different treatment arms, two of which comprised different combination chemotherapy regimens: two agents, vindesine and cisplatin (VP) or three agents, cyclophosphamide, adriamycin and cisplatin (CAP). The third arm comprised only BSC, i.e. no chemotherapy. A total of 137 patients were included in the study, 50 of whom received BSC alone. The secondary economic analysis was based solely on health system costs, including chemotherapy and radiotherapy administration, hospitalisation and clinic appointments. Economic data were only available for patients treated in two institutions (a total of 61 patients) because of non-availability of data from the 16 other study sites. Key findings of the economic analysis were that the VP arm was associated with significantly increased survival compared to BSC (median survival 24.7 weeks, compared with 17 weeks, $p \leq 0.05$), but at increased cost; and that CAP chemotherapy was associated with significantly improved median survival compared to BSC (32.6 weeks, compared to 17 weeks, $p \leq 0.01$) and at reduced cost. For both chemotherapy groups, the chemotherapy costs made up less than one-quarter of the total health care costs. The main costs in all three arms related to inpatient hospitalisation. There are several areas of methodological concern within the cost-effectiveness study, including major differences in practice between the two institutions studied (e.g. one cancer centre administered all their CAP chemotherapy as inpatients whilst the other administered all their CAP chemotherapy in outpatient settings). However, the major methodological concern that relates to both the primary RCT and the secondary cost-effectiveness study, is that the BSC arm was not defined or described at any level in terms of the care or treatment that patients received. It is simply conceptualised as the 'no chemotherapy' arm. It is therefore impossible to know whether the patients in this study arm received formal palliative care, or indeed any supportive care at all, whether from their primary care teams or the team that diagnosed their lung cancer. Given the conclusion that BSC is an expensive option, it is critical to understand what it consisted of.

A much more recent economic analysis of health system costs for people with advanced NSCLC in Canada was published in April 2019 (140). The study focused on costs for 24,729 people with unresectable stage III or stage IV non-squamous cell lung cancer in Ontario, diagnosed over a five-year period. The mean cost of health service use per patient was based on a range of expenditures including medications (including chemotherapy, but also other oral medications), cancer clinic attendances, inpatient hospitalisation, emergency department visits, radiotherapy costs. Median survival was one year (IQR 0.3-3.7 years) for the whole cohort, but only 4 months (IQR 2 months to 1 year) for the stage IV cohort. Despite this very short survival, the mean cost of care for the stage IV patients was $69,295 (Canadian dollars). Interestingly, consistent with the study reported by Jaakkimainen, the cost of chemotherapy itself was relatively low, only 6% of total costs for the stage IV cohort. The highest cost resources for the stage IV group were for inpatient admissions, followed by cancer clinic visits and then physician visits. Whilst the mechanics of the Canadian health care system are likely to be very different from cancer care in the UK, it is hard to understand how patients with stage IV disease (with a median survival of 4 months) had, on average per patient, 16.4 clinic visits, 23.3 medical oncologist visits and 106 visits by other, non-cancer, doctors. The authors acknowledged that they could not be certain about whether the identified costs related directly to the diagnosis of NSCLC. Indeed, no data relating to comorbid conditions or cause of death was presented. However, on one level, this may not matter. This study highlights the huge healthcare expenditure associated with a diagnosis of advanced NSCLC and must call into question the value that this care adds to the patients at the heart of the study. The final sentence of the conclusion was: '*The uptake of new and effective systemic therapies will result in new practice patterns and affect both resource utilization and costs.'* This may be accurate, but it was a missed opportunity to question the appropriateness (and impact in every sense) of very high expenditure for this population. It is unclear how generalisable the stated key findings are, but there are certainly questions which transcend populations and healthcare systems around the extent to which healthcare spending is benefitting patients.

3.1.1.2 Palliative chemotherapy for extensive SCLC

A Cochrane review of the evidence for palliative chemotherapy versus BSC in extensive SCLC was published in 2013 (14). This was an update to a previous Cochrane review with the same focus, published in 2003. There had been no new studies of first-line treatment since 2003 and

only two studies of first-line treatment were included in the 2013 review, one published in 1977 and the second in 1982, both by the same researcher, Kokron (141, 142). Both studies focused on treatment with ifosfamide versus BSC, although the later study included a third arm which comprised ifosfamide in combination with another agent, chloroethyl-cyclohexyl-nitrosurea (CCNU). Both studies included males only, under 70 years, with minimal comorbidity and good performance status. A total of 65 patients across the two trials completed study assessments. A lack of primary data availability for the Cochrane reviewers meant that data could not be pooled for the Cochrane 2013 analysis and the two studies' findings are presented separately in the Cochrane review. Kokron's 1977 study demonstrated a survival benefit of 79 days in the chemotherapy group compared to the BSC group. Data were not available to enable a confidence interval to be calculated. In the second study published in 1982, mean survival for patients receiving ifosfamide alone was 78 days longer than for those receiving BSC and 12 days longer than for patients receiving ifosfamide and CCNU. The quality of evidence was said to be *'very low'* for mean survival in these studies and was also low or non-existent for wider outcome measures including disease response, treatment toxicity and QoL. In part, this was due to very limited information being available about the baseline characteristics of the trial populations. The authors of the Cochrane review concluded that a survival advantage of around 80 days had been demonstrated with ifosfamide compared to BSC, with the caveat that the treatment populations had been males only, under 70 years and of very good performance status. Specific mention was given to the lack of evidence relating to poor prognosis populations and the absence of any mention of early deaths due to chemotherapy.

A large number of comparative trials of different chemotherapeutic regimes for extensive SCLC have been published, both pre-dating and since the Cochrane review in 2013. SIGN guidelines are typical of other UK and international guidelines in recommending combination chemotherapy containing one platinum-based drug for patients with extensive SCLC (130). This recommendation was informed by a meta-analysis comparing combination chemotherapy including cisplatin with combination treatment without a platinum-based agent (143). The meta-analysis, which included 19 clinical trials of 4054 patients, concluded that cisplatin-containing combination chemotherapy offered modest improvements in survival at 6 and 12 months, with no increased risk of treatment-related mortality. However, other less severe treatment-related complications including neutropenic sepsis, nephrotoxicity and neuropathy

were reported so variably across 16/19 trials that this data could not be pooled and was not included in the meta-analysis.

A Cochrane review of platinum versus non-platinum-containing chemotherapy was published in 2015 (11). 32 studies were included in the review, of which 18 presented data for patients with extensive disease. Overall, there was no significant difference in survival at 6, 12 and 24 months for the different chemotherapy regimens. However, for patients with extensive disease, there was a small but statistically significant improvement in survival at 6 months for platinum-containing regimens. By 12 months this difference was no longer evident. Platinum-based regimens were associated with higher rates of nausea, vomiting and thrombocytopenia (11).

Median OS for patients with SCLC who receive chemotherapy is consistently found to be between 8 and 12 months (144) (145) (146) (147), although a high proportion of people develop rapidly progressive disease off treatment (144).

A large-scale study analysis of English National Lung Cancer Audit and Hospital Episode Statistics data relating to treatment decisions and survival for people with SCLC was published in 2014 (148). 15,091 patients were included in the study, 55% of whom had extensive SCLC at diagnosis. This percentage is lower than has been reported elsewhere, and may be explained in part by a greater likelihood of missing data for people with more advanced disease; almost 3,000 patients in this study had missing staging data. Median OS for 8,293, people with extensive disease was 4.2 months (IQR 1.1-9.3), varying considerably in line with how many cycles of chemotherapy patients received. It has been reported that around 75% of patients with SCLC complete their chemotherapy as intended (149), although whether this observation of patients in clinical trials translates to clinical practice has been questioned (148). Of 8293 patients with extensive SCLC included in the study by Powell et al, over one-third (n=2891, 34%) did not receive any chemotherapy. Of the 5402 who received some chemotherapy, 1838 (34%) received 3 or fewer cycles. The finding by Powell et al that people who received less chemotherapy had shorter survival is important, but the reasons underlying this are not explained by the study; we do not know if patients had received more chemotherapy whether their survival would have been improved, or whether they were deteriorating fast irrespective of cancer treatment as a result of their cancer and/or other illnesses.

Real-world outcomes in extensive SCLC

A prospective cohort study of 432 patients with extensive SCLC treated with chemotherapy at 87 sites in Germany over a 6-year period was published in early 2019 (144). The aim of this study was to generate real-world data of the SCLC treatment regimens that patients receive in Germany, their PFS and OS and their disease response rates. Outcomes were comparable to those in other reported studies in terms of survival (median OS was 10.7 months for the entire cohort, with slightly longer survival for those who received cisplatin-containing regimes. These patients were typically younger and had a more favourable ECOG PS at diagnosis). No data were reported for patients who did not receive chemotherapy. Disappointingly, despite the prospective nature of the study, no outcome measures relating to symptoms or QoL are reported, nor are any details of treatment-related morbidity or mortality.

Quality of life (QoL)-related outcomes in extensive SCLC

Two studies of first-line chemotherapy were included in the 2013 Cochrane review of chemotherapy versus BSC in extensive SCLC (141) (142) (14). No validated QoL instrument was used in either study. A basic assessment of activity level was undertaken at a single time point at the start of the study. The authors of the Cochrane review, in acknowledging the highly selected populations included in these two studies (all patents were male, <70 years old and were of good ECOG PS), also describe the need for evidence to underpin *'clear and explicit criteria to guide when to stop chemotherapy with the objective of preserving quality of life'* (14). It is clear to see that without future studies incorporating validated QoL measures, such evidence will not be forthcoming.

In the 2015 Cochrane review of platinum versus non-platinum-containing chemotherapy, only 4/32 included studies incorporated QoL measures, although relevant data could not be pooled even for these studies because none reported sufficient data (11). Given that the aim of the review (and therefore of the included studies too) was to compare outcomes related to different chemotherapy regimens, the QoL measures were described in this context. Although no formal analysis was undertaken of the QoL-related findings, there were no obvious differences between regime types and resultant QoL. The authors of this Cochrane review assert that although progressive SCLC is known to be associated with a poorer QoL, it cannot be assumed that chemotherapy that leads to a reduction in cancer burden will improve QoL

(11). The authors conclude by suggesting that the only way in which QoL outcomes will be understood is if more RCTS include relevant measures as standard in their assessments.

Cost-effectiveness of treatment for extensive SCLC

Few studies have examined the cost-effectiveness of systemic treatment for extensive SCLC. There is reasonable evidence that chemotherapy can extend survival for extensive SCLC when compared to BSC (14) and, as has been discussed, chemotherapy is the UK guideline-recommended treatment for extensive SCLC where patients are of good enough performance status and wish for treatment (130) (81). UK lung cancer treatment guidelines are informed by cost-effectiveness data, with some specific mentions of cost-effectiveness of different imaging and treatment possibilities evident (130) (81). However, there is no specific mention of the cost-effectiveness of systemic treatment with chemotherapy for extensive SCLC. Newer targeted therapies are increasingly available for patients with extensive SCLC and there is some hope of improved patient outcomes with these treatments (150)**.** However, their cost-effectiveness is in question and requires further study (151).

3.1.2 The patient perspective – priorities for people living with advanced lung cancer

A descriptive meta-synthesis of what matters to people with advanced lung cancer, published in 2016, highlights a number of areas which are relevant to the present study (152). The study by Salander and Lilliehorn excluded quantitative studies based on tools and measurements, instead seeking to capture original patient perspectives on the aspects of their lives that they felt were most important in the context of their advanced lung cancer. The focus of the meta-synthesis was not emotional experiences, as these had been studied previously. Instead, the authors wished to focus on what was felt to be important to patients in relation to their daily lives. 16 studies were included in the meta-synthesis, comprising 393 patient interviews. The major theme identified within the meta-synthesis, echoed in the key findings of half of the included studies, and described in all of the other included studies, was the wish by patients that they could *'carry on as before'*. This idea was presented thematically by individual included study authors as *'living as usual', 'steadfastly living life', 'carrying on as normal'* and *'striving for pre-illness normality'* (153) (154) (155) (156) (157). Patients in several studies described a phase of despair following the diagnosis, but then striving to return to their usual roles and routines where possible. The view that treatment was '*a prerequisite for staying alive'* was identified by the authors of the meta-synthesis as important, with some evidence that patients could adapt to side-effects of treatment, especially if they were expected. Patients also described being extremely concerned by fatigue, which often hampered their ability to remain active.

The tension between living with uncertainty, but also the discomfort that knowledge of a short prognosis could bring, emerged from several studies as interfering with patients' ability to carry on as normal. Where there was uncertainty around prognosis, this left room for some people of hope of a different future.

Many other interesting findings are discussed in the meta-synthesis, all of which can serve to improve our understanding of the patient perspective in the face of advanced lung cancer. Salander and Lilliehorn conclude their meta-synthesis with these words: *'According to our findings, a "patient-centred consultation" in oncology should defer to the "voice of the real-life world", i.e. it should respect that patients want to have an idea that life carries on, even if they are quite aware that it will soon come to an end.'* (152).

It is noteworthy that very few reported studies of treatments for advanced lung cancer include measures which could be said to reflect patients' ability to carry on as normal. As has already

been described, few studies included in the meta-analyses and systematic reviews which underpin treatment guidelines have incorporated QoL measures; and where measures have been utilised in individual studies, there has typically been too much heterogeneity between studies to pool their findings. Thus, our understanding of the impact of systemic treatment on QoL and function for people with advanced lung cancer is very limited. The area of meaningful outcome measurement in cancer research is addressed in the section that follows (3.1.3).

3.1.3 Outcome measures in cancer research and the opportunities offered by population-based studies

Given that the goal of oncological treatment is to improve the quality and length of life that people with cancer experience, then it is surprising that many outcome measures and study end-points don't reflect this. The 2015 Cochrane review of platinum versus non-platinum-containing chemotherapy is a case in point (11). The primary outcome measure for this review of survival at 6, 12 and 24 months is clear and indisputably meaningful. However, two of the outcome measures relating to tumour response (objective overall response and complete response) are arguably less so. The Cochrane review authors conclude that platinum-based chemotherapy regimens led to significantly higher rates of complete response radiologically, but, critically, that this did not translate to improved survival in the short, intermediate or long term. This same review did not incorporate a meta-analysis of QoL outcomes, as already discussed, because of a lack of data (only 4 studies included any QoL measures), and inconsistently reported data between studies. The 2013 Cochrane review of first-line chemotherapy versus BSC for extensive SCLC, also discussed previously, included no QoL data at all. Thus, important recommendations for practice in advanced lung cancer originate in research that does not necessarily reflect clinically important outcomes or what matters to patients.

The concept of clinical benefit in cancer studies sounds straightforward, but is open to misinterpretation and even misappropriation. Professor Christopher Booth, a medical oncologist and clinical academic based in Ontario, has published extensively on the issue of meaningful outcome measurement in cancer research; in 2009 he asked: '*Clinical benefit in oncology trials: Is this a patient-centred or tumour-centred end-point?*' (158). Booth and his colleagues question the way in which 'clinical benefit' has become an acceptable term to describe objective tumour response, rather than outcomes which would be noticed and experienced in any real way by patients. The authors remind that the term had its origins in the 1990s, with a study of gemcitabine versus fluorouracil chemotherapy for pancreatic cancer (159). In this study, reported by Burris et al in 1997, 'clinical benefit' was clearly and precisely defined, as an improvement in any of pain, performance status or weight, sustained over a four-week period and without any of the same parameters being negative over the same time period (159).

In the 2009 paper, Booth and his colleagues describe having examined 71 trials reported in the Journal of Clinical Oncology between 1997-2008, in which 'clinical benefit' was reported explicitly as an end-point. They found that 51/71 trials (72%) described tumour-centred outcomes under the auspices of clinical benefit, whilst only 20/71 (28%) reported clinical benefit in terms that were patient-centred. 14/71 trials with patient-centred outcomes used the original Burris definition, all of which were in pancreatic cancer populations. Booth and his colleague assert that *'…the use of clinical benefit to refer to objective tumour measurements is not only inconsistent with its original definition, but is also frankly misleading to clinicians, patients and other investigators.'* (158).

In a 2012 commentary piece in the Journal of Clinical Oncology, Booth and Eisenhauer review the origins of progression-free survival (PFS) as a clinical trial end-point (160). The authors highlight that PFS was developed originally as a precisely defined end-point for phase two clinical trials where tumour response was the specific outcome of interest; and caution that its rising use in later phase studies, perhaps because it is readily and objectively measured, should be questioned. Booth and Eisenhauer remind that the radiologically-derived PFS thresholds, whereby a one or two percentage difference in tumour size can result in differing labels (e.g. partial response versus stable disease, or progressive disease versus stable disease) may well not translate to what is experienced by patients. Here again, a definition that had been developed originally with one clear intention has become commonplace in other research scenarios.

In a later publication by Booth and colleagues, also on the subject of PFS, another important issue is brought to the fore as the authors consider how studies reporting PFS as a primary end-point might influence practice (161). PFS is said to have been developed as a measure to answer the question of whether one treatment is superior to another, rather (as is critical in clinical practice) than whether a given treatment should be continued or stopped. This important distinction threatens the external validity of the studies which clinicians typically rely upon to guide their decision-making.

As an extension of Booth's interest in clinically meaningful end-points in clinical trials, he also argues for the need for observational studies which can enlighten on real-world outcomes in diverse populations who are often excluded from clinical trials (116). Here, Booth and Tannock make the case for observational studies to sit alongside RCTs, both of which should be based around outcome measures which are clinically relevant and meaningful. The authors challenge

the conventional methodological hierarchy which places RCTs at the top of the tree, and argue that these distinct methodologies are complementary, each with its place. One key area in which observational studies can enlighten is whether the outcomes demonstrated in RCTs translate to more diverse (often sicker, older and more comorbid), real-world populations.

The applicability of clinical guidelines, and the RCTs of highly selected patient cohorts that they are typically based on, to real-world populations is a concern shared by other researchers (117) (162). In a review of guideline recommended treatment (GRT) in lung cancer, Vinod proposes that population-based studies where actual treatment received can be examined, are critical to understanding how applicable clinical guidelines are in the real world (117). Vinod's review summarises the findings of three population-based studies of GRT in lung cancer, highlighting that, at best, only half of all people with lung cancer receive GRT. Several key areas are examined within this important paper, including many of the factors which are known to reduce the likelihood of patients with lung cancer receiving GRT. These are discussed in some detail, along with evidence from wider studies, in the section that follows (3.1.4).

Bonomi and colleagues propose making lung cancer trials more inclusive, with the aim of their findings being more generalisable to broader populations, but also to enable more patients to potentially benefit from clinical trial participation (162). Key groups highlighted by Bonomi et al are patients with an ECOG PS of 2, those with brain metastases (said to be 13-22% of people at presentation with lung cancer), and those who have had a prior malignancy. Outcomes for these patients are poorly understood because they are not typically eligible for clinical trial participation. This is another area where population-based research can enhance and supplement the evidence from RCTs.

Treatment-related morbidity and mortality is an area of growing focus in cancer research, in part prompted by increasing understanding of the potential harms (alongside the potential gains) that cancer treatments can bring (84) (16) (163). Chemotherapy toxicity is routinely assessed in clinical practice in the NHS using the Common Terminology Criteria for Adverse Events (CTCAE) grading system, which should allow for both individual level and whole population level evaluation of toxicity rates and severity (164). In clinical trials, chemotherapy toxicity is typically recorded and categorised using the CTCAE, or versions of it (165) (166) (167) (149) (168), enabling standardised reporting of toxicity-related outcomes. Where approaches to toxicity assessment are not standardised, data cannot be pooled for the purposes of systemic reviews and meta-analyses, and if analysis is possible, it may be

descriptive rather than quantitative (137). Treatment-related mortality (TRM) represents the most extreme end of treatment toxicity, although its definition is open to interpretation. Se-Il-Go and colleagues, in their study of predictive factors for adverse outcomes in a population with SCLC, define TRM as '*death due to any cause other than disease progression during or within 30 days of the last cycle of first-line treatment.'* (42). Details of precise causes of death may be difficult to establish, even where data is collected prospectively, as there may be clinical uncertainty about the relative contributions of cancer, comorbid conditions and acute illness such as infection. Given these challenges, another more straightforward approach is to classify any death occurring within 30 days of receiving cancer treatment a cause for concern (16). The assumption need not be that cancer treatment has definitely caused the death; rather, as Wallington et al, the authors of a large population-based study of early mortality after systemic anti-cancer treatment (SACT) describe: '*Patients dying within 30 days after beginning treatment with SACT are unlikely to have gained the survival or palliative benefits of the treatment, and in view of the side-effects sometimes caused by SACT, are more likely to have suffered harm.'* Thus, what is a hard measure at a technical level may represent a spectrum of harms by way of both direct harm and non-benefit.

Another facet of treatment-related outcomes, following on from the study by Wallington and colleagues (16) and highlighted by Vinod (117) is the extent to which people receive GRT. A range outcome measures in this area are reported on, including whether patients with a given cancer stage receive GRT (169) (170) (171); whether they require chemotherapy dose reductions (42) (149) (41), dose omissions (149) or delays (41) (40); the total number of cycles received, including early discontinuation (148) (42) (40) (172). There are no standardised approaches to categorising the non-receipt of GRT, but it is clear that there is growing interest in the extent to which patients receive their treatment as intended; and an understanding that where this isn't the case, it may be viewed as an adverse outcome of sorts.

An important question related to the issue of measuring the receipt of GRT, is what the consequences of not receiving GRT may be. There is growing interest in ensuring that people from different backgrounds, including potentially marginalised groups who may be at risk of under-treatment, are accessing the appropriate cancer care (169) (170) (171); behind such studies, the assumption is that there should be equity of access to cancer treatments which may offer significant benefits to patients. For other outcome measures relating to the receipt of treatment (e.g. chemotherapy dose reductions, delays, omissions and early

discontinuation), there is a lack of clarity surrounding their significance in relation to survival or other outcomes. Chemotherapy dose reductions and delays might reasonably be interpreted as surrogates for treatment toxicity, and often are reported as such (40) (41). However, early treatment discontinuation may be the result of any number (or combination of) factors, including: cancer progression and resultant clinical deterioration; exacerbation of a comorbid condition; intercurrent illness such as infection, which may or may not be related to the cancer treatment; cancer treatment toxicity; and patient preference. 'Adverse event' is the commonly-used umbrella term for any number of occurrences, and has been reported in one study of elderly patients with advanced NSCLC as the most common reason for early discontinuation of chemotherapy (172). Unfortunately, the generic and non-specific nature of the term 'adverse event' gives the readers no clues about what informed the decision to discontinue chemotherapy. Understanding the precise cause of treatment-related outcomes within retrospective studies is understandably more difficult than in prospective studies, but it is likely that even in prospective studies, the contributing factors may be complex and inter-dependent, and potentially not amenable to categorisation. Thus, whilst this area is important as it reflects the real world of cancer treatment, openness about what the reported outcome measures might signify appears sensible. Population-based studies offer the opportunity to examine a range of treatment-related outcome measures and to explore the potential significance of early treatment termination, dose reductions and delays on survival and other outcomes.

In 2003, Earle et al published a framework of quality indicators relating to end-of-life cancer care, all of which were theoretically available within medical insurance administrative databases (173). The suite of measures had been developed through an extensive process which included a literature review, focus groups with patients with cancer and their families and a Delphi study. Measures included: the receipt of (or initiation of) chemotherapy near to death; emergency department visits; inpatient hospital admissions; intensive care admissions near to death; late or no access to hospice care; and dying in an acute hospital. Since the measures were first published, they have been validated and utilised in a range of studies, in part to examine trends in the aggressiveness of end-of-life cancer care over time (174) (175). In a population-based study of end-of-life cancer care in Ontario, Canada, Ho at al examined a range of outcomes for 227,161 patients who had a recorded cause of death of cancer between 1994 and 2003, were over 20 years of age at death, had a valid insurance card at death and who did not die within 30 days of their diagnosis (175). The research team developed a

composite measure of aggressive end-of-life care which included the receipt of chemotherapy in the last 14 days of life; more than 1 emergency department admission in the last 30 days of life; more than 1 hospitalisation in the last 30 days of life; and more than one intensive care admission in the last 30 days of life. Almost a quarter of patients (22.4%) experienced one or more of these indicators, with identified risk factors including being male, younger and having significant comorbid conditions. Some significant differences were observed between cancer types in terms of the risk of hospitalisation and the receipt of chemotherapy close to death. Over the ten-year study period, the general trend was of increasing aggressive interventions near the end of life. This study gives a sense of some of the wider interactions between patients and the healthcare system, many of which can be viewed as outcome measures, and which may be possible to capture within UK NHS routine health data.

3.1.4 Predictive factors for adverse outcomes in lung cancer.

Beyond cancer stage, a number of factors, identifiable at diagnosis in patients with lung cancer, are known to be associated with adverse outcomes.

Poor functional status

It is well recognised that poor functional status, most commonly measured by ECOG PS, is associated with reduced survival in lung cancer (69) (70) (41) (71) (72) (73) (176) (177). However, it is also the case that ECOG PS is an imperfect and subjective measure (6), with considerable inter-observer variability (7) (8). It is generally understood that the predictive value of ECOG PS for survival in lung cancer is independent of treatment received, but it is also recognised that patients with a poor ECOG PS are less likely to receive GRT (178).

In clinical practice in the UK, cancer MDT meetings may not hold information that is up to date about the functional status of the patients whose cases are presented. Therefore, ECOG PS routinely assessed de novo when (and if) patients attend an oncology clinic to discuss their treatment options. People who are functionally well (with an ECOG PS of 0 or 1 and no or only minor limitations as a result of their illness/es) are deemed fit for most cancer treatments on this basis. People with an ECOG PS of 2 are commonly described as 'borderline fit' and whether treatment is offered often depends on other factors such as the nature and risks of the treatment, wider patient-related factors such as the presence of specific comorbid conditions or other known risk factors for adverse outcomes (10). There is growing interest in improving lung cancer treatment options for people with an ECOG PS of 2, in acknowledgement that some PS 2 patients can derive significant benefit from treatment (9). However, it has long been the case that such patients are typically excluded from clinical trials (162). Despite ECOG PS being a major deciding factor in clinical decision-making around lung cancer treatment, and despite its well-recognised predictive value, it is also the case that some studies have shown it not to be independently predictive of survival in lung cancer (108) (179) (109) (180) (181). One possible explanation is that there is confounding between ECOG PS and wider variables examined in these studies, such as those relating to systemic inflammation and weight loss. The question of what it is that ECOG PS represents, and where the overlap might be with wider clinical variables, is considered in the Discussion section, 3.4.

Systemic inflammation

The systemic inflammatory response, as measured by a range of laboratory markers, is known to be associated with reduced survival in a range of cancer types including lung cancer (66) (182) (183) (184).

The Glasgow Prognostic Score (GPS), and more recently the modified GPS (mGPS), are validated inflammation-based scores comprising C-reactive protein (CRP) and serum albumin (Alb) (109) (185) (66) (107) (70). CRP synthesis rises sharply as part of an acute inflammatory response (186) and thus, is a measurable indicator of this process. Alb is another acute phase protein, but one whose concentration falls as part of an acute phase response, possibly in part as a consequence of amino acids being diverted to synthesise other acute phase proteins (186). A rising GPS or mGPS score has been shown to independently predict survival in many different populations with incurable lung cancer (185) (109) (185) (187) (107) (70). Furthermore, a high mGPS has been shown to be significantly associated with the receipt of lower levels of chemotherapy, with a study reported by Forrest et al in 2004 revealing that only 9% of patients with a GPS of 1 or 2 received 6 cycles of first-line chemotherapy for advanced NSCLC, compared to 40% of patients with a GPS of 0 (109). However, mGPS scoring relies upon timely, reliable measurement of CRP, which at present is not standard practice in much of the UK or the rest of the world.

The most frequently studied blood-measure of systemic inflammation in advanced lung cancer is the neutrophil-to-lymphocyte ratio (NLR). The frequency with which patients have full blood counts measured has enabled many large-scale studies of the predictive value of NLR to be undertaken. A high NLR at diagnosis, pre-treatment, has been shown repeatedly to be independently predictive of reduced OS in advanced NSCLC and SCLC, in patients receiving a range of systemic treatment regimens (188) (189) (179) (190) (191) (110) (192) (108). The thresholds reported for high/low NLR status are variable between studies of different cancer types, (66), and even within lung cancer studies (189). The most commonly reported NLR threshold in studies of advanced NSCLC is 5 (107), which is consistent with studies of wider cancer groups (66). However, there are several robust studies reported where alternative thresholds were utilised. One study of 325 patients with stage IV NSCLC receiving first-line chemotherapy derived a highly discriminatory cut-point of 3.19 for NLR using receiver operating characteristic (ROC) analysis (189). In the study reported by Liu et al, median OS for patients with an NLR ≥3.19 was 13.1 months, compared to 22.3 months for those with an NLR<

3.19 (p<0.001) (189). Liu et al acknowledge that the lack of a definitive cut-point for NLR, validated in different lung cancer populations, may be limiting the use of NLR in clinical practice.

Interestingly, pre-treatment NLR has not always been found to be predictive of OS in patients with advanced lung cancer (193) (192). In a study of 199 never smokers with advanced adenocarcinoma receiving either gefitinib or standard chemotherapy as first-line treatment, Lee et al found that pre-treatment NLR was not predictive of OS (193). A study reported by Botta and colleagues, of 112 patients with advanced NSCLC receiving either bevacizumab with chemotherapy or chemotherapy alone, found that a pre-treatment high NLR was predictive of reduced PFS and OS in the group who received combination treatment including bevacizumab, but not the 'chemotherapy alone' group (192). There were significant differences in the baseline characteristics of the two cohorts in the study reported by Botta el al, with the combination therapy group on average 10 years older and with significantly higher NLR and absolute neutrophil counts at diagnosis. Thus, we do not know whether the observed differences in predicting treatment response were due to the nature of the different drug regimens, or the baseline patient characteristics.

Hypoalbuminaemia

Serum Alb levels are known to fall as part of the acute inflammatory response, but alongside this, Alb is a recognised marker of nutritional status (107) (61). The interaction between acute inflammation and nutrition is complex, with evidence that systemic inflammation brings both raised energy expenditure and reduced energy intake (194) (34).

A prospective study of 59 patients with advanced NSCLC, all of whom were over the age of 75 and had an ECOG PS of ≥2, identified low serum Alb as a significant independent predictor of poor survival (172). A cut-point of 34 was derived using ROC analysis. Interestingly, survival was equally poor for patients with a serum Alb of <34, regardless of whether they received chemotherapy, despite ECOG PS being significantly worse in the group who did not receive chemotherapy. Hypoalbuminaemia was also associated with a greater chance of discontinuation of chemotherapy after one cycle. The authors conclude that a low serum Alb may be a clinically useful marker to identify elderly patients with a poor ECOG PS who have a very low chance of benefitting from chemotherapy.

In a prospective study of 100 patients with advanced NSCLC, low serum Alb levels were independently associated with a high NLR (168). In this study by Arrieta and colleagues, patients with low serum Alb experienced significantly more chemotherapy toxicity, particularly anaemia.

Weight loss, low body mass index and unfavourable body composition status

Patient-reported weight loss at diagnosis has been shown repeatedly to be associated with reduced survival from lung cancer (33) (195) (41) (55) (59) (196) In a study of 780 patients with NSCLC, SCLC or mesothelioma, Ross et al demonstrated that weight loss at diagnosis was associated with lower levels of chemotherapy receipt for patients with NSCLC and mesothelioma, but that this was not the case for patients with SCLC (41). However, weight loss at diagnosis was associated with reduced OS in all three cancer subtype groups. It is acknowledged that the mechanism underlying weight loss may vary between cancer types and even cancer subtypes, and this may account for some of the observed differences in the study reported by Ross et al, between patients with NSCLC, SCLC and mesothelioma (41). One important question, relevant beyond lung cancer and raised by the authors of a study of weight loss in gastric cancer, is whether weight loss is simply an indicator of patients with poor outcomes, or whether it independently reduces the efficacy of cancer treatment (40).

A study reported by Scott et al in 2002 demonstrated that the magnitude of reported weight loss correlated with CRP (196). It is understood that weight loss signifies active systemic inflammation, but also that this may be caused not just by cancer but by co-existing conditions (55). Martin et al identified that a combination of low muscle attenuation (MA), skeletal muscle index (SMI) and weight loss was associated with reduced survival, in a cohort of 1473 patients that included 229 individuals with incurable lung cancer (55).

A meta-analysis of outcomes for 2583 patients with advanced NSCLC enrolled in clinical trials revealed that median survival was greatest for patients who were in the obese BMI category at diagnosis (197). Median survival fell from 11 months for these patients, to 9.3 months for patients in the overweight BMI category, to 8.6 months for patients with a normal BMI and 7 months for patients in the underweight category (BMI<20). Interestingly, response rates to treatment, as measured by PFS, was greatest in the obese BMI category; although differences in survival were only preserved to 16 months, beyond which time, being overweight was no

longer protective. The authors highlight the need for further research in order to better understand the mechanisms responsible for the observed findings; and propose that such research should incorporate data on a range of lifestyle factors including smoking, and wider health status including comorbidities (197).

BMI did not have predictive value for survival in a study of 919 patients with SCLC reported by Xuan Hong et al (108) However, the single cut-point used of a BMI of <18.5 versus ≥18.5 may have been prohibitive, not least as so few patients (7.9%) were in the low BMI category.

Kimura et al retrospectively categorised 134 patients with advanced NSCLC as having cancer cachexia (CC) or not, with CC patients having either lost >5% of their body weight at diagnosis, or >2% if they had a BMI of <20 (59). Patients with CC at diagnosis had a lower response rate to chemotherapy and a significantly reduced survival time compared to their non-CC counterparts. The authors also undertook CT-based body composition analysis and demonstrated that patients with a higher lumbar skeletal muscle index (LSMI) at diagnosis had significantly improved survival.

Se-Il Go reported a range of survival and treatment-related outcomes for a male-only population with SCLC, in whom they undertook CT-based body composition analysis (42). Chemotherapy dose reduction was significantly more common in patients with sarcopenia, defined as a (T4) SMI in the lowest quartile, although these same patients were no more likely to discontinue chemotherapy early due to toxicity than were non-sarcopenic patients. The co-existence of sarcopenia and a high NLR (with a cut-point of 4), was associated with both significantly higher rates of discontinuation of treatment due to toxicity, as well as a significantly higher incidence of treatment-related mortality (TRM, 50% versus 8% in all other patients, p<0.001). Patients with sarcopenia and a high NLR were also more likely to have a poor ECOG PS at diagnosis (50% versus 15%, p=0.016).

Older age and comorbid illness

Older age has been shown repeatedly to be associated with reduced receipt of chemotherapy for lung cancer (195) (169) (171) (198) (199) (178). There is evidence that older patients with lung cancer can have comparable outcomes to younger patients following surgery, or the receipt of radiotherapy, adjuvant chemotherapy or chemoradiotherapy for inoperable disease (200) (201) (202) (188) (137).However, it has also been demonstrated that older age is more

likely than comorbidity to limit the lung cancer treatment that people receive, despite clear evidence that comorbidity is a far stronger predictor of worse outcomes than is age (169).

The burden of comorbid illness and its impact on the receipt of treatment and outcomes following treatment can be difficult to measure. The Charlson Comorbidity Index (CCI), originally developed to predict one-year mortality for acute hospital inpatients, has been employed in countless studies in cancer populations, including lung cancer (169) (195). However, in recognition of various methodological and practical difficulties with the CCI, lung cancer-specific measures have been developed (176) (203). These appear to perform better than the CCI at identifying patients with lung cancer who are at risk of reduced survival (176) (203) The Simplified Comorbidity Score (SCS), developed by Colinet and colleagues for a population with advanced NSCLC, was independently predictive of OS, along with other variables including ECOG PS (176). The authors suggested that comorbidity may impair survival both directly, but also indirectly, by limiting the cancer treatment that patients receive. Interestingly, age over 70 was associated with reduced survival on univariate analysis but was not independently predictive on multivariable analysis, and Colinet and colleagues suggest that there may be a degree of confounding between age and comorbidity. The CCI was included in the univariate analysis and was associated with reduced survival, but it did not retain its significance in a multivariable model.

Grose et al developed an alternative lung cancer-specific comorbidity score, the Scottish Comorbidity Scoring System (SCSS), for a population of 882 people with all-stage lung cancer diagnosed in four Scottish regions (203). As with the SCS, the SCSS out-performed the CCI in its ability to predict OS. Interestingly, in the study reported by Grose et al, the SCSS was most discriminatory for patients with earlier stage disease; patients with advanced lung cancer had an almost universally poor prognosis, irrespective of their comorbidity burden. The SCSS was developed for prospective completion, and includes not only the presence or absence of comorbid illness, but also score weighting according to the severity of each condition.

Male gender and other unfavourable demographic variables

A retrospective analysis of data from four clinical trials of SCLC revealed that whilst females had significantly higher rates of chemotherapy toxicity than males, their median OS was significantly higher (1.31 years versus 0.91 years, $p < 0.001$) (149). The authors suggest one

possible reason for both the higher rates of toxicity and improved survival is that females typically have a higher proportion of body fat, which could impact on the volume of distribution of chemotherapy such that a higher response to treatment is seen (along with increased toxicity).

A further study of outcomes in patients with SCLC also revealed that males had reduced OS (177). In this study, males with extensive disease and poor performance status had the worst prognosis of all groups.

A retrospective cohort study of 32,711 patients with NSCLC identified a number of demographic factors which reduced the likelihood of patients receiving GRT of various different modalities (170). The receipt of chemotherapy was significantly reduced for patients living in more deprived areas, rural areas, and areas associated with lower levels of education. Reduced survival rates were seen for patients from more deprived areas and with lower levels of education, and the authors suggest that this is likely, at least in part, to be due to the lower levels of treatment receipt.

Predictive factors for adverse outcomes and clinical decision-making in lung cancer

The evidence base for a range of predictive factors for adverse outcomes in lung cancer is growing. However, there remains an important gap between the knowledge that research has generated and decision-making with and about patients and whether lung cancer treatment is in their best interests. It is clear that poor ECOG PS, weight loss, low BMI, systemic inflammation and unfavourable body composition are associated with reduced survival; however, no single or composite measure can reliably enough predict either prognosis or response to treatment that it has yet made it into clinical practice.

3.1.5 Rationale for the cohort under study

The cohort of interest for the present study was patients with advanced lung cancer, with whom a decision had been made to proceed with first-line systemic chemotherapy treatment.

The largest single group of patients presenting with lung cancer in Scotland has stage IV disease, and the mainstay of oncological therapy for these patients is palliative chemotherapy. It was anticipated that over a three-year period, several hundred patients would have received this treatment in SE Scotland, and as such, the cohort for study would be significantly larger than for the chemoradiotherapy study presented in Chapter 2. Survival for patients presenting with advanced disease is typically poor and optimal patient selection is a major challenge, with major differences in survival between patients with stage IV disease receiving identical treatments. Beyond cancer stage, ECOG PS is the main clinical measure which identifies patients as suitable (or not) for treatment. However, it does not reliably identify patients who fare better or worse with palliative chemotherapy. It is also recognised that some patients come to harm as a result of their treatment, either directly, through treatment toxicity and even mortality, or indirectly, through non-benefit.

Routinely collected health data offers the opportunity to study real-world populations and outcomes, and with a move towards electronic health records within the NHS, the availability of routine data for research has never been greater. Thus, a larger cohort receiving a common form of systemic cancer treatment, was chosen for study; for whom the availability of routine clinical data should permit a breadth of variables and outcomes to be investigated.

3.1.6 Study aim and research questions

The aim of the present study was to identify predictive factors for adverse outcomes in a cohort with advanced lung cancer for whom palliative chemotherapy was the agreed treatment plan. Research questions addressed by this study were:

1. What is the availability of routine electronic healthcare data relating to known risk factors for adverse outcomes in the cohort who received palliative chemotherapy for lung cancer commencing 2013-2015 in SE Scotland?
2. What are the demographic and clinical characteristics of the cohort with lung cancer who started first-line palliative chemotherapy in SE Scotland between 2013 and 2015?
3. To what extent did patients with advanced lung cancer treated between 2013 and 2015 in SE Scotland receive guideline-recommended treatment?
4. Which variables, identifiable at diagnosis and based on routine electronic healthcare data, were predictive of failure to complete first-line chemotherapy treatment as intended?
5. Which variables, identifiable at diagnosis and based on routine electronic healthcare data, were predictive of OS?
6. How do the findings of the analyses build on current understanding of the ways in which different patient and/or cancer-related factors lead to adverse outcomes?
7. What were the limitations around routine electronic healthcare data for this cohort how might these inform future research?

3.2 Materials and Methods

3.2.1 Study approvals

Ethical approval was not required for this study. However National Caldicott approval was granted for the collation of existing routine patient data from two neighbouring health boards in SE Scotland (NHS Lothian and NHS Fife). Approval was originally granted in 2014 for the first study (described in Chapter 2, relating to a cohort who received chemoradiotherapy for lung cancer) and an updated request for this study, including more recent data, was approved in 2016 (Appendix F).

3.2.2 Study logistics including information governance

This retrospective cohort study was undertaken during 2017-2019. During a 6-month period from September 2018, JB received assistance from two junior doctors working at The Edinburgh Cancer Centre to complete the routine data collection. Both completed Learnpro modules in Information Governance during this period. JB's GCP, MRC and Learnpro training has been described previously.

3.2.3 Outcomes and exploratory variables

3.2.3.1 Primary and secondary outcomes

The primary outcomes of interest for the present study were:

- **Overall survival**
- **Whether patients received four cycles of chemotherapy**

As has been discussed in 3.1.1, where chemotherapy is the preferred option for patients with advanced NSCLC and SCLC, the current national recommendation is that patients receive 4 cycles of treatment (81) (130). Thus, the intention behind this outcome measure being included was to evaluate the extent to which GRT was received by patients with advanced lung cancer in SE Scotland during 2013-2015; and to explore wider outcomes for patients who began a course of palliative chemotherapy, but who did not complete four cycles as intended.

Several secondary outcome measures were examined, including:

- Delays to first-line chemotherapy treatment
- Dose reductions during first-line treatment
- Number of acute hospital admissions following the cancer diagnosis
- Number of acute hospital inpatient bed days following diagnosis
- Whether patients died in an acute hospital.

The rationale for these broader outcome measures was to capture a more holistic view of the patient experience of advanced lung cancer and treatment with palliative chemotherapy than would be revealed by the two primary outcome measures. Inclusion of these broader measures also enabled the content of routine electronic NHS clinical data sources to be explored, in order to understand the extent to which data of interest was available for research.

A range of exploratory variables were examined in relation to the two primary outcomes. Included variables were significantly informed by the literature on known predictive factors for adverse outcomes in lung cancer (as described in section 3.1.4) and cancer more broadly. They were also influenced by what was known to be available within routine NHS healthcare data. They comprised:

- Demographics: age, gender, socioeconomic deprivation status (Scottish Index of Multiple Deprivation, SIMD)

- Cancer subtype – NSCLC or SCLC
- Functional status: ECOG PS at diagnosis
- Body Mass Index at diagnosis
- CT-derived body composition variables: skeletal muscle index (SMI) and muscle attenuation (MA)
- Blood markers of systemic inflammation: absolute neutrophil count (ANC), absolute lymphocyte count (ALC), platelet count (Plt), serum albumin (Alb), neutrophil-to-lymphocyte ration (NLR), platelet to lymphocyte ratio (PLR). All pre-chemotherapy, at the time of diagnosis

Analysis to identify the most discriminatory thresholds for key variables

An exploratory analysis was undertaken in order to identify the most discriminatory cut-points for key variables in relation to OS. Where clearly established data categories existed and could be utilised (e.g. BMI and ECOG PS, each of which has fixed categories), variables were excluded from the analysis. The variables examined in the present analysis were: ANC, ALC, Plt, Alb, NLR, PLR, SMI and MA.

Established clinical reference ranges existed for ANC, ALC, Plt and Alb, and these were included in the analysis. NHS Fife reference ranges were utilised, as follows:

- ANC: 2-7
- ALC: 1-3
- Plt: 150-410
- Alb: 35-50

Whilst systemic inflammation is typically associated with high ANC, low ALC, high Plt and low Alb, a systematic review of inflammatory biomarkers revealed some evidence that any level outside a defined reference range may have predictive significance; particularly for ALC and Plt, where both high and low levels could be predictive (66). Therefore, this was explored in the present study. In addition to the examination of established clinical reference ranges, an optimal stratification method was employed in order to identify the most discriminatory cut-points in relation to OS. This statistical technique has been reported by other researchers (ref (108) (99) (55) and was employed in the study described in Chapter 2 of this thesis, section 2.2.6, to derive cut-points for SMI and MA.

The NLR and PLR are not utilised in mainstream clinical practice, despite there being good evidence of their prognostic value (66) Therefore, there are no established clinical reference ranges. The meta-analysis of markers of systemic inflammation reported by Dolan et al revealed that the majority of included studies (n=19) had utilised an NLR threshold of 5 (66). Thus, the predictive value of < 5 versus ≥5 was examined in the present analysis. In addition, an optimal stratification-derived threshold for NLR was identified, in order to establish whether 5 was an appropriate cut-point for the present study's cohort. Odds ratios for both the Dolan threshold of 5 and the optimal stratification-derived threshold were reported. In relation to the PLR, Dolan et al described that the 12 included studies in their meta-analysis which reported PLR utilised 11 different PLR thresholds and that one study did not report a threshold. Therefore, no standardised threshold existed and so an optimal stratification-derived threshold alone was developed and utilised in this analysis.

As discussed in section 2.2.6, few studies have reported thresholds for SMI and MA derived from CT scan images from the fourth vertebral level. Optimal stratification-derived thresholds are reported in the preceding chapter for a cohort who underwent chemoradiotherapy for lung cancer. However, it was not known whether the chemoradiotherapy cohort and the palliative chemotherapy cohort in the present study would have comparable SMI and MA, or whether the same thresholds would be valid. Therefore, cohort-specific thresholds were derived for SMI and MA using optimal stratification in the present study.

Thus, the exploratory analysis resulted in the identification of optimal thresholds for key variables in relation to OS for the purposes of the stepwise analysis that followed.

3.2.4 The index dataset and identifying the study cohort

The cohort for study was identified within the online chemotherapy clinical database, ChemoCare. Patients with lung cancer in SE Scotland had their chemotherapy treatment managed within ChemoCare from the end of 2012. Beyond this time, all patients who received chemotherapy for lung cancer had their primary treatment-related encounters booked and recorded within the ChemoCare database. All patients with stage IV NSCLC or extensive SCLC who started first-line palliative chemotherapy between January 1st 2013 and December 31st 2015 in either Edinburgh or Fife were included in the study.

The decision to identify patients within ChemoCare rather than via the SE Scotland Cancer Network (SCAN) audit database was informed by the preceding study of a cohort who received chemoradiotherapy for lung cancer (described in Chapter 2). It was of interest to capture not only patients who actually received chemotherapy, but also those for whom the plan had been chemotherapy, but who, for whatever reason, did not receive this treatment. This level of detail would not be captured within SCAN audit data. Furthermore, whilst SCAN audit data was known to be relatively complete, the reliability of ChemoCare to identify *all* patients who were booked for chemotherapy was anticipated to be 100%, since patients could not be booked for chemotherapy during the study period by any other means.

For the duration of the data collection period, JB had 'read only' access to ChemoCare, via a 'book reporting' function, which allowed visualisation of patients' appointments, encounters and all clinical information which related to their chemotherapy treatment. Following Caldicott approval for the study, the ChemoCare data manager provided a minimum dataset for every patient with advanced lung cancer who was booked to commence first-line palliative chemotherapy during the designated study period. The data set provided comprised:

- CHI number
- Patient name
- Postcode
- Cancer histology and stage
- Date of first, first-line chemotherapy treatment appointment

This minimum dataset for patients was stored in an Excel spreadsheet which was sent via secure email from the ChemoCare data manager to JB. Thereafter, it was stored in a password-protected drive within the secure NHS Lothian network. A more in-depth range of data was

collected manually from ChemoCare, patient by patient, predominantly by JB, but latterly also by two junior doctors in oncology. Data was linked to several other clinical and administrative datasets and this is described in the sections that follow.

The only two exclusion criteria were:

- A diagnosis of mesothelioma
- Patients who received systemic cancer treatment other than chemotherapy, either first-line or at a later date

Basic clinical data was collected for these patients who were identified through the initial ChemoCare search by the database manager, as it was agreed that it would be of interest to explore their outcomes at a later date, beyond the MD studies.

Follow-up data was collected for all patients until a censor date of March 21st 2018.

3.2.5 Data extraction and collation

Following the receipt of the Excel spreadsheet containing details of the study cohort and basic treatment-related data (described in 3.2.4), JB extracted data for each patient from multiple different data sources. The first stage of this involved extended data collection from within ChemoCare. Details of the different data extracted from each source are presented in Table 3.1

Table 3.1 Summary of data sources and data fields of interest within each source

Data source	Data field/s
ChemoCare	• Height and weight at first chemotherapy treatment • ECOG PS at first treatment • Date of pre-first treatment bloods • Blood test results[a] • Total number of cycles of first-line chemotherapy received • If subsequent lines of chemotherapy received ○ If so, how many lines and cycles • Chemotherapy dose reductions (during first-line treatment) • Delays to planned chemotherapy cycles (first-line)[b]
TrakCare (electronic patient record in NHS Lothian)	• Gender • Pre-cycle 1 blood test results • Number of acute hospital admissions following diagnosis[c] ○ Length of stay for each admission • Date of death • Place of death
Clinical Portal (electronic patient record in NHS Fife)	• Gender • Pre-cycle 1 blood test results • Number of acute hospital admissions following diagnosis ○ Length of stay for each admission • Date of death • Place of death
Online radiology system (Picture Archiving and Communication System, PACS)	• Diagnostic CT scan date ○ Single slice image of CT from this scan, for body composition analysis • Follow-up CT scan date

[a]Details of blood parameters are described below
[b]If 'bed/chair availability' was cited as the reason, the delay was not counted
[c]Admissions were counted up until death or a censor date of March 21st 2018

ChemoCare

ChemoCare data was extracted solely from within a 'book reporting' view, in line with the read only access that JB had. Data in some domains was not in the required format, or lacked important details. One example was that the dates on which weights had been recorded were often missing. This necessitated the ChemoCare manager working with a data programmer in order to rectify the problem within the database before data could be extracted.

Data relating to chemotherapy toxicity was recorded for every patient, but inconsistently, and only variably accessible within the book reporting view. Thus, the decision was made to collect data relating to dose reductions or treatment delays, as these were reliably and consistently recorded, visible within the book reporting view. Dose reductions were easily visible with changes in the total amount of drug/s prescribed between cycles. Where patients were receiving combination treatment and both drugs were reduced between one cycle and the next, this was counted as one reduction. Where one or two drugs were reduced between two cycles, and the same or a different drug was reduced between a subsequent two cycles, this counted as two reductions. Reasons for chemotherapy cycle delay were various, but all were included and counted apart from where the reason had obviously been a resource issue.

Data relating to chemotherapy regimen type was visible, but changes were so frequent within each patient's treatment cycle, that recording the data in any consistent way was not possible. Therefore, this data was not included.

The dates when patients had their pre-treatment bloods taken were always visible within ChemoCare. However, it was commonly the case that only some blood test results were visible. Therefore, for most patients, blood test results were located within TrakCare or the Clinical Portal. Blood test results extracted for each patient comprised the following indices: ANC, ALC, Plt, Alb

TrakCare (electronic patient record in NHS Lothian) and Clinical Portal (electronic patient record in NHS Fife)

Blood test results were easily located within TrakCare or the Clinical Portal where they were missing within ChemoCare.

Hospital admissions were relatively straightforward to identify, with dates of admission and discharge which allowed a length of stay to be calculated at a later date. Reasons for admission and treatments were received during admissions were recorded too variably and qualitatively for them to be extractable in any manageable way. Therefore, this level of detail was not included.

Dates of death were extracted for all patients who had died by the study censor date of March 21st 2018. Anyone who had died within an acute hospital was identifiable, but where place of death was in the community, a community hospital or a hospice, this was often not visible.

The intention was to collect patient-reported weight loss around the time of diagnosis, where described in clinic letters or patient assessments. However, this was so inconsistently recorded that this data was not included.

As with the previous study of patients who received chemoradiotherapy, the intention at the outset was to collect detailed information about individuals' comorbid conditions. However, it became apparent that there were major issues of quality with this data, with contradicting information between data sources. And no way to verify the information. Therefore, data relating to comorbid conditions was not collected.

Online radiology system (Picture Archiving and Communication System, PACS)

Two CT scan dates were identified within PACS and were recorded for each patient. The first date was for the nearest CT scan to the date of the lung cancer MDT meeting where the patient's diagnosis was made. Diagnostic CT scans were viewed within PACS and a single image of a single slice at the level of the fourth thoracic vertebra (T4) was downloaded for each patient. This was later utilised for body composition analysis, see section 3.2.6.
The second CT scan date collected related to the post-treatment follow-up CT scan, usually after two cycles of chemotherapy. Follow-up CT scan images were examined by a specialist thoracic radiologist, Dr Alan Simms, for a sample of patients, in order to assess disease response to treatment. The exploratory study sample included patients with the highest 20% neutrophil to lymphocyte ration (NLR) and the lowest 20% NLR, within the wider study cohort. The decision to select a patient sample for CT scan analysis based on their pre-treatment NLR was informed by the literature which demonstrated the predictive value of baseline NLR for OS in advanced lung cancer (188) (189) (179) (190) (191) (110) (192) (108). The intention was to

explore whether NLR status at baseline was correlated with disease response as measured on follow-up CT imaging. Follow-up CT scan images for the combined sample of 180 patients were evaluated according to RECIST criteria, with the categories of complete response, partial response, stable disease or progressive disease allocated on the basis of detailed measurements of the primary cancer and metastases (204).

3.2.6 Body composition analysis

CT-based body composition analysis was undertaken in exactly the same way for the present study cohort as had been for the previous study (described in Chapter 2, section 2.2.6). Cohort- and gender-specific thresholds for both SMI and MA (continuous covariates) were derived in relation to OS. Optimal stratification was conducted using SAS software, as previously described.
Whole body muscle mass (muscularity) was reported as the skeletal muscle index (SMI) and muscle density was reported as muscle attenuation (MA).

3.2.7 Derived data – variables and outcome measures

Some variable and outcome data was already in its requisite format on extraction from its source, but other measures were derived from the raw data. Examples of these included age at first treatment; total number of acute hospital inpatient bed days and OS. For the purposes of the present study, the date of diagnosis was taken as the date of first intended chemotherapy dose.

Patients' postcodes were linked to the Scottish Government's Index of Multiple Deprivation (SIMD) tool, in order to categorise patients into quintiles of deprivation. This was in order that deprivation status could be tested as a predictive variable for the primary outcome measures.

3.2.8 Statistical analysis

Descriptive statistics, logistic regression and survival analysis were conducted as reported in Chapter 2.

A range of alternative thresholds for various clinical factors were examined, including the thresholds used in NHS Fife, those reported in a large meta-analysis by Dolan et al (66), and

those that were created from the optimal stratification. However, as these new thresholds have yet to be tested on an uninvolved dataset, for the examination of the primary outcomes (OS and failure to complete at least 4 cycles of chemotherapy), the analysis was restricted to those limits available in Fife, unless there were no pre-existing thresholds. In this case, the optimal stratification thresholds were used (MA, SMI, NLR and PLR).

As there were a large number of potentially significant variables, a stepwise regression method was used for both primary analyses. This involved a series of automated steps, where the statistical software works selected the most significant variable and included that in the model, then selected the next most significant variable, and so on, until there were no further significant contributors to the model. Four potential models were explored:

1) Demographic, cancer type and blood variables alone
2) Demographic, cancer type and blood variables, plus MA and/or SMI
3) Demographic, cancer type and blood variables, plus ECOG PS
4) Demographic, cancer type and blood variables, plus MA and/or SMI, plus ECOG PS

In order to be able to directly compare these models, only patients who had complete data for all these variables were included in the modelling process.

From these models, scoring systems were created by comparing the relative sizes of the parameter estimates, and assigning reasonable scores. For example, if a model contained three variables with similar estimates and one variable whose estimate was approximate twice that of the others, three variables were ascribed a score of 1 and one was ascribed a score of 2. This compound score gave a simple indication of the probability of survival or of not receiving 4 or more cycles of chemotherapy based on the presence of one or more unfavourable variables.

In addition to the primary outcomes, the number and duration of acute hospital stays were also examined. As these were likely to be influenced by the survival time (a short survival means less time available in which to go to hospital), a Poisson model was used with an offset of the log of the survival time.

3.3 Results

3.3.1 The cohort under study

473 people with lung cancer were registered within ChemoCare to begin first-line palliative chemotherapy between January 1st 2013 and December 31st 2015 in Edinburgh or Fife. 30 patients with a diagnosis of mesothelioma and 46 patients for whom first-line treatment or a subsequent line of treatment included a targeted therapy were excluded. Therefore, the study cohort included 397 patients, 259 with stage IV NSCLC and 138 with extensive SCLC. Baseline demographic and clinical characteristics of the study cohort are presented in Table 3.2.

Table 3.2 Demographic and clinical characteristics at diagnosis of 397 patients with advanced lung cancer who were booked to receive first-line palliative chemotherapy between 2013-2015 in Edinburgh or Fife.

	Overall n=397	**NSCLC n=259**	**SCLC n=138**	***p*-value** (NSCLC vs SCLC)
Age				
Median (IQR)	65 (58-70)	64 (58-70)	67 (60-71)	0.031
Gender				
Female	185 (47%)	115 (44%)	70 (51%)	0.229
Male	212 (53%)	144 (56%)	68 (49%)	
SIMD[a]				
1= most deprived	75 (19%)	49 (20%)	26 (19%)	
2	110 (28%)	65 (26%)	45 (33%)	
3	70 (18%)	46 (18%)	24 (18%)	0.523
4	65 (17%)	47 (19%)	18 (13%)	
5	67 (17%)	43 (17%)	24 (18%)	
ECOG PS[b]				
0	28 (7%)	17 (7%)	11 (8%)	
1	278 (70%)	210 (81%)	68 (50%)	
2	65 (16%)	30 (12%)	35 (26%)	<0.001
3	24 (6%)	2 (0.8%)	22 (16%)	
4	1 (0.3%)	0 (0%)	1 (0.8%)	

[a] SIMD data missing for 10/397 patients
[b]ECOG PS data missing for 1/397 patients

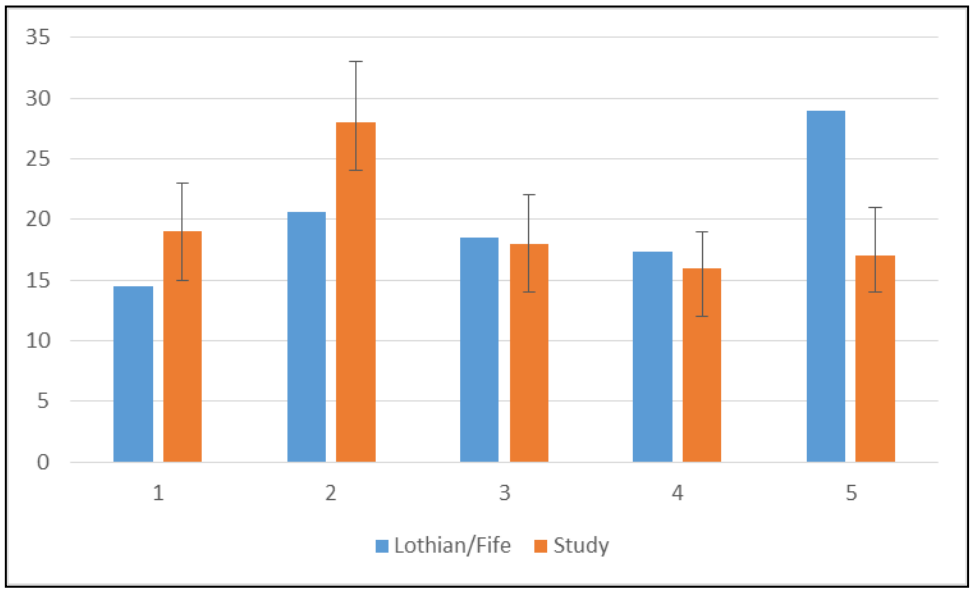
Almost two-thirds of patients (65%) had NSCLC. The majority of patients were of good performance status (ECOG PS <2), though a very low proportion were of the best ECOG PS, 0, indicating that almost all patients had some functional limitations. There were a higher proportion of patients ECOG PS ≥2 in the SCLC cohort (43%) than in the NSCLC cohort (13%).

The deprivation status of the study cohort in comparison to the general population within NHS Lothian and NHS Fife Health Board areas is presented in Table 3.3. There was a greater proportion of patients from more deprived geographical areas in the study cohort, and a smaller proportion from less deprived areas, as compared to the general population.

Table 3.3. A comparison of the deprivation status of the study cohort compared to the Lothian and Fife Health Board population in general.

SIMD quintile	Lothian and Fife actual population	Lothian and Fife actual percentage	Study cohort percentage (95% CI)
1 (most deprived)	178,017	14.52	19 (15-23)
2	252,127	20.57	28 (23-32)
3	226,716	18.5	18 (14-22)
4	212,926	17.37	16 (13-20)
5	355,564	29	17 (13-20)

Figure 3.1 A bar chart representing the relative proportions of people in each SIMD quintile, in the study cohort (red) and the general population in Lothian and Fife (blue), with 95% CI error bars



Data relating to BMI, CT-derived body composition and a range of systemic inflammatory markers are presented in Tables 3.4a and 3.4b. Data is split by both gender (3.3a) and lung cancer subtype (3.3b).

Table 3.4a Baseline BMI, CT-based body composition and systemic inflammatory status of the study cohort, by gender

	Overall n= 397		*p*-value (F vs M)
	Female	**Male**	
BMI[a]			
Mean (SD)	26.1 (6.2)	25.8 (4.4)	0.656
Underweight (<20)	26 (14%)	19 (9%)	
Normal (20-24.9)	62 (34%)	78 (37%)	0.083
Overweight (25-29.9)	56 (30%)	81 (38%)	
Obese (≥30)	41 (22%)	33 (16%)	
Muscle attenuation (MA)[b]			
Median (IQR)	37.6 (32.5-42.5)	38.2 (34.8-42.7)	0.130
Skeletal Muscle Index (SMI)[c]			
Median (IQR)	52.8 (49.7-58.4)	65.0 (58.1-72.7)	<0.001
Absolute neutrophil count (ANC)			
Median (IQR)	7.4 (5.7-11.0)	7.6 (5.2-10.2)	0.125
Absolute lymphocyte count (ALC)			
Median (IQR)	1.53 (1.03-2.10)	1.50 (1.08-2.13)	0.805
Platelet count[d]			
Median (IQR)	332 (264-404)	309 (230-395)	0.030
Albumin level[e]			
Median (IQR)	34 (30-37)	34 (30-37)	0.715
NLR			
Median (IQR)	4.90 (3.30-8.12	4.56 (2.98-8.12)	0.229
PLR			
Median (IQR)	214.5 (155.9-323.0)	206.8 (130.5-313.2)	0.252

[a] BMI missing for 1 patient with SCLC

[b]MA data missing for 14/259 patients with NSCLC and 8/138 patients with SCLC

[c]SMI data missing for 20/259 patients with NSCLC and 13/138 patients with SCLC

[d] Platelet count missing for 1 patient with SCLC

[e]Albumin level missing for 2/259 patients with NSCLC and 1 patient with SCLC

Table 3.4b Baseline BMI, CT-based body composition and systemic inflammatory status of the study cohort, by cancer type

	NSCLC n=259	SCLC n=138	*p*-value (NSCLC vs SCLC)
BMI[a]			
Mean (SD)	25.6 (4.8)	26.7 (6.0)	0.148
Underweight (<20)	28 (11%)	17 (12%)	
Normal (20-24.9)	97 (38%)	43 (31%)	0.189
Overweight (25-29.9)	93 (36%)	44 (32%)	
Obese (≥30)	41 (16%)	33 (24%)	
Muscle attenuation (MA)[b]			
Median (IQR)	39.0 (33.9-43.1)	36.7 (33.0-41.1)	0.010
Skeletal Muscle Index (SMI)[c]			
Median (IQR)	59.2 (51.9-67.2)	58.8 (52.0-67.1)	0.969
Absolute neutrophil count (ANC)			
Median (IQR)	7.14 (5.32-10.59)	7.54 (5.92-10.79)	0.293
Absolute lymphocyte count (ALC)			
Median (IQR)	1.53 (1.05-2.09)	1.44 (1.07-2.22)	0.999
Platelet count[d]			
Median (IQR)	332 (251-401)	306 (247-384)	0.128
Albumin level[e]			
Median (IQR)	34 (30-37)	34 (30-37)	0.944
NLR			
Median (IQR)	4.56 (3.00-8.71)	4.88 (3.48-8.47)	0.418
PLR			
Median (IQR)	212.8 (147.7-325.1)	210.2 (135.1-306.0)	0.483

Mean BMI was in the overweight category for females, males, those with NSCLC and those with SCLC. 11% of patients overall were in the underweight category, with a BMI <20.

Muscle attenuation (MA) was comparable between the genders, though it was significantly lower in the SCLC group. SMI did not differ appreciably between NSCLC/SCLC, but males had higher mean and median SMI than females.

Median ANC was above the normal range across all groups, and median Alb levels were below the normal range in all groups. Median ALC and Plt were within the normal ranges.

3.3.2 Outcome data

A range of outcome data is presented in Table 3.5. This includes details of the number of first-line chemotherapy cycles received; chemotherapy dose reductions or treatment delays; the number of acute hospital admissions and acute inpatient bed days between first treatment date and death; early deaths (within 30 or 90 days of the intended first treatment date); OS; place of death.

Table 3.5 Outcome data relating to chemotherapy treatment, acute hospitalisations, early mortality, overall survival and place of death.

	Overall n=397	NSCLC n=259	SCLC n=138	*p*-value (NSCLC vs SCLC)
No. of first-line chemotherapy cycles received				
0	21 (5%)	17 (7%)	4 (3%)	0.036
1	69 (17%)	49 (19%)	20 (15%)	
2	66 (17%)	50 (19%)	16 (12%)	
3	38 (10%)	23 (9%)	15 (11%)	
4+	203 (51%)	120 (47%)	83 (60%)	
Any treatment delays				
Yes	39 (10%)	28 (11%)	11 (8%)	0.365
No	358 (90%)	231 (89%)	127 (92%)	
Any dose reductions				
Yes	160 (40%)	92 (36%)	68 (49%)	0.008
No	237 (60%)	167 (65%)	70 (51%)	
No. of acute hospital admissions following diagnosis				
Median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	0.7136
Total acute hospital inpatient bed days following diagnosis				
Median (IQR)	7 (0-20)	7 (0-21)	8.5 (0-20)	0.8775
Deaths within 30 days of treatment start date				
No. (%)	27 (7%)	17 (7%)	10 (7%)	0.812
Deaths within 90 days of treatment start date				
No. (%)	83 (21%)	54 (21%)	29 (21%)	0.997
No. of people alive 12 months after treatment start date				
No. (%)	104 (26%)	67 (26%)	37 (27%)	0.431
Overall survival (days)				
Median (95% CI)	215 (191-239)	206 (177-235)	237 (203-271)	0.706
Place of death (No. and %)				
Acute hospital	94/385 (24%)	61 /250(24%)	33 /135 (24%)	0.997
Other e.g. home/ hospice	289/385 (76%)	189/250 (76%)	101/135 (76%)	
Alive on 21/03/2018	12	9	3	

Details of chemotherapy regimens received is not presented and this is discussed in the limitations section within the Discussion section, 3.4.

21/397 patients died without receiving any chemotherapy, despite having been booked for their first treatment on ChemoCare. 3/21 patients who received no chemotherapy died before the intended first treatment date. 18/21 died following the intended treatment date, but having not had treatment.

194/397 (49%) patients received 3 or fewer cycles of first-line chemotherapy, where the intention was 4 or more. Significantly more patients with SCLC received 4 or more cycles of chemotherapy than did the NSCLC Group (60% for SCLC group versus 46% for NSCLC group, p=0.009).

A minority of patients (10% overall) experienced delays to their planned treatment course, for reasons other than bed or chair availability within the cancer centre. 40% of patients overall required chemotherapy dose reductions. This was more common for people with SCLC (49%) than for those with NSCLC (36%), p=0.008.

The median number of acute hospital admissions per patient between diagnosis and death was one, with the median number of days spent as acute hospital inpatients by each patient during the same period, seven.

7% patients overall died within 30 days of their intended treatment start date and 21% within 90 days of this date. The proportion of people with NSCLC or SCLC was identical for both of these early mortality outcomes.

Median OS for the whole cohort of 397 patients was 215 days (95% CI 191-239) from the intended first treatment date. For patients with NSCLC, median survival was 237 days (203-271) and for those with SCLC it was 206 days (177-235). This difference was not statistically significant, p=0.71. Median OS for females was 241 days (200-281) and for males it was 209 days (186-232). This difference was not statistically significant (p=0.176).

Outcomes stratified by whether patients received 4 cycles of chemotherapy

Table 3.6 presents outcome data for two discrete patient groups, those who received <4 cycles of first-line chemotherapy and those who received 4 or more.

Table 3.6 Outcome data detailing patients who went on to receive second-line treatment, hospitalisation, overall survival and place of death data, stratified by the total number of first-line chemotherapy cycles received.

	Received <4 cycles first-line chemotherapy	**Received 4 or more cycles of first-line chemotherapy**	***p*-value** (<4 versus ≥4)
Patients who went on to receive second-line chemotherapy No. (%)	13/194 (7%)	44/203 (22%)	<0.0001
Total number of acute hospital admissions following diagnosis Median (IQR)	1 (0-2)	2 (0-3)	0.07
Total number of acute hospital inpatient bed days following diagnosis Median (IQR)	8.5 (0-21)	7 (0-20)	0.314
Rate of acute hospital admissions following diagnosis, per year Mean (95% CI)	2.9 (2.6-3.3)	1.6 (1.5-1.8)	<0.0001
Rate of acute hospital inpatient bed days following diagnosis, per year Mean (95% CI)	28.6 (27.8-30.0)	10.9 (10.2-11.0)	<0.0001
Overall survival (days) Median (95% CI)	112.0 (96.7-127.3)	307 (190.8-239.2)	<0.0001
Place of death (No. and %)[a,b]			
Acute hospital	46/136 (34%)	48/147 (33%)	0.835
Other e.g home/ hospice	90/136 (66%)	99/147 (67%)	

[a]Place of death excluding 12 people who were still alive at 21/03/2018 (10 people who completed ≥4 cycles of treatment and 2 people who completed < 4 cycles of treatment)
[b]Place of death is unknown for 56/192 deceased patients who completed <4 cycles treatment and 46/193 deceased patients who completed ≥4 cycles of treatment

13/194 (7%) patients who received <4 cycles of first-line chemotherapy went on to receive second-line treatment. This compares to 44/203 (22%) of the patients who received 4 or more cycles of first-line chemotherapy, $p<0.0001$.

The 13 patients who received <4 cycles of first-line chemotherapy, but who went on to receive second-line chemotherapy, had a median OS of 398 days (95% CI 373-423). This compares to a median OS of 99 days (83-115) for the 178/194 patients who received <4 cycles of first-line treatment and who did not go on to receive second-line chemotherapy, $p<0.001$.

The patient cohort who received < 4 cycles of chemotherapy had a comparable number of acute hospital admissions and acute bed days to their counterparts who received 4 or more cycles of chemotherapy. However, the <4 cycles cohort spent a significantly higher proportion of their survival time in the acute hospital than did the cohort who completed 4 or more cycles of treatment.

Median OS for the cohort who received <4 cycles of first-line chemotherapy was 112 days (95% CI 96.7-127.3). This compares to 307 days (190.8-239.2) for patients who completed 4 or more cycles. This difference was highly statistically significant, p <0.0001.

The cohort who completed <4 cycles chemotherapy was no more likely to die in the acute hospital than those patients who received 4 or more cycles of treatment (Chi-squared test, $p=0.835$)

3.3.3 Exploratory analysis of optimal thresholds for key variables in relation to overall survival.

Table 3.7 presents a range of variables and details their individual predictive value for OS at different thresholds; these are reported as variable- and threshold-specific odds ratios (OR).

Table 3.7 Hazard ratios (HR) for overall survival for a range of key variables at different thresholds

		Univariate HR (95% CI)	*p*-value
Blood markers of systemic inflammation			
Absolute neutrophil count (optimal[a], bad>=6.53)		1.73 (1.41, 2.13)	<0.0001
Absolute neutrophil count (Fife[b], bad ≥7)		1.62 (1.33, 1.99)	<0.0001
Absolute neutrophil count (Fife, bad outwith 2-7)		1.61 (1.31, 1.98)	<0.0001
Absolute neutrophil count (Fife, good 2-7)	Below 2 Above 7	1.10 (0.41, 2.97) 1.63 (1.32, 1.99)	0.8518 <0.0001
Absolute lymphocyte count (optimal, bad<1.61)		1.38 (1.13, 1.69)	0.019
Absolute lymphocyte count (Fife, bad<1)		1.58 (1.24, 2.02)	0.0002
Absolute lymphocyte count (Fife, bad outwith 1-3)		1.28 (1.03, 1.60)	0.0295
Absolute lymphocyte count (Fife, good 1-3)	Below 1 Above 3	1.55 (1.21, 1.98) 0.78 (0.52, 1.21)	0.0004 0.2806
Platelet count (optimal, bad>=329)		1.29 1.05, 1.58)	0.0137
Platelet count (Fife, bad outwith 150-410)		1.36 (1.06, 1.73)	0.0140
Platelet count (Fife, good 150-410)	Below 150[d] Above 410	2.16 (0.89, 5.25) 1.32 (1.04, 1.70)	0.0894 0.0257
Albumin level (optimal, bad<34)		1.94 (1.58, 2.39)	<0.0001
Albumin level (Fife/Dolan[c], bad<35)		1.77 (1.44, 2.17)	<0.0001
Systemic inflammation-related ratios			
Neutrophil to lymphocyte ratio (optimal, bad>=4.02874)		1.79 (1.46, 2.20)	<0.0001
Neutrophil to lymphocyte ratio (Dolan, bad>=5)		1.59 (1.30, 1.95)	<0.0001
Platelet to lymphocyte ratio (optimal, bad>244.737)		1.45 (1.18, 1.78)	<0.0005
CT-derived body composition variables			
Muscle attenuation (optimal, bad<31.5544)		1.69 (1.28, 2.24)	0.0002
Skeletal muscle index (optimal, bad<51.1818/68.6640)[e]		1.71 (1.36, 2.15)	<0.0001

[a]Optimal refers to optimal stratification-derived thresholds
[b]Fife' refers to NHS Fife normal reference ranges/thresholds
[c]Dolan refers to most commonly published threshold reported within the meta-analysis by Dolan (66)
[d]Only 6 patients in this category
[e]By gender, females then males

Selection of thresholds for key variables for the main analyses

Based on the above findings, the following thresholds were selected for each variable:

Absolute neutrophil count, ANC

The predictive value of the ANC of the four specified thresholds was similar. Therefore, the NHS Fife upper limit of normal (7) was selected for the subsequent analyses.

Absolute lymphocyte count, ALC

The predictive value of the ALC of the four specified thresholds was similar. Therefore, the NHS Fife lower limit of normal (1) was selected for the subsequent analyses

Platelet count, Plt

The predictive value of the three specified Plt thresholds were similar. Therefore, the NHS Fife upper limit of normal (410) was selected for the subsequent analyses.

Albumin level, Alb

The predictive value of the two specified Alb thresholds was similar. Therefore, the NHS Fife lower limit of normal (35) was selected for the subsequent analyses.

Neutrophil to lymphocyte ratio, NLR

The optimal predictive threshold in relation to OS for the NLR was 4.02874. For simplicity, an NLR threshold of 4 was utilised for the subsequent analyses.

Platelet to lymphocyte ratio, PLR

The optimal predictive threshold in relation to OS for the PLR was 244.737 and this was utilised for subsequent analyses.

Muscle attenuation, MA

The optimal predictive threshold in relation to OS for MA was 31.5544. This did not differ significantly between genders and so a single threshold of 31.55 was utilised for the subsequent analyses.

Skeletal muscle index, SMI

Gender-specific optimally predictive thresholds were identified for SMI. These were 51.1818 for females and 68.6640 for males. These two thresholds were utilised for subsequent analyses.

3.3.4 Stepwise analysis to identify predictive variables, identifiable at diagnosis, for overall survival

Informed by the conclusions of the exploratory analysis for optimal thresholds described in the preceding section (3.3.4), the variables and threshold that were utilised for the survival analysis were as follows:

- NHS Fife normal reference ranges:
    - Absolute neutrophil count (ANC) ≥7 = unfavourable
    - Absolute lymphocyte count (ALC) <1 = unfavourable
    - Platelet count (Plt) >410 = unfavourable
    - Albumen level (Alb) <35 = unfavourable

- Optimal stratification-derived thresholds:
    - Neutrophil to lymphocyte ratio (NLR) ≥4 = unfavourable
    - Muscle attenuation (MA) <31.55 = unfavourable
    - Skeletal muscle index (SMI) <51.1818 = unfavourable (females) and <68.6640 = unfavourable (males)

- Demographic, functional and cancer categories:
    - Age group: <65 and ≥65
    - Gender: female and male
    - Body Mass Index (BMI): 4 categories of Underweight, Normal, Overweight and Obese, plus a comparison between Underweight versus the rest
    - Scottish Index of Multiple Deprivation (SIMD) quintiles
    - ECOG Performance Status (ECOG PS): ≥2 = unfavourable
    - Cancer type: NSCLC and SCLC

Patients were only included in the stepwise analysis if they had complete data relating to all of the above variables, in order to keep the models exactly comparable (n=346). Four distinct models were constructed:

1) Demographic, cancer type and blood variables
2) Demographic, cancer type and blood variables, plus SMI and/or MA
3) Demographic, cancer type and blood variables, plus ECOG
4) Demographic, cancer type and blood variables, plus SMI and/or MA, plus ECOG

Model 1) Demographic, cancer type and blood variables

Table 3.8 Stepwise analysis including ANC, ALC, Plt, Alb, NLR, PLR, age, gender, cancer type and SIMD variables

	Degrees of freedom (DF)	Parameter Estimate	Standard Error	Chi-Square	*p*-value
NLR (≥ 4)	1	0.43949	0.11936	13.5571	0.0002
Alb (<35)	1	0.39433	0.12164	10.5089	0.0012

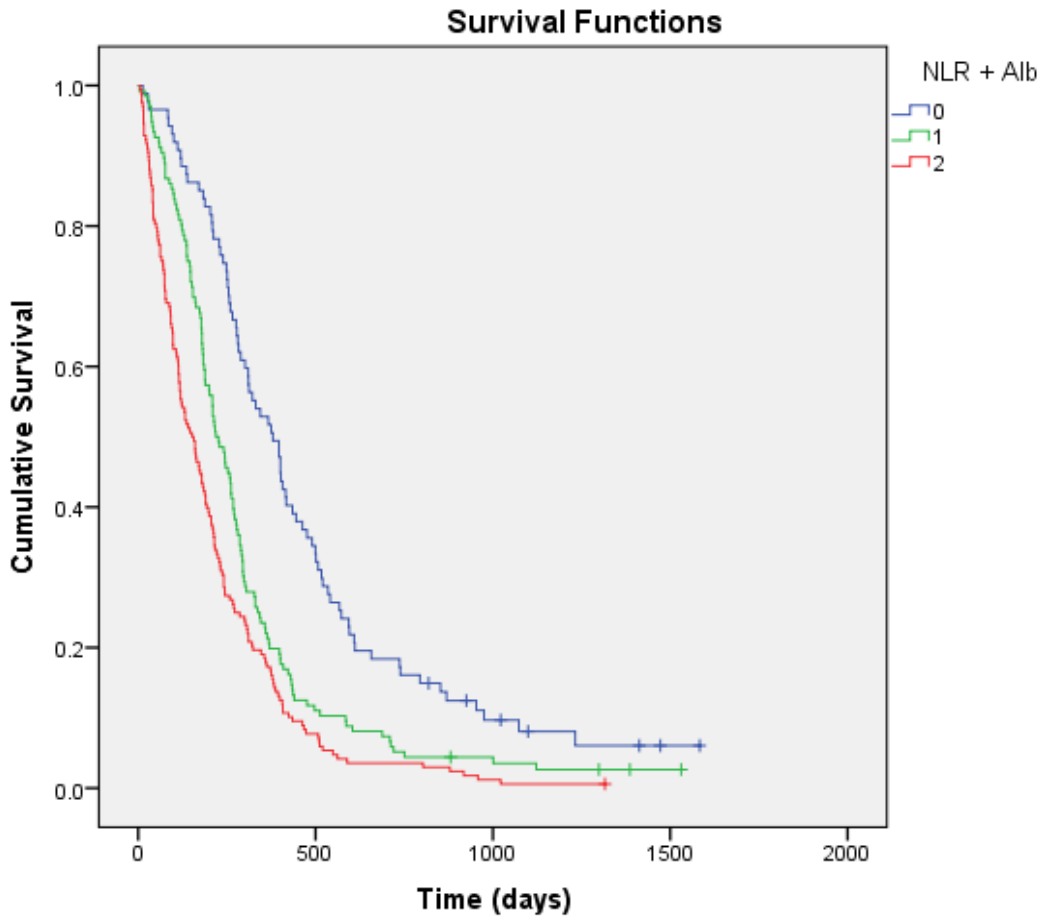
The two key variables identified through the stepwise analysis as independently predictive of OS were NLR and Alb. Parameter estimates for each of the two identified variables were roughly equivalent, and so a score of one was assigned to each. Scores within the survival model presented below are based on the presence (1 point) or absence (0 points) of the two specified variables. The number and percentage of people alive at each time point are described, stratified by their total predictive score, in Table 3.9.

Table 3.9 Predictive model for survival at 1 month, 3 months, 6 months and 12 months, based on the presence or absence of unfavourable NLR and Alb levels, or both, at diagnosis.

Score	1 month	3 months	6 months	12 months
0 (n=77)	74 (96%)	72 (94%)	64 (83%)	39 (51%)
1 (n=115)	112 (97%)	96 (83%)	67 (58%)	24 (21%)
2 (n=154)	138 (90%)	102 (66%)	67 (44%)	28 (18%)

Patients in the most favourable group (0 points, 0 unfavourable variables present at diagnosis, n=77) had the best survival at each time point, with 83% (n=64) still alive at 6 months and just over half (51%, n=39) alive at one year. Conversely, the group with both unfavourable variables at diagnosis (2 points, n=154) had the poorest survival at each time point, with less than half (44%, n=67) alive at 6 months and fewer than 1 in 6 (15%, n=28) patients alive at one year. Survival for the intermediate group (1 point, 1 unfavourable variable present at diagnosis, n=115) was significantly improved on the least favourable group over the first two time points, though this gap then narrowed and one-year survival was almost identical. This is evident in the Kaplan-Meier curve below.

Figure 3.2 A Kaplan Meier curve demonstrating the predictive value of unfavourable NLR and Alb levels at diagnosis for survival.



Model 2) Demographic, cancer type and blood variables, plus SMI and/or MA

The second analysis incorporated all of the variables from the first model (ANC, ALC, Plt, Alb, NLR, age, gender, cancer type, SIMD) but also included the two CT-derived body composition variables MA and SMI.

Table 3.10 Stepwise analysis including ANC, ALC, Plt, Alb, NLR, PLR, age, gender, cancer type, SIMD, MA and SMI variables with overall survival as the outcome.

	Degrees of freedom (DF)	Parameter Estimate	Standard Error	Chi-Square	*p*-value
NLR (≥ 4)	1	0.33469	0.12277	7.4320	0.0064
Alb (<35)	1	0.35561	0.12388	8.2408	0.0041
MA (<31.55)	1	0.38297	0.14965	6.5489	0.0105
SMI (<51.1818 or <68.6640)[a]	1	0.44157	0.12147	13.2146	0.0003

[a]Gender-specific thresholds for SMI, females and males respectively

The four key variables identified through the stepwise analysis as independently predictive of OS were NLR, Alb, MA and SMI. As the parameter estimates were similar across all variables, a score of 1 was assigned to each unfavourable variable. The number and percentage of people alive at each time point are described, stratified by their total predictive score, in Table 3.11

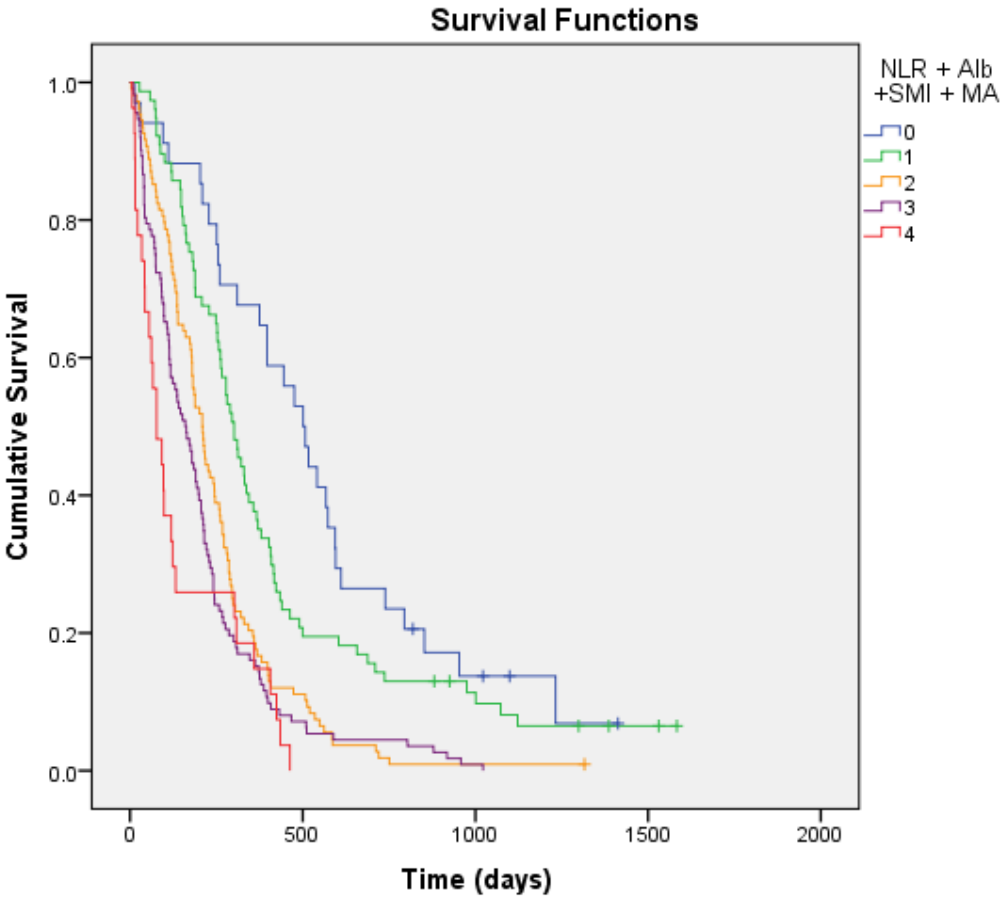
Table 3.11 Predictive model for survival at 1 month, 3 months, 6 months and 12 months, based on the presence or absence of unfavourable NLR, Alb, MA and SMI levels at diagnosis

Score	1 month	3 months	6 months	12 months
0 (n=34)	32 (94%)	32 (94%)	30 (88%)	23 (68%)
1 (n=76)	75 (99%)	68 (89%)	56 (74%)	28 (37%)
2 (n=102)	97 (95%)	82 (80%)	57 (56%)	19 (19%)
3 (n=108)	99 (92%)	75 (69%)	48 (44%)	17 (16%)
4 (n=26)	21 (81%)	13 (50%)	7 (27%)	4 (15%)

Patients in the most favourable group (0 points, 0 unfavourable variables present at diagnosis, n=34) had the best survival at each time point, with more than two-thirds of patients (68%, n=23) alive at one year. Those in the least favourable group (4 points, every unfavourable variable present at diagnosis, n=26) had poorer survival at every time point, with only half of patients alive at 3 months, just over one-quarter alive at 6 months and only 15% (n=4) alive at one year. The intermediate groups (with 1, 2 or 3 unfavourable variables at diagnosis) had

rates of survival at the various time points which reflect the predictive value of higher scores, but with variable differences between the categories over the 12-month period. By one year, those with 2 or 3 points were virtually identical in terms of survival; and are not very different from the group with all 4 unfavourable variables. These and the other observations described are evident in the Kaplan-Meier curve below.

Figure 3.3 A Kaplan-Meier curve demonstrating the predictive value of the presence of unfavourable NLR, Alb, MA and SMI levels at diagnosis for survival.



Model 3) Demographic, cancer type and blood variables, plus ECOG

The third analysis incorporated all of the variables from the first model (ANC, ALC, Plt, Alb, NLR, age, gender, cancer type and SIMD) but also included ECOG PS.

On the basis of its predictive value, ECOG PS was not selected by the program as a significant contributor. However, it was added in manually in order to explore its relative value.

Table 3.12 Stepwise analysis including ANC, ALC, Plt, Alb, NLR, PLR, age, gender, cancer type, SIMD and ECOG PS variables with overall survival as the outcome.

	Degrees of freedom (DF)	Parameter Estimate	Standard Error	Chi-Square	*p*-value
NLR (≥ 4)	1	0.42403	0.12126	12.2282	0.0005
Alb (<35)	1	0.38698	0.12202	10.0587	0.0015
ECOG PS (≥2)	1	0.09817	0.13296	0.5452	0.4603

The two key variables identified through the stepwise analysis as independently predictive of OS were NLR and Alb. With ECOG PS included manually, NLR and Alb contributed approximately 4 times as much predictive value as does ECOG PS. Therefore, given that ECOG PS was also a non-significant contributor, there was no merit in constructing a predictive model incorporating ECOG PS.

Model 4) Demographic and blood variables, plus SMI and/or MA, plus ECOG

The fourth analysis incorporated all of the variables from the second model (ANC, ALC, Plt, Alb, NLR, PLR, age, gender, cancer type, SIMD, SMI and/or MA) but also included ECOG PS.

On the basis of its predictive value, ECOG PS was not selected by the program as a significant contributor. However, it was added in manually in order to explore its relative value.

Table 3.13 Stepwise analysis including ANC, ALC, Plt, Alb, NLR, PLR, age, gender, cancer type, SIMD SMI and/or MA and ECOG PS variables with overall survival as the outcome.

	Degrees of freedom (DF)	Parameter Estimate	Standard Error	Chi-Square	*p*-value
NLR (≥ 4)	1	0.30185	0.12414	5.9126	0.0150
Alb (<35)	1	0.35731	0.12528	8.1345	0.0043
MA (<31.55)	1	0.41619	0.15082	7.6151	0.0058
SMI (<51.1818 or <68.6640)[a]	1	0.40621	0.12346	10.8620	0.0010
ECOG PS (≥2)	1	0.35866	0.22483	2.5448	0.1107

[a]Gender-specific thresholds for SMI, females and males respectively

As in Model 3, ECOG PS did not contribute any significant predictive value. Therefore, a predictive model containing ECOG PS was not constructed.

Comparison of the 4 distinct models in terms of their ability to identify patients, at the point of diagnosis, as at risk of reduced survival.

The relative utility of the models can be compared using the model fit statistics. The ideal model has the lowest -2LogL for the loss of the fewest degrees of freedom. Model 2 is an improvement over Model 1, since the reduction in -2LogL is 20.259 for a loss of 2 degrees of freedom, which is a significant improvement for the loss of the degrees of freedom ($p<0.0001$). However, the addition of ECOG PS in Model 3 compared with Model 1 is an improvement of only about 0.5 for the loss of one degree of freedom; this is not a significant improvement and it would have to be >3.84 for 1 degree of freedom. The same finding applies for Model 4, compared to Model 2, where there is an improvement of only 0.2. Thus, Model 2 is a better model than Model 1, but Models 3 and 4 do not add anything clinically useful.

Table 3.14 Comparison of utility of 4 models based on different combinations of variables

Model	**-2LogL**	**Degrees of freedom** (DF)
Model 1 (2 variables)	3285.643	2
Model 2 (4 variables)	3265.384	4
Model 3 (3 variables)	3285.107	3
Model 4 (5 variables)	3265.151	5

3.3.5 Stepwise logistic regression analysis to identify predictive variables for receiving <4 cycles of first line chemotherapy

Stepwise logistic regression analysis was undertaken to identify predictive variables for the receipt of <4 cycles of chemotherapy. The same threshold for each variable was utilised as is reported in the preceding section (3.3.5)

In this analysis, only patients with complete data for all the variables of interest were included, in order to keep the models exactly comparable (n=348).

Four distinct models were constructed, each based on different combinations of variables.

1) Demographic, cancer type and blood variables
2) Demographic, cancer type and blood variables, plus SMI and/or MA
3) Demographic, cancer type and blood variables, plus ECOG
4) Demographic, cancer type and blood variables, plus SMI and/or MA, plus ECOG

Model 1) Demographic, cancer type and blood variables

Table 3.15 Stepwise logistic regression analysis including ANC, ALC, Plt, Alb, NLR, PLR, age, gender, cancer type and SIMD variables, with <4 cycles of chemotherapy as the outcome

	Degrees of freedom (DF)	**Parameter Estimate**	**Standard Error**	**Chi-Square**	***p-value***
Cancer type (NSCLC)	1	0.4425	0.1247	12.5951	0.0004
BMI (Underweight)	1	0.7736	0.2107	13.4825	0.0002
ANC (≥7)	1	0.4828	0.1205	16.0649	<0.0001
ALC (<1)	1	0.3628	0.1436	6.3846	0.0115

Here, the parameter estimates are not all similar. Therefore, if each estimate is divided by the least strong predictor (ALC<1, 0.3628):

- NSCLC = 1.22
- BMI Underweight = 2.13
- ANC ≥7 = 1.33
- ALC <1 = 1

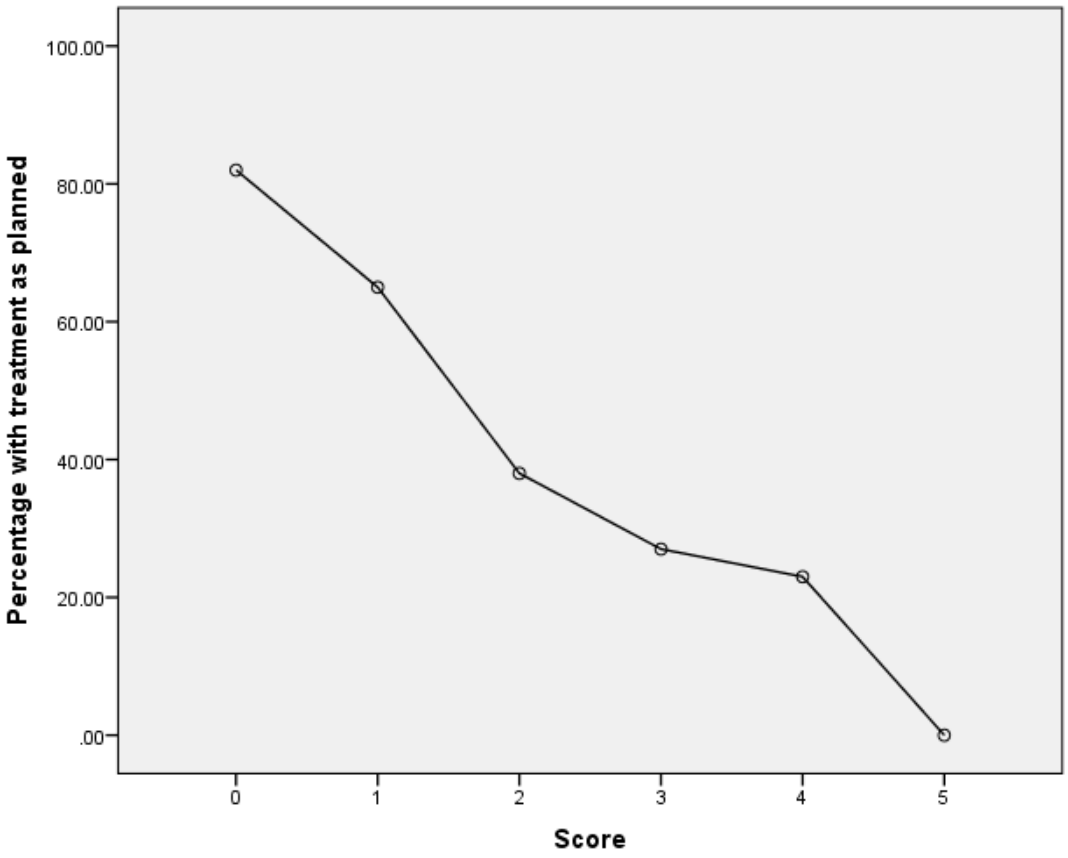
Simplifying these for the purposes of the development of a predictive model, NSCLC, ANC ≥7 and ALC <1 were each ascribed 1 point and Underweight BMI was ascribed 2 points.

Table 3.16 Predictive model for the receipt of <4 cycles of chemotherapy, based on the presence or absence of NSCLC, Underweight BMI status and unfavourable ANC or ALC levels.

Score	Received ≥4 cycles	Received 0-3 cycles
0	32 (82%)	7 (18%)
1	80 (65%)	44 (35%)
2	46 (38%)	74 (62%)
3	13 (27%)	35 (73%)
4	3 (23%)	10 (77%)
5	0 (0%)	4 (100%)

Patients in the most favourable group (0 points, n=32) had a far greater likelihood of completing 4 cycles of chemotherapy than any other group. Fewer than 1 in 4 patients (23%, n=3) with a score of 4 completed 4 cycles of treatment, with the majority in this category (77%, n=10) completing < 4 cycles. No patients with a score of 5 completed 4 or more cycles of chemotherapy, although it should be borne in mind that only 4 patients scored 5. The decreasing likelihood of completing treatment as planned for patients with a higher score is well demonstrated in Figure 3.4, below.

Figure 3.4 A Probability plot of the percentage likelihood of completing 4 or more cycles of chemotherapy at different predictive score levels, based on the presence or absence of NSCLC, Underweight BMI status and unfavourable ANC or ALC levels at diagnosis.



Model 2) Demographic, cancer type and blood variables, plus SMI and/or MA

The second analysis incorporated all of the variables from the first model (ANC, ALC, Plt, Alb, NLR, age, gender, cancer type, SIMD) but also included the two CT-derived body composition variables MA and SMI. On the basis of their predictive value, neither MA nor SMI was selected by the program. MA was marginally more predictive than was SMI and this was added manually in order to explore its relative value.

Table 3.17 Stepwise logistic regression analysis including ANC, ALC, Plt, Alb, NLR, PLR, age, gender, cancer type, SIMD, MA and SMI variables with <4 cycles of chemotherapy as the outcome.

	Degrees of freedom (DF)	Parameter Estimate	Standard Error	Chi-Square	*p*-value
Cancer type (NSCLC)	1	0.4615	0.1261	13.4058	0.0003
BMI (Underweight)	1	0.8123	0.2114	14.7630	0.0001
ANC (≥7)	1	0.4626	0.1212	14.5644	0.0001
ALC (<1)	1	0.3379	0.1445	5.4687	0.0194
MA (<31.55)	1	0.2685	0.1591	2.8478	0.0915

If the estimates are divided by 0.2685 (the estimate of the least strong predictor, MA):

- NSCLC = 1.72
- BMI Underweight = 3.03
- ANC ≥7 = 1.72
- ALC <1 = 1.25
- MA < 31.55 = 1

Therefore, for the purposes of the predictive model, MA < 31.55 and ALC <1 were each ascribed 1 point, NSCLC and ANC ≥7 were ascribed 2 points and Underweight BMI was ascribed 3 points.

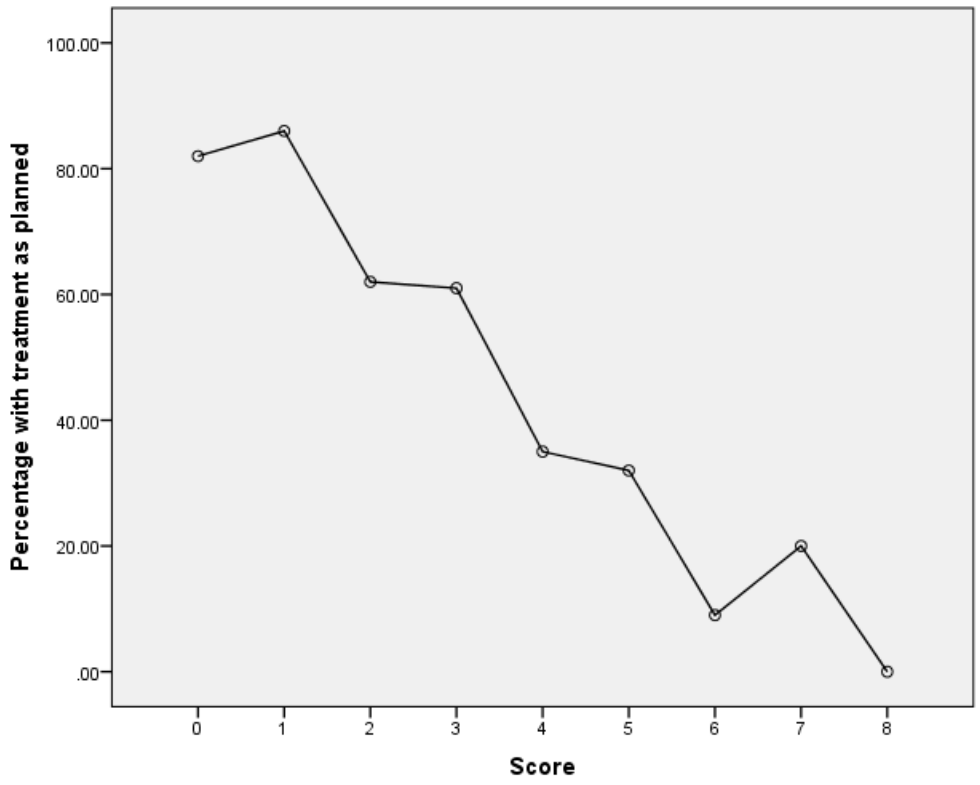
Table 3.18 Predictive model for the receipt of <4 cycles of chemotherapy, based on the presence or absence of NSCLC and/or unfavourable BMI category, ANC, ALC or MA levels at diagnosis.

Score	Received ≥4 cycles	Received 0-3 cycles
0	27 (82%)	6 (18%)
1	6 (86%)	1 (14%)
2	68 (62%)	51 (38%)
3	25 (61%)	16 (39%)
4	28 (35%)	52 (65%)
5	17 (32%)	36 (68%)
6	1 (9%)	10 (91%)
7	2 (20%)	8 (80%)
8	0 (0%)	4 (100%)

A rising score was, for the most part, associated with a lower chance of completing 4 or more cycles of chemotherapy. However, patients with a score of 1 (n=7) were more likely to

complete 4 cycles of treatment than were the 33 patients who had a score of 0. A similar anomaly is seen in the group with 6 points (n=11) and their lower chance of completing 4 cycles of chemotherapy as compared to patients with a score of 7. All 4 patients with a score of 8 received <4 cycles of chemotherapy. See Figure 3.5 for graphical representation of this analysis.

Figure 3.5 A probability plot of the percentage likelihood of completing 4 or more cycles of chemotherapy at different predictive score levels based on the presence or absence of NSCLC and/or unfavourable BMI category, ANC, ALC or MA levels at diagnosis.



Model 3) Demographic, cancer type and blood variables, plus ECOG

The third analysis incorporated all of the variables from the first model (ANC, ALC, Plt, Alb, NLR, age, gender, cancer type and SIMD) but also included ECOG PS.

On the basis of its predictive value, ECOG PS was not selected by the program as a significant contributor. However, it was added in manually in order to explore its relative value.

Table 3.19 Stepwise logistic regression analysis including ANC, ALC, Plt, Alb, NLR, PLR, age, gender, cancer type, SIMD and ECOG PS variables with <4 cycles of chemotherapy as the outcome.

	Degrees of freedom (DF)	Parameter Estimate	Standard Error	Chi-Square	*p*-value
Cancer type (NSCLC)	1	0.4824	0.1343	12.9071	0.0003
BMI (Underweight)	1	0.7695	0.2111	13.2849	0.0003
ANC (≥7)	1	0.4759	0.1209	15.5012	0.0001
ALC (<1)	1	0.3537	0.1440	6.0309	0.0141
ECOG PS (≥2)	1	0.1252	0.1498	0.6992	0.4031

It can be seen that the point estimate for ECOG PS is very small compared to all of the other variables. As a result, if it was to be included in a composite model it would score 1 and the next nearest variable would score 3. Therefore, ECOG PS would add very little to the first composite model described in this analysis (presented in Table 3.15).

Model 4) Demographic and blood variables, plus SMI and/or MA, plus ECOG

The intention had been to add ECOG PS to the second model. However, as neither SMI nor MA were significant predictors of incomplete treatment, it was decided that this would not be a useful exercise.

Comparison of models 1 and 2 in terms of their ability to identify patients, at the point of diagnosis, at risk of not completing 4 cycles of chemotherapy

As before, we aimed to identify the model with the lowest -2LogL for the loss of the fewest degrees of freedom. The reduction in -2LogL (2.89) with the Chi-squared distribution on 1 degree of freedom (5-4) are compared. This is not a significant improvement to the model (p=0.089), and so MA would not be included in the final model. Therefore Model 1 is preferred.

Table 3.20 Comparison of utility of models 1 and 2 in terms of their ability to identify patients, at the point of diagnosis, as at risk of not completing 4 cycles of chemotherapy

Model	**-2LogL**	**Degrees of freedom** (DF)
Model 1 (4 variables)	430.283	4
Model 2 (5 variables)	427.393	5

3.3.6 Exploration of value of amalgamating < 4 cycles or ≥ 4 cycles of chemotherapy with dose reduction and treatment delay outcomes

317/397 patients had one or more of the following outcomes: receiving <4 cycles of first-line chemotherapy, a chemotherapy dose reduction and/or a treatment delay. This unbalanced grouping did not allow for useful discrimination between patients, and no variables were found to be effective predictors of this outcome.

Median OS for patients who completed 4 or more cycles of treatment with no dose reductions or treatment delays was 311 days (95% CI 259.4, 362.6). For those who completed 4 or more cycles of treatment but who also experienced a chemotherapy dose reduction and/or a treatment delay, median OS was 301 days (249.9, 352.1). Therefore, OS for these two groups was not significantly different (p=0.651, Log Rank test), with no evidence that chemotherapy dose reductions or delays for this group impacted on their survival. Thus, there was no value in developing a composite variable for patients who had completed 4 or more cycles of chemotherapy and had a dose reduction and/or treatment delay.

3.3.7 CT-scan evidence of disease status following the receipt of chemotherapy, examined by NLR status at diagnosis.

Follow-up CT scans were evaluated against RECIST criteria by Consultant Thoracic Radiologist, Dr Alan Simms (introduced in Chapter 2), following the receipt of two cycles of chemotherapy for patients with the highest and lowest (top and bottom 20%) NLR at diagnosis.

One patient in the high NLR category died before their date of intended first treatment and therefore had a negative survival time. They were not included in this analysis as they did not receive chemotherapy.

Overall survival by NLR status

There were 80 patients with the highest 20% NLR. Their mean and median NLRs were 17.66 and 14.18 respectively, range 9.78-70.57. Median OS for this group was 119 days from their intended first treatment date (95% CI 92, 146).

There were 80 patients with the lowest 20% of NLR. Their mean and median NLRs were 2.05 and 2.18 respectively, range 0.11 – 2.87. Median OS for this group was 311 days (95% CI 229, 393).

Availability of CT scans for evaluation

22/80 patients (28%) with the highest NLRs did not have follow-up CT scans. The reason for this was not captured but the clinical assumption was that patients were either no longer alive or not fit enough to have the CT scan. 11/80 patients (14%) with the lowest NLRs did not have follow-up CT scans. (Chi-squared test, p=0.032).

Disease status on follow-up CT scan by NLR status

Table 3.21 Radiological evaluation of disease status following the receipt of 2 cycles of chemotherapy, for patients with available CT scans

	Lowest 20% NLR. n=69[a]	Highest 20% NLR, n=58[b]
Stable disease	38 (56%)	18 (31%)
Partial response	19 (27%)	17 (29%)
Progressive disease	12 (17%)	23 (40%)

[a]11/80 patients did not have CT scans available, therefore 69/80 patients had their disease status evaluated.
[b]22/80 patients did not have CT scans available, therefore 58/80 patients had their disease status evaluated.

Patients in the lowest NLR group were significantly more likely to have stable disease than those in the high NLR group, see Table 3.21. Partial response was similar in the two NLR groups. Patients with a high baseline NLR were more than twice as likely to have evidence of progressive disease on their CT scan, compared to the low NLR group. The difference in distribution of disease response between the two groups was statistically significant, p=0.006 (Chi-squared test).

3.3.8 Correlation between variables

Further to the planned analyses, correlation between key variables relating to skeletal muscle measures, BMI, ECOG PS, ANC and Alb were examined. These are presented in Appendix G as supplementary analyses.

3.3.9 Case studies exploring change in status of key variables following the receipt of chemotherapy.

The primary planned analyses were based on biomarker variable data that were available at the point of diagnosis for each patient. The predictive models for OS based on these biomarkers successfully identified a high proportion of patients with unfavourable variables at diagnosis who had significantly reduced survival. However, there were some patients who had several unfavourable variables at diagnosis, but whose median survival far exceeded the median OS of the entire cohort. Conversely, there were some patients who had no unfavourable variables at diagnosis, but whose OS was very short.

Thus, eight patient case studies were undertaken, in order to explore whether change in biomarker status might explain their unexpected survival outcomes. These are reported in Appendix H.

3.4 Discussion

The key findings from the present study were:

- ECOG PS did not independently predict either OS or the receipt of GRT, despite this measure being the mainstay of patient assessment for treatment.
- High NLR, low serum Alb, low SMI and low MA were independently predictive of reduced OS.
- NSCLC, low BMI, ANC and ALC were independently predictive of a failure to complete 4 GRT.
- Routine data availability did not enable patients to be classified as cachectic/non-cachectic in line with the Lancet 2011 consensus definition (46).

Palliative chemotherapy remains the oncological treatment of choice for many people with advanced NSCLC and extensive SCLC. The evidence is that it offers some patients significant benefit in terms of extended survival and/or improved QoL. However, it is also the case that some patients do not fare well in advance of, during or following treatment. The challenge is identifying patients at the point of diagnosis who stand to benefit the most from palliative chemotherapy, and those for whom the risks associated with treatment may outweigh the benefits. The clinical decision to offer patients palliative chemotherapy for lung cancer is typically based on what is known about their cancer subtype and stage, an assessment of their ECOG PS and knowledge of any significant comorbid conditions that might impact on their ability to tolerate treatment. At present it does not include any assessment of their inflammatory status. An informed discussion is held with patients who meet the selection criteria about whether chemotherapy may be the right option for them, based on how they view the potential benefits and risks of treatment and how these apply to their personal situation. However, the evidence base underpinning the discussion around risks and benefits has major limitations; both in the highly selected populations that RCTs are typically based upon, but also the narrow scope of the outcome measures they report. In this way, the lack of a real-world evidence base limits the quality of conversation that can be had with patients and those close to them about the potential spectrum of outcomes that they might expect for people like them.

Two-thirds of patients in the present study had stage IV had NSCLC, the remainder had extensive SCLC, and all were deemed appropriate to offer first-line palliative chemotherapy to; indeed, all were booked to receive their first treatment. 95% of patients received 1 or more cycles of chemotherapy.

Real world outcome headline – biomarkers can identify a poor prognosis group

Around half (49%) of the study cohort did not complete GRT, receiving 3 or fewer cycles of chemotherapy where the intention was 4 or more. Median survival for this cohort was just 112 days (3.6 months), compared with 307 days (approximately 9.9 months) for the patients who did receive GRT. Patients who received 3 or fewer cycles of chemotherapy also spent a significantly greater proportion of their life beyond diagnosis in the acute hospital, compared to their counterparts who completed GRT.

Real world outcome headline – a superficial assessment of BMI and ECOG PS alone does not identify patients with systemic inflammation who are at risk of poor outcomesAt the time of diagnosis, there was evidence of significant systemic inflammation across all patient subgroups; females, males, those with NSCLC and those with SCLC had median ANC above the upper limit of normal, median Alb levels below the lower limit of normal and median NLR above the cohort-specific optimal threshold of 4. Despite this, the majority of the patients appeared functionally favourable, with three-quarters of patients having an ECOG PS of 0/1. Furthermore, the mean BMI across all four groups was in the overweight category, with only one-quarter of patients underweight by BMI. Thus, the majority of the cohort would not have appeared conventionally cachectic or frail at diagnosis.

3.4.1 High NLR, low Alb, low MA and low SMI independently predict reduced survival in a cohort undergoing palliative chemotherapy for advanced lung cancer.

In the present study, an elevated NLR (≥4) and a low serum Alb (<35) at diagnosis were independently predictive of reduced OS. 83% of patients with a low NLR *and* a high Alb were alive at 6 months, compared with 58% with *either* high NLR *or* low Alb and only 44% with *both* unfavourable variables (Model 1).

Both CT-derived body composition variables, SMI and MA, were additionally discriminatory when added to Model 1 to create Model 2, with a low SMI and a low MA at diagnosis each

independently associated with reduced survival; 88% of patients with no unfavourable variables were alive at 6 months, compared with only 27% of patients with all 4 unfavourable variables.

Pre-treatment blood-based markers of systemic inflammation and survival in lung cancer

A high level of systemic inflammation pre-treatment has been shown repeatedly to be predictive of reduced OS in patients with lung cancer (191) (107, 108) (110) (187) (109) (185) (189) (70) (196) (42) (192) (205) (188) (179). This observation has been made in lung cancer populations receiving conventional chemotherapy (191) (107) (108) (109) (185) (189) (70) (196) (42), immunotherapy (192) (205) (188) (179) chemoradiotherapy (110) and surgery (184). The most commonly utilised measures of systemic inflammation in the referenced studies were the NLR (108) (191) (205) (188) (179) (110) (189) (42)and the GPS or mGPS (187) (107) (109) (185) (70) (184). One early study, which informed the development of the GPS, identified a high CRP as predictive of OS (196).

A retrospective cohort study of 919 patients with SCLC (39.9% of whom had extensive disease) compared the predictive value of a range of indices of systemic inflammation for OS, and found that whilst a high NLR was predictive on univariate analysis, it was the systemic inflammation index (SII, comprising Plt x NLR) that remained independently predictive on multivariable analysis (108). The SII had originally been developed for a population with hepatocellular carcinoma (HCC) (206). Interestingly, the SII cut-point in the SCLC population studied by Hong et al was almost five times the level utilised in the original HCC study, possibly reflecting typically high levels of systemic inflammation associated with SCLC. Hong et al suggest that the SII may have been more predictive of OS than the NLR or PLR because of its comprehensive nature; comprising three indices – Plt, ANC and ALC (108).

Another study which compared the predictive value of a range of composite indices (including the GPS, NLR, PLR, SII along with the advance lung cancer inflammation index [ALI= BMI x Alb/NLR] and the prognostic nutritional index [PNI= Alb+5 x ALC]) in a population with NSCLC undergoing surgical resection, found that the GPS and ALI were both independently predictive of OS on multivariable analysis (184). It is of interest that the two models reported by Tomita et al were independently predictive, despite both reflecting systemic inflammation, albeit with the ALI also capturing nutritional status with the inclusion of BMI.

Whilst serum albumin is a key constituent of the GPS, it has also been identified as independently predictive of reduced OS in a population with advanced lung cancer its own right (172); in a prospective study of 31 patients with advanced NSCLC, all of whom were 75 years or older and had an ECOG PS of 2, 3 or 4, a low serum Alb (below 34) was independently predictive of OS (172). Importantly, the study reported by Ikeda et al demonstrated that the predictive value of low Alb was significant whether patients received chemotherapy or were for BSC; with no survival advantage to receiving palliative chemotherapy in patients with a low Alb. Whilst this was a small study, it is possible to see the potential clinical application of the simplex measure of serum Alb, in identifying the elderly, poor ECOG PS patients who might be least likely to benefit from chemotherapy.

CT-based body composition variables and survival in lung cancer

Se-Il Go et al undertook CT-based body composition analysis of 117 male patients with SCLC (over half of whom had extensive disease) and examined the predictive significance of SMI in conjunction with a range of other variables, including ECOG PS, BMI and the NLR (42). Sarcopenia was defined as an SMI in the lowest quartile, based on CT images from the fourth thoracic vertebral level (T4). There was a non-significant trend for patients with sarcopenia to be older, with a poor ECOG PS and extensive disease. NLR did not differ between sarcopenic and non-sarcopenic groups. Patients with sarcopenia had significantly higher rates of chemotherapy dose reduction. However, the headline findings were that it was the combination of sarcopenia and high NLR was predictive of significantly reduced OS (median survival 3.2 months) compared with 16.0 months in patients with low SMI and a low NLR; and that sarcopenic and high NLR patients were twice as likely to discontinue treatment early because of toxicity, and more than five times more likely to die as a result of their treatment (42). Se-Il Go et al did not examine MA in their study. The finding reported by Se-Il Go et al that SMI and NLR were independently predictive of OS is consistent with the present study's findings. Another study, reported by van Dijk et al, in a population with colorectal cancer undergoing resection of liver metastases, similarly found that the combination of sarcopenia and systemic inflammation (as measured by CRP) was highly predictive of OS (56). The supplementary analysis presented in Figure 3.6, Appendix G revealed that for the present cohort, SMI and BMI were only weakly correlated. It was low SMI and not low BMI that predicted reduced OS, and it is possible that there was some confounding between these

variables, with SMI more strongly predictive. Interestingly, there was scarce correlation (r =-1.01) between SMI and ECOG PS (see Appendix G, Figure 3.8).

Martin et al undertook a large retrospective study of 1,473 patients with lung or gastrointestinal cancers, of whom 440 had lung cancer (55). All patients had CT-based body composition analysis, including SMI and MA measurements, and the predictive value of these indices for OS was examined along with a range of other variables including cancer stage, ECOG PS, BMI and weight loss. Weight loss, low SMI and low MA were independently associated with reduced OS, across all BMI categories; although patients with the lowest BMI and these three unfavourable variables exhibited the shortest survival of all (55). No blood-based markers of systemic inflammation were included in this study.

3.4.2 NSCLC, low BMI, high ANC and low ALC predict the receipt of <4 cycles of first-line chemotherapy in a cohort with advanced lung cancer

In the present study, patients with NSCLC were significantly more likely than those with SCLC to fail to complete GRT (p=0.036). The receipt of <4 cycles of chemotherapy was associated with a low median survival of just 3.3 months. Predictive variables for this outcome, identified through stepwise analysis, included NSCLC, BMI <20, ANC ≥7 and ALC <1. A BMI of <20 was twice as strong a predictor of receiving <4 cycles of chemotherapy when compared to the other predictive variables; thus, patients with this unfavourable variable were ascribed 2 points in the predictive model. 82% of patients with no unfavourable variables at diagnosis received 4 or more cycles of chemotherapy, with no patients with the highest score of 5 points receiving ≥4 cycles.

The association between NSCLC and the receipt of <4 cycles of chemotherapy

Patients in the present study with NSCLC were less likely to receive GRT. GRT for both stage IV NSCLC and extensive SCLC is 4 cycles of chemotherapy, although it is not uncommon for patients with SCLC who are tolerating and responding to treatment to continue with chemotherapy beyond 4 cycles to 6 cycles or more; a large retrospective analysis of 15,091 patients with SCLC, 8,923 of whom had extensive disease, revealed that 16.4% of patients received ≥6 cycles of chemotherapy (148). SCLC is understood to be a particularly chemo-

sensitive tumour subtype, with dramatic responses to treatment sometimes evident and relapse rates when chemotherapy has stopped are high (14). In contrast, the evidence suggests that continuing first-line chemotherapy for advanced NSCLC beyond 4 cycles does not offer additional benefit (137).

Median OS was not significantly different for patients with NSCLC and SCLC in the present study, despite the difference in the total amount of chemotherapy that patients received.

In the face of their higher rates of chemotherapy receipt, it is interesting to note that patients with SCLC were significantly more likely to have a poor ECOG PS at diagnosis. One potential explanation is the chemo-sensitivity of SCLC in some patients, and the potential reversal of cancer-induced fatigue and other symptoms which were contributing to poor functional status pre-treatment. This phenomenon is well-recognised in clinical practice.

Given the finding that patients with SCLC were more likely to have a poor ECOG PS at diagnosis, but yet were more likely to receive GRT and had comparable survival to patients with NSCLC, it was of interest to consider what changes in biomarker status on treatment might reveal. Change in biomarker status during treatment was not examined as part of the planned analysis reported in this chapter. However, a small number of patient case studies were undertaken to explore the potential relevance of change in variable status on treatment, with a view to informing future work. Four patients (patients 5, 6, 7 and 8, presented in Tables 3.26-3.29 in Appendix H) were purposively selected for case study based on their good ECOG PS and wider favourable biomarkers at diagnosis, and yet their non-receipt of GRT and very short survival. All were ECOG PS 1 at diagnosis, but none received GRT and their OS ranged from 0-111 days only. Two of these patients (patients 7 and 8) who lived long enough to have a second ECOG PS recorded prior to a second cycle of chemotherapy both had a dramatic worsening of ECOG PS from 1 to 3. Although this observation does not represent formal data analysis, it highlights a clinically important situation; namely that a changing ECOG PS may help to identify patients who are faring badly early on in their treatment. This area is of interest for further study.

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Low BMI and outcomes in lung cancer

In the present study, low BMI was the strongest predictor of the receipt of <4 cycles of chemotherapy. In a retrospective analysis of BMI and outcomes for 2,585 with NSCLC,

Dahlberg et al identified that low BMI was independently associated with poor survival, with OS rising sequentially through the BMI groups (197). In the study reported by Dahlberg et al, patients with a low BMI did not experience any more toxicity than their counterparts with a higher BMI, but they were more likely to discontinue their treatment early because of disease progression or death. Low BMI patients were more likely to have a poor ECOG PS and also to be weight-losing at diagnosis. Weight loss was not examined in the present study. However, there is extensive evidence of the predictive value of weight loss in lung cancer (33) (195) (41) (55) (59) (196) and it is possible, in the present study, that patients with a BMI<20 were more likely to be weight-losing. This observation (of reported weight loss being more prevalent in low BMI patients) was made in the preceding study presented in Chapter 2.

A high BMI was also shown to be a favourable factor for OS in the study reported by Martin et al, which included 440 patients with lung cancer(55). Patients in the lowest BMI category had the shortest survival. Interestingly, the other independently predictive variables for OS of low SMI, low MA and weight loss were less discriminatory in the low BMI group than in the high BMI groups. This may be because 92% of patients with low BMI in the Martin study had weight loss, low SMI and/or low MA. In the present study, neither low SMI nor low MA added predictive value for predicting the receipt of <4 cycles of treatment. There was a small positive correlation between BMI and SMI (r=0.24, reported in supplementary analyses, Appendix G) and a moderate negative correlation between BMI and MA (r=-0.435, Appendix G) and therefore it is possible that there was a degree of confounding between these variables.

White blood count indices ANC and ALC

It is interesting to note, in the present study, that it was the ANC and ALC (as opposed to the NLR) that were identified as significantly predictive of the receipt of <4 cycles of chemotherapy. This finding points to the balance between ANC and ALC (as expressed as NLR) as a different measure from simply high ANC and/or low ALC. Indeed, a high NLR may comprise a high ANC and a low ALC, but may also comprise a very high ANC and a normal ALC, or a normal ANC and a very low ALC. Botta et al, in their study of 112 patients with advanced NSCLC undergoing systemic treatment, identified that a high ANC, a high monocyte count *and* a high NLR were each independently predictive of reduced PFS; further evidence that absolute white blood counts and the NLR may reflect different processes. In the present study, it was the ANC and ALC as separate indices that remained independently predictive of the receipt of

<4 cycles of chemotherapy, as opposed to the NLR. Arguably, these absolute blood counts are more readily usable by clinicians, with no additional calculations needed if the indices beyond what is routinely reported.

It is not known why the independently predictive variables for the two primary outcome measures, namely OS and the receipt of <4 cycles of chemotherapy, were different. This finding is worthy of further study in larger populations with the same diagnosis and treatment strategy. It is also worthy of study in wider cancer populations. An important question is which outcome measure might be the most meaningful; with known risk factors able to inform and even influence clinical decision making.

3.4.3 ECOG PS was not independently predictive of overall survival, nor the receipt of guideline-recommended treatment

One striking finding within the present study was that a poor ECOG PS was not independently predictive of either reduced OS or the receipt of <4 cycles of chemotherapy. It is well recognised that ECOG PS is both a crude and highly subjective measure (6) (7) (8), but despite this it plays a major role in the assessment of patients' fitness for cancer treatment. Having said this, it is of interest that 42% of the present study cohort with SCLC had an ECOG PS of 2/3/4, and that despite this, all were booked to receive chemotherapy. As already discussed above, in section 3.4.2, it is recognised that SCLC is particularly chemo-sensitive, and that where patients respond, they can have dramatic reductions in their disease burden and symptoms in a short space of time. Thus, in clinical practice, it is acceptable to treat poor ECOG PS patients with SCLC on the understanding that if their disease responds quickly, they may improve physically equally quickly. This is relevant clinical context to the observation around poor ECOG PS patients being treated with chemotherapy, but it may also be one reason why ECOG PS was not predictive of either OS or the receipt of <4 cycles of chemotherapy; since it is possible that the patients with SCLC who had a poor ECOG PS at the outset improved with treatment and went on to have outcomes comparable to their counterparts with a good ECOG PS at diagnosis.

The observation that ECOG PS was not predictive of OS and/or the receipt of GRT may also reflect confounding between ECOG PS and the wider examined variables. In lung cancer populations, a poor ECOG PS has been shown to be associated with high CRP (196) sarcopenia

and a high NLR combined (42) and low BMI (197). Thus, inflammation and nutritional status, as measured in the present study by NLR, Alb, ANC, ALC and BMI are strong contenders to be confounding with ECOG PS. Fatigue was not captured by routine data or included in the present study, although it has been shown in lung cancer to be associated both with systemic inflammation and reduced OS (180) (207), and it can also be a major limiting factor when it comes to physical function, as reflected by a poor ECOG PS.

The combined predictive value in lung cancer populations of ECOG PS along with systemic inflammation (as measured by mGPS) (70) (187) and weight loss (41) has been demonstrated in certain studies . However, other studies have shown systemic inflammation to be independently predictive of OS whilst ECOG PS was not (42) (109) (185). However, it is critical to acknowledge that whilst some large studies in lung cancer have shown ECOG PS to be independently predictive of either early mortality (16) or not completing GRT (147), there were no variables reflecting systemic inflammation or body composition included in the analyses. In other words, key biomarkers were not measured.

The general fitness of the cohort under study is also likely to be important, with great variation in the relative proportion of patients in each ECOG PS group between different reported studies. The timing of ECOG PS recording and the quality of assessments may also be an issue.

In the present study, over three-quarters of patients had an ECOG PS of 0/1; unsurprising perhaps given that all had been assessed as fit to proceed with treatment. It could be argued that 'within ECOG PS' group discrimination is of greatest value in this clinical context, since in practice, patients with poorer ECOG PS are rarely offered treatment. Therefore, identifying which ECOG PS 0/1 patients are at greatest risk of adverse outcomes is of clinical interest. It is also recognised that a significant proportion of patients with lung cancer have an ECOG PS 2, and that it can be difficult to know what level of treatment is appropriate for such patients (9); hence the recommendation by Bonomi et al to expand trial eligibility to include ECOG PS 2 patients in order that an evidence base can be generated (162). The finding by Ikeda et al that serum Alb is a strong predictor or OS within a poor ECOG PS cohort (all of whom had ECOG PS of 2/3/4) is another example of the potential for for 'within group' (here, poor ECOG PS groups) discrimination (172).

3.4.4 A high NLR at diagnosis is associated with lower response rates to chemotherapy.

In the present study, patients with a high baseline NLR were significantly more likely to have CT scan evidence of progressive disease following two cycles of chemotherapy, compared with patients with a low NLR (p=0.006). This is in line with other lung cancer studies that have demonstrated both reduced OS with high pre-treatment levels of systemic inflammation, but also reduced PFS and response rates (191) (107) (108)). Given the convincing evidence that systemic inflammation is predictive of reduced survival, this finding is not surprising. However, it provides additional evidence of the importance of the systemic immune response, and indeed the inflammatory profile of the patient, as they enter into cancer treatment. It is additionally important to highlight that more than one-quarter of patients in the sample of the high NLR cohort did not have a second CT scan following treatment, and that this in itself likely reflects another dimension of adverse outcome. We cannot say precisely why this subgroup did not have a second CT scan, but it is clinically likely that the patients had either deteriorated or died, or that a follow-up scan was deemed unnecessary because further treatment was not planned. In future prospective studies, this level of information would be of interest to collect.

Whilst, in the present study, pre-treatment NLR was clearly associated with reduced OS and a lower likelihood of disease response, it is also the case that 60% of patients in the high NLR sample who had follow-up CT scans did not have progressive disease; they either had stable disease (31%) or partial response (29%). Thus, whilst patients with a high NLR were less likely to respond to chemotherapy, they still had a reasonable chance of doing so. In the section that follows, further consideration is given to the area of changing biomarkers on treatment; accepting that this was not part of the planned analyses, but rather an emerging area of interest given the primary findings of this study, and given an evolving evidence base in this area.

3.4.5 The potential significance of changes in baseline variable status after the receipt of chemotherapy

The predictive models for both reduced OS and the receipt of <4 cycles of chemotherapy can undoubtedly help to identify some patients, at the point of diagnosis, at increased risk of adverse outcomes. However, it is clear that there are a number of patients who start with one or several unfavourable variables, but who fare well, completing their chemotherapy as intended and benefitting from extended survival. Conversely, there are other patients who have no unfavourable variables at diagnosis, but who do not complete GRT and/or who have poor survival. Thus, the story is more complicated than might be first assumed.

It was with these observations in mind that eight purposively selected case studies were undertaken, presented in Appendix H. The intention was that this small-scale exploration could inform a future direction of study.

Selected patients in the present study who had unfavourable variables at diagnosis but who completed GRT and lived > 1 year

Follow-up data relating to key variables for four patients (Patients 1-4) is presented in Tables 3.22-3.25, Appendix H and is of great interest.. 3/4 patients, all of whom had several unfavourable biomarkers at diagnosis, had considerable improvements in both their NLR and Alb following the receipt of 2 cycles of treatment; and the remaining patient had a marked improvement in their NLR, whilst their Alb level remained stable at 34. Their wider variables described (including ECOG PS, weight, ANC and ALC) demonstrated a more mixed picture, with some apparent improvements and some worsening; all with the caveat that changes were described in crude terms.

Thus, the observation is that where patients had unfavourable NLR and Alb levels at baseline but completed GRT and had extended survival, changes in the status of NLR and Alb after two cycles of chemotherapy were suggestive that they may have been responding well to chemotherapy. An important question is whether these observations confer additional help to clinicians assessing patients on treatment, perhaps either in advance of, or alongside their follow-up CT scan.

Patients who had no unfavourable variables at diagnosis but who neither completed GRT nor lived long

Patients 5-8 who data is presented in Tables 3.26-3.29, Appendix H, were introduced earlier in this Discussion section. These patients had favourable biomarkers at baseline, but did not do well as might have been expected given this. The first two patients in this category (Patients 5 and 6) lived only 13 days and 30 days, with one not receiving any chemotherapy and one receiving just one cycle. Thus, no follow-up bloods or other variables were recorded for these patients. We do not know the cause of death for these patients and it is possible that they died of a sudden event such as a pulmonary embolus or a myocardial infarction. There was certainly nothing in the baseline variables for either patient that indicated that they might do badly, apart, of course, from their extensive SCLC.

The second two patients (Patients 7 and 8), who had the next shortest survival times, lived 95 and 111 days. Both received two cycles of chemotherapy only. Follow-up data was only available after their first cycle of chemotherapy, immediately before they received their final (second) treatment. The picture with regard to NLR and Alb levels for these patients was not consistent with their poor survival. Patient 7's NLR actually improved within the 'good' (i.e. low) category, and although their Alb fell, it remained within the 'good' (i.e. high) category. Patient 8's NLR remained within the good category and their Alb fell from the good to the bad category (i.e. high to low). Thus, change in NLR and Alb were not useful in the same consistent way as was observed for the first four patients (who had unfavourable variables pre-treatment, improvement in these domains, and better outcomes than might have been anticipated at diagnosis).

However, there was a striking deterioration in ECOG PS for both patients in this category (patients 7 and 8); in both cases, ECOG PS fell from 1 to 3 between their first and second cycles of chemotherapy. The circumstances of the patients' deterioration in function, and of the decision to proceed with the second cycle of chemotherapy despite their ECOG PS of 3, are not known and cannot be commented upon. Alongside the deterioration in ECOG PS, there were some wider changes in variable status from baseline to pre-cycle 2 which appeared unfavourable (e.g weight loss in both patients), but the overall picture was mixed.

An appraisal of the observational findings from the eight reported case studies in relation to the wider research literature; in populations receiving both palliative chemotherapy and immunotherapy for advanced lung cancer

Data for eight patients were highlighted for whom outcomes appeared surprising given their baseline biomarker status. The change in NLR and Alb status for patients 1-4 was largely consistent with their favourable outcomes. This observation, although based on a very small number of patients, is consistent with a growing body of lung cancer research examining inflammatory status following the receipt of systemic treatment, including immunotherapy, for lung cancer.

Lee et al studied 199 'never smokers' and measured their NLR pre-treatment and before their second cycle of either chemotherapy or gefitinib (193). An NLR that was higher post-than pre-treatment was associated with progressive disease in both treatment arms, whilst patients with a high NLR pre-treatment that fell had improved OS compared to those whose NLR remained high. Three other studies, each with small patient cohorts, examined the significance of post-treatment NLR in patients with advanced NSCLC receiving immunotherapy (208) (205) (181). All three studies reported that a high NLR post treatment was associated with adverse outcomes; Suh et al reported that a high NLR 6 weeks into treatment was predictive of OS and that no patients with a high post-treatment NLR showed an objective response to treatment (208); Kiriu et al found that where NLR rose after treatment, patients had a significantly shorter PFS and time to treatment failure (205); and Takeda et al identified that a post-treatment NLR at 4 weeks was predictive of PFS, but that at 2 weeks it was not (181)

In a study of 173 patients with mesothelioma, a thoracic malignancy that has been shown to be associated with high levels of systemic inflammation (182), Kao et al demonstrated that 43% of patients had normalisation of their NLR after just one cycle of chemotherapy, and that this was associated with increased OS compared with patients for whom the NLR remained high (209). Normalisation in NLR after one cycle of chemotherapy has similarly been shown to be associated with significantly improved OS in patients with metastatic colorectal cancer undergoing palliative chemotherapy (210).

In the same vein as the studies which examined the significance of the post-treatment NLR, others have examined the significance of change in weight and/or cachexia status in relation to OS in lung cancer populations (41) (211) (59). Ross et al studied 780 patients with NSCLC, SCLC or mesothelioma and demonstrated not only that weight loss at the time of diagnosis

predicted poor OS, but that weight stabilisation on treatment was also associated with a significant increase in OS (41). Interestingly, this was only the case for patients with NSCLC, and did not follow for those with SCLC. Ross et al suggest that the mechanism underlying weight loss may differ between these cancer subtypes, with weight loss in SCLC possibly associated with greater resting energy expenditure adjusted for fat-free mass as compared with NSCLC (41). There were only 3 patients with mesothelioma in the study by Ross et al who experienced weight stabilisation, and this did not appear to affect their survival. In their concluding comments, Ross et al question whether '*weight loss is simply a marker of patients with a poor prognosis or whether it independently reduces the ability of some patients to be treated effectively with chemotherapy.'*

Patel et al studied 421 patients with advanced NSCLC receiving chemotherapy and reported that patients who gained weight had significantly improved response rates to treatment and also OS (211). Patel and colleagues propose change in weight on treatment as a simple, practical measure of clinical benefit reflecting treatment tolerability and/or cancer control (211)

Kimura et al followed 134 patients with advanced NSCLC on chemotherapy and assessed their cancer cachexia status at baseline and at three subsequent time points (59). Cachexia was defined according to the Lancet consensus definition published by Fearon et al (46); as weight loss >5% or ≥2% in patients with a BMI <20 kg/m^2. In addition to BMI and % weight loss data, CT-based body composition analysis was undertaken by Kimura et al. 69% of patients lost weight and 79% patients lost skeletal muscle during treatment. Around one-third of patients experienced a change in cachexia status during this time. Patients who were cachectic at the outset but who moved into the non-cachectic category, gained weight but not skeletal muscle. Patients who started cachectic and remained cachectic had the poorest OS of all groups; those whose status changed in either direction had intermediate survival; and those who started and remained non-cachectic had the best OS (59). Patients with cachexia at baseline and mid-way timepoints had significantly lower response rates to chemotherapy.

Thus, the observations from these eight selected case studies are consistent with a wider emerging research literature, for populations with advanced cancer receiving both palliative chemotherapy and immunotherapy.

Case studies 5-8,, whose outcomes were poor despite their apparently favourable baseline status, were also of interest. Patients 5 and 6 are exemplars of a 'data missing not at random'

phenomenon (120). Because their survival was short, they had minimal routine clinical data, limiting what could be learned about the contributing factors to and/or circumstances of their deterioration. Follow-up data relating to patients 7 and 8 revealed a mixed picture in terms of inflammation-related blood tests, but did demonstrate a drastic worsening of ECOG PS. Thus, even for these patients, the status of their variables following the receipt of just one cycle of chemotherapy was informative. The case for further research in this area of longitudinal data capture is clear; as is the need for prospective data collection where robust and complete data can be gathered contemporaneously from patients.

3.4.6 Strengths and limitations of the present study and relevant learning to inform future study.

The present study was informed by the learning from the initial study described in Chapter 2. Several of the key limitations identified within the initial study were addressed in the present study to some extent. These areas and additional limitations, along with specific strengths, are discussed below.

The cohort under study

The present study included all patients who had been booked within ChemoCare to begin first-line palliative chemotherapy for advanced lung cancer during a three-year period. This was an improvement on the initial (chemoradiotherapy) study in that it enabled 21 patients who were booked to receive treatment, but who did not receive treatment, to be identified and included in the study (as a very poor prognosis group). This was made possible through the use of ChemoCare as a means of identifying the index dataset, as opposed to cancer audit data.

The present study cohort was more than twice the size of the chemoradiotherapy cohort, and this enabled larger sub-groups to be studied.

On the advice of a senior lung oncologist (Professor Allan Price), patients with mesothelioma and those who received immunotherapy or targeted therapy at any time during their treatment journey were excluded from the present study; this was both because their numbers were small, but also because it was anticipated that their baseline characteristics and outcomes may be very different from patients with NSCLC and SCLC receiving chemotherapy.

30 patients with mesothelioma were excluded, and 46 patients who received immunotherapy at one or more points in their treatment journey were also excluded. Immunotherapy was, and still is, a growing treatment area, with increasing numbers of patients receiving these novel treatments. However, during the time of the study cohort (i.e. 2013-2015), very low numbers of patients received immunotherapy at first line treatment. The timing of immunotherapy administration has since evolved; with many of the 46 patients identified at the outset of this study receiving immunotherapy late in their treatment journeys, compared with many more patients currently receiving first-line immunotherapy. Thus, data and associated findings from these patients, had they been included in the analyses, was deemed unlikely to be transferable to current patients. Further research, focusing on patients receiving immunotherapy as first-line treatment during a later timeframe (2016-2019) is underway within the Edinburgh Cancer Centre.

The decision was made to include patients with both NSCLC and SCLC in the present study, as although their cancer biology is recognised to be distinct, their outcomes are expected to be broadly similar. This was borne out by the comparable median OS observed in the two subgroups of the present study cohort. In recognition that there were potential differences in the characteristics and treatment receipt of the two groups, steps were taken to identify these; baseline characteristics of the entire study cohort were presented both by gender and cancer subtype, and cancer subtype was included as a variable in the stepwise analysis for the two primary outcome measures. The major identified difference between the groups with NSCLC and SCLC, was that a higher proportion of patients with SCLC had a poor ECOG PS at diagnosis, and that despite this, patients with SCLC were more likely to receive GRT. This potentially led to NSCLC being included as a key variable in the 'receipt of <4 cycles of chemotherapy' predictive model. It is acknowledged that this may not be helpful in clinical practice and it is an important area to consider for future study. The finding reported by Ross et al that weight stabilisation on chemotherapy in patients with SCLC was not associated with improved PFS or OS serves as a reminder that systemic inflammation may impact patients with NSCLC and SCLC differently (41). Further studies are needed to identify if this observation remains; and, if so, to enlighten on the potential aetiology with the inclusion of wider variables related to systemic inflammation and/or cachexia.

The study methods, including data sources, variables and outcomes under study

The present study was based on routine data that was available within electronic healthcare systems only. There was far greater availability of electronic data for the present study as compared to the chemoradiotherapy cohort, and this enabled a range of additional variables and outcomes of interest to be studied, including pre-chemotherapy blood counts and weights. The importance of indices of systemic inflammation in predicting both OS and the receipt of GRT is clear from the findings.

The advantages of the electronic data sources went beyond simply the availability of data and may have positively influenced the quality of the data. In the chemoradiotherapy study presented in Chapter 2, ECOG PS data was provided as part of the index (cancer audit) dataset. Cancer audit facilitators who attend the cancer MDT meetings record ECOG PS data based on what the clinicians who attend the meetings to present their patients recall of their earlier clinical assessment. This assessment may have been several days or even weeks before the meeting, and potentially a month or longer before cancer treatment is started. Thus, the advantage of ECOG PS data recorded at consistent time points within ChemoCare is clear; the data entry is dated and is based upon a clinical assessment that same day. The same is true of BMI.

Some ChemoCare data was provided via automatic extraction, facilitated by the database manager. This included the identification of the patient cohort who were all booked to receive their first dose of palliative chemotherapy during 2013-2015. One data domain that was initially completed using the same automated method was the number of treatment cycles that patients had completed. However, this proved to be inaccurate for several patients, revealed by cross-checking this against the prescriptions and completed treatment records. Thus, there was a significant problem with the automated extraction of accurate 'number of cycles' data and the decision was therefore made to extract this manually, patient by patient. In addition, the inaccuracies noted were fed back to the database manager and the programmers who wrote the required coding for data extraction.

Whilst the range of explanatory variables included in the present study was greater than in the initial chemoradiotherapy study, it is acknowledged that there may have been several unmeasured confounders. A key example was comorbid illness, which was so inconsistently recorded in patients' clinical records in both studies that the decision was made not to include this data. . We therefore do not have any understanding of the extent to which comorbidity

affected the variables and/or the outcomes in either study. The association between chronic obstructive pulmonary disease (COPD) and skeletal muscle wasting is one example of how comorbidity may be important; a large retrospective study of patients with COPD identified that pectoralis muscle area was significantly associated with severity indicators of COPD, including functional impairment, respiratory physiological function and disease stage (212). In the present study, low SMI was predictive of reduced OS. Lung cancer and COPD commonly co-exist, with one study of 20,511 veterans with lung cancer reporting an incidence of COPD in this population of 52% (169). Therefore, it must be a priority for future lung cancer research relating to systemic inflammation and cachexia to incorporate reliable indices of comorbidity status. Accepting that clinical records are often inconsistently completed, utilising administrative datasets to derive comorbidity scores from hospital coding of comorbid conditions would be a sensible approach.

We have to acknowledge that the amount of chemotherapy that patients received, whilst not known at the point of diagnosis, could have impacted on the outcome measures including OS. However, as the amount of treatment received is related to survival time, and as such is a confounder, we took the decision not to include it as an exploratory variable. It is interesting to note the differences within the variables which independently predicted reduced OS and the receipt of <4 cycles of chemotherapy; there was some overlap in the domain of the variables (e.g. both outcomes were predicted by white blood count levels), but for OS it was the NLR which was independently predictive and for non GRT receipt it was the component parts of NLR, separately. No other variables were common between the two outcomes. However, future studies with larger populations could explore the extent to which treatment amount contributes to survival, independently of other explanatory variables. The present study undertook to identify the most discriminatory cut-points for key variables, in order to eliminate the risk that others' published thresholds not being valid for a cohort with advanced lung cancer who received chemotherapy. The variability in published thresholds for blood markers of systemic inflammation is well recognised (66) and has been discussed earlier in this thesis. In the present study, the proximity of the optimal stratification-derived thresholds for ANC, ALC, Alb and Plt to established clinical reference ranges enabled the (NHS Fife) upper and lower limits of normal to be utilised in the stepwise analysis. If these cut-points are validated in larger populations, it is likely to be clinically helpful if predictive models are based on recognised reference ranges and do not require additional tests or complex calculations. The mGPS was not studied in the present study because CRP is not measured routinely, or at

regular time points, in clinical practice in Scotland. The ready availability of the ANC and ALC (and the resultant ability to determine the NLR) has been cited by many researchers as pointing towards the NLR being more practical to study than the mGPS (179) (208) (191) (210) (108). However, given that the measures do not include any of the same composite indices, it is also possible that they reflect different aspects of systemic inflammation and/or nutritional reserve and/or cachexia. Therefore, in future prospective studies there may be merit in examining both measures in tandem, exploring the extent to which they are correlated, but also identifying the wider variables and outcomes of interest that each are associated with. Furthermore, wider composite scores such as the ALI (BMI x Alb/NLR), SII (comprising Plt x NLR) and PNI (Alb+5 x ALC), all of which have been examined in lung cancer (184) (108) (206), may also warrant further study.

Primary outcome measures in the present study were OS and the receipt of 4 cycles of chemotherapy. Both were consistently measureable, with scarce identifiable scope for inaccuracy. A range of secondary outcomes were also examined, reflecting a broader view of what happened to patients during or following treatment. Secondary outcomes included treatment-related measures (chemotherapy dose reductions and delays), hospital admissions (number and total acute hospital inpatient bed days) and place of death. Data capture for these secondary outcomes was very high, perhaps unsurprisingly given that they had been selected on the understanding that all should be routinely recorded. It should not be possible for patients to be attend an acute hospital, either an outpatient or an inpatient, without generating an electronic record of the encounter, thus details of admissions were assumed to be reliable. Place of death, where it was the acute hospital, was assumed to be very reliable for the same reason; whilst place of death in wider locations such as hospice was not always straightforward to identify. Given the interest in over-medicalisation towards the end of life (173) (174) (213), the decision was made to focus place of death on 'acute hospital versus other', since no data relating to quality of care or death was sought which might enlighten on these wider aspects.

At the outset of the study, the intention had been to collect more detailed information about chemotherapy toxicity, as it was of interest to identify the frequency and severity of a range of toxicities and to examine which patients were at greatest risk of these. However, the low quality of this data in several senses (including the consistency in the approach taken to recording it, but also its completeness and accuracy) precluded the inclusion of this data.

Instead, measures of chemotherapy dose reduction and delay were included with the intention that they may be surrogates for treatment toxicity, along with the receipt of 3 or fewer cycles of chemotherapy. The inclusion of two outcome measures relating to acute hospitalisation added another dimension to what could be described about the experiences of the study cohort. Importantly, this included the finding that the cohort who did not receive GRT spent as much time in hospital in their typically short survival time (median OS 3.6 months) as did the cohort who completed GRT (who had a median OS of 9.9 months). The timing of admissions was not examined in relation to either treatment or death, though this could be explored in future work. Furthermore, we cannot say, for individual patients, whether such information would be of interest. However, the indicators of poor quality cancer care reported by Earle et al, and developed in part by patients with cancer and those close to them, suggest that acute hospital admissions near the end of life are viewed as undesirable (173); therefore, future studies in this area should ideally incorporate some measure of acute hospital admissions.

A small minority of the 194 patients who did not receive 4 cycles of first-line treatment went on to receive a second line of chemotherapy (n=13). The median OS of this small cohort was 398 days, compared with a median survival time of 99 days for the 178/194 patients who did not go on to receive second-line treatment. It could reasonably be argued that these 13 patients should have been excluded from the wider analysis of outcomes (including hospitalisation) for the <4 cycles of first-line treatment cohort given that they were clearly a very different group. This should be factored into any future study of this cohort, or other cohorts where similar outcomes are measured.

Inclusion of NSCLC as a predictive variable for the receipt of <4 cycles of chemotherapy may not make sense clinically. Whilst there is a validity to its presence in the model, as evidenced by the stepwise analysis, there were clear differences in the likelihood of the receipt of GRT based on cancer subtype, for reasons that have been discussed. In a future, potentially larger study, it would likely make sense to examine this outcome measure for NSCLC and SCLC subgroups separately.

3.4.7 Conclusions

The aim of the present study was to identify predictive factors for adverse outcomes in a cohort with advanced lung cancer for whom palliative chemotherapy was the agreed treatment plan. Research questions addressed by this study were:

1. What is the availability of routine electronic healthcare data relating to known risk factors for adverse outcomes in the cohort who received palliative chemotherapy for lung cancer commencing 2013-2015 in South East (SE) Scotland?
2. What are the demographic and clinical characteristics of the cohort with lung cancer who started first-line palliative chemotherapy in SE Scotland between 2013 and 2015?
3. To what extent did patients with advanced lung cancer treated between 2013 and 2015 in SE Scotland receive guideline-recommended treatment?
4. Which variables, identifiable at diagnosis and based on routine electronic healthcare data, were predictive of failure to complete first-line chemotherapy treatment as intended?
5. Which variables, identifiable at diagnosis and based on routine electronic healthcare data, were predictive of OS?
6. How do the findings of the analyses build on current understanding of the ways in which different patient and/or cancer-related factors lead to adverse outcomes?
7. What were the limitations around routine electronic healthcare data for this cohort how might these inform future research?

The present study examined a spectrum of clinical data, all sourced from routine electronic healthcare records, for a cohort of 397 patients with advanced lung cancer, all of whom were booked to receive first-line palliative chemotherapy in SE Scotland. There were some clear limitations surrounding the extent of available data, particularly with reference to known important factors such as comorbidity. However, data relating to a range of exploratory variables and outcome measures was, for the most part, available for analysis.

Key variables were identified which were independently predictive of OS; namely a high NLR, low Alb, low MA and low SMI. Of these four variables, only serum Alb is both routinely measured and reported in such a way that would allow immediate assessment of high/low

status (≥35 versus <35). However, the ANC and ALC are routinely reported and NLR is straightforward to calculate. MA and SMI assessment require examination of CT scans, and although no additional scans are needed, this is a potentially time-consuming step. Arguably however, the most important determinant of whether the predictive variables described should inform clinical practice, is the extent to which the percentage likelihood of being alive at different time points is meaningful to clinicians and their patients. In other words, how might the knowledge that a patient with a new diagnosis of lung cancer has a 44% chance of being alive 6 months later if they received chemotherapy (as Model 2 for OS would suggest if the patient had 3 unfavourable variables at diagnosis), affect whether the clinician offers chemotherapy to the patient and/or whether the patient chooses to go ahead with treatment?

Might a predictive model for the receipt of <4 cycles of chemotherapy be more meaningful? Certainly, the variables included in the predictive model for this outcome (namely NSCLC, BMI, ANC and ALC) are all readily available and do not require any additional analysis. Furthermore, not only was the receipt of <4 cycles of chemotherapy associated with significantly reduced OS, but it was also the case that this cohort spent proportionally far more of their survival time in the acute hospital than did their GRT-receiving counterparts. The decision to offer (and to choose to receive) palliative chemotherapy should be based on an understanding of the likely benefits and harms of treatment for the patient concerned. Knowledge that the patient in front of the oncologist has a very low chance of receiving GRT may usefully inform the SDM process, especially if the wider outcomes related to the receipt of GRT (namely OS and hospitalisation time) are also understood.

Ultimately, neither of the predictive models (for either OS or the receipt of <4 cycles of chemotherapy) may be enough to change clinical practice in themselves. Not least given that they require validation. The supplementary exploration through case studies described in Appendix H , revealed a more nuanced picture that is worthy of further study; in which a change in variable status following the receipt of chemotherapy may be additionally informative. As has been discussed, this is in line with a growing body of work in advanced lung cancer, for patients receiving either chemotherapy and immunotherapy.

The present study has demonstrated that the presence of a range of unfavourable biomarkers at diagnosis in patients with advanced lung cancer can help to identify individuals at risk of adverse outcomes. However, further studies are needed in order to explore the additional

discriminatory value of longitudinal measurement of key variables during treatment, and to validate the proposed and/or any refined models.

Chapter 4

Review of findings, implications for practice, future directions and conclusions

4.1 Summary of key learning from the two studies presented in this thesis

Two retrospective cohort studies were undertaken during 2015-2019, based on clinical review of individual lung cancer patient data from NHS health records to explore predictive factors for adverse outcomes with a view to:

- Developing a real-world evidence base which could inform the discussions that oncology teams have with people with lung cancer and those close to them about the likely benefits and risks of treatment.
- Supplementing the current evidence base around the prevalence and impact of cancer cachexia and how it might be evaluated in clinical practice; in order that it can be used to inform clinical decision making around the best treatment approach for individuals.

A critical finding common to both studies is that available routine clinical data did not enable any individuals to be classified formally as cachectic or non-cachectic in line with the Lancet 2011 consensus definition (46). An important limitation to highlight, again relevant to both studies, is that comorbidity data was not included for either cohort; because it was too variably recorded within clinical case records to be reliable.

The first study focused on a cohort who received chemoradiotherapy during 2008-2010. Median OS for this cohort was 19 months. Key findings from this study were that:

- Poor ECOG PS and low BMI were independently predictive of early mortality within 90 days following the completion of treatment.
- Low MA was independently predictive of significantly reduced OS.

The second study focused on a cohort with advanced lung cancer at diagnosis who were booked to receive first-line palliative chemotherapy, with treatment commencing during 2013-2015. Median OS for this cohort was 6.9 months. Key findings from this study were that:

- ECOG PS did not independently predict either OS or the receipt of GRT, despite this measure being the mainstay of patient assessment for treatment.
- High NLR, low serum Alb, low SMI and low MA were independently predictive of reduced OS.

- NSCLC, low BMI, ANC and ALC were independently predictive of a failure to complete 4 cycles of chemotherapy.

Both studies included patients with NSCLC and SCLC, and median OS did not differ between these subgroups in either study.

4.1.1 A review of the hypotheses underpinning both studies

The hypotheses underpinning both studies were introduced in Chapter 1 and these are revisited in light of learning from the two studies; both in terms of their findings, but also in relation to the study methods**:**

Hypothesis 1: Routine NHS healthcare data can be utilised in order to describe a range of real-world outcomes for two patient cohorts receiving lung cancer treatment.

The availability of routine electronic healthcare data for the cohorts of interest improved greatly over the course of the two studies. In particular, the advent of the online chemotherapy system, ChemoCare, was a major advancement that enabled ready access to a range of variable and outcome data.

Survival-related outcomes

A range of survival-related outcome measures (namely OS, 30-day and 90-day survival following the receipt of chemoradiotherapy, 30-day, 90-day and 12-month survival following diagnosis with advanced lung cancer) were included in both studies. Data relating to dates of diagnosis, treatments and dates of death were readily accessible for most patients, with only occasional difficulties identifying dates of death for patients who had died out-with an NHS institution (e.g. in an independent hospice). Therefore, it can be concluded that survival-related outcome measures are readily reportable using routine electronic NHS data. However, the extent to which the reported measures are meaningful, either in relation to a specific treatment decision and/or to patients at a more general level, is not known. Both studies incorporated survival-related outcomes that reflected both early mortality, whether in advance of, during or following treatment, and overall survival. For the chemoradiotherapy cohort, these timeframes were clearly distinct given the relatively long median OS. This distinction was less clear in the palliative chemotherapy cohort, whose median survival was less than 7 months.

Wider outcome measures

The total number of chemotherapy cycles received by patients in the chemoradiotherapy study was contained within the index (cancer audit) dataset and this was reported within the study. However, this cancer audit data was not linked to any clinical systems and so its accuracy could not be verified. Nor could it be linked to wider information about treatment type or treatment-related outcomes for each cycle.

ChemoCare was introduced in 2012 and this informed the selected timeframe for the second study cohort. Three main treatment-related outcomes were incorporated into the palliative chemotherapy study, all of which were detailed within ChemoCare; namely the total number of cycles received, chemotherapy dose reductions and treatment delays. ChemoCare also contained details of all systemic cancer treatments received by patients following first-line chemotherapy, and details of patients who received second or subsequent-line treatment were recorded. In addition, details of systemic treatment type were visible within ChemoCare, and although this level of detail was not recorded for most patients (many patients had modifications to their regimens and the data was too complex to categorise), it enabled patients who received immunotherapy or targeted therapy to be identified and excluded from the study. Information relating to chemotherapy toxicity was visible within ChemoCare for every patient in the palliative chemotherapy study. However, for reasons discussed earlier in the thesis this data was not extracted. Thus, there was a variety of available data relating to chemotherapy treatment which enabled broader outcome measures to be included in the palliative chemotherapy study. it is important to highlight that this data was extracted on a patient by patient basis by JB, aided latterly by two junior doctors. It was extremely time-consuming given the large number of patients and the multiple data entries required for every patient. In the future, it is anticipated that such data should be extractable by data managers, enabling far larger datasets to be examined with ease.

One critical area which has not been captured by the two studies presented in this thesis is the lived experience of people with lung cancer; arguably the most important 'real-world' outcomes of all. Routine healthcare data will only ever enlighten in this key area if PROMs are incorporated into clinical practice. A digital platform is currently being tested in SE Scotland with a view to capturing regular PROMs for people living with cancer. Without PROMs data, or qualitative interviews with patients and those close to them, we can only begin to imagine what the quantitatively described outcomes presented in this thesis might feel like in reality.

We do not know, for instance, whether for the individuals in the two included studies, QoL was more important than how long they lived, or vice versa. Nor do we know whether undergoing treatment with minimal or no physical benefit would be construed as the wrong decision. As was discussed in Chapter 1, we know, for some people, that having cancer treatment is extremely important, even if the likelihood of deriving real physical benefit is low. Thus, the ideal research based on routine clinical data should also include PROMs and/or other means of accessing the patient perspective. It is only with an understanding of their experience that we can honestly say we have tapped into outcomes that are unequivocally meaningful.

Hypothesis 2: Cachexia can be identified and described using routine NHS clinical data in two patient cohorts undergoing systemic treatment for lung cancer.

The diagnostic criteria for cancer cachexia, published in The Lancet Oncology by Fearon et al in 2011, are based on percentage weight loss, BMI and/or appendicular skeletal muscle mass data for individuals (46) with cachexia defined as weight loss >5%, or weight loss >2% in combination with either a BMI of <20 or sarcopenia below a defined, gender-specific, cut-off. The expert team who proposed the diagnostic criteria viewed these as a standardised starting point for future cachexia studies, with a view to validation and refinement of the criteria as needed. In addition to proposed diagnostic criteria, stages of cachexia were described with pre- (or early) cachexia (characterised by weight loss <5% alongside anorexia and metabolic changes) and refractory cachexia (with pro-catabolic cancer not responding to treatment, a poor performance status and expected survival of <3 months) featuring on the cachexia spectrum (46)

It was not possible to classify patients in either study described in this thesis as cachectic or non-cachectic in line with the Lancet Oncology definition, for the simple but fundamental reason that percentage weight loss is not routinely recorded by cancer teams in Scotland (46). In fact, even patient-reported weight loss is not recorded routinely, either in paper notes or within electronic clinical systems, and actual patient weights have only recently been captured routinely within the main electronic clinical system, TrakCare, used in SE Scotland. Patients undergoing chemotherapy in SE Scotland all have their height and weight recorded as standard, as their chemotherapy dose is calculated on the basis of these measurements and derived body surface area. However, before the advent of ChemoCare, this information was

variably available and was dependent on paper records within hard copies of case notes being available.

Thus, for the two studies described in this thesis, there was variability in terms of what routine, cachexia classification-related data was available; with weight and BMI data becoming readily accessible with ChemoCare, but before this often only being available in paper case notes, if at all.

Data relating to patients' skeletal muscle mass was routinely available if they had diagnostic CT scans that were accessible, and with images that were of an appropriate quality. This enabled formal body composition analysis to be undertaken for the majority of patients. As has been discussed previously, diagnostic CT scans for patients in SE Scotland with suspected lung cancer did not routinely extend to L3, hence the use of T4 in both studies. This meant that validated thresholds for low muscle mass could not be utilised, and thus, cohort and gender-specific cut-offs were derived and reported for each study. Therefore, even if percentage weight loss had been known, classifying patients as cachectic or non-cachectic on the basis of their skeletal muscle mass would not have been possible as the CT-based thresholds reported in the consensus definition are based on L3 images (46). Furthermore, whilst the SMI index derived from L3 images has been shown to correspond with whole body muscle mass (54), it is not known whether this is the case for T4 level muscle data. Therefore, in the two studies described in this thesis, patients with an SMI below the optimal-stratification thresholds were referred to as having 'low SMI' rather than sarcopenia. A further important point of reflection relating to body composition analysis is that neither study including fat-related measures, whether visceral, subcutaneous or both. As explained earlier in the thesis, this was because when the studies were planned, understanding of the significance that fat measures play in cancer cachexia was limited. More recently, fat measures have been included as standard in body composition-based cachexia research and it is accepted that future studies should examine both muscle and fat indices.

Given the known key difference in the two study cohorts in terms of their cancer stage at diagnosis (almost all chemoradiotherapy patients had stage III disease and all palliative chemotherapy patients had stage IV disease), and their very different median OS (the chemoradiotherapy cohort had a median OS almost three times that of the palliative chemotherapy cohort), it is of interest to compare their body composition indices at diagnosis.

Table 4.1 A comparison of median SMI and MA levels between the two study cohorts

	Female	**Male**	***p*-value** (F vs M)
Chemoradiotherapy cohort			
SMI	55.9	70.8	<0.001
Median (IQR)	49-61.3	59.2-76.3	
Palliative chemotherapy cohort			
SMI	52.8	65.0	<0.001
Median (IQR)	47.9-58.4	58.1-72.7	
***p*-value** (comparing the two study cohorts)	0.038	0.025	
Chemoradiotherapy cohort			
MA	42.5	45.3	0.026
Median (IQR)	36.6-48.8	40.5-50.4	
Palliative chemotherapy cohort			
MA	37.6	38.2	0.130
Median (IQR)	32.5-42.5	34.8-42.7	
***p*-value** (comparing the two study cohorts)	<0.001	<0.001	

Both median SMI and MA (in both females and males) were significantly lower in the palliative chemotherapy group than for the chemoradiotherapy group. This difference was highly significant for MA. This is in the context of comparable median ages and unknown comorbidity burdens for both groups. The main difference between the two cohorts at diagnosis was their cancer stage (typically stage III for the chemoradiotherapy cohort and exclusively stage IV for the palliative chemotherapy cohort). Their median OS was significantly different (19 months versus 6.9 months), but we do not understand the relationship between the observed differences in body composition measures and their survival.

Further comparison is drawn between the proportion of patients in the two studies with MA and SMI above and below the optimal stratification-derived cut-points:

Table 4.2 A comparison between the proportion of patients above and below the MA and SMI thresholds in the two study cohorts

	Female No. (%)	**Male No. (%)**	***p*-value** (F vs M)
Chemoradiotherapy cohort stratified SMI[a]			
Above threshold	77 (81.1)	44 (55.7)	<0.001
Below threshold	18 (18.9)	35 (44.3)	
Palliative chemotherapy cohort stratified SMI[b]			
Above threshold	53 (31.0)	70 (36.3)	0.288
Below threshold	118 (69.0)	123 (63.7)	
***p*-value** (comparing the two study cohorts)	<0.001	0.003	
Chemoradiotherapy cohort stratified MA[c]			
Above threshold	51 (52.6)	44 (55.0)	0.748
Below threshold	46 (47.4)	36 (45.0)	
Palliative chemotherapy cohort stratified MA[d]			
Above threshold	138 (78.9)	175 (87.5)	0.025
Below threshold	37 (21.1)	25 (12.5)	
***p*-value** (comparing the two study cohorts)	<0.001	<0.001	

[a]Stratified SMI threshold for females =46.2720, for males =67.2859.
[b]Stratified SMI threshold for females =51.1818, for males =68.6640
[c]Stratified MA threshold for females =40.45, for males =44.06
[d]Stratified MA threshold =31.5544

It is less straightforward to draw comparisons between two cohorts' data presented in Table 4.2. The SMI thresholds for the two cohorts are similar, albeit slightly higher in the palliative chemotherapy patients. A significantly greater proportion of the palliative chemotherapy patients had an SMI that was below the threshold. The MA threshold was significantly lower for the palliative chemotherapy group than for the chemoradiotherapy group, and this may partly explain the relatively low proportion of patients in this cohort who were below the threshold. The more accurate measure for comparison is likely to be the median SMI and MA levels, as described in Table 4.1.

BMI data was available for the majority of patients in both studies and this revealed that only a minority of patients was underweight at diagnosis. This is despite more than half of patients in the chemoradiotherapy group reporting that they were weight-losing at diagnosis, and high median NLR and ANC, along with low median Alb levels at diagnosis, in the palliative

chemotherapy group. Thus, there was convincing evidence of active systemic inflammation in a majority of patients in both studies, despite their apparently well-nourished body habitus.

It was not possible to classify patients in either study as having pre-cachexia or refractory cachexia as per the Lancet 2011 definition (46) because of a lack of essential data; but it is plausible that there were individuals in both studies in these categories. Fearon et al describe pre-cachexia as a state that may not progress to cachexia if the underlying cancer responds to treatment (46). In the palliative chemotherapy study, there was evidence that some individuals had active systemic inflammation at diagnosis, but that this diminished following the receipt of two cycles of chemotherapy, with associated extended survival. Arguably, such patients may have had pre-cachexia at diagnosis. At the other end of the spectrum, refractory cachexia may have been present in some of the poor prognosis patient subgroups, including those who completed fewer than 4 cycles of palliative chemotherapy in the second study. It is interesting to note that these patients had a median OS of 3.6 months, only slightly exceeding the <3 month survival described by Fearon et al (46), and furthermore, that the strongest predictor identifying these patients was low BMI. Within the chemoradiotherapy study, it was patients with a low BMI and a poor ECOG PS who were at greatest risk of early mortality. Thus, it is not a great leap to suggest that the two cohorts who died within 90 days of completing chemoradiotherapy or did not complete 4 cycles of palliative chemotherapy may have had refractory cachexia.

The two studies described demonstrate that there is a wealth of informative data held within routine NHS patient records, which enabled baseline characterisation of patients with cancer and also enabled predictive factors for adverse outcomes to be identified. However, cachexia per se could not be identified given the lack of percentage weight loss data. Given what is known about adverse outcomes in patients with cancer who report weight loss, and who have other indicators of systemic inflammation and/or cachexia, the case is strong for such data to be routinely recorded in cancer care. Without this data, it remains impossible to validate the diagnostic criteria proposed by Fearon et al, or to make informed suggestions for refinements.

Hypothesis 3: Cachexia-related biomarkers are predictive of adverse outcomes in two patient cohorts receiving lung cancer treatment.

Both studies described in this thesis identified key variables, present at diagnosis, which were predictive of adverse outcomes. However, as has previously been discussed in this thesis, we do not know the extent to which these predictive factors reflected cachexia. In part this is because we could not formally classify patients as cachectic or non-cachectic given the lack of percentage weight loss data. But it is also because we do not know whether variables such as blood markers of systemic inflammation reflected cancer cachexia, simply cancer, or other unmeasured factors such as chronic comorbid conditions.

Beyond the main palliative chemotherapy analyses, exploratory analysis of patients' routine follow-up CT scans for a sample of patients revealed that individuals with the highest NLR at diagnosis were less likely to respond to chemotherapy than were their lowest NLR counterparts. Further supplementary examination of purposively selected case study data (Appendix H) for patients with multiple adverse biomarkers at diagnosis but who survived longer than 12 months, was also informative; revealing, for the most part, considerable improvements in their NLR and Alb following the receipt of two cycles of chemotherapy. These additional analyses provided broader evidence that high levels of inflammation at diagnosis were associated with reduced disease response to systemic treatment, but also that inflammatory status was not fixed; with improvements in NLR and Alb in some individuals that appeared to translate to extended survival. These additional findings to the main analyses are worthy of further exploration with future work. However, they also enhance our understanding of the context within which certain variables are associated with adverse outcomes. We still cannot say whether the identified variables are 'cachexia-related biomarkers', as described in hypothesis 3. However, we know more about which factors, present at diagnosis, predict adverse outcomes, and we also understand that response to cancer treatment may be a key piece of the jigsaw linking unfavourable variables with reduced survival.

4.2 Implications for clinical practice

Chemoradiotherapy study

In clinical practice, ECOG PS remains a major discriminating factor for whether patients with lung cancer are deemed fit for systemic treatment. In the chemoradiotherapy study, an ECOG PS of ≥2 was, along with BMI <20, predictive of early mortality following the completion of treatment, with the caveat that there were only 4 patients with both unfavourable variables. When considering the relative risks and benefits of chemoradiotherapy, the intensive and often burdensome nature of the treatment itself is important. Where patients are anticipated to live well beyond their treatment, as the majority of the study cohort did here, the burden of treatment is likely to be outweighed by the survival advantage it confers. However, where patients are at high risk of dying in the weeks or short months following chemoradiotherapy completion, the burden of treatment may well outweigh potential benefits. Thus, identifying patients who are at high risk of dying shortly after chemoradiotherapy is of great clinical importance. The present study's findings suggest that it may be possible to identify such patients, but further validation studies should be undertaken before any clinical recommendations could be made. One final point regarding this subgroup of patients is that where it is decided, on whatever basis, that chemoradiotherapy is not an appropriate treatment modality to offer, this may not mean that other oncological treatments aren't helpful. It is possible that palliative chemotherapy alone, or indeed radiotherapy alone, are also options.

It is perhaps harder to envisage how the finding that low MA predicted significantly reduced OS in the chemoradiotherapy cohort might inform clinical practice; not least given that patients who had a low MA had a median OS of 15.2 months, suggesting that they may still have derived significant benefit from treatment. Further research is needed to explore what contributes to a low MA in patients with lung cancer, and the extent to which MA is a contributor to OS or whether it reflects other factors that are the primary determinants of poor survival. Such an understanding is critical if optimal patient selection for treatment is to be realised, but also if patients who are at risk of poor OS are to receive appropriate management of their wider health status alongside their cancer treatment. Such a strategy cannot be conceived without a deeper understanding of what low MA represents.

Palliative chemotherapy study

The finding that a high NLR, low Alb, low SMI and low MA predicted reduced OSin a population receiving palliative chemotherapy is of great interest; but is not sufficient at present to change clinical practice in any systematic or formal way. If such a model is validated in larger cohorts, one important question could be whether the additional work of undertaking body composition analysis for patients provides sufficient discrimination to the model to justify the resource. Indeed, it was high NLR and low Alb that were the most powerful predictors of reduced OS and it is possible that a future predictive model may simply contain these indices. One fundamental question is how useful it is to be able to identify patients at risk of reduced OS, and whether, in fact it is the predictive factors for the receipt of GRT that is more meaningful. As was raised for the reduced OS outcome in the chemoradiotherapy study, one possibility is that knowledge of a patient's increased risk of poor OS may prompt initiation of active supportive care alongside cancer treatment, rather than precluding the individual having cancer treatment.

Predictive factors identified for the non-receipt of GRT were NSCLC, low BMI, high ANC and low ALC. Patients who received <4 cycles of treatment had a median OS of just 3.6 months and spent a much larger proportion of their lives in the acute hospital than did their counterparts who received GRT; with a comparable number of acute inpatient bed days but over almost one third of the time. In the same vein as the chemoradiotherapy patients for whom the burden of treatment was more likely to outweigh the benefits, the cohort who did not receive GRT and had a median OS of 3.6 months were unlikely to have derived any physical benefit from palliative chemotherapy. It is possible to envisage that identifying patients at high risk of not receiving GRT could usefully inform practice, since this outcome is associated with such a short median OS and associated hospitalisation risk. However, further work is needed to validate the predictive variables in additional cohorts of patients. Where validation studies are based on retrospective data, one suggestion would be to exclude patients who went on to receive second-line chemotherapy, since survival for this subgroup has been shown to be significantly longer than for the majority who do not go on to receive further treatment. It would also make sense to undertake validation studies in patients with either NSCLC or SCLC, or to analyse this outcome separately, since it is unhelpful in clinical practice to have a risk factor that is the predominant cancer subtype. It is important to acknowledge that the two studies' findings are not transferable to the immunotherapy setting, since patients undergoing this treatment type

were excluded. This was necessary given the timeframe within which the cohorts received their treatment (a period when immunotherapy treatments were beginning to be utilised), but it remains a limitation of the findings in relation to current clinical practice. Increasing numbers of patients with advanced stage lung cancer are now receiving immunotherapy, either alone or in combination with chemotherapy, as a result of convincing evidence of benefit in certain subgroups (214) (215, 216) . First-line treatment with immune checkpoint inhibitors such as Pembrolizumab has been shown to offer extended survival over chemotherapy for patients with the programmed cell death ligand 1 (PD-L1) mutation (214). There is additional evidence that combination treatment with an immune checkpoint inhibitor and chemotherapy is superior than either drug alone for patients with both squamous and non-squamous NSCLC (215) (216). However, it is important to note that patients with adenocarcinoma NSCLC must be negative for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and Proto-oncogene tyrosine-protein kinase (encoded by ROS-1 gene) mutations in order to be eligible for consideration for immune checkpoint inhibitors. Furthermore, these treatments are currently reserved for patients with the best ECOG PS (0 or 1) because of the potential for life-changing and life-limiting toxicity, even following the cessation of the drugs. In current practice in SE Scotland, these treatments are received by around one-third of people with advanced NSCLC who are of the best performance status (ECOG PS 0 or 1). One subgroup that currently are not treatable with conventional chemotherapy are those with ischaemic heart disease, since the risk of ischaemic events on treatment is increased; and therefore immune-checkpoint inhibitors can offer a viable treatment choice if such patients are functionally fit. There is emerging evidence of some, albeit limited, survival benefit for patients with advanced SCLC treated with immunotherapy (217), although these treatments are yet to be utilised in clinical practice for this population.

Given the rising number of patients being treated with immunotherapy, the very real risk of serious complications and the high monetary cost of these treatments, improving our understanding of which patients may benefit the most (and of those who are at greatest risk of harm) is critical. In Chapter 3, section 3.4.5, the findings of the exploratory case studies analysis (in Appendix H) is presented in the context of an emerging evidence base of the significance of longitudinal biomarker measurement during oncological therapy. Several recent studies described in section 3.4.5 are based on populations receiving immune checkpoint inhibitors (181) (193) (205) (208). Thus, there is recognition that this is an important area for researchers.

At present, discussion with patients and those close to them about the potential risks and benefits of cancer treatment is informed by an evidence-base derived largely from RCTs. Such evidence is important, but it could feasibly be complemented by real-world evidence, as reported in this MD thesis; informing clinicians, as well as patients, families and carers, about the range of outcomes that people with the same diagnosis, receiving treatment in the same cancer centre or region, have experienced.

One more immediate way in which the two studies presented might inform practice is around routine data collection. As has already been discussed, we are currently unable to classify patients in SE Scotland as having cachexia as we do not routinely record their weight loss history, including percentage weight loss. Furthermore, we do not capture details of their comorbid conditions in any systematic way. Learning from routine data is one important way of improving patient outcomes, but this is limited by the scope and quality of routinely collected data. The findings from these two MD studies will be used to make the case for more comprehensive routine data collection in cancer in SE Scotland.

4.3 Implications for research

4.3.1 Additional work with the present studies' datasets

Further longitudinal data collection is underway for both study cohorts, informed by the emerging area of longitudinal biomarker assessment in patients receiving palliative chemotherapy and/or immunotherapy in the published literature, as well as the brief findings from the exploratory case studies presented in Appendix H. For the chemoradiotherapy cohort this will include examination of SMI and MA in patients' follow-up CT scans, since it is of interest to understand whether skeletal muscle characteristics change over time, and whether any changes are correlated with the primary cancer's response to treatment. In addition, measures of visceral and subcutaneous fat will be included, since there is growing evidence that these measures are also important alongside skeletal muscle measures (56). For the palliative chemotherapy cohort this will include longitudinal data relating to key variables before each cycle of chemotherapy, further enlightening on dynamic changes in indices during treatment and examining the clinical significance of these.

In addition, JB is exploring whether data relating to comorbid conditions and frailty may be accessible for the present two study cohorts; from ISD-held records comprising Scottish Morbidity Recording (SMR) data, derived from acute hospital outpatient appointments and inpatient admissions. An understanding of the prevalence of comorbid conditions in the two cohorts may help to explain some of the variation in markers of systemic inflammation, body composition and BMI. The existence of CT scans for patients in both studies from the years prior to their lung cancer diagnosis will also be explored, since body composition analysis using these images may enlighten about the extent to which the SMI and MA levels observed at diagnosis reflected active cancer, versus patients' comorbid conditions and/or were constitutional.

Finally, an examination of the two patient groups excluded from the present palliative chemotherapy study, namely those with mesothelioma and those who received immunotherapy or targeted therapy, will be undertaken. In the first instance, this will include basic description of the cohorts. Given the small size of the two cohorts, no attempt will be made to undertake formal analysis of predictive variables, but the models established for the NSCLC and SCLC cohorts will be tested in these two additional groups.

4.3.2 Future validation studies

Validation of the present two studies' findings with larger retrospective cohorts will be undertaken. Larger datasets will enable the potential impact of the amount of treatment received within patient groups with similar nutritional, inflammatory and functional profiles to be explored.

To this end, JB, her research supervisors and several co-researchers have secured funding from The Health Foundation for a study of around 10,000 patients with poor prognosis cancers across all of Scotland. The study will be based around routine cancer audit data, with formal data linkage with wider clinical and administrative datasets. The research objectives for this study are far broader than the only predictive factors for adverse outcomes, but the study will enable large scale validation of the predictive factors work in patients with several different cancer types to be undertaken. A 'whole population' approach will enable baseline characteristics, outcomes and predictive factors to also be described for patients who do not receive cancer treatment, since this BSC population is rarely studied.

Further small-scale validation studies are possible using the same data extraction techniques employed by JB for the MD, but as more sophisticated automated techniques for extracting data become possible, this may no longer be needed. Potential cohorts with other cancer types for future studies include those that are known to be associated with high levels of inflammation, e.g. mesothelioma and pancreatic cancer (182).

Ultimately, a prospective observational study of large lung cancer populations, incorporating accurate assessments of weight loss, comorbid conditions and physical functioning, should be conducted. To this end, JB, her research supervisors and other collaborators submitted a proposal to a Marie Curie funding call in December 2018, proposing a prospective study of 200 patients with lung cancer in SE Scotland. This application was not successful but it will be revised with a view to submission to an alternative funder. Alongside quantitative measures relating to systemic inflammation, cachexia and other areas, qualitative interviews will be undertaken with patients and those close to them, in order to gain insights into the lived experience of lung cancer, both for individuals who receive cancer treatment and those who do not. It is anticipated that this work will inform the development and further refinement of outcome measures for lung cancer populations that are meaningful to the people they describe.

4.3.3 Clinical trials and stratification by inflammatory status

Dolan et al recently published a systematic review of the incorporation of systemic inflammatory markers in prospective randomised clinical trials (218). Their findings were consistent with the evidence from observational studies that baseline systemic inflammatory status predicts OS. Dolan and colleagues propose prospective incorporation of systemic inflammatory indices, whether NLR and/or mGPS, in future RCTs. Given the emerging understanding that systemic inflammation is predictive of reduced PFS and disease response to treatment (as well as OS) (193) (208) (205) (181), stratifying formally by baseline inflammatory status and obtaining serial measurements on treatment may improve our ability to accurately identify patient subgroups at risk of particular outcomes.

4.4 Conclusions

The studies presented in this thesis have provided broad characterisation of two distinct cohorts diagnosed and treated with lung cancer in SE Scotland. Additionally, they have described of a range of clinical outcomes for these cohorts, including early mortality, OS and treatment-related outcomes. These descriptive findings, even in themselves, are of interest to clinicians working in cancer care in SE Scotland and beyond; since they are real-world outcomes, without the selection bias towards younger, fitter populations which can render clinical trial evidence challenging to translate to clinical practice (117). Beyond the descriptive findings, the two studies have each generated evidence of predictive factors for a range of outcomes. Data relating to each predictive factor were identified from routine clinical data from the time of diagnosis, without the need for patients to undergo additional tests. This fact is important when considering the potential clinical utility of the predictive models.

Identifying patients who are most likely to benefit from a proposed treatment for lung cancer, and least likely to come to harm, remains a major challenge for oncology teams. However, current clinical practice in SE Scotland does not involve any systematic assessment of cancer cachexia, systemic inflammation or comorbid conditions, despite a persuasive evidence base that tells us that patients with these conditions have worse outcomes. The lack of evolution of clinical practice despite this growing evidence base is not well understood.

The burden, or cost, of treatment that does not benefit patients is also not well-understood and further research is needed to investigate this critical area. Studies have been published, and discussed earlier in this thesis, relating to the economic costs of lung cancer treatments. In North America, these costs can be astronomical (140). However, in countries at the opposite end of the wealth spectrum, such as much of sub-Saharan Africa, costs to individuals and to the state are arguably just as important, with the financial consequences of cancer treatment potentially catastrophic. In the UK, the economic pressures associated with cancer care may be less visible than in either North America or sub-Saharan Africa, but they are real. The NHS has moral obligations to offer only treatments that are likely to benefit the individual, both for that individual's sake, but also to make best use of limited resources. New and emerging lung cancer treatments, such as immunotherapy and targeted therapy, come at significant cost; and it is therefore unsurprising that much of the recent research in predictive factors for PFS and OS in lung cancer has been in populations undergoing these treatments.

Electronic healthcare records offer exciting opportunities to learn from routine data about real-world populations, their pathways and outcomes. However, significant changes in practice around routine data capture are needed if observational research based on this data is to offer robust and meaningful findings. The disappointing conclusion that we could not classify the patients in either study as cachectic or non-cachectic is a case in point. It will be important to share this fact with clinical lung cancer teams and to make the case for refinements to routine data collection.

Both studies presented in this thesis were based on clinical review and extraction of individual patient data from their health records, since automated extraction was not technically possible for the majority of the data domains/sources of interest. Large scale data linkage studies using automated data extraction provide the opportunity for future validation studies, but there is a need to first establish the availability and reliability of clinical data, as well as the reliability of data extraction techniques. The studies described provide a foundation for an exciting future programme of work; with the ultimate goal of improving patient selection for a variety of lung cancer treatments, or indeed for a best supportive care approach.

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Original Article

Prediction of 90 Day and Overall Survival after Chemoradiotherapy for Lung Cancer: Role of Performance Status and Body Composition

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Abstract

Aims: If appropriate patients are to be selected for lung cancer treatment, an understanding of who is most at risk of adverse outcomes after treatment is needed. The aim of the present study was to identify predictive factors for 30 and 90 day mortality after chemoradiotherapy (CRT), and factors that were prognostic for overall survival.

Materials and methods: A retrospective cohort study of 194 patients with lung cancer who had undergone CRT in South East Scotland from 2008 to 2010 was undertaken. Gender, age, cancer characteristics, weight loss, body mass index (BMI), performance status (Eastern Cooperative Oncology Group; ECOG) and computed tomography-derived body composition variables were examined for prognostic significance using Cox's proportional hazards model and logistic regression.

Results: The median overall survival was 19 months (95% confidence interval 16.3, 21.7). Four of 194 patients died within 30 days of treatment completion, for which there were no independent predictive variables; 22/194 (11%) died within 90 days of treatment completion. BMI < 20 and ECOG performance status ≥ 2 were independent predictors of death within 90 days of treatment completion ($P = 0.001$ and $P = 0.004$, respectively). Patients with either BMI < 20 or ECOG performance status ≥ 2 had an odds ratio of death within 90 days of 5.97 (95% confidence interval 2.20, 16.19), rising to an odds ratio of 13.27 (1.70, 103.47) for patients with both BMI < 20 and ECOG performance status ≥ 2. Patients with low muscle attenuation had significantly reduced overall survival ($P = 0.004$); individuals with low muscle attenuation had a median survival of 15.2 months (95% confidence interval 12.7, 17.7) compared with 23.0 months (95% confidence interval 18.3, 27.8) for those with high muscle attenuation, equating to a hazard ratio of death of 1.62 (95% confidence interval 1.17, 2.23, $P = 0.003$).

Conclusion: Poor performance status, low BMI and low muscle attenuation identify patients at increased risk of premature death after CRT. Risk factors for adverse outcomes should inform personalised discussions with patients about the potential harms as well as the intended benefits of treatment.

Key words: Body composition; chemoradiotherapy; lung cancer; performance status; prognosis

Introduction

Lung cancer is the most common cause of cancer death worldwide. In the UK, a 10 year survival rate of 4.9% remains disappointingly low [1]. Given that most patients with lung cancer are incurable at diagnosis, with survival typically measured in 'months' [2], targeting treatments at improved quality of life, extended life or both is the priority [3]. In general, more radical treatment options carry more significant side-effects and a greater patient burden. An informed understanding of the probable outcomes following radical treatments is therefore important for clinicians and patients alike, ahead of treatment plans being made.

Clinical decision making in lung cancer in the UK is informed by national guidelines [4,5], which are underpinned by an extensive evidence base. However, the lung cancer population is typically elderly and multimorbid

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[2,4–6], and such patients are under-represented in clinical trials. Indeed, a recent review of international lung cancer guideline concordance questioned the generalisability of clinical guidelines to 'real world' patients [7].

In addition to cancer treatment modality, a number of factors are known to influence prognosis in lung cancer, including disease stage [2,6,8,9], age [2,6,8], gender [2,6], performance status [2,6,9,10], systemic inflammation [10–13], comorbidity [2,6], muscle wasting [11,14,15] and weight loss [8,15–18]. Cachexia, a complex syndrome encompassing many of these poor prognostic factors (namely weight loss, muscle wasting and systemic inflammation), is responsible for numerous negative patient outcomes in cancer [19]. However, it is not currently assessed or managed in any systematic or consistent way in the lung cancer clinic.

There is a lack of understanding about which predictive factors relate to early mortality (presumed to be a consequence of anti-cancer treatment) and which to reduced overall survival as a result of progressive cancer. The potential for severe adverse outcomes due to cancer treatment toxicity is well recognised [4,5] and death within 30 days of systemic anti-cancer treatment is now a commonly used proxy for quality of care [20]. Death within the 90 day post-treatment period is of interest in surgical cancer populations [21] and in Scotland lung cancer mortality within 30 or 90 days of the receipt of anti-cancer treatment is a routinely collected quality performance indicator [22].

Where evidence does exist around prognostic and predictive factors, assimilating this into clinical decision making can be a challenge. Furthermore, there can be a lack of understanding by some patients that cancer treatment has the potential to do more harm than good. Evidence is needed to inform discussions between lung cancer clinicians and their real world patients about the probable benefits and the potential harms of treatment. It is only with this evidence that cancer treatments can be targeted most appropriately.

The aim of this retrospective cohort study was to identify predictive factors for 30 and 90 day mortality after chemoradiotherapy (CRT) for lung cancer, and factors that were prognostic for overall survival.

Materials and Methods

All patients diagnosed with lung cancer between 2008 and 2010 in South East Scotland given CRT were included in the retrospective cohort study. National Caldicott approval was granted for the collation of existing patient data.

Population

Individuals diagnosed with lung cancer in South East Scotland between 2008 and 2010 given either concurrent or sequential CRT were included. Concurrent CRT is the UK guideline recommended treatment for patients with stage II–III non-small cell lung cancer (NSCLC) not suitable for surgery but of good performance status, and for patients with limited small cell lung cancer (SCLC) whose disease is encompassable in a radiotherapy field and are of good performance status [4,5]. Sequential CRT is less effective in NSCLC than concurrent treatment [23], although it remains an option for patients unfit for concurrent CRT at diagnosis who respond to chemotherapy [4].

Demographic and clinical information were obtained from the South East Scotland Cancer Audit Network database, including cancer histology and stage [24], Eastern Cooperative Oncology Group (ECOG) performance status [25] at diagnosis and details of completed cancer treatments. The date of diagnosis for each patient was taken as the date of their diagnostic computed tomography scan. Height, weight, weight loss history at diagnosis and details of comorbid illness were obtained from clinical notes. Routine diagnostic computed tomography scans were utilised for body composition analysis (see 'Computed tomography body composition analysis' section) and disease progression after treatment was assessed by comparing diagnostic and follow-up computed tomography scans (see 'Computed tomography evidence of progression' section). Where patients had died, details of registered causes of death were obtained from the Scottish Health Services, Information Services Division.

Body Mass Index

Body mass index (BMI) was classified into: underweight (<20), normal weight (20–24.9), overweight (25–29.9) or obese (>30) [15].

Weight Loss as a Marker of Cachexia

Patient-reported weight loss (of any specified or unspecified amount) at diagnosis was recorded, and has previously been shown to be a reliable measure [26,27]. No attempt to quantify weight loss was made, as this was inconsistently recorded or reported by patients.

Computed Tomography Body Composition Analysis

Diagnostic computed tomography scans were accessed from the Picture Archiving and Communication System (PACS) and a single cross-sectional image from the fourth thoracic (T4) vertebral level was used for body composition analysis [15,28–32]. Skeletal muscle area (cm^2) and muscle attenuation (measured in Hounsfield Units, HU) were derived for each patient by a single trained investigator using *Slice-O-Matic* V4.3 software (Tomovision, Montreal, Canada) [14,15,28,30,31]. A HU range of −29 to 150 was used to identify skeletal muscle. Whole body muscle mass (muscularity) was calculated by normalising skeletal muscle area (cm^2) for stature (m^2), and was reported as skeletal muscle index. Fatty infiltration of skeletal muscle (myosteatosis) was quantified on the basis of skeletal muscle density and was recorded as muscle attenuation.

Thresholds for high/low skeletal muscle index and muscle attenuation levels using computed tomography-based body composition analysis have been reported for

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several cancer populations [14,15,28,30,31,33,34], but not specifically in CRT for lung cancer. Given this, optimal stratification [14,35] was used to determine cut-offs for high/low skeletal muscle index and muscle attenuation (continuous covariates) in relation to overall survival. The latter was conducted using SAS software, version 9.4 of the SAS System for Windows. Gender-specific cut-offs are reported for both muscularity and muscle attenuation, in line with previous work [15,28,31].

Computed Tomography Evidence of Disease Progression

Post-treatment computed tomography scans were examined by a single thoracic radiologist for evidence of disease progression. There are recognised challenges associated with accurately assessing disease recurrence/response after high-dose thoracic radiotherapy [36,37]. Therefore, no attempt was made to quantify disease. Rather, a pragmatic assessment was made, with patients classified as having progressive disease (local and/or distant) or not. The radiologist was blind to patient outcomes during the review.

Outcome Measures

Three outcome measures were examined, 30 day, 90 day and overall survival: 30 and 90 day survival were calculated from the last day of receipt of cancer treatment (primary CRT only); overall survival was calculated from the date of diagnosis.

Statistical Analysis

Data were analysed using SPSS v19 (IBM SPSS Statistics, Ontario, Canada). Simple bivariate associations of categorical variables were analysed using the chi-squared test. The relationships between a continuous and a categorical variable were analysed with Student's *t*-test or the Mann–Whitney U for non-parametric data. Continuous variables were examined with Pearson correlation. Multivariable relationships were examined using general linear models (usually logistic regression) to explore the association between clinical and demographic factors and the outcome variables. Cox regression was used to examine the relationship between the explanatory variables and survival.

Where appropriate, odds ratios for logistic regression and hazard ratios for survival are reported. All tests are two-sided, and a significance level of 5% has been assumed.

Results

Patient Characteristics at Diagnosis

Demographic and clinical characteristics at diagnosis for all 194 patients who underwent CRT for lung cancer diagnosed in South East Scotland between 2008 and 2010 are outlined in Tables 1 and 2. Most patients had either stage III NSCLC or limited stage SCLC, and were treated with concurrent CRT. Ninety per cent of patients had an ECOG performance status of 0/1. The mean BMI for both men and women was in the overweight (BMI > 25) category, with over half of women and nearly two-thirds of men classified as either overweight or obese. Over half of the patients reported weight loss at diagnosis. Male patients typically had more muscle than females and slightly higher muscle attenuation.

Table 1
Demographic and clinical characteristics at diagnosis of 194 patients who underwent chemoradiotherapy

Characteristic	All patients, $n = 194$
Age (years)	
Median	64
Interquartile range	58–70
	No. (%)
Male	91 (46.9)
Female	103 (53.1)
NSCLC	113 (58.2)
SCLC	81 (41.8)
NSCLC	
Stage I	0 (0)
Stage II	5 (4.4)
Stage III	107 (94.7)
Stage IV	1 (0.9)
SCLC	
Limited	70 (86.4)
Extensive	11 (13.6)
Chemoradiation schedule	
Concurrent	151 (77.4)
Sequential	43 (22.2)
ECOG performance status	
0	29 (14.9)
1	147 (75.8)
2	16 (8.2)
3	2 (1.0)
4	0 (0)

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group.

Association between Body Mass Index, Weight-losing Status and Body Composition

As BMI increased, so did muscularity ($r = 0.44$, $P < 0.001$), although muscle attenuation fell ($r = 0.37$, $P < 0.001$). See 'Computed tomography body composition analysis' section for an explanation of measures. Patients reporting weight loss at diagnosis had a lower BMI (mean BMI 25.0 versus 27.7, 95% confidence interval of difference 1.23, 4.17; $P < 0.001$) than those who reported no weight loss.

Chemotherapy Completion Rates

All 194 patients received some chemotherapy, but 25 patients completed only one or two cycles (where the intention was three or more). Patients completing fewer than three cycles of chemotherapy were more likely to be

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Table 2
Body composition and weight loss characteristics at diagnosis of 194 patients who underwent chemoradiotherapy, by gender

	Males, $n = 91$	Females, $n = 103$	Overall, $n = 194$
	No. (%)	No. (%)	No. (%)
Mean (standard deviation) BMI (kg/m^2)*	26.6 (4.7)	25.8 (5.7)	26.2 (5.2)
BMI category*			
Underweight (<20)	6 (6.7)	13 (12.9)	19 (10.0)
Normal (20–24.9)	26 (29.2)	35 (34.7)	61 (32.1)
Overweight (25–29.9)	39 (43.8)	33 (32.7)	72 (37.9)
Obese (>30)	18 (20.2)	20 (19.8)	38 (20.0)
Weight-losing status†			
Weight-losing	52 (57.1)	57 (57.0)	109 (57.1)
Non-weight-losing	39 (42.9)	43 (43.0)	82 (42.9)
Computed tomography-derived skeletal muscle area (cm^2)‡			
Median	207.1	138.1	161.7
Interquartile range	182.5–226.9	122.8–153.9	135.5–202.7
$P < 0.001$§	$n = 80$	$n = 97$	$n = 177$
Skeletal muscle index (cm^2/m^2)‖			
Median	70.8	55.9	60.0
Interquartile range	59.2–76.3	49.0–61.3	53.1–69.7
$P < 0.001$§	$n = 79$	$n = 95$	$n = 174$
Skeletal muscle attenuation (HU)‡			
Median	45.3	42.5	43.5
Interquartile range	40.5–50.4	36.6–48.8	38.6–50.2
$P = 0.03$§	$n = 80$	$n = 97$	$n = 177$

BMI, body mass index.
* Data available for 190/194 patients (missing data for two men and two women).
† Status available for 191/194 patients (missing data for three women).
‡ Available for 177/194 patients (17 diagnostic computed tomography scans unavailable/poor quality image).
§ Mann–Whitney U test.
‖ Available for 174/194 patients (17 diagnostic computed tomography scans unavailable/poor quality image, plus height data not available for a further three patients).

older (67.3 years for those completing less than three cycles versus 62.3 years for those completing three or more cycles; 95% confidence interval of difference 0.84, 8.85; $P = 0.02$) and to have NSCLC (94/169) rather than SCLC (19/25); $P = 0.054$.

Follow-up Computed Tomography Scans

In total, 172/194 patients had computed tomography scans following the completion of CRT. The median time to follow-up scan from the last day of treatment was 91 days (interquartile range 55–111.5); 158/172 computed tomography scans encompassing the required fields were available for specialist radiology review; 29/158 patients had clear evidence of disease progression, either locally ($n = 5$), at a distant site ($n = 17$) or both ($n = 7$).

Survival Outcome Measures

Thirty and 90 day survival

Twenty-two of 194 patients (11%) died within 90 days of CRT completion, of whom four died within 30 days. There were insufficient deaths within 30 days for a meaningful analysis. Ten of 22 patients' follow-up computed tomography scans were available for evaluation. Only 2/22 showed clear evidence of disease progression, although the reported primary cause of death for 20/22 patients was 'lung cancer'.

Univariate analysis of variables associated with death within 90 days of treatment completion is reported in Table 3. Patients with ECOG performance status ≥ 2, BMI < 20 or who reported weight loss were significantly more likely to die within 90 days. On multivariable analysis, only BMI < 20 and ECOG performance status ≥ 2 remained independently associated with death within 90 days of CRT completion (see Table 3). Combining these significant variables to create a new variable proved additionally predictive. Nine of 29 patients with either poor ECOG performance status or BMI < 20 died within 90 days of treatment completion (odds ratio of death 5.97 [2.20, 16.19]; $P < 0.001$, when compared with patients with performance status 0/1 and BMI ≥ 20). Two of four patients with both poor performance status and BMI < 20 died within 90 days of treatment completion (odds ratio of death 13.2 [1.70, 103.47]; $P = 0.014$, when compared with performance status 0/1 and BMI ≥ 20).

Overall survival

The median overall survival was 19.0 months (95% confidence interval 16.3, 21.7). There was no significant difference in overall survival between those with different cancer type or stage, reflecting the relative homogeneity of the cohort. On univariate analysis, ECOG performance status,

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Table 3
Univariate and multivariable analysis of predictors of death within 90 days of chemoradiotherapy completion

	Died within 90 days of treatment completion		Univariate analysis Odds ratio of death within 90 days (95% confidence interval)	Multivariable analysis Joint odds ratio of death within 90 days (95% confidence interval)
	Yes ($n = 22$) n (%)	No ($n = 172$) n (%)		
Age (continuous, per year increase)	n/a	n/a	1.02 (0.97, 1.07) $P = 0.41$	–
Gender (female versus male)				
Female	8 (7.8)	95 (92.2)	0.46 (0.19, 1.16)	–
Male	14 (15.4)	77 (84.6)	$P = 0.10$	
Cancer type (NSCLC versus SCLC)				
NSCLC	14 (12.4)	99 (87.6)	1.29 (0.51, 3.24)	–
SCLC	8 (9.9)	73 (90.1)	$P = 0.59$	
NSCLC stage (III versus II)				
III	13 (12.1)	94 (87.9)	Unable to calculate odds ratio.	–
II	0 (0)	5 (100)	Fishers exact test, $P = 1.0$	
SCLC stage (Extensive versus limited)				
Extensive		10 (90.9)	0.90 (0.10, 8.11)	–
Limited	–	63 (90.0)	$P = 0.93$	
ECOG performance status (≥2 versus 0/1)				
≥2	6 (33.3)	12 (66.7)	5.00 (1.65, 15.12)	3.97 (1.20, 13.08)
0 or 1	16 (9.1)	160 (90.9)	$P = 0.004$	$P = 0.024$
BMI (<20 versus ≥20)				
<20	7 (36.8)	12 (63.2)	6.07 (2.08, 17.73)	3.91 (1.24, 12.38)
≥20	15 (8.8)	156 (91.2)	$P = 0.001$	$P = 0.020$
Reported weight loss (yes versus no)				
Yes	18 (16.5)	91 (83.5)	3.85 (1.25, 11.88)	2.89 (0.89, 9.37)
No	4 (4.9)	78 (95.1)	$P = 0.019$	$P = 0.08$
SMI at diagnosis (low versus high)*				
Low	10 (18.9)	43 (81.1)	2.33 (0.92, 5.87)	–
High	11 (9.1)	110 (90.9)	$P = 0.07$	
Computed tomography scan-derived muscle attenuation at diagnosis (low versus high)†				
Low	8 (9.8)	74 (90.2)	0.68 (0.27, 1.74)	–
High	13 (13.7)	82 (86.3)	$P = 0.42$	

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; SMI, skeletal muscle index.
* Optimal stratification SMI cut-offs for men = 67.3 ($n = 44$ above and 35 below) and for women = 46.3 ($n = 77$ above and 18 below).
† Optimal stratification muscle attenuation cut-offs for men = 44.1 ($n = 44$ above and 36 below) and for women = 40.5 ($n = 51$ above and 46 below).

patient-reported weight loss at diagnosis and low muscle attenuation were significantly associated with survival (see Table 4). Only muscle attenuation remained independently associated with survival on multivariable analysis. The median survival for patients with low muscle attenuation was 15.2 months (95% confidence interval 12.7, 17.7) and for patients with high muscle attenuation was 23.0 months (95% confidence interval 18.3, 27.8), hazard ratio 1.61, $P = 0.03$ (Figure 1).

Discussion

Treatment with CRT for lung cancer is lengthy and often burdensome. The expectation for most patients is of significantly extended survival. Current criteria for starting treatment include disease stage and performance status. In the present study, 98% and 89% of patients, respectively, survived more than 30 and 90 days after the completion of CRT, thereby suggesting that, for most, these criteria are fit for purpose. For the 22/194 (11.3%) patients who died within 90 days, BMI < 20 and ECOG performance status ≥ 2 at diagnosis were independent predictors of death.

Metabolic and Functional Bankruptcy Predicts Death within 90 Days of Treatment Completion

The present study population was selectively well, by virtue of the fact that all were deemed fit to undergo CRT; indeed, >90% of patients were of the best performance status (ECOG 0/1). Eighteen of 194 patients who had an ECOG performance status ≥2 at diagnosis had an odds ratio of death within 90 days of treatment completion of 3.97 (adjusted) compared with their fitter counterparts (ECOG performance status 0/1). A poor performance status as measured by ECOG has repeatedly been shown to be associated with reduced

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Table 4
Univariate and multivariable analysis evaluating the prognostic significance of a range of demographic and clinical variables (in relation to overall survival). The second category is the reference category

	Alive at last record	Died	Univariate analysis Hazard ratio of death (95% confidence interval)	Multivariable analysis Joint hazard ratio of death (95% confidence interval)
Age (continuous, per year increase)	–	–	1.00 (0.99, 1.02) $P = 0.68$	–
Gender (female versus male)				
Female	18 (17.5)	85 (82.5)	0.84 (0.62, 1.14)	–
Male	10 (11.0)	81 (89.0)	$P = 0.26$	
Cancer type (NSCLC versus SCLC)				
NSCLC	17 (15.0)	96 (85.0)	1.21 (0.88, 1.64)	–
SCLC	11 (13.6)	70 (86.4)	$P = 0.24$	
Cancer stage (NSCLC stage III versus II)				
III	14 (13.1)	93 (86.9)	3.64 (0.89, 14.80)	–
II	3 (60.0)	2 (40.0)	$P = 0.07$	
Cancer stage (SCLC extensive versus limited)				
Extensive	1 (9.1)	10 (90.9)	1.68 (0.85, 3.31)	–
Limited	10 (14.3)	60 (85.7)	$P = 0.13$	
ECOG performance status (≥2 versus 0/1)				
≥2	1 (5.6)	17 (94.4)	1.78 (1.04, 2.84)	1.36 (0.80, 2.30)
0 or 1	27 (15.3%)	149 (84.7)	$P = 0.035$	$P = 0.25$
BMI (<20 versus ≥20)				
<20	2 (10.5)	17 (89.5)	1.27 (0.76, 2.10)	–
≥20	26 (15.2)	145 (84.8)	$P = 0.36$	
Reported weight loss (yes versus no)				
Yes	10 (9.2)	99 (90.8)	1.43 (1.05, 1.95)	1.32 (0.95, 1.83)
No	16 (19.5)	66 (80.5)	$P = 0.025$	$P = 0.10$
Computed tomography scan-derived SMI at diagnosis (low versus high)				
Low	6 (11.3)	47 (88.7)	1.23 (0.87, 1.74)	–
High	19 (15.7)	102 (84.3)	$P = 0.24$	
Computed tomography scan-derived muscle attenuation at diagnosis (low versus high)				
Low	5 (6.1)	77 (93.9)	1.62 (1.17, 2.23)	1.61 (1.16, 2.23)
High	20 (21.1)	75 (78.9)	$P = 0.003$	$P = 0.004$

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; SMI, skeletal muscle index.

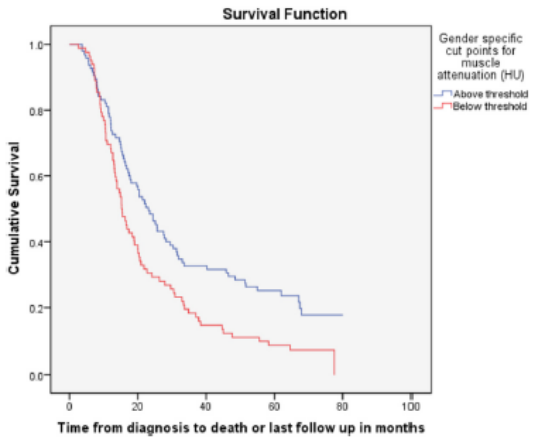

Fig 1. Kaplan–Meier curve showing the prognostic value of muscle attenuation for overall survival.

survival in lung cancer [9,10,18,38–40]. In a landmark study of weight loss in cancer [17], poor performance status (ECOG ≥ 2) surpassed weight loss as the major determinant of reduced survival.

In the present study, 10.0% of patients were underweight by BMI (BMI < 20) at diagnosis, a figure comparable with other reported lung cancer series [15,16,28]. Patients with a low BMI were at increased risk of death within 90 days of CRT completion. Previous studies have shown neoadjuvant chemotherapy to be associated with a significant loss of lean body mass [41] and one explanation for the present findings would be that during CRT those with a low BMI may reach a critical level of malnutrition that compromises survival. In a study of >8000 patients with advanced cancer prone to developing cachexia, Martin *et al.* [16] showed the importance of pre-existing reduced nutritional reserve (low BMI) as an independent adverse prognostic criterion. An earlier study by Martin *et al.* [15] similarly showed BMI to be the most important determinant of survival.

Martin *et al.* [16] have recently coined the concept of 'metabolic bankruptcy' as a description of patients with the

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lowest BMI for whom the outlook is bleak. In the present study, it was arguably both metabolic and functional bankruptcy, with BMI < 20 and ECOG ≥ 2, predicting death within 90 days of treatment completion. It is worthy of note that patients treated with CRT with BMI < 20 and ECOG ≥ 2 identified by this study were deemed fit for treatment, in contrast with other patients with disease that was theoretically treatable but who were not fit for the treatment (not included in this study). Thus, the present study's findings potentially underestimate the negative effects of a low BMI and poor ECOG in predicting early mortality after CRT. Identifying patients in the lung cancer clinic with these risk factors for early death is straightforward, and could usefully inform discussions with patients about the potential risks of proposed cancer treatment.

Gross tumour volume and pre-treatment pulmonary function have previously been shown to be independently prognostic for early mortality after CRT for lung cancer [42]. This earlier study did not include BMI, and ECOG performance status was only prognostic on univariate analysis.

Low Muscle Attenuation, Indicative of Systemic Inflammation, is Prognostic for Overall Survival

In the present study, low muscle attenuation (myosteatosis, infiltration of muscle by fat) was independently prognostic for overall survival. Individuals with low muscle attenuation had a median survival of 15.2 months (95% confidence interval 12.7, 17.7) compared with 23.0 months (95% confidence interval 18.3, 27.8), for those with high muscle attenuation, $P = 0.03$. Myosteatosis, indexed by low muscle attenuation on computed tomography scans, is associated with skeletal muscle wasting as part of the cancer cachexia syndrome [43], but may also reflect ageing, obesity or non-malignant disease [31,44]. In comparison with other studies reporting muscle attenuation values in lung cancer, the present CRT cohort had relatively high average muscle attenuation. This could be explained by the earlier disease stage and relative fitness compared with other reported populations [15,33]. The association between myosteatosis and systemic inflammation is known [31,33,44]. Systemic inflammation is a well-recognised poor prognostic factor in a range of cancer types, with several studies reporting reduced survival in lung cancer patients with active systemic inflammation [10–13,45]. The association between low muscle attenuation and adverse survival in the present study may be due to a number of different processes, including occult disseminated cancer, cachexia and comorbidity.

A history of weight loss at diagnosis has repeatedly been shown to be prognostic in lung cancer [8,15,16,18,39]. In the present study, weight loss was prognostic on univariate but not multivariable analysis, suggesting that its prognostic significance was related to low muscle attenuation and systemic inflammation. Weight loss as low as 2.4% has been linked with reduced survival [16], in line with the concept of early or 'pre-cachexia' [19]. Weight loss during the first 3 weeks of CRT treatment for lung cancer (before the onset of radiation-induced oesophagitis) has also been shown to be independently prognostic [40]. In a comparable CRT cohort, weight loss on treatment was shown to occur independently of oesophagitis and nutritional intake [46]. It therefore appears likely that cachexia drives weight loss in advance of, alongside and as a direct result of cancer treatment [19]. For most patients in the present study, cachexia would have been apparently invisible, with fewer than 10% of patients underweight by BMI. Therefore, looking beyond an apparently well-nourished exterior is needed.

Limitations

The retrospective nature of the present study brings a number of limitations. Outcome measure selection was limited by the availability of routine clinical data from 2008–2010. Therefore, measures relating to quality of life, causes of hospitalisation, actual causes of death and the incidence and severity of CRT toxicity were not included. Despite a moderately sized cohort (194) who underwent CRT, there were low numbers in some stratified analysis groups. The present study utilised cut-offs of 30 and 90 days following receipt of last cancer treatment to identify early deaths. An alternative approach identifying deaths within 180 days of starting CRT [42] would remove treatment length as a potential confounder.

Conclusions

The present study has identified three clinical variables (low performance status, low BMI and low muscle attenuation) associated with significantly reduced survival (early and late) after CRT for lung cancer. Further work is needed to validate these findings and to examine the relationship between comorbid illness, frailty and cachexia. Understanding more about actual causes of early death, including the relationship with treatment toxicity, should also be a priority. Patient selection for lung cancer treatment remains an inexact science, but could be improved by better understanding of which patients are most at risk of adverse outcomes after treatment.

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This work is dedicated to the memory of Ken Fearon, Professor of Colorectal Surgery and world leader in cachexia research. His academic expertise and mentorship were so greatly valued and he is very sadly missed. The authors also wish to acknowledge the Melville Charitable Trust (funded J. Bowden research fellowship), Professor Gerry Humpris and Dr Damien Williams, University of St Andrews (MD supervisors of J. Bowden), SCAN lung cancer team.

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Date received DPCC 13/6/14
Expected Approval date 10/7/14

NHS
Fife

APPLICATION FOR CALDICOTT APPROVAL FOR USE OF PATIENT IDENTIFIABLE DATA

User Details

Name: Dr Joanna Bowden

Position: Consultant in Palliative Medicine/Research Fellow

Organisation: NHS Fife/University of Edinburgh

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Name(s) of any co-user(s): None

You must address the 6 Caldicott Principles when submitting this request for data

1. Project/Audit title

Evaluating the role of comorbidity and muscle wasting in clinical outcomes for patients with lung cancer

2. Please provide additional background description of your project/audit to enable Caldicott Guardian to understand what outcome you trying to achieve.

Cancer cachexia is a common and highly debilitating syndrome affecting around 60% of patients with lung cancer. Its hallmarks are muscle wasting, weight loss and weakness. It limits the oncological treatments that patients can receive, and is a direct cause of death in many. Historically, there have been few effective treatments for cachexia, though there are a number of new and promising therapies on the horizon. However, these have typically only been tested in the fittest of patients who do not have comorbid illnesses (such as chronic respiratory diseases) alongside their cancer. And yet comorbidity is common in patients with lung and many other cancers and may in itself cause cachexia and premature death. Normal ageing, frailty and oncological treatments are other common causes of muscle wasting. We do not yet understand the relationship between comorbidity, frailty and other patient factors, and what this might mean for future cachexia interventions.

This evaluation will identify key variables in the development of muscle loss and shortened survival through a retrospective analysis of 2000-3000 patients presenting with lung cancer between 2008 and 2010 in Fife and Lothian. Developing an accurate picture of cachexia in the context of patients' wider health and function is critical if we are to identify the most appropriate patients, with the most to gain, for active cachexia management. Importantly, this will also involve identifying the most unwell patients for whom cachexia intervention would be futile, and for whom palliative care should be the priority.

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3. Supporting information

Proposed data for collection attached in separate document. It is mostly to come from existing Scan database (all fields in red), though some (in blue) is to be collected by me from individual patients' case records and scans. I have had several discussions with Lorna Bruce and the SCAN lung cancer team about the project and about which data is available. Colin Selby, Chair of SCAN Lung Cancer Group, has given me his approval for the study. If Caldicott approval is granted, I will submit a formal request to SCAN for access to the data outlined in the attached document.

4. Name of organisation receiving data (if not within NHS Fife)

Patient identifiable data will all be stored on password protected drives on NHS Fife and NHS Lothian servers. Anonymised data will be transferred via secure nhs email or encrypted USB stick to a password protected drive on the University of Edinburgh server.

5. What patient identifiable information are you looking to use?

CHI Number	Yes
Forename	Yes
Surname	Yes
Initials	No
Age	No
Date of birth	Yes
Gender	Yes
Address	No
Postcode	Yes
Other, please specify.....	Patients' staging CT scans (for body composition analysis) although these will be anonymised once downloaded using dicom-anonymiser software.

6. Please explain how the proposal meets the following Six Caldicott Principles. (The Caldicott Committee Report on the Review of Patient-Identifiable Information. Department of Health, December 1997)

Justify the purpose

Principle 1 Justify the purpose(s)	Every proposed use or transfer of patient-identifiable information within or from an organisation should be clearly defined and scrutinised, with continuing uses regularly reviewed, by an appropriate guardian.

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Aim:

To evaluate clinical outcomes for patients with lung cancer, comorbidity and muscle wasting, with a view to targeting future cachexia interventions most appropriately.

Objectives:

1. To describe which variables are associated with low muscularity in patients with lung cancer.
2. To identify which variables are independent determinants of low muscularity in patients with lung cancer.
3. To establish whether low muscularity is associated with reduced survival in patients with lung cancer.
4. To explore the relationship between comorbidity, muscularity and which lung cancer treatments are offered and completed.
5. To describe which variables (including cachexia, factors associated with cachexia and known prognostic variables such as cancer stage) are independently prognostic in patients with lung cancer.

Design: A retrospective case note evaluation to determine the significance of key variables to the development of muscle loss in patients with lung cancer and to determine the influence of the latter on duration of survival

Population: A retrospective electronic case note review of all patients presented at the regional lung cancer multidisciplinary team (MDT) meetings in NHS Fife and NHS Lothian between 2008 and 2010. Approximately 1000 patients are diagnosed per year in these two regions and the population for analysis is likely to be approximately 3000.

Data collection: Demographic and clinical characteristics including cancer type, stage, treatment (planned and completed) age, height, weight, weight loss and performance status. Lean body mass will be assessed using routine CT imaging and Slice-O-Matic software. Obesity will be scored using BMI and comorbidity will be scored using the Charlson Comorbidity Index (CCI) and the Simplified Comorbidity Score (SCS).

Analysis: The population will be detailed using simple descriptive statistics. The relationship between cancer type, cancer stage, age, sex, body mass index (BMI), weight-loss, co-morbidity and CT-derived muscle mass will be explored by both discriminate analysis and multivariate regression using generalised linear models. These same variables will be assessed regarding their ability to predict overall survival, using a proportional hazards model.

In 2015, if the above study has progressed sufficiently, we intend to develop a small prospective study of patients with newly diagnosed lung cancer that will look in more detail at the impact of comorbidity and frailty on their muscle mass and survival. A second Caldicott application (along with formal ethical approval) will be sought at a later date for this.

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Fife

Justify the requirement to use patient-identifiable data

Principle 2 Don't use patient-identifiable information unless it is absolutely necessary	Patient-identifiable information items should not be included unless it is essential for the specified purpose(s) of that fow. The need for patients to be identified should be considered at each stage of satisfying the purpose(s).

Patient-identifiable data is an absolute requirement of this project to allow individuals' data to be collected, traced to source and compared across exiting data sets. However, once the dataset is completed, all identifiable data will be removed for the analysis stage.

Justify the inclusion of each data field required

Principle 3 Use the minimum necessary patient identifiable information	Where use of patient-identifiable information is considered to be essential, the inclusion of each individual item of information should be considered and justified so that the minimum amount of identifiable information is transferred or accessible as is necessary for a given function to be carried out.

CHI numbers are needed as unique identifiers to allow individuals' data to be traced back to source. This may be necessary to investigate unexpected findings or simply to verify the data. It shoud also prevent double-counting of patients. CHI numbers of included patients will be stored in a password-protected database on a secure NHS server and will not be transferred to a University of Edinburgh server. Each CHI number will be allocated a participant number (1, 2, 3 etc) and it is these along with dates of birth, gender and first half of postcode that will be transferred.

Forenames and Surnames will be used in conjunction with CHI numbers to act as a double check of the patients' identities. As for CHI numbers, they will not be transferred outside NHS servers.

Date of birth will be used as a non-unique identifier, in conjunction with participant number, in the main study database on the University of Edinburgh server. It is needed in order to calculate patients' ages at different points in time (diagnosis, death).

Gender is known to influence body composition, and is required to allow lean muscle mass analysis using gender-specific reference ranges.

Postcodes (first half only) will enable the influence of deprivation status on muscle mass, comorbidity status and lung cancer outcomes to be studied.

Staging CT scans will be used to calculate patients' whole body muscularity. It is not possible to download anonymised scans, but once downloaded (to secure drive on NHS server) they will be anonymised using dicom anonymiser software.

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Fife

Please outline arrangements for access to information

Principle 4 Access to patient-identifiable information should be on a strict need-to-know basis	Only those individuals who need access to patient-identifiable information should have access to it, and they should only have access to the information items that they need to see. This may mean introducing access controls or splitting information flows where one information flow is used for several purposes.

I am a palliative medicine consultant (NHS Fife) and am also employed by the University of Edinburgh as a research fellow with an honorary NHS Lothian contract. I will assume full responsibility for collecting patient-identifiable data for the study, and for anonymising and transferring it via an encrypted USB stick or via secure NHS email, to the University of Edinburgh server. There it will be stored securely on a shared drive, protected by my username and password. Once transferred the anonymised data will be removed from the encrypted USB stick and deleted from NHS email.

Once the study is complete, the database of anonymised data on the University of Edinburgh shared drive will be removed securely.

Please outline action taken to ensure compliance with responsibilities and obligations to respect patient confidentiality

Principle 5 Everyone with access to patient-identifiable information should be aware of their responsibilities	Action should be taken to ensure that those handling patient-identifiable information - both clinical and non-clinical staff - are made fully aware of their responsibilities and obligations to respect patient confidentiality.

I completed a day's Good Clinical Practice (GCP) training in April 2013 and am aware of my responsibility to safeguard patient confidentiality. I plan to attend the next available course at the Wellcome Trust Clinical Research Facility on Safe Storage and Transfer of Research Data.

Patient-identifiable data (including CHI numbers) will be gathered from TRAK (electronic patient records) and PACS (digital radiology records) and will be stored in a password-protected database on a secure NHS server. Anonymised patient data (with only date of birth, gender, first half of postcode and participant number) will be transferred using an encrypted memory stick onto an Excel database within a password-protected University of Edinburgh server. There will be no paper copies of patient-identifiable information at any point during the study.

Please outline organisational compliance with legal requirements

Principle 6 Understand and comply with the law	Every use of patient-identifiable information must be lawful. Someone in each organisation handling patient information should be responsible for ensuring that the organisation complies with legal requirements.

The project will comply with the principles of the Data Protection Act (1998) and the General Medical Council's 2009 guidelines on confidentiality. It will be conducted under the supervision of Professor

NHS
Fife

Ken Fearon and Professor Marie Fallon as part of the Edinburgh Palliative and Supportive Care Research Team.

7. **Has your application been to Research Ethics** **NO**
If not, please explain why (i.e. not research)

The project was deemed to be a clinical evaluation, rather than research, by Alex Bailey at R+D in Lothian and Amanda Wood at R+D in NHS Fife, and therefore not needing ethical approval. I was advised to submit my proposal for Caldicott approval.

8. **Who is the data custodian for the NHS data?**

Name: Dr Joanna Bowden

Position: Consultant in Palliative Medicine/Research Fellow

Organisation: NHS Fife/University of Edinburgh

Address: Palliative Care Research Team, Edinburgh Cancer Research Centre, Western General Hospital, Crewe Road, Edinburgh.

Postcode: EH4 2XR

Tel. No:

E-mail: joannabowden@nhs.net

Signature: See scanned signature page emailed separately Date: .....

Counter-signature by Line Manager

Name: Professor Ken Fearon

Job Title: Consultant in Colorectal Surgery

Signature: See scanned signature page emailed separately Date: .....

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Please outline organisational compliance with legal requirements

Principle 6 Understand and comply with the law	Every use of patient-identifiable information must be lawful. Someone in each organisation handling patient information should be responsible for ensuring that the organisation complies with legal requirements.

7. Has your application been to Research Ethics **YES/NO**
If not, please explain why (i.e. not research)

8. Who is the data custodian for the NHS data?

Name: DR JOANNA GOUDGE

Job Title: CONSULTANT IN PALLIATIVE MEDICINE (NHS FIFE)/RESEARCH FELLOW

Return Address: UNIVERSITY OF EDINBURGH
PALLIATIVE CARE RESEARCH TEAM, EDINBURGH CANCER RESEARCH CENTRE, WESTERN GENERAL HOSPITAL, CREWE ROAD, EDINBURGH EH4 2XR

Email Address: joanna.goudge@nhs.net

Telephone Number:

Signature: Date: 3/6/14

Counter-signature by Line Manager

Name: PROFESSOR KENNETH FEARON

Job Title: CONSULTANT IN COLORECTAL SURGERY

Signature: Date: 3/6/14

NHS
Fife

Counter-signature by Acute Services/Primary Care Caldicott Guardian

Name:

Job Title:

Signature: Date: 16/6/14

I authorise access to the data as noted above:

Signature: ..... Date: 19/6/14

DR EDWARD COYLE
Caldicott Guardian for NHS Fife

Expiry Date

An expiry date of 01/06/15 has been set for this application. If your audit, project or evaluation runs over that date, you must submit a Continuation request. See C9 Confidentiality Policy Appendix 9.

ADMIN USE ONLY

Applicant's Name & Project Title Bowden, Joanna Evaluation – Co-morbidities in Lung Ca Patients	
Date application received Data Protection Caldicott Coordinator (DPCC)	
Expected Approval Date (20 working days)	
Date sent for approval to CG Acute/PC	
Date sent to Board CG for formal approval	
Date received by DPCC	
Date applicant informed	
20 days time scale met?	(Y) N

clinical research facility EDINBURGH

Certificate of Attendance

NHS Lothian

Good Clinical Practice & the EU Directive

Joanna Bowden

Wellcome Trust Clinical Research Facility, Edinburgh

Tuesday 9th April 2013

Course content:

- History of Clinical Trials and the development of GCP
- Informed Consent
- Pharmacovigilance
- Principles of GCP
- Responsibilities of Research personnel
- Monitoring Workshop

Training provider: Michelle Evans Date: 09.04.13

CPD Accredited 81614, 5 credits

THE UNIVERSITY OF EDINBURGH

clinical research facility EDINBURGH

NHS Lothian

Good Clinical Practice & EU Directive Half Day UPDATE

Thursday 28th May 2015

Edinburgh WTCRF, Education Programme

This is to certify that

Joanna Bowden

Attended the above workshop

Course Objectives

- Recognise the regulations that govern clinical trials
- Describe the roles and responsibilities in research
- Create a Trial Master File or Study Site File and understand the archiving requirements
- Participate in the informed consent process
- Recognise a serious breach and process for reporting
- 04830

CPD Accreditation: 94839 3.00 Credits

Reference: 42114

NHS
SCOTLAND
NHS RESEARCH SCOTLAND

This is to certify that

Joanna Bowden

Attended

NRS Good Clinical Practice (GCP) Update

Date: 19th January 2017

Course Content:

- UK legislation – Statutory Instrument
- What's new in regulations and frameworks
- Safety reporting
- Informed Consent Process
- Recruitment
- Documentation and data management
- Principles of GCP

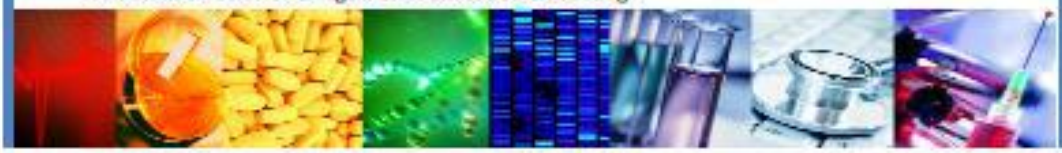
This ICH E6 GCP Investigator Site Training meets the Minimum Criteria for ICH GCP Investigator Site Personnel Training identified by TransCelerate BioPharma as necessary to enable mutual recognition of GCP training among trial sponsors.

RCPS Code: :101009

Signed:

Shona McDermott

Assistant Director of Glasgow CRF: Education & Training



NHS
National Institute for Health Research

CERTIFICATE of ACHIEVEMENT

This is to certify that:

Joanna Bowden

has completed the course

Good Clinical Practice (GCP) Refresher: eLearning

28 January 2019

A practical guide to ethical and scientific quality standards in clinical research

Including EU Directives, Medicines for Human Use (Clinical Trials) Regulations & the Department of Health UK Policy Framework for Health & Social Care Research, as applied to the conduct of Clinical Trials & other studies conducted in the NHS

Modules completed:

Core
Team Roles
Eligibility
Safety Reporting
Electronic Studies and Source Text
Summary

This course is worth 2 CPD credits

Delivering research to make patients, and the NHS, better

This is to certify that

Joanna Bowden

completed the following e-learning course assessment for Scotland with a score of
84%

Research Data and Confidentiality e-learning course

Covering:
- The concept of confidentiality and how to work within the law
- Principles 1, 2, 7, 8 and section 33 of the Data Protection Act
- Consent and the issues in accessing data for research without consent
- Appropriate disclosure and routes for access without consent
- Accessing data from ONS and the NHS
- Archiving and sharing research data

on Wed Dec 3 2014

learnPro

Certificate of Achievement

★ ★ ★ ★ ★

Name:	Joanna Bowden
Health Service:	NHS Scotland
Registration Date:	02/07/2014 10:47:21
Job Family:	Medical Staff
Role:	Not Specified
Division / Trust:	NHS Fife
Hospital:	SES VIP - Specialities
Ward:	Medicine - Palliative Medicine
Sub Family:	Doctor
Date Generated:	29/06/2019 11:33:53

Successfully Completed Assessments:

FIFE: INFORMATION GOVERNANCE

All Assessments Completed. This course will elapse on 23/01/20 and will expire on 23/01/23.

Information Governance - Passed on 23/01/17 at 18:35

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Fife

Appendix 9

APPLICATION FOR CONTINUATION or AMENDMENT TO CALDICOTT APPROVAL FOR USE OF PATIENT IDENTIFIABLE DATA

83935

Continuation of project, evaluation or audit X please tick
Amendment to approved project, evaluation or audit X please tick. Details of significant changes should be shown in red.

User Details

Name: Dr Joanna Bowden

Position: Consultant in Palliative Medicine/Research Fellow

Organisation: NHS Fife/University of Edinburgh

Address: Palliative Care Research Team, Edinburgh Cancer Research Centre, Western General Hospital, Crewe Road, Edinburgh.

Postcode: EH4 2XR

Tel. No:

E-mail: joannabowden@nhs.net

Name(s) of any co-user(s): none

You must address the 6 Caldicott Principles when submitting this request for data

1. Project/Audit title

Evaluating the role of comorbidity and muscle wasting in clinical outcomes for patients with lung cancer

2. Please provide additional background description of your project/audit to enable Caldicott Guardian to understand what outcome you trying to achieve.

Cancer cachexia is a common and highly debilitating syndrome affecting around 60% of patients with lung cancer. Its hallmarks are muscle wasting, weight loss and weakness. It limits the oncological treatments that patients can receive, and is a direct cause of death in many. Historically, there have been few effective treatments for cachexia, though there are a number of new and promising therapies on the horizon. However, these have typically only been tested in the fittest of patients who do not have comorbid illnesses (such as chronic respiratory diseases) alongside their cancer. And yet comorbidity is common in patients with lung and many other

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cancers and may in itself cause cachexia and premature death. Normal ageing, frailty and oncological treatments are other common causes of muscle wasting. We do not yet understand the relationship between comorbidity, frailty and other patient factors, and what this might mean for future cachexia interventions.

The original evaluation aimed to identify key variables in the development of muscle loss and shortened survival through a retrospective analysis of patients presenting with lung cancer between 2008 and 2010 in Fife and Lothian. This was then supplemented by adding patients from 2011-2013. However, data relating to patients' chemotherapy treatments completed and their treatment toxicities was not collected routinely electronically (within 'Chemocare') until 2013 for patients with lung cancer in Lothian. Therefore, one further extension is requested, to include patient data from 2014 and 2015 (to allow for 3 years' of patient data to be incorporated). My earlier work using patient cohorts from 2008-10 has revealed that this information would be of interest (as it may relate to why some patients die soon after treatment.) I have applied for and been granted access to Chemocare, the electronic chemotherapy patient record, which holds this information. Developing an accurate picture of cachexia in the context of patients' wider health and function is critical if we are to identify the most appropriate patients, with the most to gain, for active cachexia management. Importantly, this will also involve identifying the most unwell patients for whom cachexia intervention would be futile, and for whom palliative care should be the priority.

2. Supporting information

Data to be collected is detailed in an attached in separate document.

Data will mostly come from an existing SCAN database (all fields in red) and accessing this data for the original cohort from 2008-2013 has been straightforward, following Caldicott approval and SCAN approval. I plan to apply to SCAN for this to be extended to patients from 2014-15.

Additional data (in green) will be accessed through Chemocare, the online patient chemotherapy database which I have been granted access for already for 2013 patients, but which I will apply to be extended to 2014-15 patients.

Some (in blue) is to be collected by me from individual patients' case records and scans, or through ISD. I have had data through for the 2008-2010 cohort from ISD and if this proves useful I will also likely apply to extend that to patients from 2011-2015 also.

4. Name of organisation receiving data (if not within NHS Fife)

Patient identifiable data will all be stored on password protected drives on NHS Fife and NHS Lothian servers. Anonymised data will be transferred via secure nhs email

NHS Fife

or encrypted USB stick to a password protected drive on the University of Edinburgh server.

5. What patient identifiable information are you looking to use? (please tick where relevant)

CHI Number	Yes
Forename	Yes
Surname	Yes
Initials	No
Age	No
Date of birth	Yes
Gender	Yes
Address	No
Postcode	Yes
Other, please specify.....	Patients' staging CT scans (for body composition analysis using a single anonymised cross-sectional image).

6. Please explain how the proposal meets the following Six Caldicott Principles. (The Caldicott Committee Report on the Review of Patient-Identifiable Information. Department of Health, December 1997)

Justify the purpose

Principle 1 Justify the purpose(s)	Every proposed use or transfer of patient-identifiable information within or from an organisation should be clearly defined and scrutinised, with continuing uses regularly reviewed, by an appropriate guardian.

Aim:

To evaluate clinical outcomes for patients with lung cancer, comorbidity and muscle wasting, with a view to targeting future cachexia interventions most appropriately.

Objectives:

1. To describe which variables are associated with low muscularity in patients with lung cancer.

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2. To identify which variables are independent determinants of low muscularity in patients with lung cancer.

3. To establish whether low muscularity is associated with reduced survival in patients with lung cancer.

4. To explore the relationship between comorbidity, muscularity and which lung cancer treatments are offered and completed.

5. To describe which variables (including cachexia, factors associated with cachexia and known prognostic variables such as cancer stage) are independently prognostic in patients with lung cancer.

Design: A retrospective case note evaluation to determine the significance of key variables to the development of muscle loss in patients with lung cancer and to determine the influence of the latter on duration of survival

Population: A retrospective electronic case note review of all patients presented at the regional lung cancer multidisciplinary team (MDT) meetings in NHS Fife and NHS Lothian between 2008 and 2013. And now to be extended to 2014-2015. Approximately 1000 patients are diagnosed per year in these two regions.

Data collection: Demographic and clinical characteristics including cancer type, stage, treatment (planned and completed) age, height, weight, weight loss and performance status. Lean body mass will be assessed using routine CT imaging and Slice-O-Matic software. Obesity will be scored using BMI and comorbidity will be scored using the Charlson Comorbidity Index (CCI) and the Simplified Comorbidity Score (SCS).

Analysis: The population will be detailed using simple descriptive statistics. The relationship between cancer type, cancer stage, age, sex, body mass index (BMI), weight-loss, co-morbidity and CT-derived muscle mass will be explored by both discriminate analysis and multivariate regression using generalised linear models. These same variables will be assessed regarding their ability to predict overall survival, using a proportional hazards model.

Justify the requirement to use patient-identifiable data

Principle 2 Don't use patient-identifiable information unless it is absolutely necessary	Patient-identifiable information items should not be included unless it is essential for the specified purpose(s) of that flow. The need for patients to be identified should be considered at each stage of satisfying the purpose(s).

Patient-identifiable data is an absolute requirement of this project to allow individuals' data to be collected, traced to source and compared across existing data

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Fife

sets. However, once the dataset is completed, all identifiable data will be removed for the analysis stage.

Justify the inclusion of each data field required

Principle 3 Use the minimum necessary patient identifiable information	Where use of patient-identifiable information is considered to be essential, the inclusion of each individual item of information should be considered and justified so that the minimum amount of identifiable information is transferred or accessible as is necessary for a given function to be carried out.

CHI numbers are needed as unique identifiers to allow individuals' data to be traced back to source. This may be necessary to investigate unexpected findings or simply to verify the data. It should also prevent double-counting of patients. CHI numbers of included patients will be stored in a password-protected database on a secure NHS server and will not be transferred to a University of Edinburgh server. Each CHI number will be allocated a participant number (1, 2, 3 etc) and it is these along with dates of birth, gender and first half of postcode that will be transferred.

Forenames and Surnames will be used in conjunction with CHI numbers to act as a double check of the patients' identities. As for CHI numbers, they will not be transferred outside NHS servers.

Date of birth will be used as a non-unique identifier, in conjunction with participant number, in the main study database on the University of Edinburgh server. It is needed in order to calculate patients' ages at different points in time (diagnosis, death).

Gender is known to influence body composition, and is required to allow lean muscle mass analysis using gender-specific reference ranges.

Postcodes (first half only) will enable the influence of deprivation status on muscle mass, comorbidity status and lung cancer outcomes to be studied.

Staging CT scans will be used to calculate patients' whole body muscularity. A single anonymised image from each patient's diagnostic CT scan will be downloaded to an encrypted NHS USB device for transfer to a secure personal folder on the University of Edinburgh network drive (no identifiable data will be transferred to University of Edinburgh server)

Please outline arrangements for access to information

Principle 4 Access to patient-identifiable information should be on a strict	Only those individuals who need access to patient-identifiable information should have access to it, and they should only have access to the information items that they need to see. This may mean introducing access controls or splitting information flows where one information flow is used for several purposes.

NHS
Fife

need-to-know basis	

I am a palliative medicine consultant (NHS Fife) and I am also employed by the University of Edinburgh as a research fellow with an honorary NHS Lothian contract. I will assume full responsibility for collecting patient-identifiable data for the study, and for anonymising and transferring it via an encrypted USB stick or via secure NHS email, to the University of Edinburgh server. There it will be stored securely in a personal folder on a shared drive, protected by my username and password. Once transferred the encrypted NHS USB device will be destroyed by NHS Lothian and deleted from NHS email.

Once the study is complete, the database of anonymised data on the University of Edinburgh shared drive will be removed securely.

Please outline action taken to ensure compliance with responsibilities and obligations to respect patient confidentiality

Principle 5 Everyone with access to patient-identifiable information should be aware of their responsibilities	Action should be taken to ensure that those handling patient-identifiable information - both clinical and non-clinical staff - are made fully aware of their responsibilities and obligations to respect patient confidentiality.

I completed a whole day's Good Clinical Practice (GCP) training in April 2013 and a half day update in May 2015. I completed an online module in 'Research Data and Confidentiality' in December 2014 and a course on Data Management in May 2015. I am aware of my responsibility to safeguard patient confidentiality.

Patient-identifiable data (including CHI numbers) will be gathered from TRAK (electronic patient records) and PACS (digital radiology records) and will be stored in a password-protected database on a secure NHS server. Following a lengthy application process ISD have also granted permission for me to use their data on patients' comorbid illnesses and frailty status, which ISD have now given me access to for the 2008-2010 patient cohort. If this proves useful, I shall be applying to extend this access to include patients from 2011 to 2015. Anonymised patient data (with only date of birth, gender, first half of postcode and participant number) will be transferred by secure NHS email to a secure personal folder in a shared drive on the University of Edinburgh server. There will be no paper copies of patient-identifiable information at any point during the study.

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Fife

Please outline organisational compliance with legal requirements

Principle 6 Understand and comply with the law	Every use of patient-identifiable information must be lawful. Someone in each organisation handling patient information should be responsible for ensuring that the organisation complies with legal requirements.

The project will comply with the principles of the Data Protection Act (1998) and the General Medical Council's 2009 guidelines on confidentiality. It will be conducted under the supervision of Professor Ken Fearon and Professor Marie Fallon as part of the Edinburgh Palliative and Supportive Care Research Team.

Legal basis: Schedule 2 "for the exercise of functions of a public nature exercised in the public interest by any person" and Schedule 3 – medical purposes (extended: research and management of services).

7. Has your application been to Research Ethics **NO**
If not, please explain why (i.e. not research)

The project was deemed to be a clinical evaluation, using existing patient data, rather than research, by Alex Bailey at R+D in Lothian and Amanda Wood at R+D in NHS Fife. I was advised to submit my proposal for Caldicott approval rather than to Ethics.

8. Who is the data custodian for the NHS Fife data?

Name: Dr Joanna Bowden

Job Title: Consultant in Palliative Medicine/Research Fellow

Return Address: Palliative Care Research Team, Western General Hospital, Crewe Road, Edinburgh. EH4 2XR

Email Address: joannabowden@nhs.net

Telephone Number:

Signature:

..... Date: ...23.08.2016.....

Counter-signature by applicant's Line Manager

Name: Professor Ken Fearon

NHS
Fife

Job Title: Consultant in Colorectal Surgery

Signature: ..... Date:23.08.2016.....

Please forward to:

Data Protection & Caldicott Coordinator
NHS Fife
Information Services Department
Lynebank Hospital
Dunfermline KY11 8JH

NHS
Fife

Counter-signature by Acute /Primary Care Caldicott Guardian

Name:

Job Title:

Signature: ..... Date: .....

I authorise access to the data as noted above:

Signature: Date: 2 Oct 2016

DR FRANCES ELLIOT
Caldicott Guardian for NHS Fife

Expiry Date

An expiry date of / / has been set for this continuation. If your audit, project or evaluation runs over that date, you must submit a further continuation.

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Applicant's Name & Project Title	
Date application received Data Protection Caldicott Coordinator (DPCC)	
Expected Approval Date 20 working days	
Date sent for approval to CG Acute/PC	
Date sent to Board CG for formal approval	
Date received by DPCC	
Date applicant informed	
20 days time scale met?	Y N

Supplementary analysis to Chapter 3: Correlation between key variables

Additional exploratory analysis was undertaken to examine the correlation between skeletal muscle indices, BMI, ECOG PS, ANC and Alb. These are presented in the Figures that follow.

Figure 3.6 A scatter plot of BMI by muscularity (SMI)

There was a small positive correlation between BMI and SMI, r=0.24. However, as the correlation coefficient is close to zero, there is only a weak relationship between BMI and SMI (*p*<0.01).

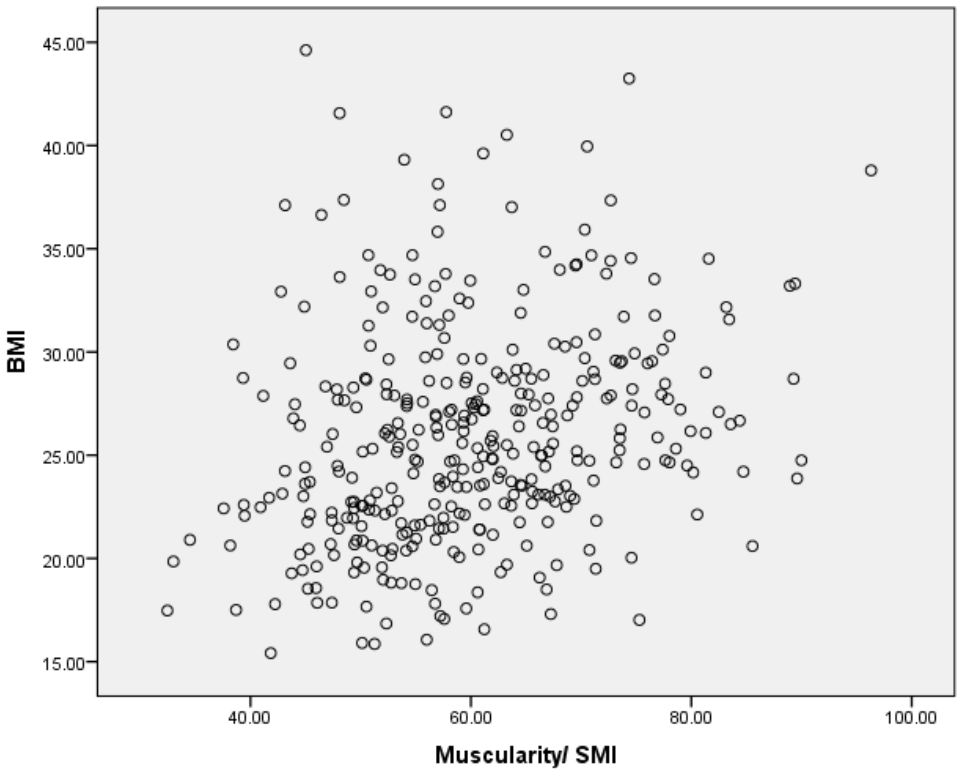


Figure 3.7 A scatter plot of BMI by muscle attenuation (MA)

There was a moderate negative correlation between BMI and MA, r=-0.435, with higher BMI typically associated with low MA. However, there remains a significant degree of variability (p<0.01).

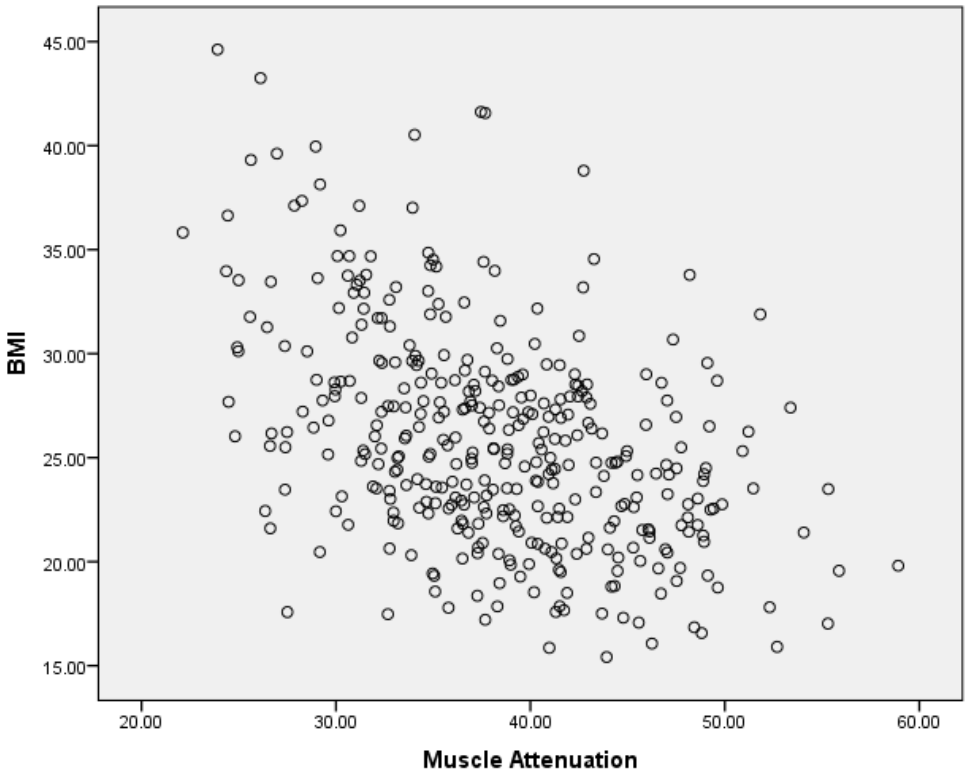


Figure 3.8 A box plot of SMI by ECOG PS

There was a minimally significant negative correlation between SMI and ECOG PS, r=-0.101, with a slight trend for higher SMI to be correlated with more clinically favourable (lower) ECOG PS (*p*=0.054).

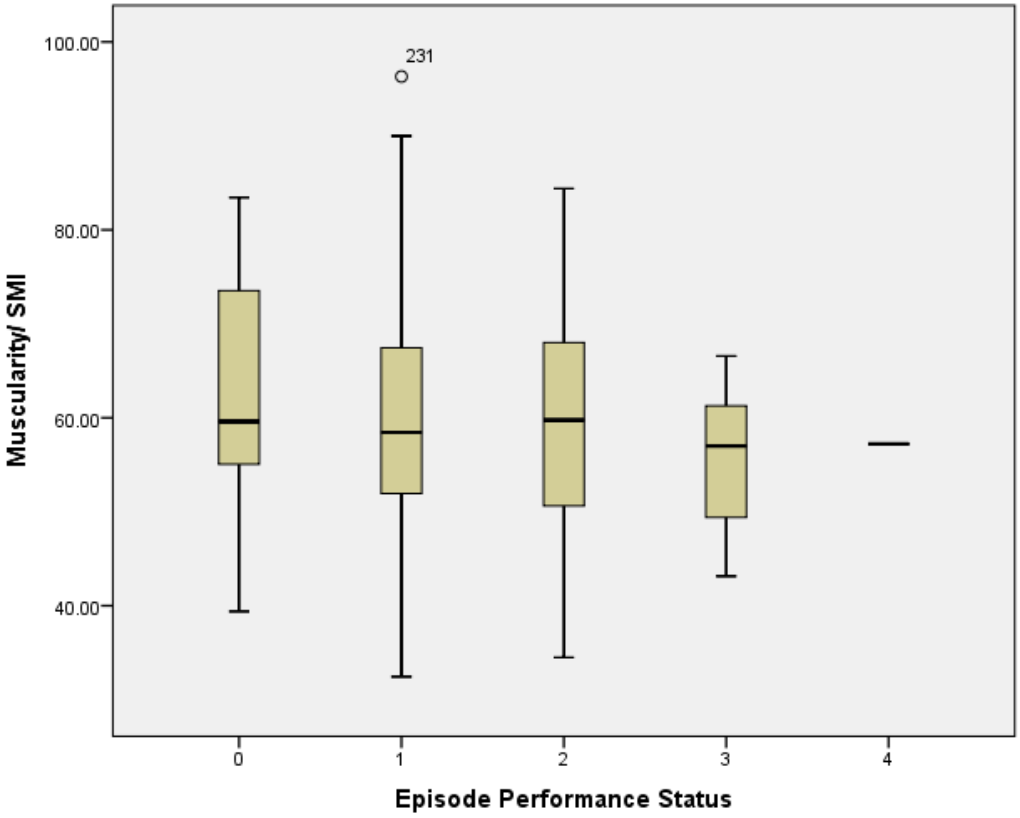


Figure 3.9 A box plot of MA and ECOG PS

There was a minimally significant negative correlation between MA and ECOG PS, r=-0.131, with a trend for higher MA to be correlated with lower (more clinically favourable) ECOG PS (*p*=0.011).

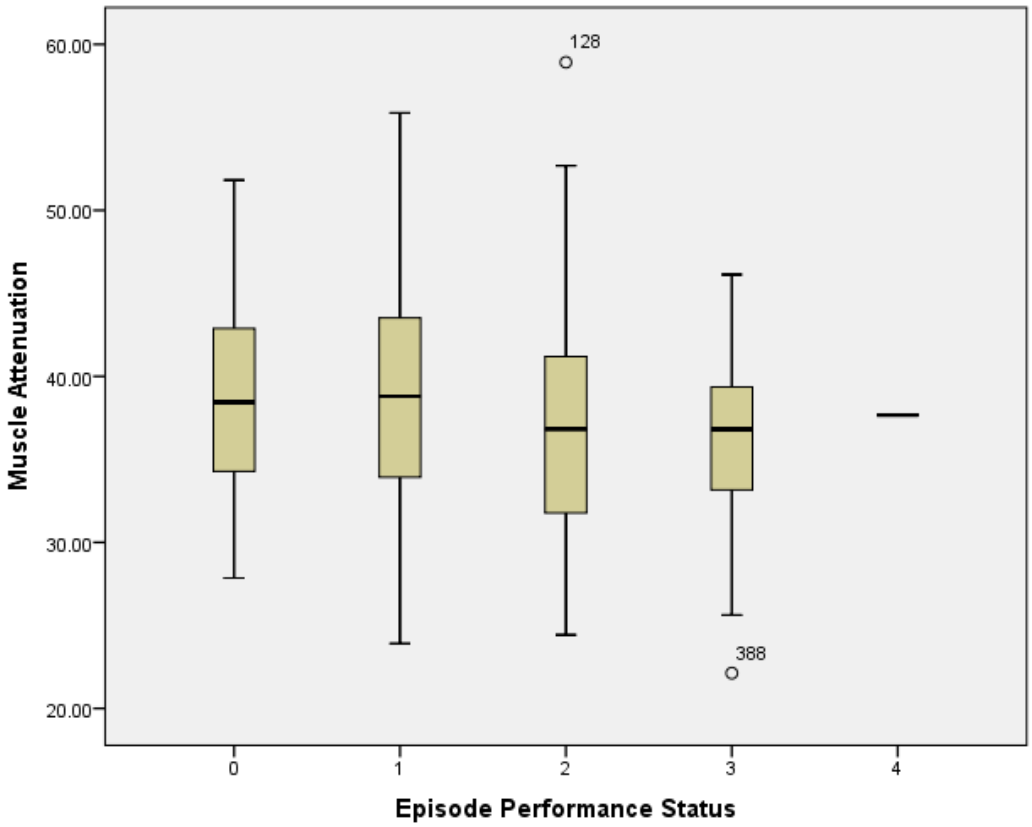


Figure 3.10 A scatter plot of SMI and neutrophil counts.

There was a minimally significant negative correlation between SMI and ANC, r=-0.15, with a slight trend for a higher SMI and lower neutrophil counts to be correlated (*p*=0.003).

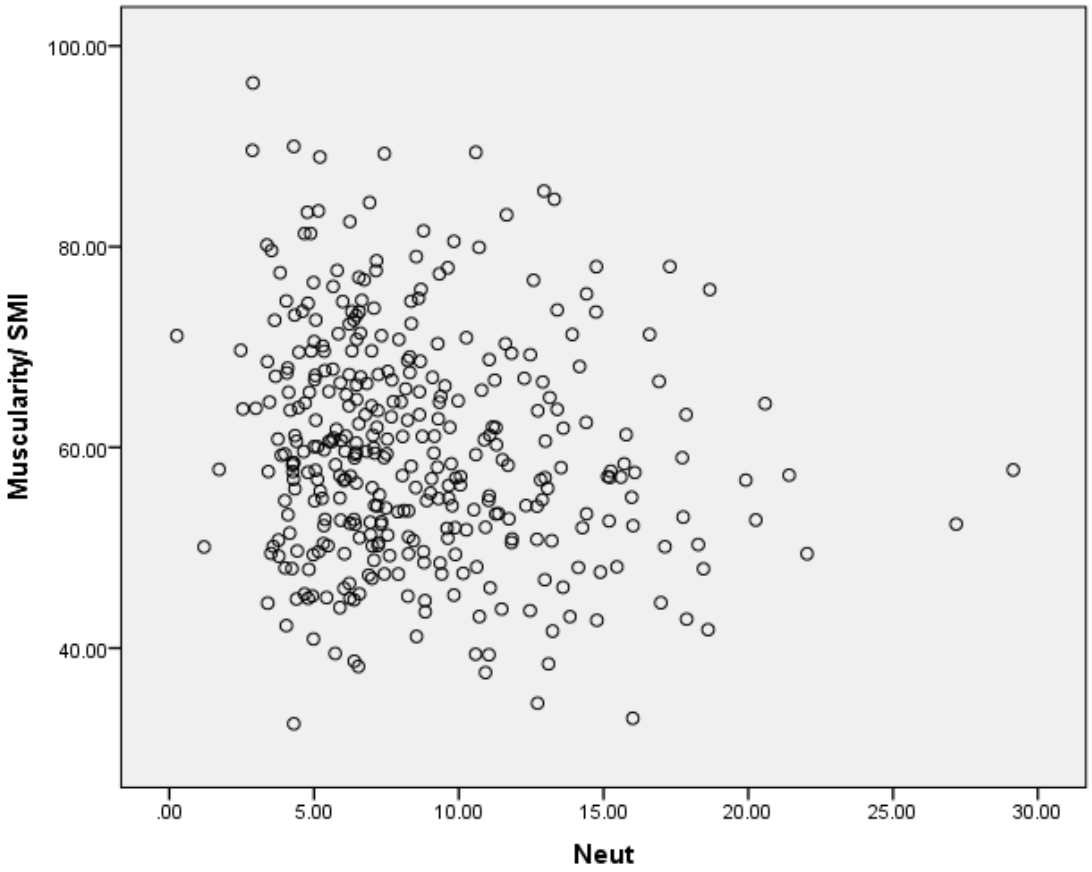


Figure 3.11 A scatter plot of SMI and albumin levels

There was a minimally significant positive correlation between SMI and Alb, r=0.144, with a small trend for higher SMI and albumin levels to be correlated (*p*=0.006).

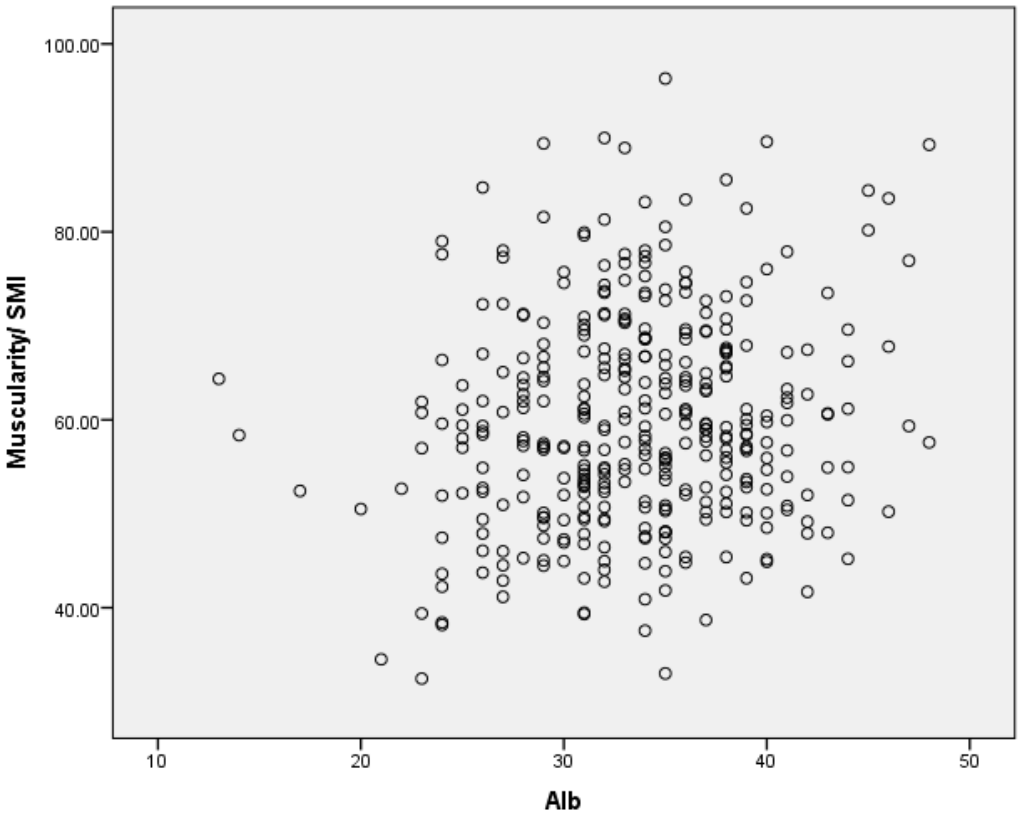


Figure 3.12 A scatter plot of MA and neutrophil counts

There was virtually no correlation between MA and ANC levels, r=-0.069 (*p*=0.363).

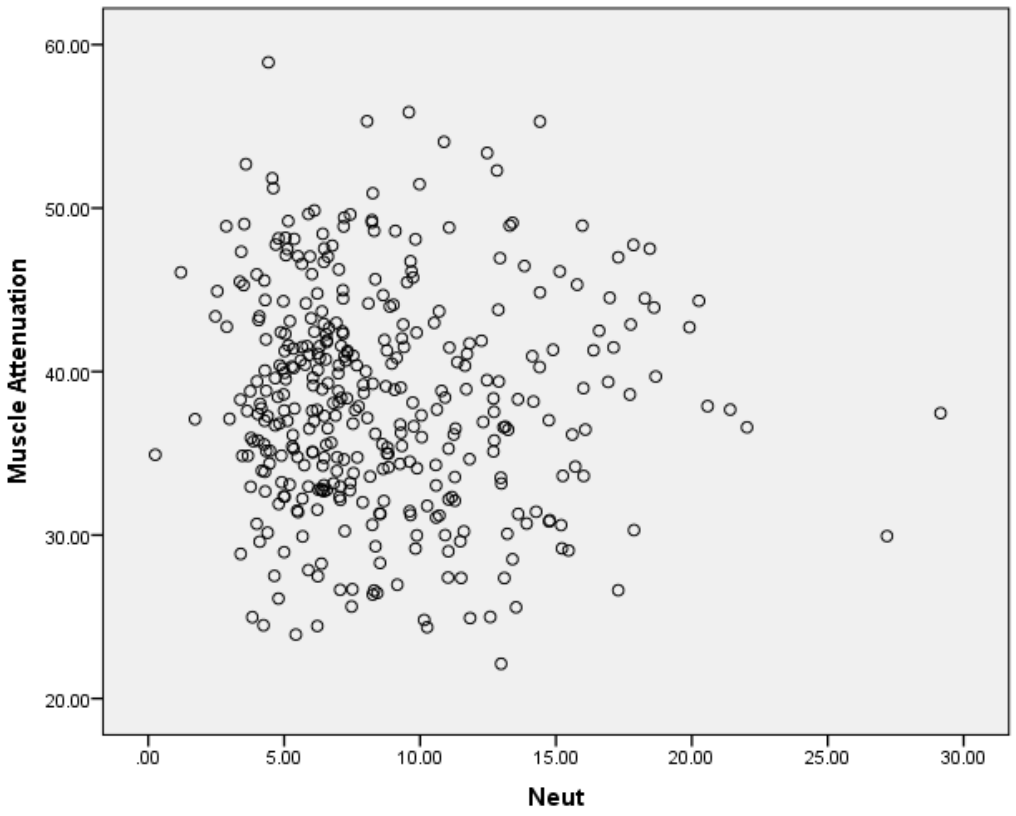
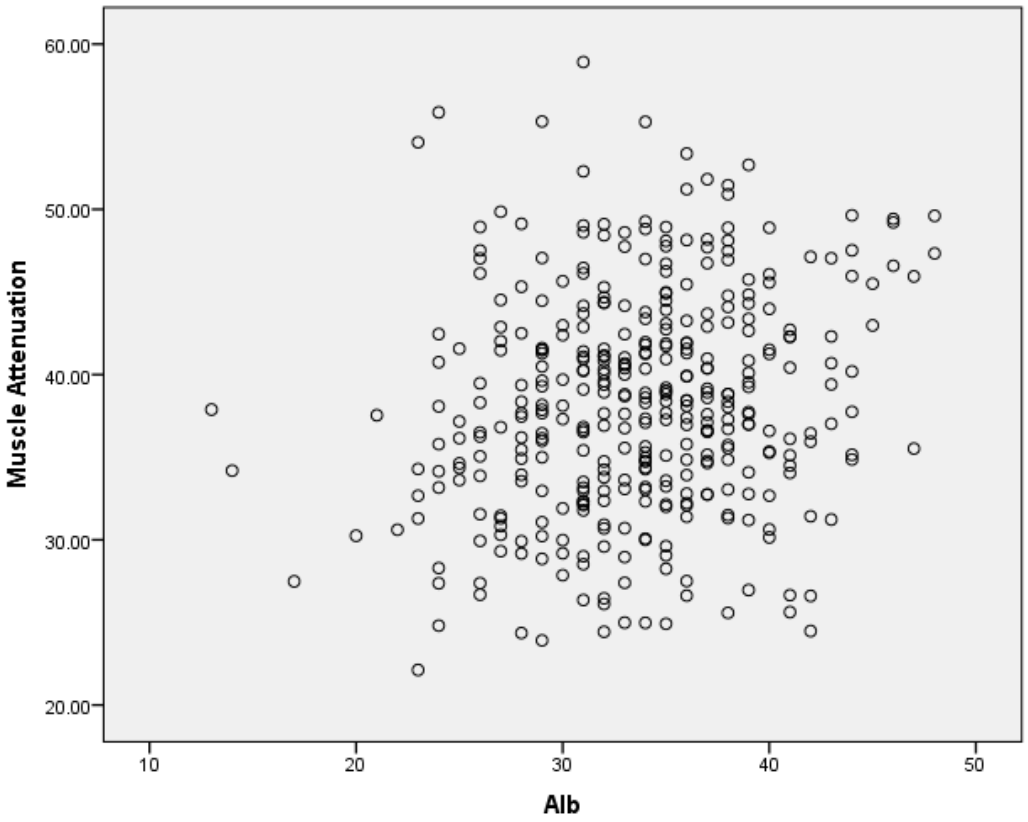


Figure 3.13 A scatter plot of MA and albumin levels

There was a minimally significant positive correlation between MA and Alb levels, r=0.181, with a trend for higher MA levels and higher albumin levels to be correlated (p<0.001).



Supplementary analysis to Chapter 3: Case study exploratory examination of change in status of key variables following the receipt of chemotherapy

Model 2, as described in Table 3.10, was chosen for this analysis because it was the most discriminatory model for OS.

Patients who had a high score at baseline but who lived >12 months, Patients 1-4

Four patients in Model 2 each had all 4 unfavourable variables (high NLR, low Alb, low MA and low SMI) at diagnosis, but lived >12 months. Basic follow-up data was collected for these 4 patients following the receipt of 2 cycles of chemotherapy; these were 'pre-cycle 3' bloods and other measures recorded within ChemoCare. Follow-up CT-derived body composition analysis was not undertaken.

The four patients who each had a 'full house' of unfavourable variables, but who lived >12 months from the first treatment date, are individually described below. Changes in the status of their key variables are described in relation to the specified thresholds used in the main analyses.

Patient 1:

Baseline characteristics: Male, NSCLC, BMI=26.2, **SMI=59.35 (bad), MA=26.68 (bad)**

Treatment received: 4 cycles of first-line chemotherapy and went on to receive second-line treatment

Survived**:** 463 days

Table 3.22 Baseline and follow-up variables and any changes in status between the two time points during first-line chemotherapy for Patient 1.

	Pre-cycle 1	**Pre-cycle 3**	**Status change summary**
NLR	**5.48**	**1.67**	**Improvement from bad to good**
Alb	**26**	**29**	**Improvement to less bad**
ECOG PS	2	1	Improvement
Weight (Kg)	82.9	76.0	Weight-losing (8%)
ANC	7.51	3.14	Improved from bad to good
ALC	1.37	1.88	Improved from slightly less good to good
Plt	426	579	Increased from high (bad) to higher (worse)
PLR	310.95	307.98	Stable

Patient 2:

Baseline characteristics: Female, NSCLC, BMI=31.27, **SMI=50.71 (bad), MA=26.48 (bad)**

Treatment received: 5 cycles of first-line chemotherapy and no second-line treatment

Survived: 424 days

Table 3.23 Baseline and follow-up variables and any changes in status between the two time points during first-line chemotherapy for Patient 2.

	Pre-cycle 1	**Pre-cycle 3**	**Status change summary**
NLR	**5.14**	**1.97**	**Improvement from bad to good**
Alb	**32**	**36**	**Improvement from bad to good**
ECOG PS	1	1	No change
Weight (Kg)	71.3	68.3	Weight loss (4%)
ANC	8.43	2.62	Improvement from bad to good
ALC	1.64	1.33	Fall from good to less good
Plt	398	308	Improved within normal range
PLR	242.68	231.58	Stable

Patient 3:

Baseline characteristics: Male, SCLC, BMI=23.46, **SMI=58.76 (bad), MA=27.38 (bad)**

Treatment received: 6 cycles of first-line chemotherapy and went on to receive second line treatment

Survived: 435 days

Table 3.24 Baseline and follow-up variables and any changes in status between the two time points during first-line chemotherapy for Patient 3.

	Pre-cycle 1	Pre-cycle 3	Status change summary
NLR	**5.56**	**1.00**	**Improvement from bad to good**
Alb	**26**	**36**	**Improvement from bad to good**
ECOG PS	2	2	No change
Weight (Kg)	63.1	64.4	Minor weight gain (2%)
ANC	11.51	2.30	Improvement from very bad to good
ALC	2.07	2.29	Improvement from good to slightly better
Plt	550	458	Improvement from bad to less bad
PLR	265.7	200	Improvement from bad to good

Patient 4:

Baseline characteristics: Male, NSCLC, BMI=22.43, **SMI=37.57 (bad), MA=30.00 (bad)**

Treatment received: 4 cycles of first-line chemotherapy and went on to receive second line treatment

Survived: 406 days

Table 3.25 Baseline and follow-up variables and any changes in status between the two time points during first-line chemotherapy for Patient 4.

	Pre-cycle 1	Pre-cycle 3	Status change summary
NLR	**10.92**	**6.72**	**Improvement from bad to less bad**
Alb	**34**	**34**	**No change**
ECOG PS	1	1	No change
Weight (Kg)	75.1	73.6	Slight weight loss (2%)
ANC	10.92	3.56	Improvement from bad to good
ALC	1.00	0.53	Fall from borderline bad to worse
Plt	410	395	Improved to within normal range
PLR	410.0	745.28	Bad to worse

Patients who had a low score at baseline but whose survival was very limited, Patients 5-8

Four patients described in Model 2 had 0 unfavourable variables (low NLR, high Alb, high MA and high SMI) at diagnosis, but did not live very long. All 4 patients are described below, 3 of whom had SCLC. 2/4 patients died in 30 days or less from the date of first intended treatment; one of whom did not receive any chemotherapy and one of whom only received one cycle. No routine follow-up data was available for these patients as neither made it to either 2 or 3 cycles of chemotherapy. However, their baseline and survival data is presented below (Patients 5 and 6).

2/4 patients survived beyond 30 days but had the next poorest survival of all the patients with 0/4 unfavourable variables at diagnosis. They are Patients 7 and 8. Each received 2 cycles of chemotherapy and their baseline, pre-cycle 2 and survival data are described below.

Unfortunately, we were unable to determine the cause of death for these patients.

Patient 5:

Baseline characteristics: Male, SCLC, BMI=25.19, **SMI=69.62 (good), MA=38.81 (good)**

***Treatment received*:** none

***Survived*:** 13 days

Table 3.26 Baseline variables and an interpretation of variable status for Patient 5.

	Pre-cycle 1	**Interpretation of baseline variables**
NLR	**3.12**	**Good**
Alb	**38**	**Good**
ECOG PS	1	Good
Weight (Kg)	75.4	Slightly overweight
ANC	6.99	Only just in good
ALC	2.24	Good
Plt	205	Good
PLR	91.52	Good

Patient 6:

***Baseline characteristics*:** Male, SCLC, BMI=25.86, **SMI=76.93 (good), MA=35.52 (good)**

***Treatment received*:** one cycle of first-line chemotherapy only

***Survived*:** 30 days

Table 3.27 Baseline variables and an interpretation of variable status for Patient 6.

	Pre-cycle 1	**Interpretation of baseline variables**
NLR	**3.88**	**Just good**
Alb	**47**	**Good**
ECOG PS	1	Good
Weight (Kg)	66.2	Slightly overweight
ANC	6.55	Good
ALC	1.69	Good
Plt	249	Good
PLR	147.34	Good

Patient 7:

***Baseline characteristics*:** Female, SCLC, BMI=25.4, **SMI=65.7 (good), MA=38.82 (good)**

***Treatment received*:** 2 cycles of first-line chemotherapy only

***Survived*:** 111 days

Table 3.28 Baseline and follow-up variables and any changes in status between the two time points during first-line chemotherapy for Patient 7.

	Pre-cycle 1	**Pre-cycle 2**	**Status change summary**
NLR	**4.00**	**2.94**	**Improvement within good**
Alb	**38**	**37**	**Slight fall, but still good**
ECOG PS	1	3	Significant worsening
Weight (Kg)	63.4	61.2	Weight losing (3%)
ANC	10.79	7.38	Improvement, but still bad
ALC	2.70	2.51	Fall, but still good
Plt	421	500	Worsening within bad
PLR	155.93	199.20	Substantial increase, but still good

Patient 8:

***Baseline* characteristics:** Male, NSCLC, BMI=21.82, **SMI=71.38 (good), MA=36.53 (good)**

***Treatment received*:** 2 cycles of first-line chemotherapy only

***Survival*:** 95 days

Table 3.29 Baseline and follow-up variables and any changes in status between the two time points during first-line chemotherapy for Patient 8

	Pre-cycle 1	**Pre-cycle 2**	**Status change summary**
NLR	**2.91**	**2.44**	**Slight fall, but still good**
Alb	**37**	**33**	**Worsening from good to bad**
ECOG PS	1	3	Worsening
Weight (Kg)	58.7	55.7	Weight losing (5%)
ANC	6.60	2.44	Improvement from good to better
ALC	2.27	1.00	Worsening from good to borderline bad
Plt	447	389	Improvement from bad to good
PLR	196.92	389	Worsening within good