Physical performance and muscle mass in the assessment of sarcopenia and its association with receipt and completion of planned treatment in non-small cell lung cancer

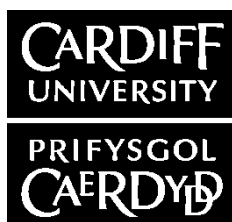**Jemima Tunung Tagal Collins**

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to

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Acknowledgements

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Table of Tables and Figures

List of Commonly Used Abbreviations

ASMI	Appendicular skeletal muscle index
BIA	Bioelectrical impedance analysis
BMI	Body Mass Index
BSA	Body surface area
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DXA	Dual-energy X-ray absorptiometry
ECOG	Eastern Cooperative Oncology Group
FM	Fat mass
FMI	Fat mass index
FFM	Fat-free mass
FFMI	Fat-free mass index
MDT	Multi-disciplinary team
MMI	Muscle mass index
MUAC	Mid upper arm circumference
MUST	Malnutrition Universal Screening Tool
NSCLC	Non-small cell lung cancer
OR	Odds ratio
PET	Positron emission tomography
PET-CT	Positron emission tomography-computed tomography
PPM	Permanent pacemaker
PS	Performance status
RALCC	Rapid Access Lung Cancer Clinic
RTOG	Radiation Therapy Oncology Group
SCLC	Small cell lung cancer
SD	Standard deviation
SPPB	Short Physical Performance Battery
STS	Sit to stand (5 times)
TKI	Tyrosine kinase inhibitor
TNM	Tumour, Node, Metastasis
TST	Triceps skinfold thickness
UK	United Kingdom
95% CI	Confidence intervals at the 95% confidence level

Abstract

Lung cancer is the third most common cancer in the United Kingdom, and the most common cancer worldwide, where approximately 1.61 million new cases are diagnosed every year. The prognosis is bleak as many present at advanced stages, despite advances in systemic anticancer-treatment, including targeted treatment. In the United Kingdom, at 5 years only 11-16% are still alive, with this proportion decreasing to approximately 5% at 10 years.

Survival is dependent on many factors, one of which is whether or not treatment is received. In advanced lung cancer, survival was poorer in those who did not receive treatment, regardless of performance status (PS). However, many lung cancer patients who are initially considered eligible for treatment do not go on to receive it, as a result of declining physical function. The importance of receiving and subsequently completing treatment planned by the multidisciplinary team, as an endpoint, has been overlooked thus far, in favour of survival. Although survival is undoubtedly important, understanding factors which may be predictive of receipt and completion of treatment will enable better stratification of risks and benefits of treatment.

Sarcopenia is a condition which is defined as depletion of muscle mass, and either poor physical performance or low muscle strength. It was originally recognised in the context of older people, but is also prevalent in many cancer groups. In non-small cell lung cancer (NSCLC), muscle mass depletion has been associated with poor survival, and potential increased risk of chemotherapy toxicity. However, in this context muscle mass is rarely assessed with physical function, and the latter may also have predictive potential. Whether or not bioelectrical impedance (BIA)-measured muscle mass is associated with treatment outcomes in NSCLC is also unclear. The overall aim of this thesis was to examine the value of

muscle mass and physical performance measurements in predicting receipt and completion of treatment in NSCLC.

Chapters 2 and 3 concern the primary and secondary aims of the thesis, as well as details of recruiting participants, the study protocol and techniques used.

In chapter 4, the body composition of all participants, including muscle mass, fat mass and body mass index (BMI) was described. None of these parameters had any association with treatment receipt or completion. However, a subset analysis of muscle mass values from BIA compared with dual energy x-ray absorptiometry (DXA) values showed that BIA consistently overestimated DXA values. BIA-derived values consistent with sarcopenia were present in 19.4% of participants. Although individually sarcopenic participants had worse outcomes than their counterparts in surgery and chemotherapy groups, statistically this was not significant.

In Chapter 5, the predictive value of nutritional status on receipt and completion of treatment is presented. Nutritional status parameters of weight loss, BMI, albumin, C-reactive protein and malnutrition universal screening tool (MUST) were evaluated for prediction of treatment-related outcomes. Weight loss of 10% or more was predictive of being less able to complete of treatment in all groups, as well as being less likely to receive chemotherapy. A higher CRP was associated with being less able to complete treatment in all groups, and a higher albumin associated with completion of 3 or more cycles of chemotherapy in the group planned for chemotherapy. BMI and MUST were not predictive of treatment outcomes.

In Chapter 6, the predictive value of physical performance assessed by the Short Physical Performance Battery and its component parts was evaluated. In the chemotherapy group, total SPPB, gait speed and sit-to-stand were all predictive of completion of more cycles

of chemotherapy. We also found that for every unit increase in SPPB score, there was a 28.2% decrease in chemotherapy toxicity events. There was no relationship between muscle mass and SPPB score, and between SPPB score and PS.

Chapter 7 investigates the relationship between both physician and patient-rated Eastern Cooperative Oncology Group (ECOG) and Karnofsky PS, and whether any of these are predictive of receipt or completion of treatment. PS between physician and patient was poorly correlated for both scores, but there was no tendency for the physician to over- or under-estimate patients' scores. In terms of predicting completion of treatment in all groups, only patient-rated ECOG PS showed an association. However, in the chemotherapy group only, physician-rated ECOG PS was predictive of receipt of chemotherapy.

The results of the chapters taken together demonstrate that PS which is currently used to evaluate NSCLC patients' fitness for treatment is insufficient to predict receipt or completion of treatment. SPPB as a marker of physical performance shows promise as a simple bedside test for predicting chemotherapy completion, and may be able to predict risk of chemotherapy toxicity. Patient-rated PS as well as some nutritional status markers such as weight loss of 10% of more, CRP and albumin, could add to the robustness of future studies looking at creating a predictive model for treatment receipt and completion.

Publications and Presentations

Published Work

- Collins J, Noble S, Chester J et al. The assessment and impact of sarcopenia in lung cancer: a systematic literature review. *BMJ Open* 2014; 4:e003697 doi:10.1136/bmjopen-2013-003697.

- Collins JT, Noble S et al. Association of sarcopenia and observed physical performance with attainment of multidisciplinary team planned treatment in non-small cell lung cancer: an observational study protocol. *BMC Cancer* 2015; Jul 24;15:544. doi: 10.1186/s12885-015-1565-6.

- Collins JT, Noble S et al. The value of physical performance measurements alongside assessment of sarcopenia in predicting receipt and completion of planned treatment in non-small cell lung cancer: an observational, exploratory study. *Support Care Cancer* 2018; 26(1):119-127. Epub Jul 2017.

Invited Oral Presentations

British Thoracic Oncology Group (BTOG) Cachexia Study Day: Definition, clinical implications and treatment. 25th November 2016, Wellcome Collection, London.

Oral Presentations

South Wales Cancer Network. Sharing Good Practice Conference. 16th May 2014, Princess of Wales Hospital, Bridgend.

Posters and published abstracts

- Collins J, Noble S, Byrne A. Assessment and impact of sarcopenia in lung cancer: a systematic review highlighting implications for research and clinical practice. *Lung Cancer* 2013; 81(s1):1-144. Presented at the British Thoracic Oncology Group conference, Dublin, January 2013.

- Collins J, Noble S, Chester J, Byrne A. The value of assessing muscle depletion in lung cancer (sarcopenia) rather than body surface area, in the work-up to chemotherapy: reflections from a Systematic Review. *J Thorac Oncol* 2013; 8:s1015-16. Presented at the World Conference for Lung Cancer, Sydney, October 2013.

- Collins JT, Noble SI, Davies HE, Parry D, Lester JF, Chester J, Byrne A. Assessing physical performance in non-small cell lung cancer: Is the Short Physical Performance Battery acceptable, feasible and able to predict receipt of treatment? Presented at the British Thoracic Oncology Group conference, Dublin, January 2015.

- Collins JT, Noble SI, Chester J, Davies HE, Lester JF, Parry D, Byrne A. Assessing physical performance in non-small cell lung cancer: is the Short Physical Performance Battery acceptable, feasible and able to predict completion of treatment? Presented at the European Association for Palliative Care Congress, Copenhagen, May 2015.

Thesis Short Summary

INTRODUCTION:

The presence of muscle mass depletion is associated with poor outcomes and survival in cancer, and assessment of muscle strength or physical performance is essential for the diagnosis of sarcopenia. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) is commonly used to assess patients' suitability for treatment, in non-small cell lung cancer (NSCLC). However, a significant proportion of patients with good PS are unable to complete multidisciplinary team (MDT)-planned treatment. Little is known about whether objective measurements of physical performance can predict patients' ability to complete MDT-planned treatment in NSCLC.

OBJECTIVES:

Our main aim was to evaluate whether physical performance, utilising the short physical performance battery (SPPB), and muscle mass measurements, were able to predict receipt and completion of MDT-planned treatment.

MATERIALS AND METHODS:

NSCLC participants from a single centre MDT and ECOG PS 0-2 were recruited and the following assessed: body composition [bioelectrical impedance (BIA) and whole body dual-energy X-ray absorptiometry (DXA) in a subgroup], physical performance (SPPB), PS and nutritional status.

RESULTS:

We included a total of 62 participants with NSCLC, and 26 of these were planned for chemotherapy. Participants with early stage disease and weight loss of <10% were more likely to complete MDT-planned treatment ($p < 0.001$ and $p < 0.05$). A higher total SPPB score were associated with completion of more cycles of chemotherapy as well as the full course

(p < 0.05). For every unit increase in SPPB score, a 28.2% decrease in adverse events, hospitalisations and delays of chemotherapy (incidence rate ratio 0.718, p = 0.001) was seen, whilst ECOG PS showed no correlation with these outcomes.

CONCLUSION:

Assessing physical performance by SPPB may give a better indication of likelihood of completion of the chemotherapy course, compared to muscle mass alone and ECOG PS, with an impact on MDT decision-making and prudent use of resources.

Statement of Authorship

I declare that the work presented in this thesis was carried out solely by myself, as Clinical Research Fellow in the University Hospital of Wales (UHW), Cardiff and University Hospital Llandough (UHL), Penarth, except where indicated below:

- Measurement of haematological and biochemical data was performed by the hospitals' laboratory service.

- Dual energy X-ray absorptiometry (DXA) scans for a subset of participants were carried out in the Medical Physics department by Mrs. Rebecca Pettit, and reports were generated in the department.

- Participants' heights were measured by clinic staff in the Rapid Access Lung Cancer clinic in UHL using a wall mounted stadiometer.

Statistical analysis was performed by myself, and the results checked with the assistance of Dr Daniel Farewell, Cardiff University.

DECLARATION

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

Signed ……………………………………………. (candidate)   Date ……………………………………………

STATEMENT 1

This thesis is being submitted in partial fulfillment of the requirements for the degree of ………(insert MCh, MD, MPhil, PhD etc, as appropriate)

Signed …………………………………….……… (candidate)   Date ……………………………………………

STATEMENT 2

This thesis is the result of my own independent work/investigation, except where otherwise stated, and the thesis has not been edited by a third party beyond what is permitted by Cardiff University's Policy on the Use of Third Party Editors by Research Degree Students. Other sources are acknowledged by explicit references. The views expressed are my own.

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Chapter 1:
Lung Cancer and Sarcopenia

1   CHAPTER 1: LUNG CANCER AND SARCOPENIA

Lung cancer is a common, poor prognostic disease with a rising incidence. In 2000, the worldwide incidence of lung cancer was estimated to be 1.5 million (Parkin, 2001) and in 2008 this rose to 1.61 million (Ferlay et al., 2010). In the United Kingdom (UK), it accounts for approximately 13% of all new cases of cancer, and in 2011 there were approximately 43,000 new cases (Office for National Statistics, 2013 , Welsh Cancer Intelligence and Surveillance Unit, 2011, Northern Ireland Cancer Registry, 2011, Information Services Division, 2013). In 2009, it was the second most common cancer among men and women in the United Kingdom after prostate cancer and breast cancer respectively (Office for National Statistics, 2012); it is also the most common cause of cancer death in both men and women in the United Kingdom (Office for National Statistics, 2013).

In 2014, 35,895 patients died from lung cancer in the United Kingdom (Cancer Research UK, Office for National Statistics, 2015b). Overall survival is still poor – representative figures of one-year and five-year survival for men in England were 34% and 11% respectively; for women in England, they were 40% and 16% respectively (Office for National Statistics, 2015a). Only an overall estimated 5% are expected to still be alive at 10 years after diagnosis (Office for National Statistics, 2011). These figures are poor, despite advances in surgery, radiotherapy and chemotherapy over the last two decades. In contrast, over the same time period, there have been improvements in survival rates in other common cancers such as breast, colorectal and prostate cancers (Berrino et al., 2007, Coleman et al., 2003).

The International Cancer Benchmarking Partnership (ICBP) is an international collaborative to study international variation on cancer survival, and to inform policy on improving it (Butler et al., 2013). Compared to other countries in the developed world, the

United Kingdom has consistently lower figures of age standardised relative survival. Worldwide data from 2005-2009 showed that the 5-year survival rate for UK was 9.6%, compared with 14.8% in the Netherlands, 17.3% in Canada, and 15% in Australia (Allemani et al., 2015). Within each tumour-node-metastasis (TNM) stage I-IV, comparative survival was 10-16% lower in the UK than in Sweden, and 9-19% lower in TNM stages I-III than in Canada (Walters et al., 2013).

The reasons for this difference in survival are complex and varied (Holmberg et al., 2010). For example, the UK had lower proportions of histologically confirmed subtypes, and where this was the case they were grouped with NSCLC, potentially leading to some cases of SCLC and other poorer-prognosis cancers being misclassified as NSCLC. UK also had the lowest percentage of adenocarcinomas, which in general have better prognosis. More advanced stage distribution in the UK may be due in part to a higher incidence of smoking, or diagnostic delays (World Health Organisation, 2008). Furthermore, patients with lung cancer who consult their general practitioner more frequently prediagnosis, are more likely to have early mortality compared to those who present less frequently. This suggests some missed opportunities for early diagnosis and a need for judicious and timely use of chest x-rays at high risk, especially those who are elderly and socially-deprived (O'Dowd et al., 2015).

Another important explanation for UK having poorer outcomes is TNM stage at presentation, where 14.8% of patients with NSCLC presented with stage 1 disease in the UK, compared to 19.7% in Sweden. The reasons for presentation at a less early, or more advanced stage, are complex. Suboptimal staging could be relevant, with potentially different staging procedures, leading to misclassification of stage and subsequent inappropriate treatment. We consider stage-specific survival in greater detail in section 1.1.5.1. Whilst it is acknowledged that UK may have relatively poorer stage-specific treatment, studies are not directly comparable, due to differences in data, time periods and methods.

Comparing TNM stage specific data, the UK still performed worse compared with other developed countries, with best performances in Sweden. For data between 2004-2007, encompassing over 57,000 patients with lung cancer, UK net survival for TNM stage 1 non-small cell lung cancer (NSCLC) was 16% lower than Sweden, and TNM stage 4 NSCLC 10% lower than in Sweden (Walters et al., 2013). Within a global context of poor survival, prognosis is worse in the UK than in most developed countries, and is therefore a cause for concern and justifies research into the reasons behind this and methods to address it.

1.1 BACKGROUND TO LUNG CANCER: EPIDEMIOLOGY AND PATHOGENESIS

In the majority of cancers, the causative factors tend to be multifactorial, however, approximately 90% of lung cancers are the direct result of cigarette smoking (Peto et al., 1994). This link has been known since 1950 (Doll and Hill, 1950), and is attributed to carcinogens amongst the 4800 identified chemicals in cigarette smoke (Hecht, 2002, Hoffmann et al., 2001) which together cause the development of many lung cancers.

Not only does cigarette smoking contribute directly to the risk of developing lung cancer, it is also linked to other major co-morbidities such as chronic obstructive pulmonary disease, heart failure, ischaemic heart disease and hypertension (Lopez-Encuentra, 2002). The early warning symptoms of lung cancer such as cough and breathlessness are similar to that of smoking-related chronic lung diseases, and mistaking the symptoms of a new lung malignancy for chronic lung disease could lead to a delay in presentation. Conversely, this patient group have relatively more hospital admissions for other smoking-related diseases, where radiology may detect early signs of malignancy. Complete and timely resection of the tumour remains the definitive treatment for lung cancer, where possible. However despite

improvements in surgical resection rates over the last decade, the UK still lags behind other European countries with rates of 9-14% (Beckett et al., 2012). This is largely attributed to the majority of lung cancers being diagnosed late when surgery is not possible. Even when lung cancers are diagnosed at an early stage, poor lung reserve in patients with smoking-related co-morbidities such as COPD may render the patient at high anaesthetic risk for surgery.

1.1.1   A brief history of smoking and trends with the disease

At least a century has passed since lung cancer was recognised and reported. In 1912, Adler published a book entitled Primary Malignant Growths of the Lungs and Bronchi, in which he presented a case series of all 374 known bronchogenic cancers worldwide (Adler, 1912). However, it was not until much later in the 20th century that the link between cigarette smoking and the development of lung cancer became widely known. Cigarette smoking was popularised during the First World War, and smoking rates were at their peak in Europe and the United States after the Second World War. At that time, physicians were seen advocating smoking in tobacco advertisements, and claims by the tobacco industry that smoking was safe went unchallenged (Spiro and Silvestri, 2005a).

Later, two important breakthrough reports linking lung cancer to smoking occurred. The first was published in the British Medical Journal in 1950 by Doll and Hill, confirming the link between the increase in rates of tobacco consumption, and deaths due to lung cancer (Doll and Hill, 1950), and the second was a report by the U.S. Surgeon General, stating that smoking was harmful to health and calling for efforts to quit (US Advisory Committee to the Public Health Service, 1964). Since then, smoking rates have dramatically reduced in both men and women. Nevertheless, in 2010 an estimated 20% of both British men and women continued to smoke (Office for National Statistics, 2010).

Smoking and lung cancer are so closely linked that the rise and decline of the incidence of lung cancer parallels that of past trends of cigarette smoking. Once the direct link between smoking and lung cancer was known, efforts were made to reduce relative risk by changing the tobacco composition and makeup of cigarettes, and cigarette filters were also introduced. However, the anticipated improvement in mortality rates among cigarette smokers did not occur, primarily because smokers increased the depth of inhalation and subsequently their intensity of smoking. Risk of developing lung cancer is based on the duration and intensity of smoking. Recent models of the effect of smoking on the risk of developing lung cancer have shown that this risk is more dependent on the duration of smoking, rather than on the level of consumption. For example, smoking 20 cigarettes a day for 40 years is more hazardous than smoking 40 cigarettes a day for 20 years (Lubin et al., 2007, Lubin and Caporaso, 2006).

Environmental tobacco smoke, otherwise known as passive smoking, is also a risk factor for developing lung cancer, particularly in never-smokers. Meta-analysis data of exposure to environmental tobacco smoke at home or at work in non-smokers has shown an increased risk of developing lung cancer (Taylor et al., 2007, Stayner et al., 2007). In non-smoking British patients diagnosed with lung cancer in 2010, approximately 15% were due to environmental tobacco smoke (Parkin, 2011). There were gender differences in workplace-related risk of developing lung cancer. Women had a higher risk of developing lung cancer from environmental tobacco smoke (for example, working in smoky environments such as restaurants or bars) compared to men, however men were much more at risk of developing lung cancer from industry-related carcinogens such as asbestos, metals, and polycyclic aromatic hydrocarbons (PAHs). This was probably because a much lower proportion of women work in industries with exposure to asbestos, metals and PAHs, therefore proportionally their risk was much less compared to men (Veglia et al., 2007).

At a molecular level, the mechanisms by which carcinogens from cigarette and other secondhand smoke cause the development of lung cancer has been extensively studied. There are over 5000 identified compounds in cigarette smoke, including approximately 73 compounds which are considered carcinogenic to humans (Perfetti and Rodgman, 2008). Cigarette smoke is thus a concoction of the highly addictive nicotine, together with carcinogens, irritants, toxicants and inflammatory agents. Among the many carcinogens in cigarette and second hand smoke, polycyclic aromatic hydrocarbons (PAHs) and the tobacco-specific carcinogen 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) have robust evidence that they directly cause the development of lung tumorigenesis (International Agency for Research on Cancer, 2007).

Drug metabolising enzymes convert carcinogens to more water-soluble forms that can be detoxified and thereafter excreted. However, during this process, electrophilic intermediates such as carbocations and epoxides are produced, which then react with neutrophilic sites in DNA. These carcinogenic products covalently bind to DNA causing the formation of DNA adducts, which, if they persist unrepaired, result in genetic mutations (Beland and Poirier, 1994). If these mutations occur in the region that codes for an oncogene such as K-RAS or a tumour suppressor gene such as TP53, this may result in loss of normal cellular growth control mechanisms and the development of cancer (Hecht, 2012).

1.1.1.1   Causative factors other than cigarette smoke

Certain environmental carcinogens, apart from tobacco smoke, have been causally linked to lung cancer. The most significant after cigarette smoke is radon, which is the second leading cause of lung cancer in the United States. It is a naturally occurring gas, arising from the breakdown of uranium-238 which is present throughout the earth's crust. Once inhaled, radon gives off progeny which are deposited on the bronchial epithelium which exposes cells

to radiation (Darby et al., 2005). It was the first occupational carcinogen to be identified as a cause for lung cancer amongst underground miners where radon is present in high levels (Samet, 1991, Lubin et al., 1995). Systematic analysis data of residential radon exposure and risk of developing lung cancer showed that risk increased with higher levels of environmental radon concentrations in a linear fashion (Krewski et al., 2006). Certain regions have higher levels of radon, for example a substantial proportion of houses in Iowa in the United States had radon levels exceeding acceptable environmental levels, posing an obvious public health risk (Field et al., 2001). In the United Kingdom, Pembrokeshire and Cornwall are the most affected regions (Public Health England, 2007).

As mentioned in the section 1.1.1, certain occupations confer a higher risk of developing lung cancer. These occupations are those that involve working with asbestos, heavy metals, and polycyclic aromatic hydrocarbons – industries that involve mining, welding, machining, manufacturing and transport. These occupations and industrial areas have been highlighted for prioritisation of risk reduction strategies (Rushton et al., 2008) however, at present it is unclear what these strategies are in practical terms. However, the first and most important step is that public health authorities recognise the link between these occupations and the risk of developing lung cancer, in order that appropriate preventative measures and health screening can be taken for the employee.

Worldwide, occupational risks for developing lung cancer differ. For example, fumes produced by high-temperature oil-frying has been recently classified by the International Agency for Research on Cancer (IARC) as probably carcinogenic to humans (Straif et al., 2006). Such cooking is typical in countries such as China and Hong Kong, where cigarette smoking among women is low (3-5%) compared to women in western countries such as the United States (22%). Despite this, there is a high incidence of lung cancer among Chinese

women, and in recent years the link between cooking fumes from deep frying and the development of lung cancer has been recognised (Yu et al., 2006).

Race and ethnicity also impact on the risk of developing lung cancer, which is not wholly attributable to cigarette smoking. Large observational studies on the effect of ethnicity on the risk of developing lung cancer have been done in the United States of America. One large study of 183,813 participants of five American ethnic groups found that African Americans and Native Hawaiians were most at risk of developing lung cancer, compared to other ethnicities (Haiman et al., 2006). These racial trends were echoed in another publication (Berger et al., 2007), which also showed a gender disparity in incidence of lung cancer, reflecting a lower smoking rate in women compared to men. Native Hawaiians had a higher prevalence of lung cancer than whites and Asians, despite similar smoking habits (Menck and Henderson, 1982).

Race/Ethnicity	Men	Women
All Races	82.1	52.3
White	81.7	54.7
Black	112.2	53.1
Asian/Pacific Islander	55.7	27.3
American Indian/Alaska Native	55.5	33.8
Hispanic	44.7	24.0

Table 1.1 : Lung cancer incidence rates per 100,000 and age adjusted to year 2000 standard (from Berger et al, 2007)

There are multiple proposed reasons for the increased prevalence of lung cancer in Black Americans. Firstly, it has been reported that Black Americans inhale more nicotine per

cigarette smoked compared to whites, and therefore have increased exposure to carcinogens. In addition, Black Americans metabolise cotinine (the proximate metabolite of nicotine) slower than White Americans, given the same number of cigarettes smoked (Perez-Stable et al., 1998). These differences are in part due to genetic differences between blacks and whites.

Lung cancer is most likely to occur in the poor and less well educated, and these soci-economic trends are echoed worldwide. In Canada, the risk of developing lung cancer was inversely associated with income, education and social class, even after adjusting for smoking habits (Mao 2001). In the Netherlands, this trend was mirrored, and was not attributable to occupational exposures (van Loon 1997). This is probably because socioeconomic status determines multiple external factors of lung cancer risk, such as smoking, diet and exposure to inhaled carcinogens in the workplace and environment. A low socio-economic status is associated with an adverse profile to all of these factors (Alberg 2007).

1.1.1.2   Related comorbidities

As the majority of lung cancers are caused by cigarette smoking, it is not surprising that most patients at diagnosis will have other smoking related comorbidities. These are varied, but some important related diseases are chronic obstructive pulmonary disease (COPD), ischaemic heart disease, cardiac failure and hypertension (Lopez-Encuentra, 2002).

Many patients who develop lung cancer have some degree of COPD, and by definition, reduced overall lung function. Age and reduced lung function have frequently been cited as the two predominant reasons precluding patients from curative surgical resection of lung tumours. Lung cancer and COPD are both diagnoses which become increasingly prevalent with advancing age. A large Dutch study with almost 8000 participants

showed that the incidence was 9.2 per 1000 person-years in patients 55 years and older, with increasing incidence through ages 75-79 years (van Durme et al., 2009). Lung cancer, too, increases with age, and the median age of diagnosis is at 70 years of age, peaking in those aged 75-79 (O'Rourke et al., 1987, SEER Database, 2008).

The consequences of pre-existing COPD in elderly lung cancer patients are significant, particularly impacting on treatment. In early stage lung cancer, the only current curative treatment options are surgery and radical radiotherapy. In patients with early stage non-small cell lung cancer, lobectomy or pneumonectomy and pathologic mediastinal node staging offers the best overall survival, and is the treatment of choice (Scott et al., 2007). However, the high rate of medical comorbid illnesses, together with poor baseline pulmonary function in this population make many such early stage patients medically inoperable. There is some evidence which suggests that fewer older patients with early stage disease receive definitive surgical treatment for lung cancer compared to their younger counterparts (Guadagnoli et al., 1990). This is due to a combination of factors; the most compelling being that it was previously thought that there is increased perioperative mortality in older patients (Berry et al., 2009, Damhuis and Schutte, 1996), and also some surgeons' perception that the long term benefits in this cohort are likely to be limited. In addition, as previously mentioned, older patients are more likely to have other comorbidities such as COPD, which make surgery a higher risk procedure given increased anaesthetic risks associated with age and reduced overall lung function.

However, in the fit elderly patient with NSCLC, this is not the case, and in fact those over the age of 70 have been shown in several large prospective trials to respond as well as younger patients to lung resection, in terms of morbidity, mortality and quality of life (Chambers et al., 2010). In a large study of 316,682 NSCLC patients, older patients were offered surgery far less than younger patients; nevertheless, in those who underwent

surgery, their 5-year survival rates were comparable to that of younger patients (Owonikoko et al., 2007). Another large, population-based study in the United States of America, in over 17,000 stage I and II non-small cell lung cancer patients found that patients were more likely to undergo surgical resection of their tumours in high-surgery areas, which resulted in improved one-year all-cause and lung cancer-specific mortality figures, even in older and sicker patients (Gray et al., 2012).

1.1.2   Histological classification

The term lung cancer is an umbrella term for a range of cell types, with an evolving system of classification based on histological subtype. The earliest system of classification was proposed by Marchesani in 1924 (Marchesani, 1924), who identified four broad histological subtypes: squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell carcinoma. This was later expanded by the World Health Organisation in 1967, with further modification in a second edition in 1981 and 2001, recognising variations in differentiation and subtypes (World Health Organisation, 1967, World Health Organisation, 1981, Brambilla et al., 2001). However despite further refinement of this classification, the most commonly used broad classification still echoes the earliest classification by Marchesani – non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Of these, adenocarcinoma and squamous cell carcinoma are most common (50% and 30% of all NSCLC subtypes respectively), and the rest are made up of large cell carcinoma and undifferentiated NSCLC. There is no further subclassification for SCLC. The clinical relevance of differentiating NSCLC from SCLC lies in their differing clinical course and therapeutic options available.

The close relationship between the exposure to tobacco smoke and the subsequent development of lung cancer years later, means that there is a long latent period, during which sequential pre-neoplastic changes take place. The different histological subtypes of lung cancer are determined by the type of cells affected and their location in the lung. The lung has central and peripheral compartments; the central compartment comprising large and medium sized bronchi, and the peripheral compartment smaller bronchioles and alveoli. The central airways are lined by basally located basal cells and neuroendocrine cells, luminal tall ciliated cells and mucus secreting cells. The peripheral terminal bronchioles however have short stubby ciliated cells, secretory Clara cells, and type I and II alveolar pneumocytes (Gazdar and Brambilla, 2010).

Early research has postulated that lung tumours arise from cancer stem cells (CSCs) in both these compartments of the lung. It is thought that central airways stem cells give rise to both neuroendocrine small cell lung tumours and squamous cell lung tumours, while adenocarcinomas arise from peripheral airways stem cells (Sullivan et al., 2010). The clinical importance of the CSC theory is that although they comprise less than 1% of the overall tumour, they are its crucial component. They are able to proliferate extensively, form new tumours, leading to recurrence, therapy resistance, and metastasis (Wu et al., 2012, Reya et al., 2001). For this reason, the presence of CSCs have been implicated in chemotherapy resistance and radiotherapy failure (Ajani et al., 2009, Koch et al., 2010, Raguz and Yague, 2008), and some authors have called for new therapeutic strategies to target CSCs, in addition to traditional chemo-radiotherapy (Han et al., 2013). However, while there is currently evidence for the CSC theory, its precise biology and clinical implications are incompletely understood. Nevertheless, the potential for CSCs as targets for therapeutic strategies is enormous.

1.1.2.1   Squamous cell carcinoma

As mentioned previously, squamous cell carcinoma is often preceded for many years by squamous cell dysplasia or metaplasia in the respiratory epithelium of the bronchi, later becoming carcinoma in situ. Atypical carcinoma in situ cells may be identified from cytological smear cells from sputum, bronchoalvealar lavage, or endobronchial brushing samples. It accounts for 20-30% of all lung cancers (Travis, 2011), and until the 1960s was the most frequent subtype of non-small cell lung cancer, when its prevalence decreased in proportion compared to adenocarcinoma (Dodds et al., 1986). Out of all the subtypes of NSCLC, squamous cell carcinoma is most strongly associated with cigarette smoking, and the overall reduction in prevalence of squamous cell carcinoma has been ascribed to changes in cigarette design and composition, and a change in smoke inhalation patterns.

Squamous cell carcinoma most often arises centrally in larger bronchi, but tumours arising from the lung periphery are becoming increasingly common (Funai et al., 2003). Clinically, patients may present with cough, dyspnoea, and fever resulting from atelectasis and post-obstructive pneumonia, particularly with centrally located tumours. Larger tumours may necrose and cavitate, occasionally causing haemoptysis. Squamous cell carcinomas tend to be locally aggressive, and metastasise to distant organs less frequently than adenocarcinoma.

1.1.2.2   Adenocarcinoma

Adenocarcinoma is currently the most commonly occurring lung cancer type, accounting for around 50% of all subtypes of NSCLC. It occurs more commonly in smokers, but is the most common lung cancer amongst non-smokers. They may occur almost anywhere in the lung but tend to arise peripherally.

In the last decade, the histopathological differentiation between squamous cell carcinoma and adenocarcinoma has emerged to be of great importance for a number of reasons, particularly with regards to choice of therapeutic options. Firstly, the presence of epidermal growth factor receptor (EGFR) mutations in patients with adenocarcinoma confers a greater responsiveness to tyrosine kinase inhibitors such as erlotinib and gefitinib, and phase III trials have shown a significant progression-free survival benefit (Mok et al., 2009, Mitsudomi et al., 2010). Secondly, patients with adenocarcinoma have an improved outcome with permetrexed therapy, compared to those with squamous cell carcinoma (Scagliotti et al., 2009, Ciuleanu et al., 2009). Thirdly, whilst the monoclonal antibody vascular endothelial growth factor (VEGF) inhibitor bevacizumab, in combination with carboplatin, is associated with increased overall survival and progression-free survival, there is an increased risk of potential life-threatening haemorrhage in squamous cell carcinoma (Johnson et al., 2004).

1.1.2.3   Large cell carcinoma

Large cell carcinoma is the least frequently occurring type of NSCLC. It commonly arises from the lung periphery, but may be located centrally. Macroscopically, it tends to be a large necrotic tumour and is a diagnosis of exclusion, after the presence of squamous cells and glandular differentiation is excluded by light microscopy. Large cell carcinomas are a heterogenous group comprising histological variants such as large cell neuroendocrine carcinoma (LCNEC), basaloid carcinoma and clear cell carcinoma. As such, there is scant clinical trial data on clinical outcomes and response to therapy (Travis, 2011). However, the fact that they present in advanced stages makes them a highly aggressive form of lung carcinoma with a poor prognosis (Downey et al., 1989).

1.1.2.4   Small cell lung cancer

Small cell lung cancer is highly associated with smoking, and is characterised by aggressive growth patterns and disseminated metastases. Approximately 60-70% of SCLC patients present with advanced (extensive stage) disease, and for this reason surgery (and therefore cure) is rarely possible. Clinically, small cell lung tumours present as a central mass, with bronchial obstruction caused by circumferential compression, causing localised symptoms such as cough and dyspnoea (Travis et al., 2004, Sangha and Lara Jr., 2011). Extensive lymph node metastases are common. It is recognised histologically by malignant epithelial tumour consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli (Travis et al., 2004). There is a rapid growth rate caused by a high mitotic count. The diagnosis of small cell lung cancer rests primarily on morphologic assessment, however immunocytochemistry also plays a key role, where almost all small cell lung tumours immunostain for keratin and epithelial membrane antigens. Small cell lung cancer is recognised as a neuroendocrine tumour, with immunohistochemical analyses consistently displaying the presence of neurosecretory-like granules (Cook et al., 1993). This has led to it being associated with a variety of endocrine and neurological paraneoplastic syndromes such as syndrome of inappropriate antidiuretic hormone secretion, and Cushing's syndrome. In fit patients with localised disease, the treatment of choice is concurrent chemotherapy and radical radiotherapy. Despite high tumour response rates to platinum-based chemotherapy, many develop drug resistance and progression during, or relapse soon after, first-line chemotherapy is common, with consequent poor prognosis (Califano et al., 2012).

1.1.3   Metastasis

Cells that have undergone malignant transformation exhibit these six traits or hallmarks (Hanahan and Weinberg, 2011):

1. Ability to sustain long term prolifetiation

2. Evasion of growth suppressors

3. Resistance to cell death or apoptosis

4. Ability to replicate indefinitely

5. Stimulation of angiogenesis

6. Activation of invasion and metastasis

This ability to metastasise is a unique and distinct ability of cancer cells. At a cellular level, it a sequence of direct steps, termed the invasion-metastasis cascade (Talmadge and Fidler, 2010). The process of metastasis begins with local invasion, then intravasation of cancer cells into adjacent blood and lymphatic vessels, where it is carried through the lymphatic system and bloodstream. This is then followed by cancer cells escaping from the lumina of these vessels into distant tissues (extravasation), and subsequently the creation of small nodules of tumour cells (micrometastases), leading eventually to the formation of macroscopic tumours (colonisation). The presence of metastases to distant organs is a characteristic of aggressive disease. Further to these six well-established hallmarks of metastasis, two new concepts are emerging: the ability to re-programme energy metabolism, and evade immune destruction (Hanahan and Weinberg, 2011).

1.1.3.1   Metastastic sites in lung cancer

At the time of diagnosis, approximately 56% patients with lung cancer will have advanced or metastatic disease (Howlader et al., 2011). Lung cancer spreads outwards from

the mediastinum, affecting the local lymph nodes areas to include mediastinal, supraclavicular, and paratracheal nodal groups. As it metastasises to distant organs, it affects commonly but not exclusively the brain, bone, liver and adrenal glands.

Lung cancers have a high predisposition for spread to the brain. At autopsy of 400 people with lung cancer, 36% had brain metastases, with a higher prevalence found in those with adenocarcinoma histology (45%) (Cox and Yesner, 1981) and in small cell lung cancer this can be as high as 80%, at two years from diagnosis (Gavrilovic and Posner, 2005). Although the prognosis of patients with brain metastases is generally very short, with a median of 4-7 weeks untreated, survival can be increased to a median of 5 months, by means of cranial irradiation (Sen et al., 1998) and further to a median of 10-12 months following metastasis resection in selected patients (Noordijk et al., 1994).

The next most common extra-thoracic spread of lung cancer is to bone, the distribution being most frequent in the axial skeleton (spine and ribs), although lesions in the large bones such as the humerus and femur are also common, sometimes presenting with pathological fractures. At time of diagnosis, the incidence of bone metastases is highest in small cell lung cancer and lowest in squamous cell carcinomas. As with intracranial disease, prognosis for patients with lung cancer and bony metastases is generally poor, with a median survival of 7.2 months. However, a more favourable prognosis is conferred if it is a solitary lesion, if there are no pathological fractures, and if treated with an epidermal growth factor receptor inhibitor (Sugiura et al., 2008). The use of bisphosphonates such as zoledronic acid is also widely used to prevent skeletal related events such as pathological fractures, spinal cord compression and hypercalcaemia (Coleman, 2004).

1.1.4   Staging

For all patients presenting with lung cancer the first and foremost question that requires an answer is whether their disease is potentially curable? This will depend on multiple prognostic variables but none more so than the stage of disease at presentation. Other important patient-related prognostic markers such as baseline performance status, quality of life and weight loss should also be taken into account when planning appropriate treatment for the patient.

As well as giving important prognostic information, accurate staging of the disease is a vital step in identifying therapeutic options available. Not uncommonly, tests to provide a diagnosis and stage the disease occur simultaneously, for example in surgical exploration of the mediastinum to confirm technical resectability, and to provide adequate nodal samples for histological examination. However, recent advancements in techniques in the staging of lung cancer has enabled a less invasive, more targeted approach to classification of the tumour and its treatment.

1.1.4.1   Radiological methods for staging

Alongside histological staging, the use of radiological investigations to characterise tumour bulk is of great importance. The radiological mainstay of current lung cancer staging is with computed tomography (CT) images, which has a more modest sensitivity value of 57% when staging the mediastinum. In the absence of metastatic disease, accurate mediastinal staging is crucial to guide therapeutic options, and increase chance of cure. Meta-analysis data have demonstrated that the accuracy of CT scanning in mediastinal staging had not improved from the 1980s and 1990s, despite improvements in CT scan resolution (Toloza et al., 2003b). However, the emergence of another imaging modality, Positron Emission

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Tomography (PET) scanning, has proven to be superior to CT scanning in sensitivity and specificity in detecting mediastinal nodal metastases. Since 2001 the accuracy of lung cancer staging has been improved by combining both CT and PET (CT-PET) which is achieved practically by superimposing CT and PET images one on another. The diagnostic capability of CT-PET is superior to that of CT alone and PET alone (Lardinois et al., 2003), and has improved rationalisation of services, by reducing the total number of thoracotomies (Fischer et al., 2009).

Although staging of the mediastinum is essential, the evaluation of possible distant metastases is equally important. Modalities for evaluating this include non-invasive techniques such as ultrasound, magnetic resonance and computed tomography imaging, PET and CT-PET as discussed above. Biopsies of discrete lesions, such as skin, bone, and lung lesions if accessible, will help to further characterise disease spread. Evidence of metastatic disease, either proven clinically or radiologically will limit therapeutic options, in particular surgery.

1.1.4.2   Invasive staging techniques

The accurate staging of the mediastinum is essential as prognostic information in order to guide appropriate treatment for individual patients, as well as to compare staging data between studies. The evaluation of cancerous involvement of mediastinal lymph nodes can be based on size (CT, MR or other imaging) or metabolic properties (PET). However, these techniques lack specificity unless multiple sites are involved on imaging. Hence, tissue examination is frequently required for further consideration of surgical exploration or treatment.

The role of surgery within the multidisciplinary assessment of lung cancer, as a diagnostic and therapeutic modality should not be understated. Surgical exploration of the mediastinum can be for staging purposes initially, but proceed as therapy. Complete resection remains the best chance of cure for lung tumours which are confined to the lung. Hence, surgical exploration in order to characterise disease extent and technical resectability is vital, and imaging modalities do not give the same accuracy. Finally, surgical techniques allow adequate sampling for histological examination, with lower rates of false-negatives (Catarino and Goldstraw, 2006).

The gold standard investigation is surgical mediastinoscopy, which gives a pooled diagnostic sensitivity of 78-81%, and a negative predictive value (NPV) of 91% (Toloza et al., 2003a). However, this procedure is invasive and skill-dependent. Video assisted thoracoscopy (VATS) enables lung resection and lymph node biopsy, and has been shown to have lower systemic recurrences and improved 5-year survival figures compared to open lobectomy (Yan et al., 2009). Bronchoscopy with trans-bronchial needle aspiration has been a long established practice of sampling bulky subcarinal and paratracheal lymph nodes for diagnostic and staging purposes. The main drawback of this procedure is that the nodal sampling is `blind', accessing only limited groups of nodes. However, it is a well-tolerated, minimally invasive procedure with a sensitivity of 76-78% and an NPV of 71-72% (Toloza et al., 2003a).

In contrast, endobronchial ultrasound (EBUS) has the advantage of improving diagnostic utility where there is discrete nodal enlargement. Systematic review pooled data for EBUS shows a 90% sensitivity and 76% NPV, making it superior to transbronchial needle aspiration (Detterbeck et al., 2007). Another endoscopic modality used for staging lung cancer is endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), which is achieved by sampling mediastinal nodes through the wall of the oesophagus. It can be used as an

adjunct to mediastinoscopy. The sensitivity is 84-88% and NPV 77-81% (Detterbeck et al., 2007). In the United Kingdom, the National Institute of Health and Care Excellence (NICE) recommend the use of CT-PET as the preferred first test after CT to evaluate mediastinal lymph nodes, if there is low probability of mediastinal malignancy. For patients with intermediate probability of mediastinal malignancy, NICE recommend PET-CT, EBUS-guided TBNA, or EUS-guided FNA to investigate; for patients with high probability, neck ultrasound with lymph node sampling (National Institute for Health and Care Excellence, 2011).

1.1.4.3   Tumour Node Metastasis Staging

The diagnosis of lung cancer frequently relies on the use of a combination of radiological and histological methods, as described above. Subsequently, the disease is staged according to spread and invasion, using the tumour, node, metastasis (TNM) staging system. There is strong evidence of the association between TNM stage on survival in lung cancer, and as such the accurate determination of this is crucial. From January 2017, the eighth edition of the TNM staging in lung cancer was published by the International Association for the Study of Lung Cancer (IASLC) based on their database analyses of 77,156 patients with lung cancer from 1999 to 2000 (Rami-Porta et al., 2017).

T	Primary Tumour
Tis	Pure lepidic adenocarcinoma less than 3cm in size
T1m1	Lepidic predominant adenocarcinoma less than 3cm in total size
T1a	≤1cm
T1b	>1cm but ≤2cm
T1c	>2cm but ≤3cm
T2a	>3cm but ≤4cm; bronchus <2cm from carina or total atelectasis/pneumonitis
T2b	>4cm but ≤5cm; bronchus <2cm from carina or total atelectasis/pneumonitis
T3	>5 but ≤7cm
T4	>7cm or tumour that invades the diaphragm

N	Regional Lymph Nodes
Nx	Unassessable regional lymph nodes
N0	No lymph node metastasis
N1	Involvement of ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M	Distant Metastasis
M0	No distant metastasis
M1a	Metastasis within thoracic cavity
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases

Table 1.2: 8th Edition TNM Classification for Lung Cancer, from Rami-Porta et al 2017.

Occult carcinoma	Tx	N0	M0
Stage 0	Tis	N0	M0
Stage 1A1	T1mi or T1a	N0	M0
Stage 1A2	T1b	N0	M0
Stage 1A3	T1c	N0	M0
Stage 1B	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a,b,c	N1	M0
	T2a,b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,b,c	N2	M0
	T2a,b	N2	M0
	T3	N1	M0

	T4	N0,1	M0
Stage IIIB	T1a,b,c	N3	M0
	T2a,b	N3	M0
	T3,4	N2	M0
Stage IIIC	T3,4	N3	M0
Stage IVa	Any T	Any N	M1a,b
Stage IVb	Any T	Any N	M1c

Table 1.3: Stage groupings according to 8th Edition TNM Classification, from Rami-Porta et al, 2017.

1.1.5   Tumour-related factors affecting clinical outcomes in NSCLC

The assessment of prognosis is important in determining the likely clinical outcome and the selection of treatment from suitable options for each individual. However, length of survival does not merely depend on whether one is suitable for systemic treatment, but also on one's physical fitness to undertake and complete rigorous treatment. All these factors that have a bearing on survival can be grouped into two categories: tumour-related and patient-related factors, and these are now discussed.

Possibly the most important factor determining cure is operability and suitability for radical radiotherapy. This is largely dependent on the stage at diagnosis, as only stage I and II tumours are considered resectable. Unfortunately, many lung cancers are diagnosed at a late stage, when surgery or radical radiotherapy are not options and overall survival figures are poor. Approximately 65% of lung cancers present at a locally advanced stage IIIB or metastatic stage IV disease, where the median survival is 4 to 6 months with best supportive

care (Spiro and Silvestri, 2005b). Despite this fact, staging is still an independent predictor of survival even amongst advanced non-operable lung cancers. Furthermore, the number of metastatic sites involved (Lee et al., 2013), particularly liver metastases (Hilsenbeck et al., 1993) is associated with reduced survival. A malignant pleural effusion is also considered a negative prognostic factor (Sugiura et al., 1997).

American data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database revealed that over the last 2 decades, from 1996 to 2010, while survival has changed little for stage I and II patients (median survival of 51 to 64 months), it has improved for stage IIIA and IIIB/IV patients (median survival of 11 to 23 months, and 4 to 5 months respectively) (Kaniski et al., 2017). The table below illustrates 5-year survival rates for NSCLC patients according to TNM stage, with Australian data as representative.

TNM Stage	5-year survival %
I	67
II	34
III	24
IV	10

Table 1.4: Five year survival figures for non-small cell lung cancer based on tumour stage, adapted from Australian data, Denton et al 2016.

Net survival data vary according to geographical location, for varied reasons such as local rates of surgery, screening, early diagnosis and treatment options available. Data in over 5 million patients in both the developed and developing world (CONCORD data, Global Surveillance of cancer survival 1995-2009) show that the net 5-year survival for patients with lung cancer is low, at 10-20%. In 2009, this ranged from 18.7% in North America, 17.5% in China, 16.2% in Germany, 15% in Australia, and 9.6% in the UK (Allemani et al., 2015). Lower stage-specific survival could be indicative of lower treatment rates, as previously it was

reported that the UK had lower rates of surgery for lung cancer, as well as uptake of radiotherapy and chemotherapy, compared to other European countries (NHS Information Centre (NHSIC), 2011, Riaz et al., 2012). In 2004, the National Lung Cancer Audit database was set up to improve data collection and ensure targets of care were achieved. A recent report showed that, while improvements were made particularly to surgical resection rates, this only resulted in a 1% annual improvement in survival, suggesting that relatively poorer survival in the UK is only partly explained by previously low surgical rates (Khakwani et al., 2013).

Within the past two decades, there have been vast improvements in knowledge of the development and progression of lung cancer at a cellular and molecular level. Despite this, NSCLC remains the leading cause of cancer-related mortality (Siegel et al., 2017). The well-established link between cigarette smoking and the development of lung cancer does not explain the disease occurrence in never-smokers, nor does it explain why only around 15% of smokers develop lung cancer (Brennan et al., 2006). With this in mind, it is highly likely that other biological factors may influence the development of lung cancer and response to treatment. In recent years, there has been a plethora of new research and knowledge regarding the processes of cellular transformation, tumour invasion and metastasis. These biomarkers and genetic alterations have also been evaluated for their prognostic potential. Whilst isolated individual findings are of little practical value, some of the more common genetic alterations with more robust evidence are presented here.

A defining trait of cancer cells is their ability to escape normal growth control mechanisms (Hanahan and Weinberg, 2011), and this is achieved in part by the aberrant production of, and response to, growth factors. The epidermal growth factor receptor (EGFR) is part of the ERBB superfamily of trans-membrane signalling molecules – EGFR (also known as ERBB1), ERBB2 (also known as Her2/Neu), ERBB3 (also known as Her3) and ERBB4 (also

known as Her4). All these growth factor receptors have a similar structure, comprising an extracellular ligand-binding region, a membrane-spanning region and a cytoplasmic domain containing tyrosine kinase, and they are involved in the control of multiple cellular processes, such as proliferation and survival (Hynes and Lane, 2005). The ERBB receptors are implicated in the development of many types of human cancers. In lung cancer patients, EGFR is particularly important. The expression of EGFR, which is generally low in normal lung tissue, is enhanced in metaplastic, preneoplastic and neoplastic lesions (Rusch et al., 1995). While it was previously thought that over-expression of EGFR was key in determining suitability for anti-EGFR targeted treatment, EGFR mutations are now considered much more significant (Siegelin and Borczuk, 2014).

The major importance of EGFR mutations is in guiding targeted treatment using tyrosine kinase inhibitor (TKI) drugs, which work by counteracting the abnormal signal transduction pathways between the cell membrane and nucleus in cancer cells. As EGFR is a cell-surface protein, it binds to and activates epidermal growth factor, inducing phosphorylation of tyrosine residues in a variety of target proteins (and autophosphorylation), leading to altered intracellular signal transduction and cell proliferation. Licensed anti-EGFR TKIs for lung cancer include erlotinib, gefitinib and afatinib. Gefitinib and erlotinib work by reversibly binding to the adenosine triphosphate-binding pocket of the EGFR tyrosine kinase domain. This counteracts abnormal downstream signalling pathways, resulting in increased apoptosis and inhibition of proliferation in cancer cells. 10-15% of patients with non-squamous NSCLC have an EGFR positive (EGFR+) mutation, and in this group patients are more likely to have adenocarcinoma, be of East Asian ethnicity and have never smoked (Greenhalgh et al., 2016, Rosell et al., 2009).

The discovery of the value of EGFR mutations found that most mutation-positive tumours exhibited increased sensitivity and favourable clinical response to TKIs (Lynch et al.,

2004, Pao et al., 2004). This has heralded a new era of 'precision medicine' for patients with advanced lung cancer. EGFR mutation-positive patients treated with erlotinib or gefitinib versus standard chemotherapy have shown increased progression-free survival, in phase III trials, in both European and Asian patients (Rosell et al., 2012, Mok et al., 2009). Meta-analysis data of phase III trials in EGFR mutation-positive patients receiving erlotinib or gefitinib alone or with standard chemotherapy as first line treatment showed statistically significant improved overall response rate and progression free survival (Gao et al., 2012). TKIs are now first-line for EGFR+ tumours, having a superior progression free survival compared to conventional chemotherapy (Peters et al., 2012). Furthermore, in the UK patients with advanced lung cancer are now routinely screened for EGFR mutation status, and if positivie, prioritised for treatment with oral TKIs rather than intravenous chemotherapy.

Another very important antitumour mechanism involves T-cell immunity – the advent of immune checkpoint inhibitor drugs promises to be a paradigm shift in the management of advanced lung cancer. Programmed cell death 1 (PD-1) and its ligand, PD-L1, which are part of the B7-CD28 superfamily, are cell surface proteins found in NSCLC patients. Cells that express these proteins evade T cell immunity via inhibitory and suppressive signals to T-cells, thereby defending tumour cells from cytolysis (Zou and Chen, 2008). Clinically, those with higher levels of PD-L1 expression are more likely to have poorly differentiated tumours, and lower overall survival (Wang et al., 2015).

Nivolumab and pembrolizumab are human IgG4 immune checkpoint inhibitor antibodies, which work by disrupting PD-1-mediated signalling, and may restore anti-tumour immunity. The rate at which these tumours express PD-1 or PD-L1 on their surface varies, but in patients with advanced NSCLC with expression of PD-L1 on at least 1% of tumour cells, pembrolizumab demonstrated superior survival benefit compared to standard

chemotherapy, validating the use of PD-L1 selection in this patient group (Herbst et al., 2016). Nivolumab was also superior to docetaxel in improving overall survival and reduced adverse events, in patients with advanced squamous and non-squamous NSCLC (Borghaei et al., 2015, Brahmer et al., 2015). However, in non-squamous NSCLC patients, this survival benefit was not seen in PD-L1 mutation negative patients.

1.1.6   Patient-related factors affecting outcomes in NSCLC

1.1.6.1   Performance Status

Resectability of the tumour depends heavily on disease stage at presentation, as only stage I and II tumours are considered operable, and radical radiotherapy with curative intent also demands early stage disease. However, early stage disease does not on its own predict suitability for a resection. Other patient related factors must be taken into account, including the likelihood that the patient will survive the operation. Performance status (PS) has long been used to estimate a patient's ability to perform daily living activities, and is a subjective, surrogate measure of their fitness for treatment. In addition to this, a patient's individual co-morbidities and predicted post-operative lung function need to be taken into account. Therefore, a patient with poor pre-existing lung function and significant comorbidities may have technically operable disease (based on stage) but be medically unfit for surgery.

Grade WHO / ECOG	Description of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Table 1.5: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale, from Oken et al 1982.

Karnofsky score	Description of activity	Equivalent WHO Performance Status score
100%	normal, no complaints, no signs of disease	0
90%	capable of normal activity, few symptoms or signs of disease	1
80%	normal activity with some difficulty, some symptoms or signs	
70%	caring for self, not capable of normal activity or work	2
60%	requiring some help, can take care of most personal requirements	
50%	requires help often, requires frequent medical care	3
40%	disabled, requires special care and help	
30%	severely disabled, hospital admission indicated but no risk of death	4
20%	very ill, urgently requiring admission, requires supportive measures or treatment	
10%	moribund, rapidly progressive fatal disease processes	
0	Death	5

Table 1.6: Karnofsky Performance Status scale and corresponding ECOG scale, from Karnofsky and Burchenal 1949 and the European Society for Medical Oncology (ESMO) webpage.

In the United Kingdom, the ECOG PS score (also known as World Health Organisation, WHO Performance Status) is widely used, together with the stage of disease, to determine treatment options. It is a 6-point scale ranging from 0 (normal) to 5 (dead). Another widely used score is Karnofsky PS, which is an 11-point scale ranging from 100% (normal) to 0 (dead) (Karnofsky and Burchenal, 1949, Oken et al., 1982). The importance of accurately gauging patients' fitness for systemic anticancer treatment becomes more pronounced when patients present with advanced disease. In lung cancer, the association between poor PS and poor survival is well documented, even after controlling for age and TNM stage (Hespanhol et al., 1995, Buccheri et al., 1996).

While there is plenty of literature that supports PS as a strong predictive factor for survival, not much is known regarding its effect on treatment-related outcomes such as tolerance to and successful completion of chemotherapy. This is perhaps surprising, given that PS so profoundly affects treatment decisions made by the MDT. For example, at the same TNM stage a patient with PS 3 may receive best supportive care, whereas a patient with PS 2 may be offered palliative chemotherapy; this cut-off is also often used for clinical trials (Sorensen et al., 1993). Even some with good baseline PS and considered suitable for active treatment by the MDT do not go on to receive it due to declining PS (Vinod et al., 2008, Vinod et al., 2010), suggesting that clinician-assessed PS, on its own, may not be a reliable indicator of true fitness for treatment.

A major disadvantage of PS is that it is a subjective measure, with significant inter-observer variability (Dajczman et al., 2008, Ando et al., 2001). Where PS have been evaluated by different observers concomitantly, the level of agreement has been cited as moderate between physicians, physician and patient, and physician and nurse (kappa statistics 0.4-0.74) (Blagden et al., 2003, Ando et al., 2001, Sorensen et al., 1993, Zimmermann et al., 2010, Conill et al., 1990), with few exceptions (Taylor et al., 1999, Roila et al., 1991). Furthermore,

physicians tend to rate patients as healthier, compared to other healthcare professionals, and even patients themselves (Zimmermann et al., 2010, Ando et al., 2001, Dajczman et al., 2008).

The likelihood of successful systemic anti-cancer treatment depends on patients completing the course at an optimal dose. Disease that is inoperable may be amenable to chemotherapy or combined chemo-radiotherapy, but these treatments have been found to be poorly tolerated in patients with performance status 2 (PS 2) or worse (Gridelli, 2002). This poor tolerance is partly due to increased chemotherapy toxicities in those with a poorer baseline functional status.

In advanced stage PS 2 patients, with so-called "marginal performance status", it can be difficult to decide on the risk-benefit ratio of giving systemic anti-cancer treatment, in contrast to clearer consensus on PS 0-1 patients (West, 2013). PS 2 patients have shorter median survival compared to their better PS counterparts, irrespective of treatment, and a worse PS tends to correlate with a poorer response to treatment. Despite this, the current recommendation is that patients with advanced disease and PS 2 should be considered for single agent chemotherapy, with the aim of symptom alleviation and also to confer a survival advantage (Gridelli et al., 2004).

Despite PS being the most widely accepted measure of the likelihood of tolerability of chemotherapy, it has inherent problems. The main problem is that of bias; it is scored by the clinician, based on their perception of a patient's functional status. A phase III trial with paclitaxel poliglumex versus standard paclitaxel specifically in PS 2 patients, showed no benefit for either arm, yet the authors observed that "PS designation remains highly subjective and open to debate". This was based on the finding that patients recruited in Eastern Europe had conspicuously higher median overall survival than those recruited in North America and Western Europe (Langer et al., 2008, West, 2013), an observation which

was corroborated by the same pattern in another parallel PS 2 trial comparing paclitaxel and single agent gemcitabine or vinorelbine (O'Brien et al., 2008).

1.1.6.2   Body Composition

The idea of the ideal weight corrected for height range of 18.5-25 kg/m^2 is based on the U shaped curve of mortality seen in the general population, where obesity (BMI ≥30) and underweight (BMI ≤18.5) were associated with increased mortality compared to those in the ideal range (Flegal et al, JAMA 2005). Being underweight is a poor prognostic factor in lung cancer, with consistently worse risk-adjusted outcomes (Zogg et al., 2015). There is good evidence of this particularly in surgical candidates, where patients with a BMI of 18.5 and below have increased post-operative pulmonary and cerebrovascular complications, as well as postoperative mortality, compared to normal weight or obese counterparts (Matsunaga et al., 2015, Ferguson et al., 2014). An underweight BMI was also predictive of poorer survival in locally advanced lung cancer patients treated with chemotherapy (Park et al., 2016).

The interplay between lean and fat body compartments, particularly muscle mass, in NSCLC patients, is the subject of further scrutiny in this thesis and is considered in detail in section 1.2 and chapters 3 and 4.

1.1.6.3   BMI and the obesity paradox

In patients with malignancy, increasing BMI has been associated not only with the development of certain cancers, but also with greater rates of cancer specific death in the

highest BMI categories (Renehan et al., 2008, Calle et al., 2003). However, being obese seems

to be associated with favourable surgical outcomes and even increased survival compared to

those with normal weight (Lam et al., 2017). This is perhaps surprising, as obesity is well

known to be linked to hypertension, dyslipidaemia, and insulin resistance, all of which

contribute to the development of cardiovascular disease and its related increased risk of

mortality. It is likely that being obese confers certain short-term benefits, particularly in the

peri-operative period, where it offers an initial protective physiological reserve, after which

time disadvantages on general health and mortality increases.

Whatever the case, the role of BMI on survival in many cancer populations is

inconsistent (Vrieling and Kampman, 2010, Renehan, 2014) and can seem counter-intuitive.

The relationship between high BMI and low mortality has been called the obesity paradox,

which has been reported in several large lung cancer clinical trials. Yang et al studied the

effect of weight loss and obesity in over 76,000 patients with lung cancer. They found that

obesity was an independent predictor of improved survival, and those presenting with

unplanned weight loss worsened survival (Yang et al., 2011). Another study in over 64,000

elderly people showed a strong inverse association between BMI and lung cancer specific

mortality, regardless of smoking status (Leung et al., 2011). This relationship has been

observed in other studies. One study from China observed this only in current smokers, whilst

another from America found that excluding smokers from analysis yielded non-significant

results (Yang et al., 2009, Calle et al., 2003). The clear message from these large cohort

studies is that excess body weight for height, in lung cancer patients seems to have a positive

effect for cancer-specific survival.

Aside from BMI being a sub-optimal measurement of adiposity, other possible

explanations for the obesity paradox are that some tumours may be biologically less

aggressive, and that excess weight may provide reserves against the physiological stress of

malignancy (Renehan, 2014). Another hypothesis, particularly for improved post-operative outcomes in obese patients is that chronic low-grade inflammation allows them to better withstand the stress of surgery (Mullen et al., 2009). Whatever the cause, BMI does not provide an accurate picture of one's phenotype, particularly in categorisation for treatment-related risk.

1.1.6.4   BMI and its predictive value in surgery and chemotherapy outcomes

Underweight patients with lung cancer undergoing resection had significantly increased post-operative pulmonary complications and mortality, but being overweight or obese did not increase this risk (Matsunaga et al., 2015, Ferguson et al., 2014). Even though overweight and obese patients with lung cancer had a greater number of comorbidities including diabetes, hypertension and cardiovascular disease, there was no increase in morbidity and 30-day mortality in this group, compared to normal weight patients (Mungo et al., 2015).

In contrast to evidence for BMI and surgical outcomes, there is not a great deal of evidence with regards to BMI and chemotherapy-related complications in NSCLC. This is the subject of further discussion in Chapters 4 and 7, where BMI and chemotherapy-related complications is explored in our study. Fujiwara et al found that overweight patients were more likely to experience grade 2 or worse hepatic dysfunction during chemotherapy than their non-overweight counterparts. The authors conjectured that this may be due to impaired pharmacokinetics and impaired drug distribution (Fujiwara et al., 2007). On the other hand, low muscle mass and underweight NSCLC patients treated with afatinib were found to be more likely to develop dose-limiting toxicities (Arrieta et al., 2015). While low BMI and muscle

mass have both been implicated as risk factors for developing chemotherapy toxicities in other cancers (Tan et al., 2015a, Prado et al., 2009, Antoun et al., 2010), there is not enough evidence to conclude that BMI is an independent risk factor in predicting dose-related chemotherapy toxicities in NSCLC.

1.1.6.5   Weight loss

Pre-diagnosis, unintentional weight loss is another factor that affects prognosis as well as clinical outcomes in lung cancer. In a study with 76,086 lung cancer patients, weight loss at presentation was predictive of reduced survival time across all stages and histological subtypes. Furthermore, the absence of weight loss was an independent predictor of improved survival (Yang et al., 2011). In a smaller study with 780 patients with stage III and IV non-small cell lung cancer, small cell lung cancer and mesothelioma, Ross et al demonstrated that weight loss at presentation is an independent prognostic factor for progression-free and overall survival, particularly in NSCLC. Furthermore, NSCLC patients with weight loss were less likely to complete at least three cycles of chemotherapy, and were more likely to develop chemotherapy-related toxicities (Ross et al., 2004).

These uncertainties pose interesting questions with regards to the phenotype of patients who are more, or less likely to do well, with regards to systemic treatment. While unintentional weight loss confers a poor prognosis, the mechanism is unclear at present. What is clear however, is that involuntary weight loss is a central feature of cancer cachexia, a metabolic syndrome conferring a poor prognosis (Blum et al., 2011b). In recent years the diagnosis of cachexia has been refined to include sarcopenia, or loss of muscle mass and function, as a defining criterion (Fearon et al., 2011). Sarcopenia is already a recognised

marker of frailty in the elderly, and amongst cancer patients there is increasing evidence that its presence is associated with poorer performance status and reduced survival (Prado et al., 2008, Prado et al., 2009, Martin et al., 2013). Thus the importance of recognising the unit of weight lost in the lung cancer patient is timely, as is further evaluation of its significance in the work-up to systemic anti-cancer treatment.

1.2   CACHEXIA AND SARCOPENIA IN CANCER – TWO LINKED, BUT DISTINCT PROCESSES

The majority of work pertaining to weight loss, reduced physical function and poor survival in advanced cancer is widely recognised to be associated with the cachexic state. However, there is an increasing body of evidence which recognises the importance of sarcopenia as a separate but closely-related entity. Figure 1.1 refers to a Venn diagram of the degree of overlap of not just cachexia and sarcopenia, but also of starvation and frailty – all conditions which reflect a bleak prognosis. In the following section, cachexia and sarcopenia will be considered individually, while their similarities and degree of overlap will also be discussed.
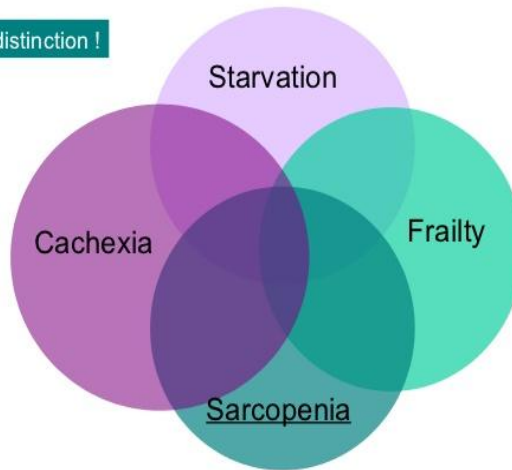
Figure 1.1: Adapted from Rolland Y, Evaluation of Sarcopenia. 4th International Seminar on Preventive Geriatrics (Rolland, 2011)

1.2.1   Current definition of cancer cachexia

Cachexia, which originates from the Greek words *cac* (bad) and *hexos* (condition) is a recognised syndrome in many chronic illnesses, including cardiac failure, chronic kidney disease, and chronic obstructive pulmonary disease. It is also a common manifestation of advanced malignancy, and in those with advanced disease its prevalence has been cited as 60-80%, with over half of patients with cancer having a degree of cachexia at the time of their death (von Haehling and Anker, 2010). Whilst cancer cachexia has regularly been associated with reduced physical function, reduced tolerance to anticancer therapy, and reduced survival, there has been, until recently, a lack of an internationally accepted cancer-specific definition of cancer (Blum et al., 2011b).

The most recent comprehensive definition of cancer cachexia was a collaborative consensus between the European Palliative Care Research Collaboration (EPCRC), the Society

on Cachexia and Wasting Disorders, the National Cancer Research Institute (NCRI) Palliative Care Clinical Studies Group (UK), and the European Society for Clinical Nutrition and Metabolism Special Interest Group on Cachexia in 2011, summarised by Fearon and co-workers (Fearon et al., 2011). They define cancer cachexia as being a "multifactorial syndrome characterised by a progressive loss of skeletal muscle mass, with or without loss of fat mass, that cannot be fully reversed by standard nutritional support and which leads to progressive functional impairment". In practical terms, cancer patients are classified as being cachectic when there is weight loss of >5% over the past 6 months, or any degree of weight loss >2% with a BMI of <20, or any degree of weight loss >2% with sarcopenia as defined by a low skeletal muscle mass.

1.2.2   Sarcopenia, its aetiology and current definition

The word sarcopenia is derived from the Greek words *sarx* (flesh) and *penia* (lack of). Originally, the term was coined in 1989 at a meeting for Elderly Care physicians, where Rosenberg observed that there was no age-related decline potentially more significant than the decline in lean body mass (Rosenberg, 1989). Since then, the area of sarcopenia has been studied extensively amongst the elderly, and received particular attention with the possibility that the decline in muscle mass and function was amenable to intervention (Rosenberg, 1997).

One of the inherent difficulties in researching a relatively new clinical entity is that the definition changes over time, as more is understood about the condition and its clinical implications. As such, whilst the original meaning of sarcopenia was purely one of loss of muscle mass, later findings of the close association between a reduced muscle mass and reduced muscle strength and physical function prompted calls for a broader, widely accepted definition of sarcopenia for use in research and clinical practice (Cruz-Jentoft et al., 2010).

As a result, the European Working Group on Sarcopenia in Older People (EWGSOP) who are represented by the European Geriatric Medicine Society, the European Society for Clinical Nutrition and Metabolism, the International Association of Gerontology and Geriatrics-European Region, and the International Association of Nutrition and Aging, have agreed a working definition and criteria for diagnosis. Sarcopenia is a syndrome of progressive and generalised loss of skeletal muscle mass and strength associated with adverse outcomes such as poor quality of life and death. The presence of both a low muscle mass and low muscle function (either strength or performance) is required for a diagnosis of sarcopenia to be made (Cruz-Jentoft et al., 2010). Sarcopenia was later recognised as a disease entity with the awarding of an ICD-10 code (Anker et al., 2016).

While the widely-accepted definition of sarcopenia involves low muscle mass and low muscle strength or physical performance, in cancer literature, sarcopenia is defined as solely muscle mass depletion. While low muscle mass is the central feature of sarcopenia, the arguments for recognising poor muscle function as well as muscle mass are many, not least in streamlining diagnostic criteria, to enable direct comparison in research and clinical practice. As a result, our study on which this thesis is based, set out to evaluate muscle mass and physical performance together in NSCLC. One of our hypotheses was that physical performance measurements might prove to be as useful as muscle mass measurements in the diagnosis of sarcopenia and its predictive ability of receipt and completion of treatment. The results are detailed in Chapters 4 and 6.

1.2.3   Cachexia and sarcopenia in context of one another

The recognition of sarcopenia as a key component of the definition of cancer cachexia is significant, not least because previous definitions did not include muscle mass as a major criterion (Evans et al., 2008, Fearon et al., 2006b), see Table 1.x. Loss of muscle mass is

usually gradual and not necessarily associated with significant or sudden weight loss. In the

context of lung cancer, cachexia and sarcopenia frequently coexist and may be clinically

indistinguishable. It is also important to consider that sarcopenia may itself pre-date

cachexia. Therefore, in established cachexia, most patients will have sarcopenia, whereas

sarcopenic patients are often not cachectic. Having clear working definitions may allow

earlier recognition of both conditions and provide a framework for research to identify early

markers and focused interventions.

Whilst loss of function is a recognised later consequence of cancer cachexia, muscle

strength or physical performance have not been routinely measured as part of the initial

assessment of cachexia severity, despite being central to the current, broader definition of

sarcopenia. As clear consensus emerges on the definitions of cachexia, a better

understanding of the inter-dependence between cachexia and sarcopenia suggests that early

recognition of sarcopenia as part of, or prior to, cachexia in NSCLC may yield improvements in

patient outcomes.

	Cachexia	**Sarcopenia**
Source		
Fearon et al (Fearon et al., 2011)	Weight loss >5% OR Weight loss >2% and BMI <20 OR Weight loss >2% and sarcopenia	
Evans et al (Evans et al., 2008)	Weight loss of >5%, with at least 3 of the following: - Decreased muscle strength - Fatigue - Anorexia - Low FFMi index - Abnormal biochemistry	
Lasheen and Walsh (Lasheen and Walsh, 2010)	Cancer anorexia-cachexia syndrome: Anorexia AND weight loss >10% compared to pre-illness weight	
Cruz-Jentoft et al (Cruz-Jentoft et al., 2010)		Low muscle mass AND - Low muscle strength OR - Poor physical performance

Muscaritoli et al (Muscaritoli et al., 2010)		Low muscle mass >2 SD below mean of healthy young population AND Low gait speed <0.8 m/sec

Table 1.7 Definition of cachexia and sarcopenia in the current literature

1.2.4   Characteristics, aetiology, mechanisms and current management of cancer cachexia

The causes of cachexia are complex and multifactorial, with no established final common pathway. Overall, chachexia is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism. In cancer patients, this can be largely attributed to humoural and tumoural factors. The key humoural factors involved in cancer cachexia are cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor (TNF) and interferon-gamma (IFN-γ). These factors contribute to abnormal metabolism in the host that leads ultimately to a nett protein imbalance, by means of anorexia, proteolysis, and reduced protein synthesis (Argiles et al., 2005a).

Many humoural factors induce cachexia by means of anorexia – a severely reduced dietary intake. Cytokines have a key role in inducing anorexia as they have a direct effect on the gastro-intestinal tract and the brain to suppress or allow satiety, which affects gastric motility and emptying. For example, the suggested mechanism by which IL-1 and TNF-α contribute to anorexia is by increasing levels of the central nervous system neurotransmitter corticotrophin-releasing hormone (CRH) which acts to suppress appetite (Argiles et al., 2005b). Other studies involving tumour-bearing mice have shown that inhibition of IL-6 and IFN-ɣ led to reversal or inhibition of cachexia, indicating that endogenous production of these cytokines is instrumental in producing some of the metabolic changes characteristic of cancer cachexia (Zaki et al., 2004, Matthys et al., 1991).

Tumoural factors are molecules which are produced by cancer cells. These are capable of producing cytokines which may act on cancer cells in an autocrine fashion, or on supporting tissues such as blood vessels to produce an environment which is conducive to tumour growth. Proteolysis-inducing factor (PIF) is one example of a tumoural factor that promotes skeletal muscle atrophy, contributing to weight loss and cachexia (Tisdale, 2009).

These tumoural and humoural factors act at a cellular level to bring about cachexia by means of anorexia and an abnormal hypermetabolic state characterised by protein catabolism, decreased protein synthesis, and an increased resting energy expenditure (REE) (Bosaeus, 2008). The phenomenon of anorexia, characterised by a severely reduced energy intake, is well recognised in cancer patients, particularly in the advanced stages. There are various tumour-related and iatrogenic causes for anorexia, among them stomatitis, constipation and pain. Other causes include a reduced central drive to eat, disturbances of taste and smell – particularly as side effects of chemo-radiotherapy – and gastric dysmotility which are more challenging to treat (Fearon et al., 2011). Whatever the cause, the severely reduced energy intake is insufficient to cope with the body's metabolic demands, contributing to loss of weight.

Anorexia alone is insufficient to account for weight loss in cachexia. A study of 297 unselected cancer patients showed that weight loss could not be explained by a diminished calorie intake, since the absolute amounts of energy intake did not differ. In addition, weight loss was not compensated for by an increase in energy intake (Bosaeus et al., 2001). Body composition changes in cachexia differ to that in pure anorexia, where most of the weight lost in anorexia is fat, with a small amount of loss of muscle (Moley et al., 1987), whereas in cachexia there is loss of muscle with or without loss of fat (Fearon et al., 2011). Therefore anorexia, defined as a severely reduced energy intake, is not the major mechanism involved in cancer cachexia, although these two circumstances usually go hand in hand.

Despite the fact that anorexia plays an important role in the development of malnutrition, the tumour-bearing host also exhibits hypercatabolism caused by abnormal tumour metabolism and systemic inflammation. In normal metabolism, body fat stores are mobilised when energy intake is lower than required to meet requirements, generally sparing the fat-free body mass. In contrast, patients with active malignancy experience systemic inflammation, which activates protein catabolism from skeletal muscle, leading to a loss of muscle mass.

Clinically, the most widely used marker of systemic inflammation is C-reactive protein (CRP). Several scoring systems incorporating inflammatory markers, of which the most widely used was CRP, and albumin, another marker of systemic inflammation and poor nutrition, have been used in the prediction of prognosis in advanced lung cancer (Simmons et al., 2015, Jafri et al., 2013). The Glasgow Prognostic Score (GPS) has been widely used, and is a score based on CRP and albumin which is reported to increase the accuracy of PS in predicting survival (Simmons et al., 2015). Furthermore, high CRP and low albumin have been associated with depletion of weight and muscle, as well as low PS (McMillan, 2013). All this underlines a few key points regarding cancer cachexia: it is multifactorial, and systemic inflammation is a key process driving it; PS remains a subjective measurement with inter-rater variability (c.f. Section 1.1.6.1); and there may be other objective measurements, such as CRP, weight and muscle loss and physical performance, which add value to PS.

In terms of current management of cancer cachexia, there is currently no successful treatment. Cancer cachexia is associated with a poor prognosis, and, as such, the aim of treatment should be improvement of symptoms and quality of life. There have been some targeted efforts at modulating the effects of anorexia and hypermetabolism which ultimately lead to cachexia. Over the last decade there has been interest in managing cancer cachexia by supplementation with fish oil (omega-3 fatty acids or eicosapentaenoic acid). Four systematic

reviews evaluating the efficacy of fish oil were carried out between 2007 and 2012 and only one gave a weak recommendation (grade B) of its use in advanced cancer patients with weight loss (Colomer et al., 2007). The other reviews found no clear advantage with treatment (Dewey et al., 2007, Mazzotta and Jeney, 2009, Ries et al., 2012), therefore there is no clear consensus of the benefits of taking fish oil in managing cachexia.

Steroids have long been used in the management of anorexia, mainly through their actions as appetite stimulants. Another two compounds from the steroidal progestin family, medroxyprogesterone acetate and megestrol acetate have also been used as appetite stimulants in cancer patients. Among these orexigenic drugs, megestrol acetate is the most widely prescribed, and appears to have a positive effect on cancer patients, resulting in significant gain in appetite and weight (Pascual Lopez et al., 2004). However, despite the appreciable gain in weight, meta-analysis data with mainly lung cancer patients, showed that there was no benefit in global quality of life (Berenstein and Ortiz, 2005). Anorexia is seldom an isolated symptom in those with advanced cancer, and tends to be accompanied by symptoms such as pain, fatigue, dry mouth and nausea. This could account, in part, for the discordance between non-improvement in quality of life despite weight gain, as other symptoms persist.

The gain in weight seen with appetite stimulants is primarily gains in fat rather than muscle mass (Simons et al., 1998, Loprinzi et al., 1993). In itself, gains of fat mass have not been found to have a beneficial effect, whereas it is the loss of fat-free mass that leads to reduced functional status, morbidity, and mortality. Gains in fat-free mass (which includes functionally active muscle mass), are more difficult to achieve than gains in body fat. Therefore, studies that show increased body weight may not translate into improvements in morbidity or improvements in functional status (Donohoe et al., 2011). Indeed, with appetite stimulants come the well-recognised benefits of improved appetite and gain of body fat, but

not appreciable improvements of quality of life or physical function (Jatoi et al., 2003, Vadell et al., 1998, Westman et al., 1999).

In order for patients to experience improvements in physical function and hence improved quality of life, not only do they need to maintain the weight they put on, but also to regain muscle mass lost during the cachectic process. In addition to the international acceptance of sarcopenia as being a key component in the definition of cachexia, it is being increasingly recognised in its own right in the cancer population, as muscle mass depletion being associated with increased morbidity, poorer functional status, and increased mortality. Perhaps more importantly however, it can be present in all strata of body mass indices and without the presence of weight loss, making it clinically difficult to recognise in its early stages. When present, it has been associated with increased chemotherapy toxicities, making it a worthwhile subject of further scrutiny, particularly with regards to patients receiving systemic anti-cancer treatment for NSCLC.

1.2.5   Pathophysiology and categories of sarcopenia

As mentioned in section 1.2.2, sarcopenia in the cancer literature is defined as muscle mass depletion only. However, the more widely accepted definition of sarcopenia is depletion of muscle mass and function (cf section 1.2.2). Sarcopenia can further be divided into primary and secondary categories of aetiology (Table 1.7), where secondary sarcopenia is caused by activity, disease or nutrition, whereas in primary sarcopenia there is no other cause evident but ageing.

Primary Sarcopenia	
Age-related	No other cause evident but ageing

Secondary Sarcopenia	
Activity-related	Can result from bed rest, sedentary lifestyle, deconditioning, or zero-gravity conditions
Disease-related	Associated with advanced organ failure (heart, lung, liver, kidney, brain), inflammatory disease, malignancy or endocrine disease
Nutrition-related	Results from inadequate dietary intake of energy and/or protein, as with malabsorption, gastrointestinal disorders or use of medications that cause anorexia

Table 1.8: Sarcopenia categories by cause, from Cruz-Jentoft et al. 2010.

Given that sarcopenia was first recognised as a geriatric syndrome, much of the literature regarding the pathophysiology of sarcopenia is connected with the biology of aging. Indeed, loss of muscle mass in the cancer literature has been largely concentrated in the development of cancer cachexia. Whilst there is some degree of overlap in the pathophysiology of muscle mass depletion in sarcopenia and that of cachexia, the degree of overlap is unclear at present. Two major mechanisms that are implicated in secondary sarcopenia are decreased protein synthesis and an increased protein breakdown, resulting in a nett negative protein balance. However, whether this negative balance is predominantly a result of reduced protein synthesis or increased proteolysis is still under debate (Argiles et al., 2005a, Johns et al., 2013).

Much of the current understanding of cancer-related loss of muscle mass and function has been derived from animal models of cancer cachexia. Some well used models are the murine adenocarcinoma 16 (MAC16) model, the XK1 model, and the colon 26 adenocarcinoma (C26) model (Bennani-Baiti and Walsh, 2011, Johns et al., 2013). Whilst these models have been useful in understanding the processes of cachexia and sarcopenia, in humans there is heterogeneity in tumour metabolism, growth, and other patient-specific factors, such as co-morbidities. For example, the MAC16 model appears to be independent of

systemic inflammation, whereas the C26 model is said to be mainly dependent on interleukin-6 (IL6) (Strassmann et al., 1992). The inherent problem of whether there is much translational value, or indeed whether these models can be representative of the majority of cancer patients, remains to be seen.

Skeletal muscle atrophy contributes directly to muscle mass depletion. Skeletal muscle atrophy occurs via four major proteolytic pathways – the ubiquitin proteasome-dependant, lysosomal, caspase-dependent and calpain-dependant enzyme pathways – all of which may be involved in the processes of sarcopenia and cachexia.

The ubiquitin-proteasome pathway mediates proteolysis by means of ubiquitin-conjugated proteins being targeted for degradation by an adenosine triphosphate (ATP)-dependant protease, but in sarcopenia there remains debate as to whether this is or is not increased (Tisdale, 2009, Bossola et al., 2008). The ubiquitin proteasome system is activated by inflammatory cytokines such as tumour necrosis factor alpha (TNFα) and interleukin-1 (IL1), which in turn activates the NF-kappaβ pathway, influencing pathways involved in apoptosis, inflammation and differentiation. The transforming growth factor beta (TGFβ) family, particularly myostatin, also activate the ubiquitin proteasome system. An excess of myostatin causes an increase in skeletal muscle atrophy (Zimmers et al., 2002), whereas its inhibition results in an increase in muscle mass (Welle et al., 2007).

While hyperactivation of the ubiquitin proteasome system has been heavily implicated in muscle wasting in cancer, there is newer evidence that the lysosomal or autophagy pathway also has a role, by means of inducing the activity of enzymes required for the digestion of macromolecules. The mechanism by which this pathway works is to drive substrates to lysosomes, where lysosomal proteolysis depends on the activity of proteases called cathepsins (Attaix and Bechet, 2007), with increased activity of cathepsins found in cancer models. Strengthening this concept is the finding that in tumour-bearing rats, muscle

depletion could be prevented by treatment with leupeptin, an inhibitor of proteases such as cathepsins (Penna et al., 2013, Tessitore et al., 1994).

The most studied group of calcium-dependant enzymes are the calpains. These work by initial degradation of myofibrillar proteins during the process of muscle wasting. While calpain activity has been shown to contribute to muscle wasting in non-cancerous chronic diseases such as muscular dystrophy (Tidball and Spencer, 2000), there is little evidence in the literature of the assessment of the role of calpains in models of cancer cachexia (Johns et al., 2013).

The presence of a tumour elicits a systemic inflammatory response which alters the patient's metabolism. Inflammatory cytokines such as tumour necrosis factor (TNF – formerly known as TNFα) and interleukin-6 (IL-1) have been implicated in the development of sarcopenia, either directly or indirectly. In animal models, chronic treatment with TNF results in increased muscle proteolysis (Flores et al., 1989). Furthermore, in a cohort of over 2000 older people, higher levels of TNF were associated with a decline in muscle mass as well as grip strength (Schaap et al., 2009). The mechanism by which TNF contributes to sarcopenia during tumour growth is direct, by stimulating protein loss from muscle via the ubiquitin-proteasome pathway (Llovera et al., 1997, Tisdale, 1997).

Whilst the presence of tumour cells can induce muscle loss via inflammatory cytokines, circulatory factors have also been implicated in the initiation of muscle loss. In a rodent model of the MAC16 adenocarcinoma proteolysis inducing factor, serum from cachectic animals induced an increase in protein degradation from gastrocnemius muscle (Smith and Tisdale, 1993). While preliminary evidence in human patients with cancer showed that proteolysis inducing factor was associated with loss of weight (Cabal-Manzano et al., 2001, Wigmore et al., 2000), other studies found that it had no relation to weight loss, prognosis, survival, or loss of muscle mass (Deans et al., 2006, Wieland et al., 2007).

Utilising animal models, the ubiquitin proteasome system is thought to be essential in the process of skeletal muscle atrophy. This, thus far, has not been proved conclusively in humans. In one study, levels of ubiquitin proteasome activity as well as muscle mass comparing lung cancer patients with weight loss to healthy controls did not differ (Op den Kamp et al., 2012). However, the lysosomal autophagy pathway may have a greater effect on muscle atrophy (Op den Kamp et al., 2013). A lysosomal proteolytic enzyme called cathepsin B has also been shown to have a strong inverse relationship with fat free mass (an indirect measure of skeletal muscle) in patients with pre-operative lung cancer patients. Furthermore, no association was found with components of the ubiquitin proteasome pathway (Jagoe et al., 2002). This was echoed in a study which examined mechanisms associated with muscle wasting in patients with oesophageal cancer. The authors found that only activity of the lysosomal autophagic pathway was increased, whereas proteasome, calpain and caspase activities were not different compared to controls (Tardif et al., 2013).

Hypercatabolism of skeletal muscle, or proteolysis, is thought to be the main mechanism by which overall protein imbalance contributes to muscle wasting in cancer. On the other hand, while hypoanabolism of skeletal muscle is considered to have a role in its pathogenesis, its impact is less clear. In pathological conditions, skeletal muscle tissue is capable of self-repair, using key satellite cells, in order to prevent the loss of muscle mass (Zammit et al., 2004). Upon activation, satellite cells start proliferating and expressing genes which enable production of new muscle fibres. In a study with gastric cancer patients undergoing surgery, the expression of these genes was increased compared to controls (Pessina et al., 2010), however elsewhere in post-operative gastrointestinal cancer patients, the levels of these genes, whether anabolic or catabolic, were found to be similar to that of controls (Gallagher et al., 2012). It is therefore unclear at present whether there is any potential for targeted management of hypoanabolism in cancer-associated muscle wasting.

1.2.6   Heterogeneity of measurements of muscle mass and cut-off thresholds for the diagnosis of sarcopenia in cancer

The human body is made up of different compartments, which can be divided according to cell type, more broadly into fat and fat-free compartments. The table below illustrates this:

Body Composition by percentage, estimate values			
Fat mass (FM)			20%
Fat free mass (FFM)	Body cell mass	Body protein	13%
		Intracellular water	36%
	Extracellular mass	Extracellular water	24%
		Bone tissue	7%

Table 1.9: Body composition by percentage, adapted from Thibault et al 2012.

The above estimated figures are dynamic throughout the aging process. Furthermore, there exist differences between the sexes, such as a higher body fat percentage and lower fat-free mass in females (Chumlea et al., 2002). However, one relatively constant figure is the proportion of body water in fat-free mass, which is roughly 73% (Brozek et al., 1963, Heymsfield et al., 1993, Pace and Rathbun, 1945). There are two main approaches adopted in measuring muscle mass: indirect and direct measurements.

The estimation of FFM by indirect measurements such as anthropometric measurements of mid upper arm muscle circumference (MUAC) and triceps skinfold thickness (TST) have been used for many decades, primarily to assess nutritional status. In elderly care, the use of MUAC in particular has evolved to include prediction of functional performance and mortality risk (de Hollander et al., 2013, Landi et al., 2010). In cancer patients, MUAC is used primarily to assess nutritional status (Bovio et al., 2008, Jagoe et al.,

2001), but TST has also been used (Harvie et al., 2003) (Agteresch et al., 2002). As anthropometric measurements are quick and easy to perform, they are particularly useful in the ambulatory setting; however, the main drawback is that they are inclined to inter-observer error and thus cannot be recommended for routine use in the diagnosis of sarcopenia.

Other indirect measurements of muscle mass consist of measuring total body water, and total body potassium, thereby deriving estimates of skeletal muscle mass. As bodily water occupies a relatively fixed fraction of FFM, investigators have used isotopes of hydrogen, deuterium, and tritium to quantify body water volumes and hence fat free mass (Lukaski, 1987). These measurements have been used in gastric cancer patients (Liedman et al., 1997) and lung cancer patients (Jatoi et al., 2001, Scott et al., 2001) to assess body composition and nutritional status in the research setting. While these techniques enable an estimation of FFM it has not been validated for use in determining sarcopenia in cancer, in routine clinical practice. Indeed, as there are more direct imaging methods of measuring muscle mass such as computed tomography, as below, techniques involving estimations of body water to provide estimations of muscle mass may well prove obsolete.

An indirect method of assessing muscle mass and sarcopenia, which is gaining popularity in the cancer population, is bioelectrical impedance analysis (BIA). The principle underlying this method is that the human body contains intra- and extra-cellular water that act as electrical conductors, and cell membranes that are involved with capacitance (Lukaski, 1987). By applying a small current to the body electrodes placed on the feet and hands, BIA measures capacitance and resistance by recording the drop in voltage. The use of BIA has its advantages: it is a non-invasive, easy to use and reproducible technique, and is widely used in the evaluation of body composition and nutritional status in cancer patients (Gupta et al., 2004, Sarhill et al., 2003, Fearon et al., 2006a). Although it has not, as yet, been validated as a

technique of measuring sarcopenia, it is one of the key methods of assessment of muscularity cited in the definition of cancer cachexia (Fearon et al., 2011). The main disadvantage of BIA is that it is dependent on hydration status of the patient, therefore may be inaccurate in cases of under- or over-hydration (Thibault et al., 2012). Furthermore, in the presence of a large tumour mass, BIA will overestimate muscle bulk as it does not differentiate between organ or tumour mass and skeletal muscle, therefore a more direct measurement is preferred (Fearon et al., 2011). Provided that these limitations are borne in mind, the ease of use, portability, and low cost of BIA makes it an attractive method for further research in the assessment of sarcopenia in cancer, particularly in relation to patient-related outcomes.

In the last 20 years, diagnostic imaging techniques such as computed tomography (CT), magnetic resonance (MR) and DXA have changed our ability to quantify muscle mass and its change over time. The obvious disadvantages are clear – they are expensive techniques requiring specialist equipment and operators, and, in the case of CT, involve a significant risk of exposure to ionising radiation. However, they are the gold standard techniques for assessing muscularity in sarcopenia because they allow direct measurement of muscle cross-sectional area in single images, or of muscle volume in a succession of images encompassing an entire organ (Baracos and Kazemi-Bajestani, 2013). In all these techniques, there is good precision for measuring skeletal muscle cross sectional area (MacDonald et al., 2011); this level of sensitivity enables the detection of small, but potentially significant changes over time.

The way in which CT measures skeletal muscle is by calculating the area of skeletal muscle at the third lumbar vertebra level (L3), which includes the psoas; the paraspinal muscles erector spinae and quadratus lumborum; and the abdominal wall muscles rectus abdominus, transversus abdominus, and external and internal obliques. The area of muscle at L3 is highly correlated with total body skeletal muscle mass (Shen et al., 2004), and this value

is then divided by height in squared metres to produce the skeletal muscle index (SMI). Cut-off values for sarcopenia were produced using regression equations (Mourtzakis et al., 2008), and the values detailed in Table 1.9.

The main advantages of CT in diagnosing sarcopenia, are twofold. Firstly, most patients have routine CT scans of their chest, abdomen and pelvis as part of the diagnostic work-up process for any cancer diagnosis. Scans at the level of L3 will therefore be available to the MDT clinicians for most patients, and thus CT may represent a useful and accessible tool in diagnosing sarcopenia. Secondly, and perhaps more importantly, while loss of muscle mass is important, so too is the change in muscle quality. This can be seen clinically on CT scans with muscle attenuation (MA), where a low attenuation or low skeletal muscle density is reflective of muscle which has been infiltrated with fat, thereby making it poorer quality (Aubrey et al., 2014, Daly et al., 2018). The normal muscle attenuation range is between -30 and 150 Hounsfield Units (HU), but in healthy young adults this value is typically 50 HU. Muscle with attenuation of <30 HU is deemed less functional and found in chronic conditions such as diabetes. It has been said that the increases in lipid content in muscle actually precedes the loss of muscle mass (Chu et al., 2015), and that MA is a better marker of prognosis, compared to muscle mass (Sjoblom et al., 2016).

This being said, CT-derived muscle values still require technical ability, confer radiation, and require a level of training to interpret the scans themselves. A more pragmatic approach to body composition, such as BIA, may be a better and more feasible option. This technique has been compared to DXA and CT before, in research settings, but its main inadequacy is overestimation of DXA- and CT-derived values of fat-free mass by up to 9 kilogrammes difference (Mourtzakis et al., 2008, Trutschnigg et al., 2008). Whilst at face value, BIA may be an inaccurate predictor of muscle mass and sarcopenia, the main problem with interpreting this data is one of comparison. It is recognised that sarcopenia can be

diagnosed with a variety of techniques, and with resulting data expressed in various ways. For example, CT expresses skeletal muscle index at L3, in cm^2/m^2; DXA as appendicular skeletal muscle index (ASMI) in kg/m^2; and BIA as fat-free mass index or ASMI in kg/m^2. The papers by Mourtzakis et al and Trutschnigg et al compared the FFM derived from BIA to that of DXA, rather than ASMI which might be a more accurate comparison, as 75% of body skeletal muscle is located in the limbs (Gonzalez and Heymsfield, 2017).

A further discordance in comparison relates to cut-offs for diagnosing sarcopenia. The consensus statement on the diagnostic criteria of cancer cachexia (Fearon et al., 2011) mentions the cutoff for BIA-derived FFM without bone, as well as CT-derived skeletal muscle (see Table 1.9), which are not exactly the same. The equations used to derive these cutoff values, as well as the validation population, are also dissimilar. While interest in the predictive value of muscle mass, muscle quality and body composition in cancer intensifies, there should also be a focus on development of a consensus in both sarcopenia terminology and cut-off values. For the present, BIA is still a valid and acceptable method in sarcopenia research.

The heterogeneity of methods used to assess muscle mass has meant that to date, there is no single universally-accepted cut-off value employed in the diagnosis of sarcopenia. However, in considering sarcopenia as a condition which becomes more prevalent with age, it is useful to consider how cut-off values in bone mineral density in diagnosing osteoporosis. Muscularity is greatly determined by gender, and thus gender-specific cut-off values must exist in sarcopenia, as for osteoporosis. Furthermore, the relationship between bone mineral density and risk of fracture provides a clinical outcome-specific threshold, which in osteoporosis is defined as two standard deviations (SD) below the norm of healthy young adults.

Adopting the principles employed in the diagnosis of osteoporosis, current thresholds for the diagnosis of sarcopenia are 2 SDs below the mean values for muscularity in healthy young adults (Table 1.9):

Method	Measurement	Men	Women
DXA	ASMI	<7.26kg/m^2	<5.45kg/m^2
CT	Skeletal muscle index at L3	<55cm^2/m^2	<39 cm^2/m^2
BIA	Whole body FFMI	<14.6kg/m^2	<11.4kg/m^2
Anthropometric measurements	MUAC	<32cm^2	<18cm^2

Table 1.10: Cut-off points associated with the diagnosis of muscle mass depletion (or sarcopenia) in cancer. Adapted from Fearon et al. (Fearon et al., 2011).

These values, whilst providing a useful benchmark in the diagnosis of sarcopenia, have their limitations. Current standardised values were derived from a large elderly cohort whilst the cut-off values are based on healthy young adult reference values. The applicability of this approach to cancer patients is debatable, for a number of reasons. Firstly, sarcopenia manifests in cancer patients of all ages and is not confined to the elderly. Secondly, the pathophysiology of sarcopenia in cancer patients may differ at least in part to that of the non-cancer elderly population (Argiles et al., 2005a). Finally, the recognition of muscle function as a defining component of sarcopenia needs consideration, within the context of cancer cachexia, and not solely as muscle mass depletion.

Ongoing research into population-specific and outcome-specific cut-offs will, in time, provide a standardised definition of cancer-related sarcopenia which can be used clinically and in the research setting, which in turn will harmonise reporting, allowing for direct comparison of results as well as meta-analysis of data. For the present, however, the above values are helpful, at least until debates around specific cut-off values for sarcopenia in cancer patients are resolved.

1.2.7   Relationship between muscle mass, muscle strength and physical performance

While much of the sarcopenia literature has concentrated on muscle mass, whether in elderly, cancer, or other populations, there is evidence to support the incorporation of muscle function as part of the disease spectrum. The rationale for this is that loss of muscle mass causes a loss of strength, which ultimately leads to functional impairment and physical disability. It is well known that amongst the elderly, a low muscle mass gives rise to increased disability and morbidity, as well as increases risk of mortality (Janssen et al., 2002, Baumgartner et al., 1998, Landi et al., 2012). In addition, low muscle strength, which is sometimes termed dynapenia, also leads to mobility limitations and declines in physical function such as gait speed (Visser et al., 2005, Stenholm et al., 2009).

In the elderly, the relationship between muscle mass and strength is closely associated, with changes in muscle strength being reflected by changes in muscle mass. A study of almost 1900 older adults found that a loss of muscle mass was independently associated with a decline in strength, but that this strength decline was much more rapid than the concomitant loss of muscle mass, suggesting a decline in muscle quality (Goodpaster et al., 2006). In 4000 community-dwelling Chinese adults, muscle mass, strength and performance declined over time, with rapid declines in strength and performance compared with modest declines in mass (Auyeung et al., 2014). However, a smaller study of 120 adults aged between 45 and 78 showed that there were declines in strength despite maintenance or even gains in muscle mass (Hughes et al., 2001). While there may be a role for recognition of dynapenia on its own, the reality is that muscle mass and function are indeed associated and should be measured in tandem. International recognition of this led to the diagnosis of sarcopenia based on both muscle mass and muscle strength or physical performance (Cruz-Jentoft et al., 2010).

In cancer populations, while muscle function is rarely measured as part of the work-up to sarcopenia, it is measured in the context of nutritional status, quality of life, and as a measure of fatigue in cancer cachexia. In lung cancer patients, for example, a systematic review of sarcopenia in lung cancer (Collins et al., 2014) found that there was very little direct evaluation of the relationship between muscle mass and muscle function. Where studies evaluated muscle mass alongside muscle function, there was limited correlation. Muscle strength seemed to be affected, regardless of loss of muscle mass. In pre-cachectic patients, exercise capacity was significantly reduced, despite maintenance of muscle mass (Op den Kamp et al., 2012), and resistance exercise training increased all parameters of muscle strength and physical performance, with no difference in muscle mass (Peddle-McIntyre et al., 2012). Cachectic patients showed reduced strength in terms of walking distance (Martinez-Hernandez et al., 2012) and quadriceps strength (Op den Kamp et al., 2013) compared to controls.

Muscle function can be described and measured in many ways, the commonest being measures of muscle strength and assessments of objective or subjective physical performance. Muscle strength is measured primarily in terms of hand grip and quadriceps strength, with the use of dynamometers. Physical performance has been objectively measured with many different tools, amongst them gait speed, six minute walk test (6MWT), timed get-up-and-go test, and mean daily step count using accelerometers. Apart from performance status, other subjective methods used to measure physical performance includes patient-reported activity and levels of functioning in quality of life questionnaires.

The temporal relationship of depletion of muscle mass, muscle strength, and physical performance is at present unclear. In the elderly, it is suggested that loss of muscle mass predates loss of muscle function, and this stage should be termed pre-sarcopenia. Further loss of either muscle strength or clinically evident impairment of physical performance is

suggested to be termed sarcopenia, and depletion of muscle mass, strength and physical performance is termed severe sarcopenia. While this is a useful model to guide practice, it assumes that muscle mass is the first to be lost in the sarcopenic process, however it is unclear whether this is the case. Furthermore, it is not known, particularly in the cancer population, at what level depletion of muscle mass becomes sufficiently severe to cause clinically significant deterioration in muscle strength and physical performance.

1.2.8   Clinical findings and patient related outcomes of sarcopenia in cancer

There is growing evidence that depletion of muscle mass is a key process driving cachexia within the oncology setting. Whilst the hallmark of cancer cachexia is involuntary weight loss of multifactorial causes, it is the on-going loss of skeletal muscle mass, with or without the loss of fat mass, which leads to progressive functional impairment. As in the elderly, sarcopenia is an independent indicator of a poor prognosis in patients with cancer. In patients with lung cancer, sarcopenia is an independent negative predictor of survival (Martin et al., 2013), and the addition of the skeletal muscle variable to existing prognostic scoring systems increases its accuracy (Veasey Rodrigues et al., 2013).

Perhaps most strikingly, sarcopenia may be predictive of increased risk of chemotherapy related toxicities, and of poorer response to chemotherapy. In breast cancer patients treated with capecitabine, half of the patients who were classified as being sarcopenic had toxic side effects after one cycle, compared with 20% of non-sarcopenic patients. The study also showed a significantly shorter time to progression in sarcopenic patients, versus non-sarcopenic patients (Prado et al., 2009). In hepatocellular carcinoma patients treated with sorafenib, sarcopenic patients experienced significantly more toxic side effects than non-sarcopenic patients (Mir et al., 2012), and in renal cancer patients receiving

sunitinib, this was also the case (Huillard et al., 2013). All these toxicities were dose-limiting for the participants involved.

Body surface area (BSA) is the current method used in calculating chemotherapy dosage, but it is far from perfect (Beumer et al., 2012). A population-based study of 250 obese patients with lung and gastrointestinal tract cancers, of which 15% were classified as sarcopenic, found a poor correlation between FFM and BSA (r^2=0.37). Moreover, individual variation in FFM could account for up to three times variation in effective volume of distribution of fluorouracil, per unit of BSA. Hence, the authors argue that the reason for increased chemotherapy toxicity in sarcopenia is the poor relationship between fat-free mass (FFM) and body surface area (BSA) (Prado et al., 2008).

Exactly how systemic anti-cancer treatment affects sarcopenic individuals temporally is as yet unknown. While weight loss is a recognised side effect of chemotherapy, it is unclear whether loss of muscle mass occurs over the course of chemotherapy, nor is it known whether or not pre-existing sarcopenia increases this likelihood. Small observational studies in patients with lung cancer have so far proved inconclusive – two studies in stage III and IV NSCLC patients showed no significant change in FFM over the course of chemotherapy, with an overall objective response rate of 22-33%, although FFM was not directly analysed with regards to response rates (Harvie et al., 2005, Harvie et al., 2003). Larger, appropriately-powered studies are needed to understand these associations better. At present, there is insufficient evidence that depletion of muscle mass at presentation is associated with increased chemotherapy toxicity, or change in FFM over time in NSCLC.

1.2.9   Sarcopenia, physical performance and the rationale for the study design

In cancer, the impact of muscle mass depletion (or sarcopenia) is that muscle stores are depleted, causing altered pharmacokinetics in chemotherapy metabolism (Prado et al., 2009, Gusella et al., 2002), reduced muscular strength and increased fatigue (Kilgour et al., 2010), poorer functional status (Prado et al., 2008) and increased mortality (Martin et al., 2013).

Since sarcopenia is associated with poor outcomes, the implications for patients with cancer are far-reaching. While consensus-based guidelines as to best practice when evaluating muscle mass in cancer have agreed that muscle mass depletion is a critical prognostic clinical indicator (Fearon et al., 2011), there is lack of a standardised approach and reference populations, resulting in largely heterogeneous studies and hindering routine measurement of muscle mass in cancer care (Rier et al., 2016). Furthermore, timings as to assessment of muscle mass are not well-defined in cancer. Research into sarcopenia in older people is more robust, with age-standardised reference populations and agreed techniques and thresholds for the diagnosis of sarcopenia. There are also ethnicity-specific thresholds amongst older people (Chen et al., 2014). While research into sarcopenia in cancer is emerging as an important clinical variable, a main priority for the future is for consensus as to diagnosis and management, similar to that available in the literature for the geriatric population.

Sarcopenia is associated with lower PS scores in cancer (Prado et al., 2008), and poor muscle strength is associated both with lower PS and low muscle mass (Kilgour et al., 2013). The PS score is still the most widely used scoring system of physical function, (Section 1.1.5.3) and is used to determine patients' treatment options and prognosis, particularly in the multidisciplinary team (MDT) setting. However, this score is subjective, with inter-observer

variability (Sorensen et al., 1993), and some data indicate only a modest correlation between PS and observed physical performance (Montoya et al., 2006). Furthermore, inter-clinician discordance in performance status scoring may result in less PS 0 and 1 patients receiving chemotherapy (May et al., 2012), even when treatment is recommended by the MDT, mainly due to declining physical function (Vinod et al., 2010).

The significance of non-treatment is that it is a predictor of worse survival, compared to those who did receive treatment (Grivaux et al., 2016). In advanced NSCLC, poor survival in those who did not receive systemic treatment was independent of PS (Brule et al., 2016), which suggests that PS may not be the only evaluable physical factor in predicting receipt of systemic treatment. Objective evaluation of physical performance, alongside PS and together with muscle mass may give essential information to the MDT in recommending treatment. This may allow more reliable prediction of receipt of MDT-planned treatment, ensure more effective resource use and identify targets for intervention to optimise patient performance in anticipation of systemic treatment. In light of this, the overall thrust of this thesis is to evaluate muscle mass and physical performance in tandem, and how they impact on predicting receipt and completion of MDT-planned treatment.

Chapter 2:
Aims of the Thesis

2   CHAPTER 2: AIMS OF THE THESIS

The main aim of the thesis is to explore the utility of skeletal muscle mass and physical performance measurements in predicting receipt of treatment offered by the multidisciplinary team (MDT) to patients with NSCLC.

Important secondary aims of this thesis are as follows:

i) To explore whether physical performance, measured objectively by the Short Physical Performance Battery, more accurately predicts completion of chemotherapy than subjective clinician-measured ECOG performance status. This is described in Chapter 6.

ii) To explore the relationship between sarcopenia, physical performance, and degree of chemotherapy toxicity as defined by the proportion of CTCAE grade 3-4 toxicities. This is described in Chapter 6.

iii) To establish whether baseline nutrition status has an effect on fitness for chemotherapy and ability of patients to complete the chemotherapy course. This is described in Chapter 5.

iv) To explore the relationship between performance status (as measured by ECOG and Karnofsky scores) with sarcopenia, nutrition status, and SPPB. This is described in Chapter 6.

v) To investigate the concordance between physicians' and patients' independent assessments of performance status, and to explore which score correlates better with receipt and completion of treatment. This is described in Chapter 7.

vi) To explore the utility and feasibility of BIA as a practical clinical tool for estimating body composition in the routine clinical setting, using DXA as the gold standard comparator in a subgroup of patients. This is described in Chapter 4.

Chapter 3: Participants, Materials and Methods

3   CHAPTER 3: PARTICIPANTS, MATERIALS AND METHODS

3.1   PARTICIPANTS

We recruited participants from the Rapid Access Lung Cancer Clinic (RALCC) in University Hospital Llandough, Penarth in South Wales. Potential participants meeting the inclusion criteria, which included a suspected diagnosis of non-small cell lung cancer (NSCLC) were identified for study screening by chest physicians, and introduction to the study investigators was at the discretion of the physician. Patients only received information about the study once it was clear to the chest physician that they understood the possibility of a diagnosis of lung cancer, and that it was appropriate to offer information based on the likelihood of NSCLC diagnosis and level of emotional distress. Every effort was taken to be as sensitive as possible to the patient's psychological situation, as patients were being recruited before formal confirmation of lung cancer. A favourable ethical opinion was obtained from the South East Wales Research Ethics Committee (REC) in November 2013, REC reference 13/WA/0254.

3.1.1   Inclusion Criteria

- Patients with suspected non-small cell lung cancer (NSCLC) based on clinical and radiological features. Prior data from other RALCCs suggested that approximately 57% of those presenting had a high probability of lung cancer warranting further investigation (Rajasekaran et al., 2006), and 36% had a subsequent diagnosis of primary lung malignancy, of which 81% had NSCLC (Dunican et al., 2011).
- Clinician-scored World Health Organisation ECOG PS 0-2 at presentation.
- Age 18 years or more.

- Willing to participate and able to give informed consent.

3.1.2   Exclusion Criteria

- The presence of implantable cardioverter defibrillators or pacemakers. This was contraindicated because of risks associated with BIA.

- Strenuous activity or excessive alcohol 24 hours prior to the study, or significant peripheral oedema, which would alter the accuracy of BIA measurements.

- Significant neurological or physical impediment that impedes the participant from performing tests of physical performance.

- Insufficient ability to understand and communicate in English; however, all participants subsequently screened and included were able to understand and communicate in English.

3.2   MATERIALS AND METHODS

3.2.1   Baseline study investigations and collected data

The entire study protocol has already been published (Collins et al., 2015). In keeping with the exploratory nature of this study, we captured only baseline data, in order to record function at a pre-MDT discussion stage. The following information was collected from participants' medical notes, in order to document baseline body composition and performance status: weight, height, and physician-assessed PS (both ECOG and Karnofsky). We also collected the following information to account for possible sources of bias: co-

morbidities, including severity of chronic obstructive pulmonary disease (COPD) if present; use of non-steroidal anti-inflammatory medicines (NSAIDs) or steroids; and routine blood test results (haemoglobin, albumin, and C-reactive protein) (see the Case Report Form in Appendix A).

Where it is used throughout this thesis, unless explicitly stated, the term `chemotherapy' refers to all intravenous cytotoxic agents, as well as targeted systemic anti-cancer treatment such as TKIs. In participants planned for chemotherapy, we recorded CTCAE grade 3 or 4 adverse events, number of hospitalisations and delays of treatment during the chemotherapy course (collectively reported as `adverse events'), where CTCAE is the common terminology criteria for adverse event reporting , grade 1 indicating a mild and grade 4 a life threatening event (National Cancer Institute, 2009).

3.2.1.1   Measurement of body composition

Muscle mass was measured using the BIA technique on the Tanita bioimpedance analyser model BC-418 (Leicester, UK). This machine resembles weighing scales with a vertical rod and two paddles for gripping, attached at waist level (see Figure 3.1). The science of this technique was explained in greater detail in section 1.2.6. Operationally, participants were asked to remove their footwear and socks before placing their feet on to the machine. Participants were then asked to grip the paddles gently while the machine measured their body composition by the application of a small, painless electrical current which passed through their body. A printout of total fat mass and FFM, and individual fat mass and FFM of all four limbs was generated, taking into account the participant's age and gender. This assessment took roughly 1 minute, and was repeated twice to ensure reproducibility of data.

To assess the accuracy of BIA as a non-invasive, outpatient test of muscle mass, it was compared to whole body DXA measurements (Hologic Discovery A), which is the gold standard investigation for body composition. This was done in a subgroup of participants (n=16), which was performed within three days of BIA. DXA measurement involved lying supine for ten minutes under the DXA scanner, whilst the scanning arm of the machine ran over the participant's body. This was done at the Medical Physics Department in University Hospital of Wales, Cardiff. Each whole-body DXA scan gives an estimated 4.2 microSieverts of radiation, which is approximately equivalent to one day's worth of background radiation (Blake et al., 2006).

Figure 3.1: Bioimpedance analysis machine, model Tanita BC-418 (image from www.tanita.com)

3.2.1.2   Measurement of physical performance

Physical function, or physical performance, has been assessed in cancer patients in a myriad of ways, all of which evaluate one or more of functional capacity, physical activity, or muscle strength.

The gold standard measurement of functional capacity is clearly cardiopulmonary exercise testing (CPET) – a comprehensive test which evaluates the physiological response to exercise and then provides an objective measure of exercise capacity. This test is predominantly used before surgery, and exercise capacity can predict post-operative outcome, reflecting the available physiological reserve to withstand the stress of surgery. The test involves a battery of cardiovascular, pulmonary, haematological and metabolic measurements to standardised exercise protocols, including cycle ergometry and spirometry (Levett et al., 2018). The clear disadvantage of this test is that a large proportion of palliative-stage patients will not tolerate it, and therefore more pragmatic tests of physical function must be utilised.

A number of tests, mainly centred around gait speed, have been developed to test lower limb strength and endurance, functional capacity and cardiovascular fitness, in order to simulate CPET. The incremental shuttle walk test (ISWT) and stair-climbing test (SCT) have both been validated against CPET with evidence of strong correlation (Win et al., 2006, Koegelenberg et al., 2008). However, once again, these tests preclude many patients with poor pre-existing functional ability and frailty. Furthermore, while they are validated against CPET mainly in pre-operative patients, this may not be the case in the palliative group of patients, and associations with tolerance to chemotherapy and patient-rated outcomes such as quality of life are as yet unknown.

Gait speed is a test which has been called the `sixth vital sign' of geriatric assessment. Low gait speed is an independent predictor of adverse outcomes, cardiovascular mortality and all-cause mortality in older people (Kuys et al., 2014, Hsu et al., 2018). It has also been used extensively in oncology settings, being of diverse utility in the prediction of anticancer treatment-related complications, functional decline as assessed by Activities of Daily Living scales, disability and survival (Verweij et al., 2016, Pamoukdjian et al., 2015, Owusu et al., 2017). Gait speed is most commonly assessed by means of the six-minute walk test (6MWT), and 4 metre gait speed. The appeal of gait speed as a predictor of outcomes in cancer is clear: it is a simple test, easily performed, and cost-effective. The cutoff for good outcomes for the 6MWT in lung cancer patients is a walking length of 400m (Miller et al., 2005, Kasymjanova et al., 2009), which may not be achievable for many patients, and is not thus practical for everyone. The results can also be affected by the age, sex, weight and height of the patient, as well as poor cognition, peripheral arterial disease, and musculoskeletal problems. The 4 metre gait speed test would seem to be better tolerated, given the shorter distance, although it also is not immune from some of the limitations of the 6MWT.

Physical activity is measured by means of accelerometers, such as the ActivPAL^{TM} accelerometer and pedometers, such as the OMRON pedometer. These gadgets essentially measure the number of daily steps one does, and can be used to correlate with Performance Status. A major issue with this is the introduction of bias – participants may be more likely to alter their activity levels whilst wearing the device, or even forget to wear it. While they have been associated with poorer patient-rated outcome measures, their use has not been validated against outcome measures such as treatment-related adverse events (Granger et al., 2013).

Handgrip strength (HGS) is lower in advanced lung cancer patients, compared to controls (Brown et al., 2005), and is said to be able to add value to predictive scores of all cause

mortality, and more specifically, mortality from lung cancer (Celis-Morales et al., 2018). Those

with scores in the lowest 10th percentile were much more likely to be sarcopenic (Kilgour et

al., 2013). HGS is one of the cited assessments by the Sarcopenia Working Group, for

assessing muscle strength loss associated with sarcopenia (Cruz-Jentoft et al., 2010), but

whether it is responsive to changes over time remains to be seen. Furthermore, it only

measures one value of upper limb muscle strength, which may not give a complete picture of

functional ability.

Tests that involve measurement of more than one parameter of physical function, such

as muscle strength and lower limb endurance, and the Short Physical Performance Battery

(SPPB) is one such test of an integrated approach to physical performance. The SPPB was

developed in order to assess physical performance objectively (Guralnik et al., 1994), and is a

reliable and feasible measure of physical performance in older people (Mijnarends et al.,

2013, Freiberger et al., 2012). It is also the test of choice of physical performance,

recommended by international consensus (Cruz-Jentoft et al., 2010, Working Group on

Functional Outcome Measures for Clinical Trials, 2008). It is quick to perform, easily

reproducible, requires little additional equipment, and with basic training can be performed

by most healthcare personnel.

The SPPB consists of a series of tests assessing balance, gait speed, and chair stand

tests which take between 7-10 minutes to perform (see Appendix B for schematic diagram of

SPPB scoring). For balance, there were 3 tests: timed side-by-side stand, in which the

participant places both feet together and holds this position for 10 seconds; timed

semitandem stand, in which the participant places the heel of one foot touching the big toe

of the other and holds this position for 10 seconds; and timed tandem stand, in which the

participant places the heel of one foot in front of and touching the toes of the other and

holds this position for 10 seconds. The gait speed test involved two timed walks of 4 metres

each, to a marked point and back again, at the participant's usual walking pace. The shortest

time of the two is taken, and scored accordingly. The chair stands test involved five timed

stands from a sitting position without the use of arms. The time taken to stand from sitting

five times consecutively is noted and scored. All tests were timed with the same stopwatch.

The chair used for testing lower limb strength was armless and standardised with regards to

seat height. All participants were given the option of having the test performed, within 3 days

after clinic, in a place of their choice. However, none of the participants took this option; all

had SPPB performed in the RALCC on the day of recruitment.

3.2.1.3   Performance status

Both physician- and patient-assessed PS scores (ECOG and Karnofsky scales) were

performed independently and noted. For the purposes of patient-assessed PS, we used lay

wording taken directly from the Cancer Research UK website, with permission (Cancer

Research UK). Patients were shown the two PS scales on paper and asked to check one

statement per scale which best represented their functional status at that point in time.

Participants were asked to score themselves against both scales. We omitted the descriptions

of 5 on the ECOG scale and 0 on the Karnofsky scale (both corresponding to death) to

minimise potential distress. The cut-off criterion of clinician-assessed PS 2 (i.e. those scoring

PS 0-2 were included) was made as those with poorer PS were less likely to be planned for

active treatment.

3.2.1.4   Nutrition status

Routine baseline serological tests of C-reactive protein and albumin were recorded, as were BMI, degree and percentage weight loss in 3-6 months prior to first presentation. The Malnutrition Universal Screening Tool (MUST) (Stratton et al., 2004) is a simple and quick three-component method of screening for malnutrition in at-risk patients, and can be performed by any health professional. MUST allocates points based on body mass index (BMI), unplanned weight loss in the last 3-6 months, and any acute illness or no nutritional intake for >5 days. The components are scored and classified into low, medium and high risk of malnutrition (Figure 3.2). In addition, we documented participants' recollections of food and drink intake during the 12 hours prior to BIA, to account for possible bias when calculating muscle mass, which is dependent on hydration status.
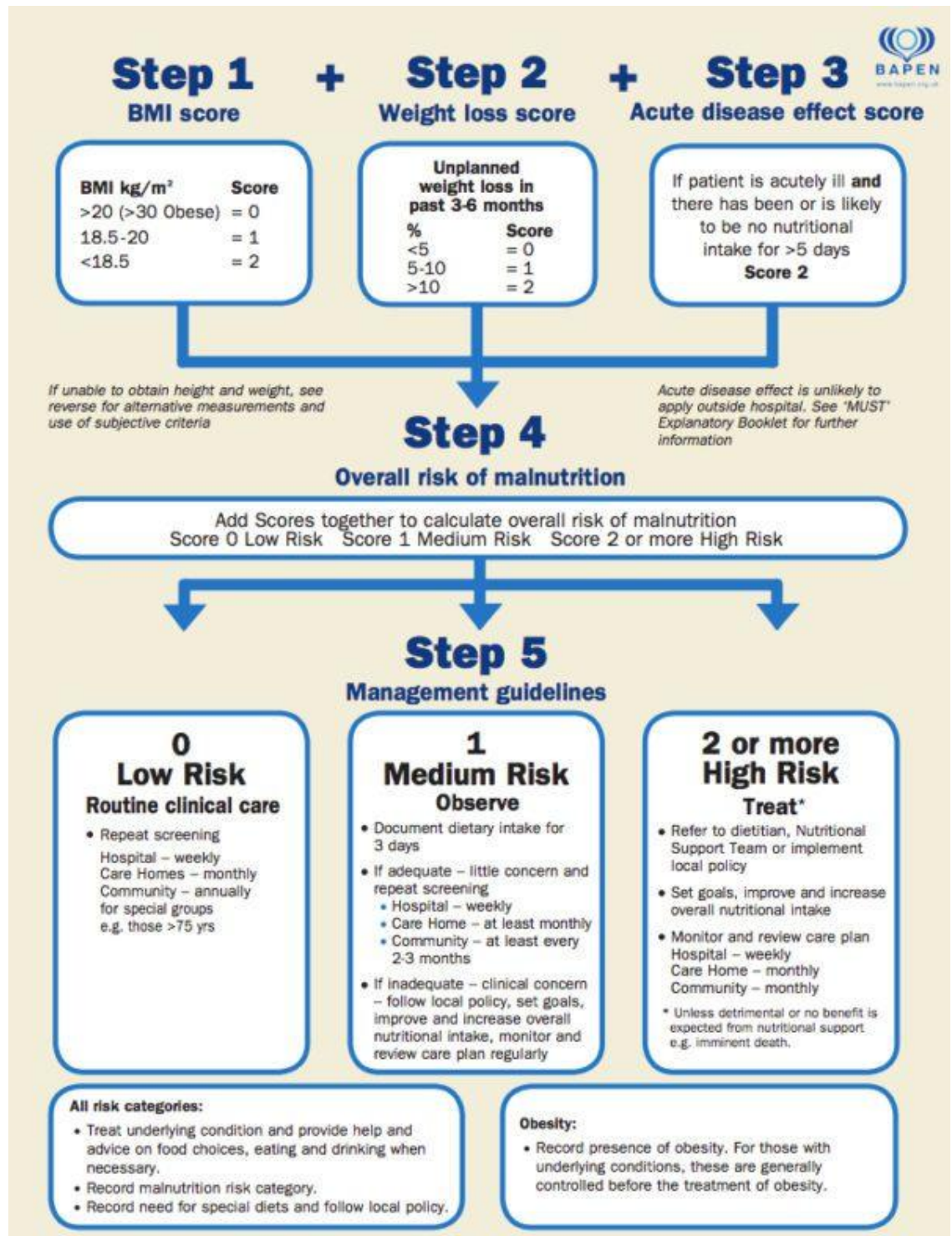
Figure 3.2: The Malnutrition Universal Screening Tool (MUST) from the British Association for Parenteral and Enteral Nutrition, www.bapen.org.uk/pdfs/must/must_full.pdf

3.2.2   Statistical Analysis and Outcome Measures

This was an exploratory study with a pre-agreed recruitment aim of 75-100 participants with suspected NSCLC. The exploratory nature meant that the sample was collected in order to inform powering of future studies. This sample size was based on the fact that we planned on a recruitment rate of 1-2 per week, over an 18 month time period. Descriptive statistics were employed for demographics, TNM stage, and histological diagnosis.

The independent variables were: body composition variables including muscle mass, SPPB score, MUST score, demographics and serological tests as detailed in section 1.2.1. Outcome measures were divided broadly into receipt and completion of MDT-planned treatment. Receipt of treatment was defined as: receipt of planned surgical procedure, receipt of the first dose of radiotherapy, or receipt of the first dose of chemotherapy. Completion of treatment was defined as: completion of planned surgical procedure, completion of planned fractions of radiotherapy, or completion of planned cycles of chemotherapy. In the case of chemotherapy, completion (yes/no) was determined *a priori* by the Clinical Oncologist and Palliative Care physician, and we also noted how many cycles of chemotherapy were completed.

Correlations between the independent variables, and receipt of treatment, completion of treatment and completion of chemotherapy cycles, were analysed using logistic regression as well as graphically. Derived odds ratio (OR) and corresponding p-values and 95% confidence intervals (CIs) were tabulated. Where the outcome measure was analysed according to number of cycles of chemotherapy, we utilised regression analysis for each outcome measure of interest, and present in tabular form the unstandardised regression coefficient, and corresponding p-values and 95% confidence intervals (CIs).

For adverse events during chemotherapy, we presented its association with SPPB using Poisson regression analysis and reported the Incidence Rate Ratio. Both ECOG and Karnofsky physician-patient agreement were determined by kappa statistics. The Wilcoxon signed rank test was employed to determine any differences between raters' scoring. Each predictive factor was tested against binary outcomes of receipt and successful completion of MDT-planned treatment with the chi-squared test or Fisher's exact test, where appropriate.

Chapter 4:
Body composition in NSCLC, and its association with predicting receipt and completion of MDT-planned treatment.

4   CHAPTER 4: BODY COMPOSITION IN NSCLC AND ITS ASSOCIATION WITH RECEIPT AND COMPLETION OF MDT-PLANNED TREATMENT

4.1   INTRODUCTION

In this study, our aim was to characterise not only baseline body composition, but importantly muscle mass values, its prevalence and implications, of NSCLC patients attending a RACC. While the study's overall objective was to measure muscle mass together with physical performance, as in the more widely used diagnosis of sarcopenia, in this chapter we focus on body composition and how it impacts on outcome measures of interest. We chose to assess BIA as a simple and accessible potential alternative method to DXA assessments of body composition, and aimed to evaluate its accuracy and feasibility.

4.2   PARTICIPANTS, METHODS AND STATISTICAL ANALYSES

We screened 89 potential participants, excluding one prior to the consent process (who had a PPM, a study contraindication), and a further two due to research error (incorrect height measured with the stadiometer, an issue which was quickly acknowledged and addressed) (Figure 4.1). We therefore recruited 86 participants in total who had a potential diagnosis of NSCLC. After subsequent investigation, 62 of these participants were diagnosed with NSCLC. The participants were planned for surgery, radiotherapy, and chemotherapy, to include systemic anti-cancer treatment; or a combination of chemo- and radiotherapy. In this chapter we focus on the predictive value of body composition measurements, specifically muscle mass, on all patients with NSCLC (Table 4.1), with a focus on those planned for chemotherapy (n=26). While BMI of participants is presented descriptively in this chapter, its value as a predictive marker of receipt and completion of planned treatment is explored in greater detail in Chapter 5, alongside other nutrition status parameters.

4.3   RESULTS

4.3.1   Descriptive analysis of all participants
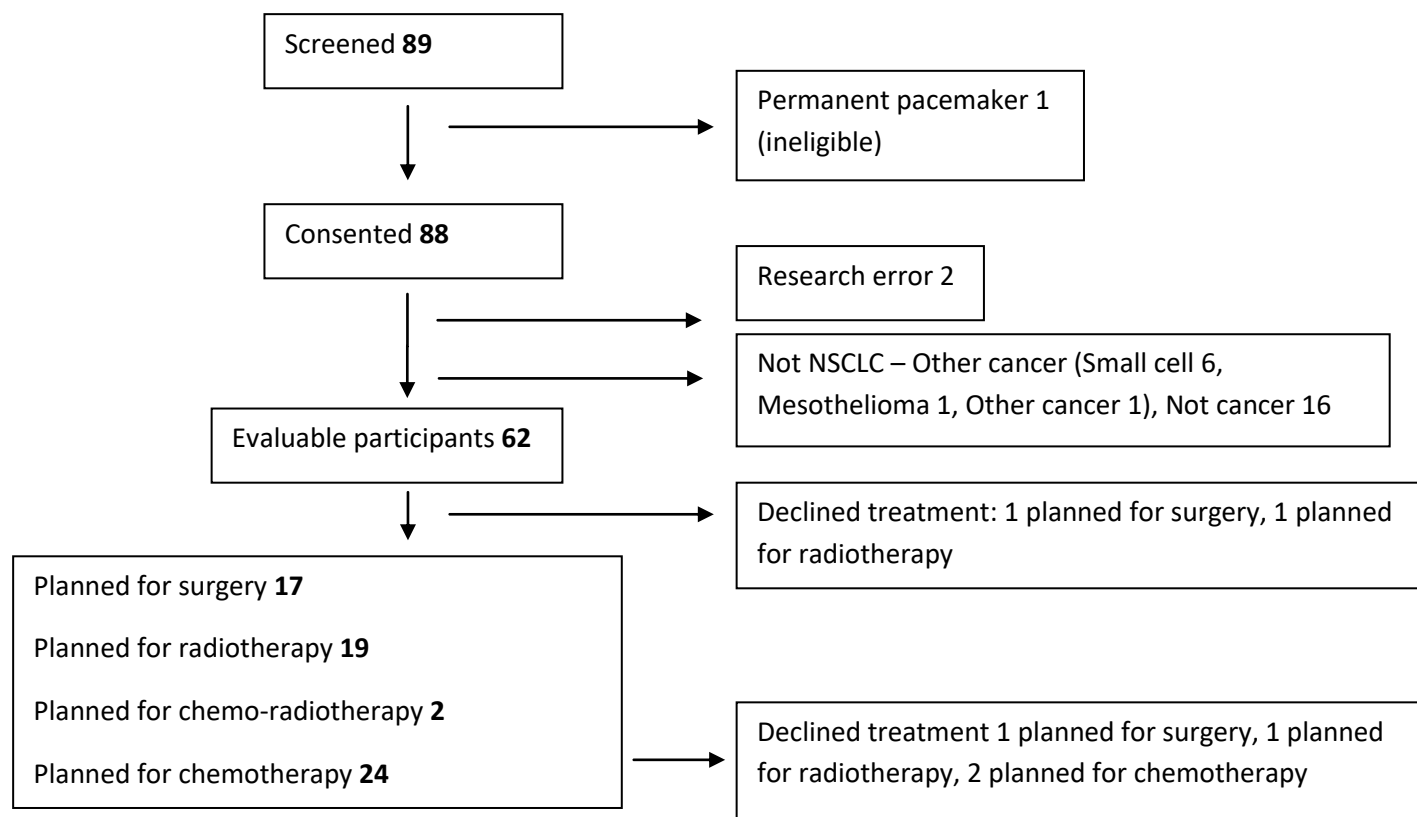
Figure 4.1: Consort diagram of all participants and subgroups

	Men	Women	All participants	Participants with NSCLC only	Participants planned for Chemotherapy
N	55	31	86	62	26
Age, *years,* mean ± SD	68.7 ± 8.5	65.3 ± 10.8	67.5 ± 9.5	68.2 ± 9.6	64.4 ± 9.4
Weight loss, % over last 6 months	4.6 ± 6.7	7.2 ± 7.9	5.6 ± 7.2	6.5 ± 7.6	9.5 ± 8.5
Histology, n (%)					
Squamous cell	14 (25.4)	10 (32.2)	24 (27.9)	24 (38.7)	9 (34.6)
Adenocarcinoma	18 (32.7)	9 (29)	27 (31.4)	27 (43.5)	14 (53.8)
NSCLC other	4 (7.2)	0 (0)	4 (4.7)	4 (6.5)	3 (11.5)
No tissue diagnosis[¶]	2 (3.6)	5 (16.1)	7 (8.1)	7 (11.3)	0
Other cancer	6 (10.9)	2 (6.5)	8 (9.3)	0	0
Not cancer	11 (20)	5 (16.1)	16 (18.6)	0	0
Comorbidities[†], n(%)					
< 2	17 (30.9)	10 (32.3)	25 (29.1)	21 (33.9)	15 (57.7)
≥ 2	38 (69.1)	21 (67.7)	61 (70.9)	41 (66.1)	11 (42.3)

	Men	Women	All participants	Participants with NSCLC only	Participants planned for Chemotherapy
Presence of COPD, n (%)					
Nil	36 (65.5)	24 (77.4)	60 (69.7)	44 (71.0)	22 (84.6)
Mild	3 (5.5)	1 (3.2)	4 (4.7)	3 (4.8)	1 (3.8)
Mod	11 (20)	4 (12.9)	15 (17.4)	12 (19.4)	3 (11.5)
Severe	5 (9.1)	2 (6.5)	7 (8.1)	3 (4.8)	0

Table 4.1: Descriptive analysis of all participants, with subset of those planned for chemotherapy only. [¶]Denotes radiological diagnosis of NSCLC only. [†]Denotes comorbidities at time of recruitment. Common diagnoses include hypertension, ischaemic heart disease, diabetes mellitus and obstructive airways disease.

	Men	Women	All participants with NSCLC	Participants planned for Chemotherapy
TNM Stage, n (%)				
I	9 (23.7)	9 (37.5)	18 (29)	0
II	5 (13.2)	4 (16.7)	9 (14.5)	2 (7.7)
III	12 (31.6)	6 (25)	18 (29)	9 (34.6)
IV	12 (31.6)	4 (16.7)	16 (25.8)	15 (57.7)
Staging unavailable	0	1 (4.2)	1 (1.6)	0
Planned Treatment, n (%)				
Surgery	9 (23.7)	8 (33.3)	17 (27.4)	0
Radical radiotherapy	5 (13.2)	4 (16.7)	9 (14.5)	0
Palliative radiotherapy	5 (13.2)	5 (20.8)	10 (16.1)	0
Chemotherapy	17 (44.7)	7 (29.2)	24 (38.7)	24 (92.3)
Chemo-radiotherapy	2 (5.3)	0	2 (3.2)	2 (7.7)

Table 4.2: Descriptive analysis of all participants with NSCLC (n=62) by gender, n (%), and the subset of those who were planned to receive chemotherapy only.

The mean age and SD were 67.5 ± 9.5 years. Of 86 recruited participants, only 62 subsequently had a diagnosis of NSCLC (72.1%), which is comparable to 70.4% of that found in a previous study of the prevalence of NSCLC diagnoses in a RALCC (Dunican et al., 2011). Over 71% of all participants presented with 2 or more comorbidities, of varying type and severity, but mainly comprised of hypertension, ischaemic heart disease, diabetes mellitus, arthritis, and chronic lung disease. This figure was slightly less in the subset of those with NSCLC (66%). The presence of COPD was not as high as might be expected, with almost 70% presenting with no diagnosis of COPD. In those who did have COPD, the proportion of those with severe COPD was slightly higher in all participants (8.1%), compared to the subset of those with NSCLC only (4.8%) (Table 4.1).

For the 62 with NSCLC (38 men and 24 women), the mean age and SD were 68.2 ± 9.6 years (Table 4.2). In terms of histology in those with NSCLC, adenocarcinoma was the most prevalent (43.5%), followed by squamous cell carcinoma (38.7%), other NSCLC (6.5%) and radiological diagnosis only (11.3%). TNM stage ranged from early stage I (29%) and stage II (14.5%) disease, to advanced stage III (29%) and metastatic disease (25.8%). In the subset planned for palliative chemotherapy, almost 60% had stage IV disease. There were 26 participants planned for chemotherapy, alone or in combination (24 planned for chemotherapy alone, 2 planned for chemo-radiotherapy), 17 participants planned for surgery, and a total of 19 planned for radical and palliative radiotherapy. The vast majority of participants who were planned for chemotherapy were planned for intravenous cytotoxic treatment, with only one out of 26 planned for the TKI afatinib.

4.3.2   Body composition – All consented participants and subset of participants with NSCLC

	All participants	Men	Women	Only NSCLC	Men	Women
Number	86	55	31	62	38	24
BMI	26.6 ± 6.4	26.8 ± 5.5	26.3 ± 7.8	26.6 ± 6.4	26.5 ± 5.2	26.9 ± 7.9
Total MMI (BIA)	17.8 ± 2.9	19.0 ± 2.5	15.5 ± 2.3	17.6 ± 2.6	18.7 ± 2.2	16.0 ± 2.3
ASMI (BIA)	7.6 ± 1.4	8.1 ± 1.3	6.7 ± 1.1	7.6 ±1.3	8.1 ± 1.2	6.9 ± 1.2
FMI (BIA)	8.1 ± 4.4	7.2 ± 3.4	9.6 ± 5.4	8.3 ± 4.7	7.0 ± 3.4	10.2 ± 5.6
Total MMI (DXA, n=16)	16.6 ± 2.4	17.1 ± 2.3	14.5 ± 1.9	16.6 ± 2.2	16.9 ± 2.2	15.2 ± 2.1
ASMI (DXA, n=16)	7.2 ± 1.0	7.4 ± 1.0	6.3 ± 0.8	7.2 ± 1.0	7.3 ± 1.0	6.7 ± 0.6

Table 4.3: Descriptive analysis of the body composition of all consented participants, and the subset of those who had a subsequent diagnosis of NSCLC, kg/m2 values of mean ± SD unless specified. BMI, body mass index; MMI, muscle mass index, ASMI, appendicular skeletal muscle index; BIA, bioimpedance analysis; DXA, dual energy x-ray absorptiometry; FMI, fat mass index.

Table 4.3 shows body composition reported by gender as there are different reference ranges (see Appendix C for age-stratified reference ranges of fat mass and fat-free mass in healthy adults). The mean BMI for the whole group, and for both genders was 26.6 kg/m^2. Women had a higher total FMI, lower MMI and ASMI (means 9.6, 15.5 and 6.7 kg/m^2 respectively) than men (means 7.2, 19 and 8.1 kg/m^2 respectively), in keeping with known anatomical variances in healthy subjects. As this was a prospective, pragmatic, non-randomised study, we did not statistically compare the body composition between groups.

Comparing all participants and the subset of those who were subsequently diagnosed with NSCLC, there was not much difference between body composition values of BMI, FMI, total MMI and ASMI. Twelve of 62 participants (19.4%) had sarcopenia according to BIA-derived cut-offs of ASMI.
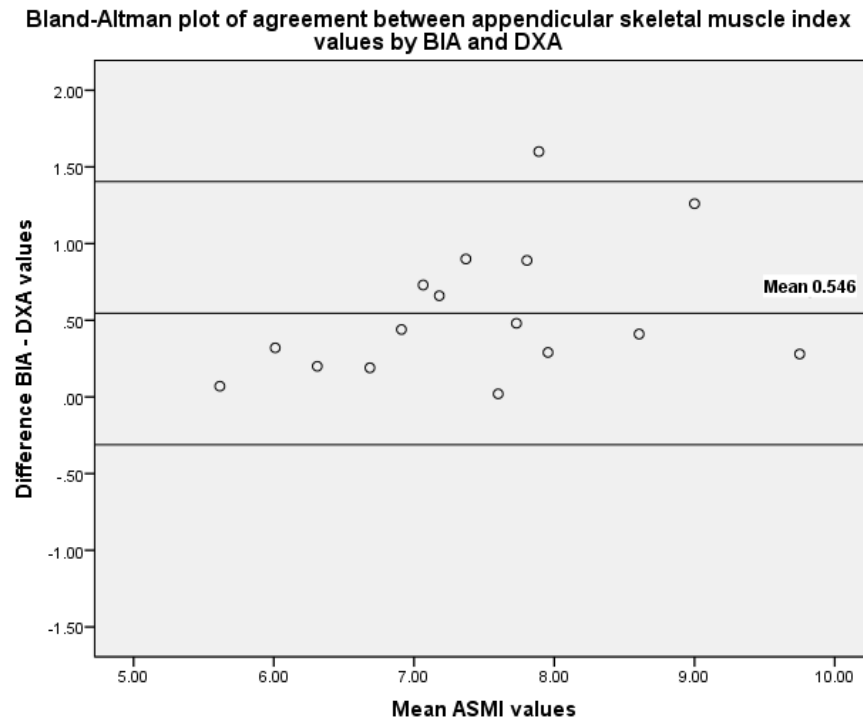
Figure 4.2: Bland-Altman plot of agreement between DXA- and BIA-derived ASMI values

Comparing the agreement between BIA and DXA-derived ASMI values, using DXA as the gold standard investigation, BIA-derived values consistently overestimated DXA-derived values (mean difference 0.546, 95%CI -0.312,1.404, p<0.001, Figure 4.2). This meant that BIA-derived values of ASMI were inaccurate and BIA may not be an appropriate investigation for this purpose, in this patient population. There was no clear trend between the difference between BIA- and DXA-derived ASMI values, and muscle mass i.e. with increasing or decreasing muscle mass, there was no clear trend in the overestimate.

4.3.3   Body composition and associations with outcome measures of interest

For the group as a whole, BMI and ASMI did not have any statistically significant association with receipt of any mode of MDT-planned treatment. In addition, these parameters were not associated with completion of treatment (see Table 4.4 and Figure 4.3).

Predictor variables	Receipt of MDT-planned treatment			Receipt and completion of MDT-planned treatment		
	OR	95% CI	p-value	OR	95% CI	p-value
BMI	1.036	0.93 to 1.16	0.523	1.065	0.97 to 1.17	0.194
ASMI for men	1.073	0.50 to 2.30	0.856	1.455	0.76 to 2.78	0.255
ASMI for women	2.458	0.76 to 7.94	0.133	1.701	0.69 to 4.18	0.246
Presence of sarcopenia (BIA-derived values of ASMI)[†]			0.424			0.473

Table 4.4: Odds ratios (OR) and corresponding p-values and 95% confidence intervals of logistic regression analyses, and †Fisher's exact test for the assessment of BMI and ASMI in predicting receipt and successful completion of all modes of MDT-planned treatment.
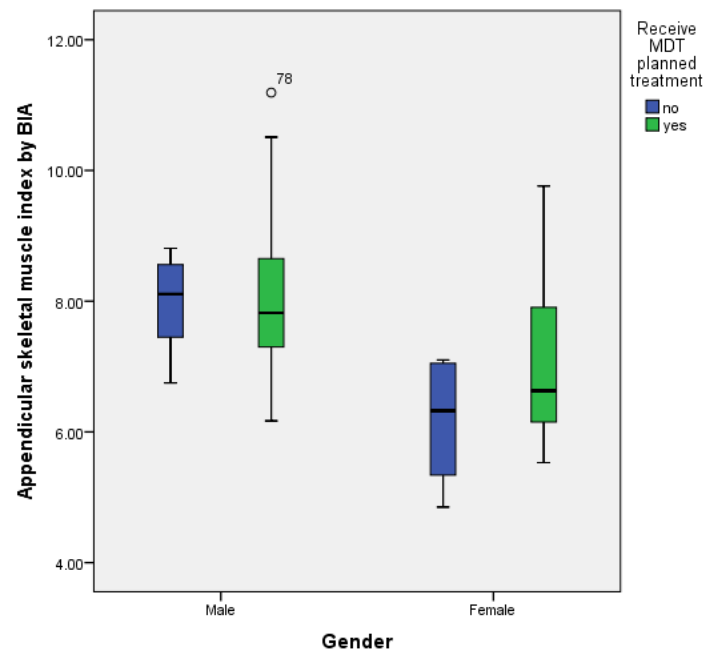
Figure 4.3: ASMI of all participants with NSCLC, and association with receipt of MDT-planned treatment.

4.3.3.1   Body composition of participants planned for surgery and radiotherapy, and associations with outcome measures of interest

Among 17 participants planned for surgery, only one declined treatment; all the rest received and completed the intended surgical procedure. 2 of 16 surgically-treated participants (12%) were sarcopenic, and both required further surgical procedures and consequently had a prolonged length of stay (>10 days) (Table 4.5).

Of the 19 participants who were planned for radiotherapy, 1 participant declined treatment, and 2 did not receive a dose of planned radiotherapy, one because of death prior to receipt of treatment and the other because of prolonged admission to hospital. Neither of these participants were sarcopenic at the time of baseline assessment. Two participants were sarcopenic, but they both received and completed the radiotherapy course (Table 4.5). A third patient treated with concurrent chemo-radiotherapy was sarcopenic, and received treatment, but died before completing it (this participant is included in the chemotherapy

data). None of the participants treated with radiotherapy had grade 3 or 4 toxicities

according to Radiation Oncology Therapy Group (RTOG) criteria.

	Participants planned for Surgery		Participants planned for Radiotherapy	
	Men	Women	Men	Women
FMI, mean ± SD	6.9 ± 3.4	11.9 ± 5.1	7.5 ± 4.6	8.8 ± 3.4
ASMI, mean ± SD	8.1 ± 1.2	7.3 ± 1.2	7.9 ±1.2	6.6 ± 0.8
Sarcopenia, n (% of all participants)	2 (11.8%)	0	2 (10.5%)	0

Table 4.5: FMI, ASMI and prevalence of sarcopenia in participants planned for surgery and radiotherapy

4.3.3.2   Body composition of participants planned for palliative chemotherapy, and association with outcomes of interest

The 26 participants planned for chemotherapy or chemo-radiotherapy were

considered separately, as a cohort of special interest. There was no significant difference

between the FMI of those who did and did not complete the chemotherapy course.

However, male participants who received and successfully completed chemotherapy had

higher median ASMI than those who did not, but this did not achieve statistical significance

(see Figure 4.4 and Table 4.6). Out of 26 participants, 7 (26.9%) were sarcopenic according to

BIA-derived ASMI cut-off values of less than 7.26 for men and 5.45 for women. Only one of

these completed the course; 3 others did not receive chemotherapy due to poor fitness; and

an additional 3 received chemotherapy but did not complete the full course due to worsening

fitness. Statistically, however, the presence of sarcopenia was not significantly associated

with receipt or completion of chemotherapy. The small number of women in the

chemotherapy group (n=7) precluded the statistical analysis of ASMI and other body

composition values as predictors of chemotherapy receipt and completion.
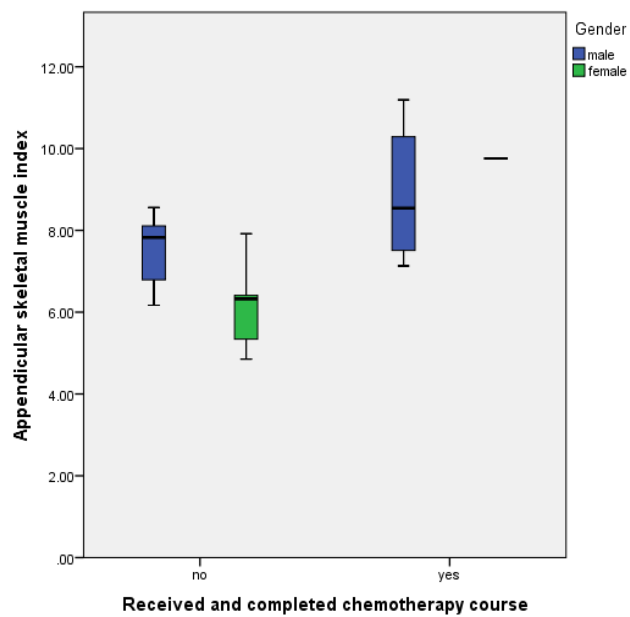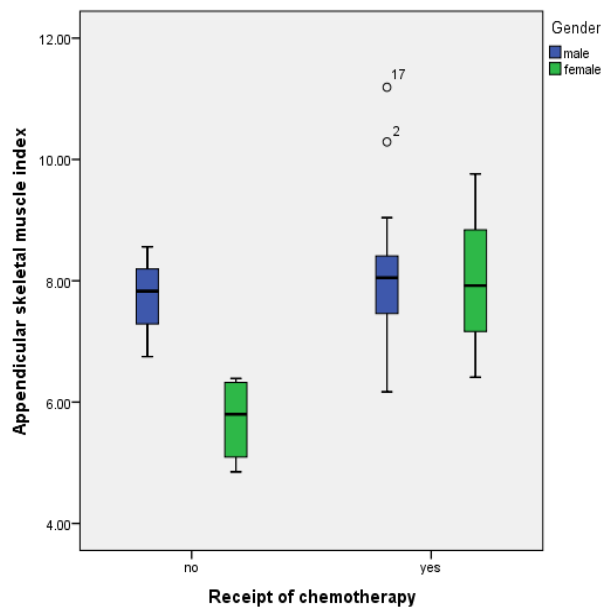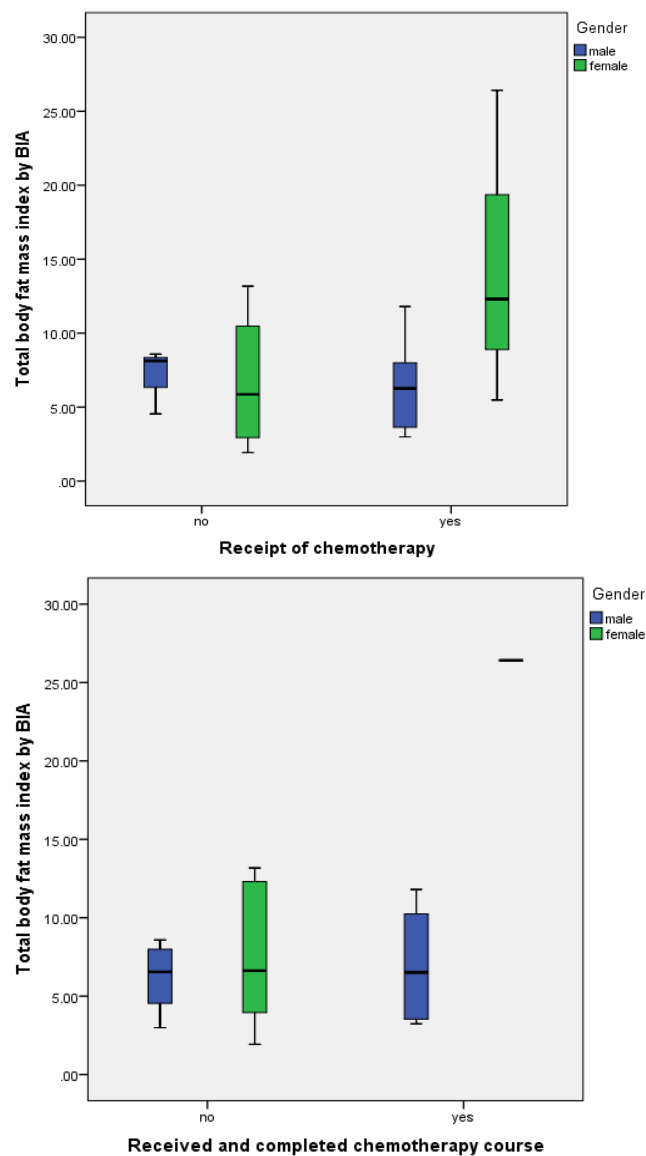
Figure 4.4: ASMI and FMI of participants planned for chemotherapy, and associations with receipt and completion of chemotherapy course

Predictor variables	Receipt of chemotherapy		Receipt and completion of chemotherapy course		Completion of 3 or 4 cycles of chemotherapy	
	OR (p-value)	95% CI	OR (p-value)	95% CI	OR (p-value)	95% CI
ASMI for men[‡]	1.40 (0.581)	0.43 to 4.61	2.882 (0.104)	0.81 to 10.33	2.705 (0.118)	0.78 to 9.42

Sarcopenia as defined by ASMI <7.26 for men and <5.45 for women (BIA)[†]	0.318	0.621	0.621

Table 4.6: Odds ratios (OR) and corresponding p-values and 95% confidence intervals for and logistic regression‡, and p-values of Fisher's exact tests† for muscle mass values and cutoffs for sarcopenia, and receipt and completion of chemotherapy course.

4.4 DISCUSSION

Body mass index is used in many areas of healthcare as a surrogate for body composition. Whilst it is generally regarded that having a low body weight for height is associated with poorer outcomes and worse survival, not much is known about whether it has any bearing on receipt and completion of treatment. Our focus on muscle mass values, rather than BMI, in this chapter (BMI and its association with outcomes of interest are considered in Chapter 5) was based on pre-existing reports that those with muscle mass depletion, or sarcopenia, had worse survival than those who had normal muscle mass levels (Prado et al., 2009, Martin et al., 2013). The ability of muscle mass depletion to predict prognosis suggests that it might also be predictive of tolerance to treatment, as those who are too frail to complete their treatment course in general have a shorter prognosis than those who do complete treatment.

Surprisingly, none of the body composition parameters investigated here (ASMI and FMI) were able to predict treatment related outcomes. Sarcopenia in our group was not significantly predictive of receipt of and successful completion of any mode of treatment, nor was it associated with adverse events during chemotherapy (cf SPPB in Chapter 6). Several studies in other cancer-specific groups have suggested an increased incidence of adverse events in sarcopenic patients (Tan et al., 2015a, Cushen et al., 2014, Antoun et al., 2010)

however we found this not to be the case. One important reason for this negative finding may be the use of bioelectrical impedance in this study, in contrast to more commonly used CT values. While CT is used widely in cancer, perhaps because it is a convenient investigation given that most cancer patients will have it in their work-up to the diagnosis, its accuracy in predicting muscle and fat mass is flawed in terms of having a wide range of agreement differences, compared to DXA (Kilgour et al., 2016).

BIA has been used to determine muscle mass and body composition in cancer (Gonzalez et al., 2014, Fearon et al., 2006a, Sarhill et al., 2003), and was one of the cited techniques of evaluating sarcopenia in consensus-based guidelines in cancer cachexia (Fearon et al., 2011). Despite a previous report that BIA overestimates muscle mass in lung cancer patients (Trutschnigg et al., 2008), an important research question was whether this overestimate was clinically relevant, and whether BIA-derived muscle mass was able to predict treatment-related outcomes with adequate certainty. Unfortunately, we found that BIA-derived muscle mass consistently overestimated DXA-derived values and was not significantly predictive of treatment-related outcomes. Therefore, we cannot recommend that BIA be routinely used in predicting muscle mass, in the diagnosis of sarcopenia in lung cancer patients.

The overestimation of BIA-muscle mass compared to DXA-muscle mass may be due to a number of reasons. Firstly, BIA does not directly measure muscularity, in contrast to DXA. Instead, it utilises a prediction equation developed using a DXA- or CT-derived reference method, producing a weight of muscle mass which is then expressed divided by the square of height ("index"). Cut-off values are based on comparative standard deviations below young adult values (Janssen et al., 2002, Janssen et al., 2000), or risk of physical disability (Janssen et al., 2004). As validation studies for BIA have not been based in cancer patients, with their own specific patient-related outcomes, this may explain the inaccuracy in part.

Furthermore, BIA works on the basis of a normal hydration status. While every effort was taken to ensure that we did not recruit participants who had had too much or too little to drink within 24 hours of the study, and ensured that all participants emptied their bladder immediately prior to the test, it is unclear how small inevitable variations in participants' hydration status might affect the test. It was also important to assess the utility of BIA as a routine clinical test, with patients `coming as they are', rather than be subject to test restrictions prior to enrolment.

Over the years, BIA-evaluated muscularity has been expressed in a variety of ways, common values being total skeletal muscle mass index (MMI) and appendicular skeletal muscle mass index (ASMI). While BIA-MMI estimates all skeletal muscle in the body including the head and neck and trunk, ASMI measures the fat- and bone mineral-free tissue in all four limbs. This tissue component is mainly muscle, accounting for 73-75% of total body skeletal muscle, with a small amount of skin and connective tissue (Gonzalez and Heymsfield, 2017) and may be a more accurate assessment of muscularity. CT-muscle mass is expressed using direct visualisation of muscularity at the 3rd lumbar vertebra, where muscle mass at this level is said to be linearly related to whole body muscle mass (Shen et al., 2004). We described cut-offs for sarcopenia, strengths and limitations of the commonly used methods of assessing muscularity in Section 1.2.6.

Given the consistent overestimate of muscularity in our cohort, it is possible that we underestimated the prevalence of sarcopenia, and subsequently, its association with receipt and completion of treatment. A significant proportion (19.4%) of our all participants with NSCLC, irrespective of treatment plan, had BIA-muscle mass values under the threshold for sarcopenia. Other studies in NSCLC have estimated 47% with sarcopenia (Baracos et al., 2010) but this difference was probably due to the difference in techniques.

Sarcopenia can also occur as a consequence of having COPD. As detailed previously in Section 1.2.5, the aetiology of sarcopenia may be related to chronic disease, inadequate nutrition, or lack of activity. In patients with both COPD and lung cancer, it is unclear whether sarcopenia is more prevalent given dual pathology, or whether this is only significant for patients with severe COPD, for example. COPD might even be considered a confounding factor when accounting for the prevalence of sarcopenia, as sarcopenia and poor physical function may predate the cancer diagnosis in the patient with COPD.

In over 2000 patients with COPD, where body composition was evaluated by BIA, sarcopenic obesity was found to be associated with reduced gait speed, and increased systemic inflammation, after adjusting for age, smoking, and BMI (Joppa et al., 2016). In 263 patients with COPD, the prevalence of sarcopenia increased with COPD severity, and there were obvious changes in BIA parameters in malnourished patients with systemic inflammation (de Blasio et al., 2018). This highlights a number of observations: cachexia and sarcopenia are closely linked, BIA is an accepted and useful measurement of muscle mass, and that being both sarcopenic as well as obese is an indicator of markedly poor prognosis (see Section 5.4). In our study, a relatively small proportion (29%) had COPD, and regression analyses did not reveal significant associations between muscle mass and outcome measures of interest. Where secondary analysis with prediction regression models might have been created, the presence of COPD would be accounted for as a confounding factor.

As mentioned previously, a normal hydration state is essential for the accurate reading of body composition, using BIA. Other indirect tests of body composition such as measurement of body cell mass measurement by means of dilution with deuterium and resting energy expenditure (Scott et al., 2001, Richards et al., 1992) are also reliant on hydration status and fasted participants in order to achieve this. However, as this was a pragmatic study, this was not achievable. We did, however, ensure that participants' body composition was measured

at the same time of day (i.e. the morning), that they had not had excessive alcohol in the last 24 hours and that they emptied their bladder prior to the test. We also made a note of what they had had to eat in the last 12 hours, and while there were variations in the amount of food and fluid intake, most participants had an average breakfast consisting of a hot drink and cereal or toast. While variations in short-term nutrition and hydration status must introduce some bias to BIA measurements of body composition, it may be of interest to compare these measurements amongst the under- and over-hydrated, and assess their accuracy with normal-hydration participants, controlling for age, weight, height and BMI. In addition, we noted the use of long term steroids, as it could also be a confounding variable with regards to reducing systemic inflammation and the incidence of anorexia by stimulating appetite, but less than 5% of our NSCLC cohort was taking this, so its impact would likely be negligible.

As noted previously, sarcopenia is associated with poor survival, although its association with treatment receipt and completion has never been evaluated. In stage I patients treated with surgical resection, sarcopenia was associated with poorer 5-year survival (Suzuki et al., 2016), although no associations were found with post-operative morbidity. In our surgical cohort, 2 of 17 participants were sarcopenic, and both of these had prolonged post-operative length of stay, but whether this was associated with sarcopenia is speculative. Not much is known on the effects of sarcopenia on patients treated with radiotherapy, however early weight loss has been associated with concurrent chemo-radiotherapy (Op den Kamp et al., 2014). Similarly, we did not find any associations between the presence of sarcopenia and radiotherapy outcomes.

In our cohort, 7 out of 26 participants (26.9%) planned for chemotherapy were sarcopenic. It is noteworthy that 6 out of 7 of these either did not receive, or did not complete the course, due to poor or worsening fitness levels. The effect of SPPB scores on

these outcomes are discussed in detail in the next chapter. While there was no statistically

significant effect of sarcopenia on receipt or completion of the chemotherapy course, this

may be due to our small sample size. We also did not find an association between sarcopenia,

or muscle mass, and adverse events during chemotherapy (cf effect of SPPB in Chapter 6).

This is in contrast to the literature which finds increased frequency of toxic events in

sarcopenic patients with renal cell, colorectal, and breast cancer (Antoun et al., 2010, Cushen

et al., 2014, Barret et al., 2014, Prado et al., 2009). These papers also had small sample sizes

(n<100), but used CT and its relevant cut-offs to diagnose sarcopenia. Furthermore, there are

no prospective published studies finding this association in NSCLC patients, despite previous

reports that sarcopenia is prevalent and a predictor of poor survival in this population (Martin

et al., 2013).

Our study had some limitations. An unexpected finding was the consistent

overestimation of muscle mass values by BIA compared to DXA. One of the aims of this study

was to test whether BIA-derived muscle mass measurements were accurate and clinically

relevant in lung cancer. This study suggests, within its limitations, that this is not the case. As

a result of the inaccurate BIA-derived muscle mass measurements, we were unable to test

the relationship between muscle mass and physical performance – another aim of our study

– with any confidence. A further limitation was that this was an observational cohort study,

with some analyses not reaching statistical significance due in part to small numbers.

Furthermore, the loss of some participants from longitudinal analysis was due to the study

design, whereby participants were recruited at first presentation to the RALCC. While this

enabled true baseline data to be captured, it also meant that some participants were

recruited prior to histological confirmation of NSCLC, leading to loss of these participants

from follow-up. Finally, having more than one time-point when body composition and

physical performance were recorded would have enabled further analysis of changes over

time, and the response of these parameters to systemic treatment.

4.5 Conclusion

In this section of the thesis, we evaluated the association of BIA-derived body composition values with receipt and completion of any mode of MDT-planned treatment. We found that BIA overestimated muscle mass values, compared to the gold standard investigation DXA, and that BIA-derived sarcopenia had no association with receipt and completion of MDT-planned treatment. We explore other variables – physical performance, Performance status, and nutrition status – in the following chapters.

Chapter 5: Nutrition status as a predictor of treatment delivery in NSCLC patients.

5   CHAPTER 5: NUTRITION STATUS AS A PREDICTOR OF TREATMENT DELIVERY IN NSCLC PATIENTS.

5.1   INTRODUCTION

A possible association between body composition and the delivery of treatment in NSCLC patients was explored in Chapter 4, above. Body composition and nutritional status are closely linked. It is therefore of interest to see whether there might be an association between nutritional status and treatment delivery.

The World Health Organisation (WHO) definition for nutritional status is based on body mass index (BMI), where being underweight, or having a BMI of less than 18, is associated with increased morbidity and mortality in cancer (Thomas et al., 2014). However, utilising BMI alone in the context of cancer does not account for rate and degree of weight loss, protein stores, ratio of fat to fat-free mass (FFM), nor metabolic alterations in the patient. Weight loss has long been associated with a poor prognosis in cancer, and is widely used to evaluate nutritional status (Dewys et al., 1980). A robust grading system incorporating degrees of weight loss and BMI graded between 0 and 4 has been developed, which is independently associated with prognosis (Martin et al., 2015), and will, in this study, be tested in the context of receipt and completion of treatment.

The Malnutrition Universal Screening Tool is scored according to 3 components – BMI, weight loss in last 3-6 months, and projected nutritional intake in the next 5 days. It has been used in many healthcare settings including oncology, and has been validated in patients with cancer (Boleo-Tome et al., 2012, Leuenberger et al., 2010), although not specifically in lung cancer. It is quick and simple to perform in clinical practice, compared to other tools such as the SGA which requires specific expertise. MUST is used to predict malnutrition risk in cancer, but less is known about its predictive value of treatment outcomes. The Glasgow Prognostic

Score (GPS) combines CRP and Albumin into a inflammation-based scoring system that predicts prognosis; a score of 0 is given if CRP is less than 10 and albumin is more than 35, a score of 1 given if CRP is more than 10 or albumin is less than 35, and 2 is given if CRP is more than 10 and albumin less than 35 (McMillan, 2013). It has been validated in patients with varied cancer types for prognostic purposes.

While BMI and weight loss are important established parameters in predicting outcomes in cancer, an internationally accepted definition of nutritional status in cancer is warranted, as there remains heterogeneity its definition. Apart from BMI and degree of weight loss, serological markers such as albumin and C-reactive protein (CRP), malnutrition assessment tools such as the SGA, or a combination of these (Attar et al., 2012, Tan et al., 2015b) have been used to define nutritional status in cancer. In this chapter, the focus is on the predictive value of commonly used nutritional status parameters in association with receipt or completion of MDT-planned treatment in NSCLC.

5.2 PARTICIPANTS, METHODS AND STATISTICAL ANALYSES

Recruitment of study participants, together with methods and statistical techniques are presented in detail in Chapter 3. In this chapter, the predictive value of BMI, weight loss, MUST score and CRP and albumin levels in all patients with NSCLC is evaluated (n=62), with an emphasis on those planned for chemotherapy (n=26).

5.3 RESULTS

BMI in all participants with NSCLC is presented in greater detail in Chapter 4, above. The mean BMI was similar in all NSCLC participants, whether planned for palliative

chemotherapy or other treatment modalities (Table 5.1). However, weight loss at

presentation was higher in participants planned for chemotherapy, with a mean of 8.2 kg

(9.5% of baseline body weight) over the preceding 6 months, compared to 5.3 kg (6.5%

baseline body weight) in participants with NSCLC (Table 5.1). Although sarcopenia is

considered in greater detail in Chapter 4, none of our participants with NSCLC were both

obese according to BMI, and sarcopenic. There were wide variances in weight loss and BMI,

however this occurred in NSCLC participants planned for all modes of treatment, as well as

the subset planned for chemotherapy. Both BMI and weight loss were not normally

distributed, in all NSCLC participants as well as participants in the chemotherapy group (all

Shapiro-Wilk test p-value >0.05) with a left skew for weight loss, and right skew for BMI.

	All NSCLC (n=62)	Participants planned for chemotherapy (n=26)
BMI	26.6 ± 6.4	26.3 ± 7.1
Weight loss (kg)	5.3 ± 6.5	8.2 ± 7.7
Weight loss (%)	6.5 ± 7.6	9.5 ± 8.5

Table 5.1: Mean ± SD of BMI and weight loss of all NSCLC participants at first presentation, and the subset of 26 patients planned for palliative chemotherapy.

In terms of nutrition status parameters, we found a number of significant associations

between measures of nutrition status – BMI, MUST score, serum CRP, serum albumin and

GPS – and the receipt or completion of chemotherapy (Table 5.2). In all participants with

NSCLC, those with weight loss greater than 10% were significantly less likely to successfully

complete MDT-planned treatment. In the chemotherapy group, weight loss of greater than

10% was significantly predictive of non-receipt of chemotherapy. However, when weight loss

was calculated as a continuous variable (percentage weight loss), there was no significant

association with either receipt or completion of all modes of treatment as well as

chemotherapy. BMI and weight loss graded together according to the Martin classification (Martin et al., 2015) did not show any significance with receipt or completion of treatment.

A higher albumin concentration was significantly associated with completion of 3 or more cycles of chemotherapy (OR 1.46), although not associated with other outcome measures. Higher CRP concentrations were associated with non-completion of all modes of treatment, although the effect size was small (OR 0.985). CRP and albumin scored together within the GPS showed a significant association with completion of 3 or more cycles of chemotherapy (p=0.003). MUST scores had no significant association with any outcomes of interest. Although these significant associations might seem promising, it is important to bear in mind that there was no pattern to these associations – with receipt or completion of MDT-planned treatment or chemotherapy. This raises the possibility of chance associations to account for our significant findings.

	MDT-planned treatment		Chemotherapy		
Predictor variables	Receipt, OR (p-value)	Successful completion, OR (p-value)	Receipt, OR (p-value)	Successful completion, OR (p-value)	Completion of 3 or 4 cycles, OR (p-value)
Weight loss %	0.959 (0.289)	0.93 (0.061)	0.908 (0.102)	0.913 (0.159)	0.920 (0.164)
Weight loss <10% vs ≥10%	3.182 (0.085)	0.29 (0.039)*	0.091 (0.045)*	0.280 (0.190)	0.200 (0.096)
BMI (kg/m^2)	1.036 (0.523)	1.065 (0.194)	1.127 (0.198)	1.212 (0.065)	1.221 (0.060)
BMI/Weight Loss grade[†]	(0.798)	(0.478)	(0.909)	(0.456)	(0.585)
MUST 0, 1, ≥2	0.757 (0.424)	0.638 (0.131)	0.378 (0.117)	0.440 (0.107)	0.459 (0.107)
Albumin	1.051 (0.383)	1.053 (0.318)	1.187 (0.134)	1.203 (0.163)	1.46 (0.025)*
CRP	0.995 (0.474)	0.985	0.996 (0.604)	0.769 (0.127)	0.920 (0.122)

			(0.035)*		
GPS[†]	(0.469)	(0.188)	(0.698)	(0.08)	(0.003)*

Table 5.2: Regression analyses showing associations of commonly used measures of nutrition status with receipt and completion of planned treatment in NSCLC. *Denotes significance at the 95% confidence level. [†]Denotes Chi-squared or Fisher's exact test, expressed as p-values.GPS: Glasgow Prognostic Score.

In terms of BMI, the median BMI of those who successfully completed chemotherapy was higher than the BMI of those who did not (Figure 5.1), however this did not reach statistical significance. In contrast to the sub-group planned for chemotherapy, the median BMI of those completing all MDT-planned treatments was similar to those who did not.
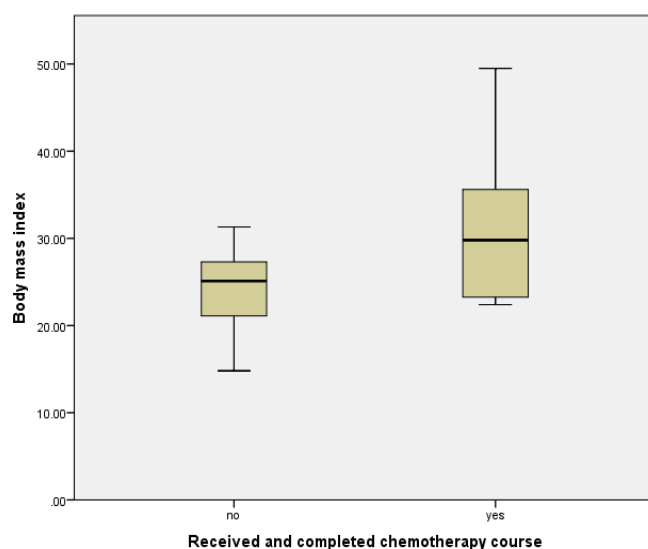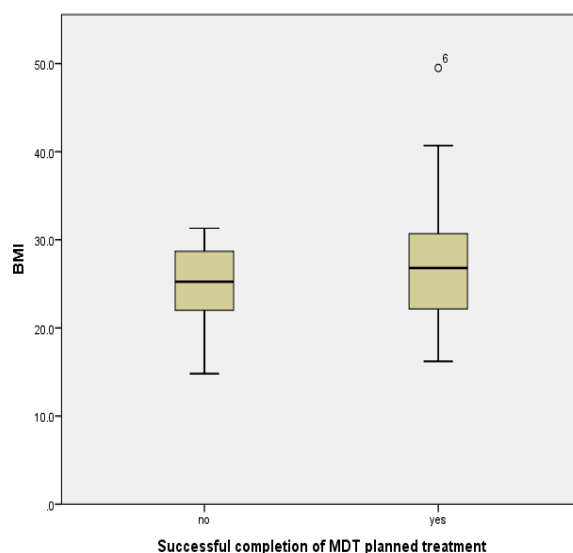
Figure 5.1*: Relationship between BMI and completion of MDT-planned treatment in all 58 participants with NSCLC (top diagram) and the subgroup of 24 participants planned for palliative chemotherapy (bottom diagram).*

5.4 DISCUSSION

Nutritional status in cancer is varied and ill-defined. Many nutritional screening tools are available, and some have been validated for certain cancers. This has resulted in a heterogeneous mix of approaches to define nutritional status, with no consensus on their use in clinical practice, prognostic abilities, and therapeutic options. However, many scoring tools and clinicians use BMI, weight loss, and albumin levels, singly or in combination to define nutrition status in cancer, and our findings are now compared to what is known from the literature.

Body mass index (BMI) is a convenient measurement, with two easily measured parameters required for its calculation – weight and height. However, compared with BMI, body composition parameters of muscularity and adiposity may be more precise predictors of cancer-related outcomes. Indeed, many body composition experts have called BMI "an imperfect measure of body fatness" (Baracos et al., 2010, Dixon and Egger, 2014), recognising that it is not primarily the unit of weight that is important, but the composition, distribution and fluctuations in fat and muscle (cf Chapter 4), which may be more significant (Larsson and Wolk, 2008).

While the health risks of obesity are numerous, it is the combination of both excess adiposity and skeletal muscle depletion, termed sarcopenic obesity, which seem to confer the greatest health risks in cancer patients (Prado et al., 2012), irrespective of BMI. Poor survival regardless of BMI is also reported in the sarcopenic obese population in lung cancer; whereas BMI was not found to be predictive of survival (Baracos et al., 2010, Martin et al., 2013). In advanced lung cancer, BMI-underweight is associated with poorer overall survival (Kim et al.,

2013, Dahlberg et al., 2013, Luo et al., 2012), however, sarcopenic obesity in other cancer-specific groups resulted in mixed reports (Psutka et al., 2015, Gonzalez et al., 2014). Despite this, it is generally agreed that being underweight, and having excess fat mass compared to muscle mass is associated with poor survival in cancer.

Much of the literature considering BMI and body composition has evaluated its predictive potential in survival, and not treatment receipt and completion. In our study, out of 62 participants, none were characterised as having sarcopenic obesity, so it was not possible to evaluate whether there were worse outcomes in this group. One consideration is that we used BIA to analyse muscle mass, which we found in a subgroup of participants to consistently overestimate measurements compared to DXA (Chapter 4), and much of the literature assessing body composition have used CT. This may have led to underestimation of the prevalence of sarcopenia in our cohort. We considered successful completion of treatment, particularly chemotherapy, as endpoints in themselves, and found no significant association between BMI and receipt of, or completion of planned treatment.

In general, weight loss is associated with a poor prognosis. Both 5% and 10% weight loss thresholds are widely used in the cancer literature (Blum et al., 2011a), and are associated with anorexia, increased catabolic drive and increased metabolism, and low albumin levels. Weight loss is also an independent risk factor for poorer outcomes, be it in early or advanced stage disease – weight loss was associated with increased mortality in early stage lung cancer patients undergoing surgery (Fiorelli et al., 2014), as well as patients with advanced disease (Moumtzi et al., 2016). However, other studies found that weight loss alone was an insufficient predictive factor, and more comprehensive nutritional assessments incorporating other parameters such as albumin outperformed weight loss alone in predicting prognosis (Gioulbasanis et al., 2011).

In lung cancer, a greater degree of weight loss correlated with a shorter time from diagnosis to death (Sarhill et al., 2003) and early mortality (Grivaux et al., 2016). This may reflect an increased rate of catabolism in the host, which gives rise to the anorexia-cachectic state and thus a more aggressive disease process. In our study, weight loss of ≥10% was significantly associated with being less able to complete MDT-planned treatment, as well as non-receipt of palliative chemotherapy. Our finding that weight loss of ≥10% was associated failure to receive palliative chemotherapy in NSCLC is in keeping with other data (Brule et al., 2016), in which the authors also report that patients who did not receive treatment had significantly reduced survival. However, the fact that weight loss as a continuous variable was not associated with receipt of chemotherapy, versus the finding that weight loss of ≥10% was significantly associated with failure to receive chemotherapy, should prompt cautious interpretation of these positive associations.

Malnutrition assessment tools such as the SGA may be helpful, particularly in detecting malnutrition risk and proactively managing it, in cancer populations where malnutrition is prevalent (Abbott et al., 2016). While these assessments provide a more comprehensive assessment than nutritional screening tools, they are time consuming and require formal training and expertise. The importance of nutritional screening tools is that they identify patients at risk of malnutrition, highlighting these patients for more in-depth assessment. The many tools available for screening malnutrition, with no clear guidelines on which is most appropriate for use in lung cancer make it difficult to choose, for example when designing a study, or in everyday clinical practice. Our evaluation of MUST showed that it had no relationship with receipt and completion of MDT-planned treatment, or receipt and completion of chemotherapy, hence its use in this context will remain solely a nutritional screening tool. In practice, however, weight loss on its own might be just as useful a tool, compared with MUST, to prompt more in-depth evaluation of nutritional status.

In our study, higher albumin was significantly associated with successful completion of 3 or more cycles of chemotherapy. Similarly, lower CRP was significantly associated with successful completion of MDT-planned treatment, although the effect size was small. Although albumin and CRP were not significantly predictive of all treatment-related outcomes, these associations hint that these parameters may have potential in predicting completion of treatment in NSCLC. This is in keeping with other data which suggest that both albumin and CRP, the most widely used marker of inflammation have prognostic value. Both these markers have been used together with other body composition parameters such as weight loss and BMI to create nutritional indexes. For example, the Prognostic Nutritional Index (PNI) incorporates albumin into its calculations and the Glasgow Prognostic Score (GPS) utilises both CRP and albumin. In particular, the GPS has been reported to be able to predict development of cachexia, a poorer response to treatment, and poorer survival (Shimizu et al., 2015, McMillan, 2009).

5.5 CONCLUSION

Our study showed that weight loss, albumin and CRP had significant associations with either receipt or completion of treatment in NSCLC patients. However, there was no clear trend to these associations and as such the inconsistency prevented firm conclusions from being drawn. Rather, this data suggests that together with objective physical performance and other body composition parameters, there may be a role for baseline nutritional status in predicting receipt and/or completion of treatment in NSCLC.

Chapter 6: Physical performance as a predictor of treatment delivery in patients with NSCLC.

6   CHAPTER 6: PHYSICAL PERFORMANCE AS A PREDICTOR OF TREATMENT DELIVERY IN PATIENTS WITH NSCLC.

6.1   INTRODUCTION

The interaction between muscle mass, muscle strength and physical function is intriguing, as part of the wider interest in the role of physical function and performance in determining fitness for treatment. Currently, the subjective performance status (PS) score is widely used to help determine which patients receive systemic anti-cancer treatment, and other palliative treatment options in patients at the same disease stage.

While PS is a prognostic factor for survival, relatively little is known about its ability to predict whether patients are fit to receive guideline-based treatment or not – the very objective of establishing baseline PS in the first place. This paradox is illustrated by the fact that a significant proportion of patients with lung cancer do not go on to commence MDT-planned treatment, the main reason for this being a lower PS than at baseline (Vinod et al., 2008, Vinod et al., 2010). A declining PS may signify many things: a patient population with rapidly progressing disease trajectory resulting in rapidly declining function, inter-observer variability in assessing PS, or simply that PS is not a sufficiently sensitive predictor of fitness for treatment.

As a result, there is a requirement for a more objective evaluation of physical performance or muscle strength which may complement, or even outperform, PS (Sonpavde et al., 2012). The Short Physical Performance Battery (SPPB) tests lower limb strength and endurance, incorporating gait speed which is similar to the six-minute walk test (6MWT) more commonly used in lung cancer research (Kasymjanova et al., 2009, Sommer et al., 2014). The SPPB is used widely to test the physical performance of older people, where the

age cut-off for research purposes is 65 years, although this may be greater or less depending

on comorbidities and individual circumstances (Cruz-Jentoft et al., 2010).

Other objective tests such as the 6MWT and handgrip strength have been shown to

predict survival (Kasymjanova et al., 2009, Kilgour et al., 2013), however their use in routine

clinical practice is not yet established. Whilst the predictive abilities of physical performance,

strength and muscle mass have been considered separately in patients with cancer (Kilgour et

al., 2013, Peddle-McIntyre et al., 2012), they have not yet been considered in combination.

Given the non-linear relationship between physical performance and muscle mass in the

elderly (Goodpaster et al., 2006), a similar relationship might exist in cancer. In this chapter,

we focus on the whether or not physical performance has any bearing on receipt and

completion of chemotherapy. Establishing predictive, prognostic and clinically relevant tests

of physical performance which are both simple and quick to use in the outpatient clinic, in

parallel with muscle mass assessment may provide essential information to clinicians when

evaluating treatment options.

6.2 METHODS, PARTICIPANTS AND STATISTICAL TECHNIQUES

Recruitment of the study's participants, together with methods and statistical

techniques was presented in detail in Chapter 3. In this chapter, we focussed on objective

measures of physical performance, as assessed by using SPPB (see Appendix B for SPPB

scoring), of all patients with NSCLC (n=62). We were especially interested in whether SPPB is

able to predict receipt and completion of MDT-planned treatment, and adverse events in

chemotherapy. We used Poisson regression to evaluate the relationship between SPPB score

and adverse events in participants planned for chemotherapy, and reported the incidence

rate ratio (IRR) as an expression of the odds of having adverse outcomes with every unit

increase in SPPB. *B* refers to the unstandardised regression coefficient.

6.3 RESULTS

6.3.1   Physical performance in all participants with NSCLC

Predictor variables	Receipt of MDT-planned treatment		Receipt and completion of MDT-planned treatment	
	OR (p-value)	95% CI	OR (p-value)	95% CI
Total SPPB score (range 0-12)	1.039 (0.79)	0.78 to 1.38	1.023 (0.854)	0.81 to 1.30
Gait speed categories 0-2 vs 3-4	1.033 (0.962)	0.27 to 3.98	1.299 (0.648)	0.42 to 3.99
Gait speed (m/sec)	4.97 (0.449)	0.08 to 316.06	1.947 (0.707)	0.06 to 63.2
5 times sit-to-stand categories 0-2 vs 3-4	1.556 (0.498)	0.43 to 5.58	2.40 (0.115)	0.81 to 7.13
Balance categories	0.745 (0.798)	0.08 to 7.06	0.295 (0.281)	0.03 to 2.71

Table 6.1: Regression analyses expressed as odds ratios (OR) with p-values and 95% confidence intervals of total and component SPPB scores, and associations with receipt and completion of MDT-planned treatment.
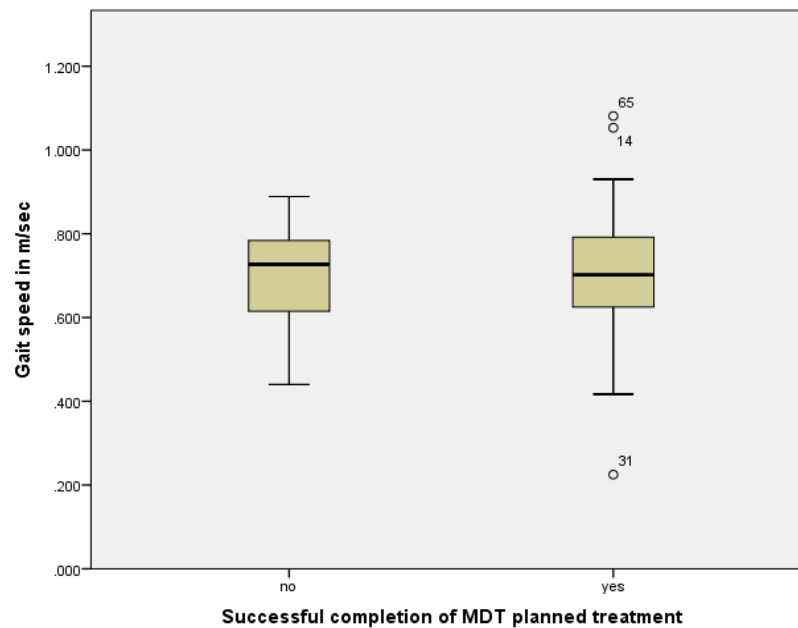
Figure 6.1: Relationship between gait speed and successful completion of MDT-planned treatment, all patients with NSCLC

A description of all participants, those with NSCLC and those planned for chemotherapy only is presented in the Results section of Chapter 4. In terms of physical performance and all modes of MDT- planned treatment, there was no significant association between total SPPB score and receipt of MDT-planned treatment (p=0.79), or completion of MDT-planned treatment (p=0.854) (Table 6.1). Gait speed, as a continuous variable as well as in SPPB categories, was also not associated with completion of MDT-planned treatment (see Figure 6.1).

6.3.2   Physical performance – participants planned for palliative chemotherapy

Having considered all patients, irrespective of treatment modality, in the previous section, we now consider only the group of special interest – those receiving chemotherapy. Total SPPB score, as well as its component tests – balance, gait speed and five times sit-to-stand – were considered separately, in order to gauge whether any one component had a greater predictive effect than another on chemotherapy outcomes (Table 6.2).

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Predictor variables	Receipt of chemotherapy		Receipt and completion of chemotherapy course		Completion of 3 or more cycles of chemotherapy		Completion of number of cycles of chemotherapy	
	Odds ratios (OR) and corresponding 95% Confidence Intervals (CI)						Beta (*B*), unstandardised regression coefficient and 95% CI	
	OR (p-value)	95% CI	OR (p-value)	95% CI	OR (p-value)	95% CI	*B* (p-value)	95% CI
Total SPPB score	1.282 (0.272)	0.82 to 2.00	1.903 (0.047)*	1.01 to 3.60	1.849 (0.043)*	1.02 to 3.36	0.351 (0.023)*	0.05 to 0.65
Gait speed <0.8/sec vs ≥0.8m/sec	4.200 (0.227)	0.41 to 43.04	4.333 (0.124)	0.67 to 28.12	7.222 (0.042)*	1.08 to 48.48	1.313 (0.055)	-0.03 to 2.66
Gait speed (m/sec)	20.5 (0.349)	†	473.9 (0.106)	†	959.5 (0.076)	†	3.913 (0.077)	-0.46 to 8,29
5 times sit-to-stand categories 0-2 vs 3-4	1.905 (0.478)	0.32 to 11.31	8.571 (0.070)	0.84 to 87.83	11.667 (0.039)*	1.14 to 119.54	1.552 (0.014)	0.35 to 2.76
5 times sit-to-stand (sec)	0.962 (0.698)	0.79 to 1.17	1.00 (0.682)	0.99 to 1.02	1.00 (0.658)	0.99 to 1.02	0.001 (0.665)	-0.00 to 0.00
Balance categories[‡]	(0.076)[‡]		(1.000)[‡]		(1.000)[‡]		1.826 (0.272)	-1.53 to 5.19

*Table 6.2: Regression analyses expressed as odds ratios (OR) or B (unstandardised regression coefficient) with p-values and 95% confidence intervals of total and component SPPB scores, and associations with receipt and completion of cycles of chemotherapy. B is the unstandardised regression coefficient. *Denotes statistical significance at the 95% confidence level. ‡Calculations of Odds Ratios failed to converge, therefore only p-values for Fisher's exact test or chi-squared test reported, where applicable. †Error in calculation of confidence intervals*
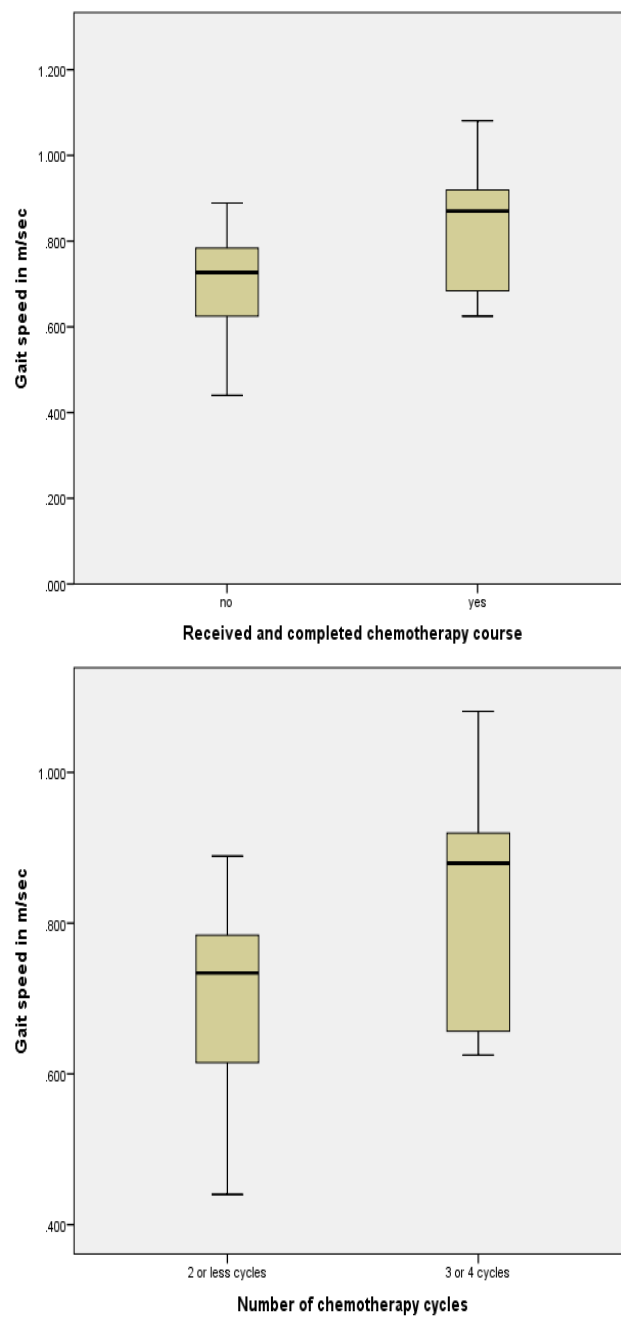
Figure 6.2: Relationship between gait speed, and completion of chemotherapy course, and completion of 3 or more cycles of palliative chemotherapy

The collated results for the total and components of the SPPB, as predictors for

chemotherapy outcomes, are shown in Table 6.2. The higher the SPPB score, the more likely

one was to complete more cycles of chemotherapy (*B*=0.351, p=0.023). The odds of receiving

3 or more cycles of chemotherapy was increased by around 85%, for each unit increase in

SPPB score (OR 1.849, p=0.043), and the odds of completing the full course of chemotherapy

was increased by 90% (OR 1.903, p=0.047), for each unit increase in SPPB score.

The five times sit to stand (STS) test was not discriminatory for receipt of

chemotherapy. However, the odds of completing 3 or more cycles of chemotherapy were 11

times higher in those with quicker STS speeds (categories 3-4 on the SPPB component score)

than slower STS speeds (categories 0-2) (OR=11.667, p=0.039). In terms of gait speed, the

odds of completing 3 or more cycles of chemotherapy were 7 times greater in those with gait

speeds of 0.8m/sec or more, than those with gait speeds of less than 0.8m/sec (OR=7.22,

p=0.042). However, when gait speed was tested as a continuous variable, this failed to show

a significant association with completion of cycles of chemotherapy (Figure 6.2). Balance was

not found to be associated with either receipt or completion of chemotherapy. This data

suggest that SPPB total score, and in particular the STS component, is positively associated

with completion of the chemotherapy course, and more cycles of chemotherapy. The balance

component did not show an association with prediction of chemotherapy completion, but

gait speed may have a role.
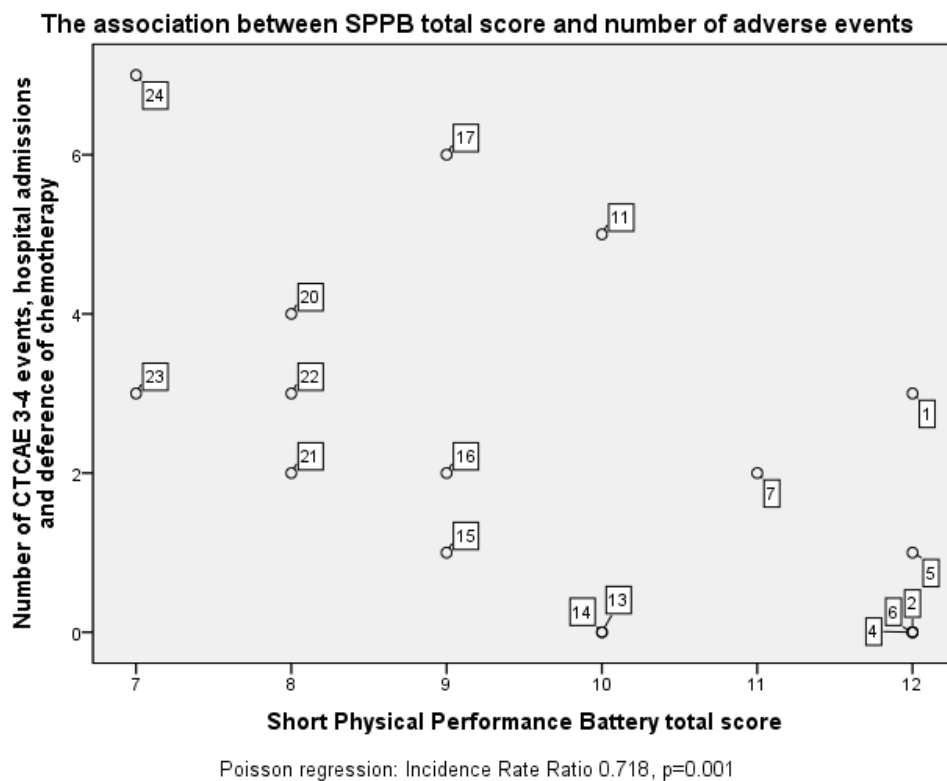
Figure 6.3: Relationship between SPPB total score and number of CTCAE grade 3-4 adverse events, hospitalisations, and delays in chemotherapy, IRR 0.718, p=0.001.
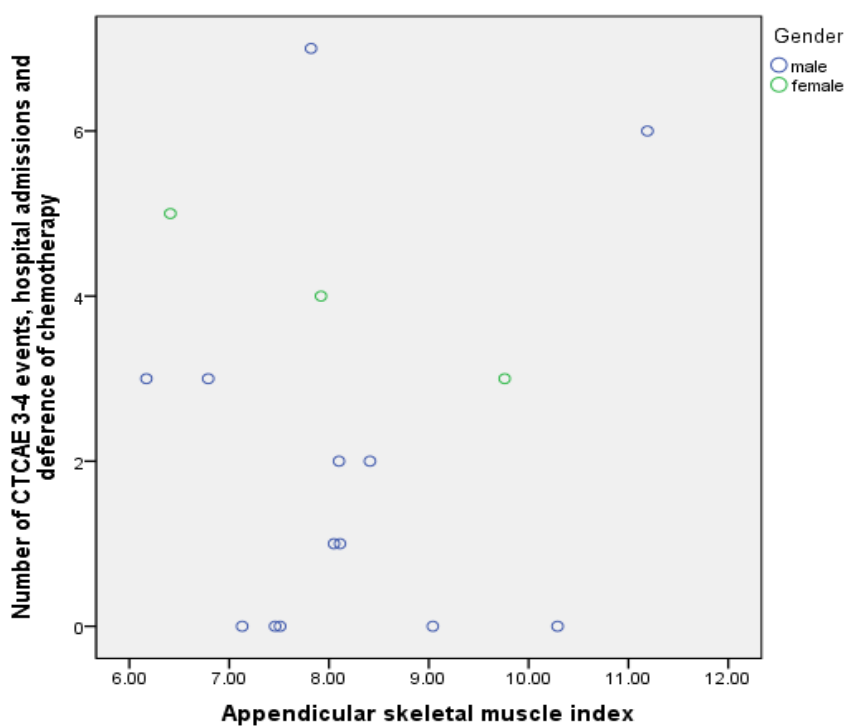
Figure 6.4: The relationship between ASMI and frequency of CTCAE grade 3-4 adverse events, hospitalisations and delays of chemotherapy.

With regards to numbers of adverse events, an association was seen between this and SPPB scores (IRR=0.718, p=0.001), where for every unit increase in SPPB score, there was a 28.2% decrease in adverse events (Figure 6.3). In contrast, there was no significant association between ASMI and adverse events during chemotherapy (Figure 6.4).

In those who completed 3 or more cycles of chemotherapy, there was no apparent correlation between dose reductions and SPPB score. Five participants had dose reductions, mainly due to adverse events after cycle 1 – one had worsening renal function, one had a mild allergic reaction, a further participant had severe vomiting, and another had non-febrile neutropenia. The other participant was deemed not fit for full dose chemotherapy. These participants' SPPB scores ranged from 9 to 12. Three participants did not have dose reductions; all these participants had SPPB scores ranging from 7 to 12. This needs more detailed scrutiny with a larger cohort, especially as there is a statistically significant association between frequency of adverse events, and SPPB.

6.3.3 Physical performance and associations with muscle mass and ECOG PS
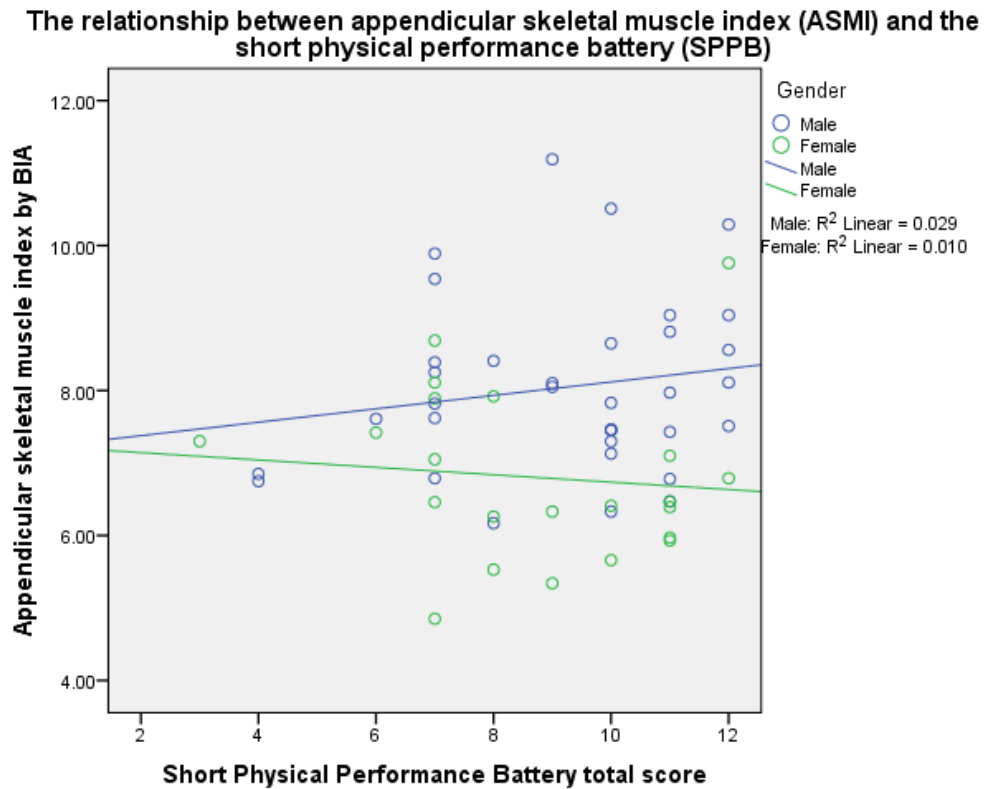
Figure 6.5: The relationship between ASMI and SPPB total scores, by gender, all patients with NSCLC.

A secondary aim of this thesis was to describe the relationship between the two main parameters of interest – muscle mass (here, represented by BIA-derived ASMI) and physical performance as assessed by SPPB. In evaluating this, we found no significant relationship between them (Figure 6.5), as mentioned in section 4.3.2 and 4.4, in contrast to the previously described linear relationship that exists in older people (Goodpaster et al., 2006).
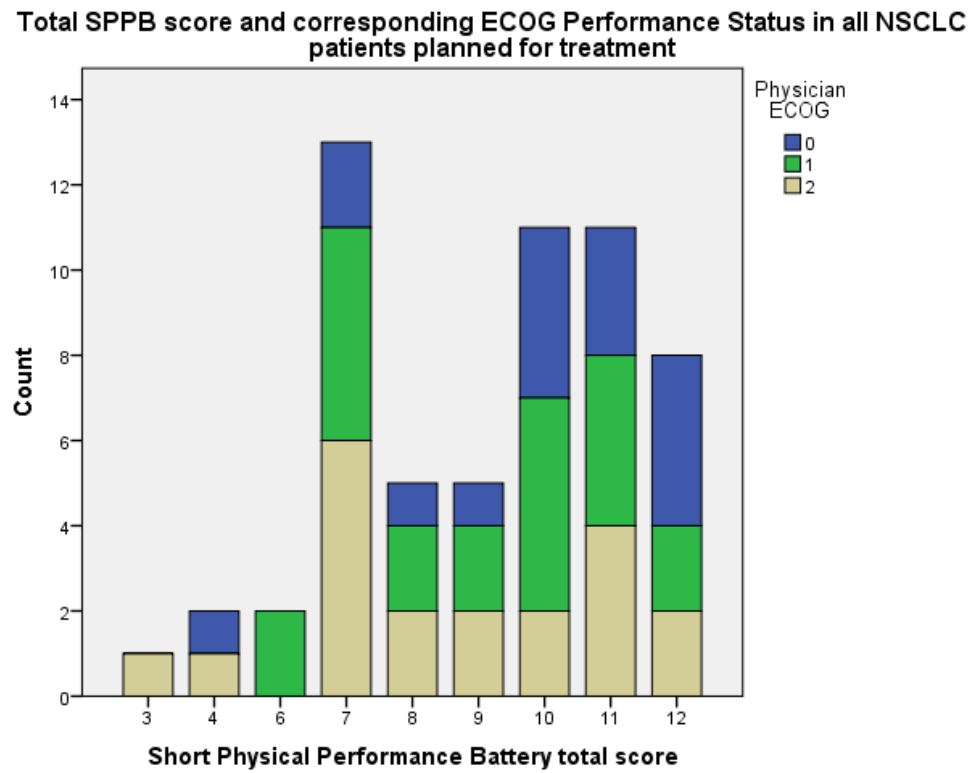
Figure 6.6: *SPPB total score and proportions of physician-rated ECOG PS, all participants with NSCLC.*
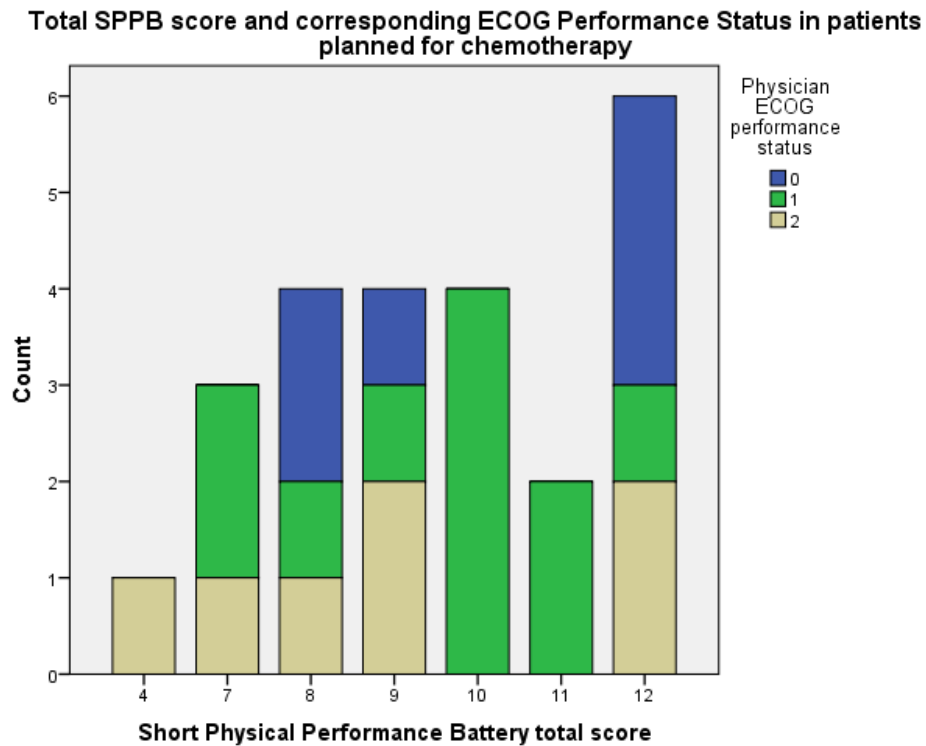
Figure 6.7: SPPB total score and proportions of physician-rated ECOG PS, only participants planned for chemotherapy.

A good PS (0-1) was assigned to patients with SPPB scores as low as 4, and borderline

PS (2) was assigned to the patients with (best) SPPB scores of 12, in all participants with

NSCLC planned for any mode of treatment. We concluded therefore that there was no

relationship between SPPB and physician-assessed ECOG PS, in all participants with NSCLC, as

well the subset of those planned for chemotherapy. Figures 6.6 and 6.7 illustrate this

relationship in all NSCLC participants, and the subset of participants planned for palliative

chemotherapy, respectively.

6.4 DISCUSSION

While current advances in NSCLC, and other tumour types, tend to focus efforts on improving survival, our study considers the factors that may contribute to barriers to treatment receipt and completion, from a different perspective. Multiple phase III clinical trials have demonstrated that receiving palliative systemic treatment results in prolonged survival (Non-Small Cell Lung Cancer Collaborative Group, 2010, Rapp et al., 1988, Paz-Ares et al., 2012). However, a significant proportion of advanced NSCLC patients do not receive treatment at all, many due to poor PS (Sacher et al., 2015, Brule et al., 2016). Our study suggests that PS is not the best marker of fitness for treatment, as even in those with good or borderline PS, treatment is not always tolerated, let alone begun (cf Chapter 7). Non-receipt of treatment might then result in poorer overall survival, as previously reported (Brule et al., 2016). Much of the existing literature supporting the use of physical performance tests in predicting cancer-related outcomes have looked at survival (Brown et al., 2015, Ward et al., 2014, Hamaker et al., 2014), but to the best of our knowledge this is the first study to prospectively assess the role of the SPPB in predicting receipt and successful completion of treatment in lung cancer patients.

Our most significant findings were that SPPB total scores, in contrast to non-predictive values of muscle mass, were predictive of completion of a higher number of cycles of chemotherapy, completion of 3 or more cycles of chemotherapy, and successful completion of the chemotherapy course. In terms of the components of the SPPB, higher sit-to-stand category values and gait speed ≥0.8 m/sec were associated with completion of 3 or more cycles of chemotherapy. Together, this may suggest a link between observed task performance and an underlying physical resilience to withstand treatment. A recently published study of 413 older cancer survivors also used SPPB to assess survival outcomes over time. It found that older cancer survivors with low total SPPB and gait speed scores had

increased all-cause mortality relative to their counterparts with high scores. Furthermore, each unit increase in SPPB score predicted a 12% reduction in mortality (Brown et al., 2015).

Our smaller study in a population receiving palliative chemotherapy had similar findings, where for every unit increase in SPPB score, there was a 28% decrease in adverse events, hospitalisations and delays of chemotherapy. We found that the highest SPPB score category was significantly predictive of fewer adverse events including hospitalisation, delays of chemotherapy and associated toxicities. The fact that physician-rated PS, the currently used gold standard marker of fitness for withstanding treatment, was not predictive of completion of treatment or adverse events was in contrast to the positive association between high SPPB score and completion of more cycles of chemotherapy, as well as fewer adverse events. This, again, highlights the potential of the SPPB as a clinical tool in the pre-treatment evaluation of patients with NSCLC, and suggests the need for a larger study with appropriate power to validate these findings.

It seemed timely to test the predictive value of physical performance in lung cancer, utilising SPPB – a responsive and reliable test which was created for and validated in the elderly population (Freiberger et al., 2012). The fact that SPPB was significantly associated with chemotherapy completion and adverse events was interesting as the mean age of all our participants, and those planned for palliative chemotherapy only, was 67.5 and 64.4 respectively. Although it is a reliable and valid test of physical performance in older people, the SPPB has not been much used in patients of all ages. The utility and validity of SPPB as a routinely performed test in the diagnostic work-up in lung cancer, would be an appropriate future step.

Muscle mass depletion is reported in the literature to be associated with increased frequency of chemotherapy toxicity, as discussed in Chapter 4. However, whilst this seems to be the case in a variety of solid tumour groups – gastrointestinal, breast and renal cancers

(Chemama et al., 2016, Cushen et al., 2014, Shachar et al., 2017) – there are few data to support this in lung cancer patients. In fact, one article published recently showed no conclusive association between muscle mass depletion (characterised by CT), and chemotoxicity, in NSCLC patients (Srdic et al., 2016). There may be many reasons for little data to support muscle mass depletion being associated with adverse chemotherapy events. Firstly, different chemotherapeutic regimens, with differing pharmacokinetic and toxicity profiles are used in different tumour types. Secondly, treatment in NSCLC tends to be palliative rather than neoadjuvant or adjuvant. Lastly, it may be that patients with NSCLC differ from other solid cancer groups in their body composition or physical function decline, prior to overt loss of muscle mass. It is also worth noting that these studies have very small numbers (typically n<150). A larger, appropriately powered study evaluating the value of SPPB in NSCLC, alongside or instead of muscle mass, may provide a clearer picture of its predictive potential.

Although the SPPB seems to be a promising test in terms of prediction of completion of chemotherapy, when tested against all MDT-planned treatment types, including surgery with curative intent and radical radiotherapy, it failed to show any clear association with receipt or completion of treatment. It may be that the SPPB is better suited to patients with more advanced disease being treated with palliative intent. More traditional prognostic markers such as weight loss and ECOG PS were also not predictive of chemotherapy completion and adverse events in our small cohort. Overall, the SPPB, as an easily applied clinical measure, appears to be a better indicator of tolerance of palliative chemotherapy than body composition parameters alone, and may highlight targets for functional intervention earlier than weight loss alone.

Previous reports have found that physical performance declines during the course of chemotherapy in advanced lung cancer (Kasymjanova et al., 2009, Shallwani et al., 2016), and

there is mounting interest in the benefits of structured exercise, prior to or alongside

systemic treatment, including in those with advanced disease (Bade et al., 2015). The uptake

rate of prescribed exercise in lung cancer has been traditionally poor (Granger et al., 2013,

Granger et al., 2017), and while the reasons behind this may be multifactorial, a key question

should be what patients' baseline physical performance is. Tailored exercise regimes may be

more suitable, compared to a `one size fits all' approach. The results of our study bring a new

dimension to this notion, where the value of baseline physical performance in predicting

important outcomes related to chemotherapy is underlined.

This exploratory study highlights the fact that the current focus on survival must be

broadened to incorporate reasons for non-receipt and non-completion of systemic

treatment, and include predictive factors for the same. Going forward, our results show that

SPPB has potential as a pre-diagnostic test in the work-up to treatment in NSCLC. This finding

is similar to that seen with other elderly care tests such as the Comprehensive Geriatric

Assessment (CGA), which has been shown in Phase III trials in NSCLC to have superior

predictive value for chemotherapy toxicity, compared with PS and age alone (Corre et al.,

2016). Other assessments in cancer patients in general, including assessment of activities of

daily living and of frailty, have also been found to be predictive of completion of

chemotherapy and mortality, regardless of PS (Hamaker et al., 2014, Hamaker et al., 2012).

While a case can be made for utilising many tests in this setting, important test characteristics

should be ease of use and validity for important outcomes.

The SPPB is a much quicker test than CGA, and warrants testing in a similar scenario,

in order to prove its worth. The SPPB is reported to be predictive of survival in other cancer

groups (Cesari et al., 2013, Klepin et al., 2013, Verweij et al., 2016), but not specifically in

NSCLC. Understanding any associations between SPPB at baseline and prognosis will be of

benefit whilst making treatment decisions within the MDT. This test needs to be validated in

a larger cohort, with sequential measurements taken over time to enable longitudinal

analysis. Evaluating its worth in terms of prognosis is also desirable, therefore future work

should include whether there is any relationship between SPPB and survival.

6.5 CONCLUSION

A greater understanding of the baseline physical function of patients who are most

likely to have chemotherapy-related adverse events, and declining physical function

throughout the treatment course, will be valuable to the MDT. The SPPB is an objective test

of physical performance, and is simple, quick to perform and may have predictive value in

NSCLC. The fact that baseline SPPB scores were associated with adverse events during

chemotherapy including number of hospitalisations, provide early insight into some

uncertainty surrounding patient optimisation for treatment.

Chapter 7: Performance status as a predictor of treatment delivery in NSCLC patients.

7   CHAPTER 7: PERFORMANCE STATUS AS A PREDICTOR OF TREATMENT DELIVERY IN NSCLC PATIENTS.

7.1   INTRODUCTION

Performance status (PS) is a well-recognised prognostic tool, guiding the multidisciplinary team (MDT) in its decision treatment decision-making. Patient-reported outcome measures (PROMs), of which quality of life (QoL) scores are the most widely used , also have predictive value (Montazeri et al., 2001). QoL – a well-established method of measurement of physical function – significantly predicts survival, prompting suggestions that patient-rated data provide more sensitive prognostic information than physician-rated PS (Montazeri, 2009, Gotay et al., 2008). Patient-rated ECOG and Karnofsky PS, as well as other patient-rated scales of physical performance and ambulation have even been found to outperform clinician-rated PS in terms of predicting rate of decline and survival (Gotay et al., 2008, Suh et al., 2011). This raises the question of whether they might also be useful in predicting the delivery of chemotherapy.

The main endpoint in the literature evaluating PS as a predictive factor is survival (Suh et al., 2011, Ando et al., 2001). Whilst this is undoubtedly important, it is also useful to ascertain if PS has any bearing on treatment delivery. Receipt and completion of treatment as endpoints in themselves could allow stratification of patients according to fitness levels, enabling better informed treatment decisions, especially given the context of non-small cell lung cancer (NSCLC), where patients not uncommonly present with advanced disease. In addition, patient-rated PS may provide added accuracy and prognostic information over clinician-rated PS with regards to their projected ability to undertake and complete MDT-planned treatment.

7.2   METHODS, PARTICIPANTS AND STATISTICAL TECHNIQUES

Recruitment of the study's participants, together with methods and statistical techniques are presented in detail in Chapter 3. In this chapter we focus on both ECOG and Karnofsky physician-rated and patient-rated PS of all recruited participants (n=86), as well as in the subset who were subsequently diagnosed with NSCLC (n=62). In the latter group, we evaluated whether any PS was able to predict receipt and completion of MDT-planned treatment (where n=58 as 4 participants declined treatment).

As stated in Chapter 3,` receipt of treatment' means receipt of planned surgical procedure; receipt of the first dose of planned radiotherapy; or receipt of the first cycle of the planned chemotherapy course. `Completion of treatment' means completion of the planned surgical procedure; or completion of planned fractions of radiotherapy; for chemotherapy, `completion of chemotherapy' means completion of the planned course of chemotherapy, which is usually 3 or 4 cycles. Completion of chemotherapy was confirmed (Yes/No) jointly by the treating Oncologist and Palliative Care physician.

7.3   RESULTS

7.3.1   Performance Status of all recruited participants

The initial 86 participants recruited into the study, prior to diagnosis of NSCLC, are presented descriptively in Table 4.1 in Chapter 4. Here, we present agreement between physician and patient-rated scores for ECOG (Table 7.1) and Karnofsky (Table 7.2) for all study participants presenting to the RALCC. In both cases, agreement was poor, with kappa statistics of 0.275 and 0.172 respectively.

	Patient-rated ECOG score, n	0	1	2	3	4
Physician-rated ECOG score, n	0	18	7	0	1	0
	1	12	9	6	4	1
	2	3	4	14	7	0

Table 7.1: Agreement in assessment of ECOG PS between patients and physicians, n=86; kappa statistic 0.275.

	Patient-rated Karnofsky score, n	50	60	70	80	90	100
Physician-rated Karnofsky score, n	60	1	0	1	0	0	0
	70	1	2	5	6	2	0
	80	1	3	2	5	1	1
	90	0	2	2	7	11	11
	100	0	0	0	1	4	5

Table 7.2: Agreement in assessment of Karnofsky PS between patients and physicians, n=74 as 12 missing values for Karnofsky data among all participants; kappa statistic 0.172.

7.3.2   Performance Status of those with NSCLC

Amongst the 62 participants diagnosed as having NSCLC, the difference between physician and patient scores were not significantly skewed to a preference for physicians scoring patients higher or lower, and vice versa. Among the ECOG scores, 31 of 62 (50%) participants scored themselves the same as the physician. Of the other participants, almost equal numbers scored lower and higher than the physician (15 and 16 respectively). There

were 9 fewer paired values for Karnofsky scores, but of the 53 scores from both NSCLC

patient and physician, there were almost equal proportions of participants scoring

themselves greater than, less than, and equal to physician scores (18, 17 and 18 respectively)

(Table 7.3).

	Physician score > patient, n (%)	Physician score = patient, n (%)	Patient score > physician, n (%)	Significance level
ECOG	15 (24.2)	31 (50)	16 (25.8)	0.724
Karnofsky	18 (33.9)	18 (33.9)	17 (32.1)	0.534

Table 7.3: Difference between physician-patient scores, Wilcoxon signed ranks test, n=62; 9 missing values for Karnofsky data among NSCLC participants only.

In terms of correlation between physician ECOG and Karnofsky scores, as well as

patient ECOG and Karnofsky scores, these were highly correlated (Spearman's rho -0.79 and -

0.828, both p<0.001). This was expected as each set of ECOG and Karnofsky scores, was

collected from the same physician and the same participant, i.e. choosing a higher

functioning (lower) score for ECOG meant that one was likely to choose a higher functioning

(higher) score for Karnofsky.

Predictor variables	Receipt of MDT planned treatment, p-value	Successful completion of MDT planned treatment, p-value
Physician ECOG score	0.236	0.142
Physician Karnofsky score	0.869	0.264
Patient ECOG score	0.063	0.007*
Patient Karnofsky score	0.521	0.625

*Table 7.4: p-values of Fisher's exact and chi-squared tests of associations between physician- and patient-rated PS and receipt and completion of MDT-planned treatment in 58 NSCLC participants. *Denotes significance at the 95% confidence level.*

While physician-rated ECOG and Karnofsky and patient-rated Karnofsky scores showed no association with receipt and completion of treatment (Table 7.4), when tested with chi-squared test the patient-rated ECOG PS was significantly associated with successful completion of treatment (p=0.007). However, it was difficult to quantify the value of this significance, given that the chi-squared test can only show an association, hence we can only present this finding as tentative.

7.3.3   Performance Status of those planned for chemotherapy only

Predictor variables	Receipt of chemotherapy treatment, p-value	Successful completion of chemotherapy, p-value
Physician ECOG score	0.100	0.446
Physician Karnofsky score	1.000	0.316
Patient ECOG score	0.192	0.087
Patient Karnofsky score	0.221	0.158

Table 7.5: p-values of Fisher's exact and chi-squared tests of associations between physician- and patient-rated PS and receipt and successful completion of chemotherapy course in 24 participants.

Out of our main cohort of participants, 24 were specifically planned for chemotherapy, and 2 for chemo-radiotherapy. Of the chemotherapy group, 2 participants declined, therefore 24 in total were analysed for outcomes of interest. There was no association between all PS scores, rated by physician or patient, and receipt or completion of chemotherapy (Table 7.5).

7.4 DISCUSSION

An accurate baseline assessment of physical function is essential in treatment decision-making for patients diagnosed with malignancy. In lung cancer, curative treatment options are reserved for fit patients with early stage disease. Similarly, those with advanced disease have the option of systemic anti-cancer treatment only if their fitness allows. Whilst PS is the mainstay of cancer MDTs in assessing physical performance, the fact that some patients with good baseline PS do not go on to receive nor to complete treatment warrants investigation.

As mentioned in greater detail in Chapter 6, the SPPB is a test which is validated in older people and not widely used in cancer populations. There were a few important reasons why we chose to evaluate the role of SPPB alongside subjective routine PS scores, in this cohort. A good proportion of patients who have lung cancer are older people, with a median age of 70 at diagnosis (Howlader et al., April 2016). Even in patients with good PS, geriatric impairments such as cognitive impairment, malnutrition and decreased mobility are prevalent and have prognostic significance (Schulkes et al., 2016), and geriatric assessment (GA) is reported to be able to detect deficiencies which are not reflected in ECOG PS. This has led to previous guidance from the International Society for Geriatric Oncology for GA to be implemented for all older patients with cancer (Extermann et al., 2005). While previous studies have evaluated GA alongside PS (Schulkes et al., 2016), there is much heterogeneity of data and varied use of GA domains. These domains include activities of daily living (ADL), cognition, and objective physical performance. We showed, in Chapter 5, that physical performance as assessed by SPPB was associated with completion of completion of chemotherapy, and predictive of chemotherapy-associated adverse events.

In this chapter, the main finding was that, in contrast to SPPB having some value in predicting completion of treatment, physician-assessed PS was not associated with receipt or

completion of any mode of treatment. Although this was not a statistically significant finding, it was a notable outcome because it was negative. As PS is used as a key part of the MDT decision-making process, one would expect PS to be able to predict whether patients are fit enough to start treatment, and having started treatment, to withstand the course. We found this not to be the case; but on the other hand, finding that the SPPB was able to predict chemotherapy completion was intriguing. While a larger study with appropriate power might be able to definitively state the utility of both PS and SPPB in predicting receipt and completion of treatment, these early findings provide some insight and credence to using objective tests of physical performance in the work-up to diagnosis in NSCLC.

While both PS scores assessed by physician and patient did not show an association with chemotherapy receipt and completion, we did find a tentative association between patient-rated ECOG PS and completion of MDT-planned treatment. However, the strength of this correlation could not be established. Therefore, at present, this link remains theoretical and should be clarified with a larger, appropriately powered study, which could be reasonably performed as part of the validation of the role of SPPB in receipt and completion of treatment.

As previously suggested, there may be better tests that outperform physician-assessed PS (Sonpavde et al 2012), and patient-rated PS may represent a simple candidate to this suggestion, if it can be shown more robustly that it is a predictor of treatment-related outcomes. Completion of planned treatment results in reduced disease progression and ultimately improved survival (Fry et al., 1999, Non-Small Cell Lung Cancer Collaborative Group, 2010), highlighting the importance of completion of treatment as a crucial endpoint in itself. Very few previous studies have looked at similar variables – only one reported that better ADL and physical functioning scores were predictive of completion of chemotherapy (Biesma et al., 2011). This tentative data suggest that there is a role for additional

information, particularly related to physical performance, alongside PS in the work-up of patients with lung cancer.

The fact that physician-assessed PS is an outsider's appraisal of a one's physical abilities is what makes it so subjective. Overestimation of patients' PS by physicians is a well-recognised phenomenon (Schnadig et al., 2008, Loprinzi et al., 1994). The patient who spends most of their waking hours in a chair and is largely housebound, but manages to attend clinic well-dressed may give the impression of being PS2 but in reality be PS3 or worse. This can produce the result that many patients with seemingly good baseline PS are deemed unfit to commence treatment, just a few days or weeks later (Vinod et al., 2008). In our cohort, we found that physician-patient agreement was poor for both ECOG and Karnofsky scales (kappa statistic 0.275 and 0.172). However, there was no significant tendency for physicians to over- or underestimate scores based on patients' ratings of themselves.

Karnofsky PS was not significantly associated with completion of treatment, despite ECOG and Karnofsky being highly correlated. While the Karnofsky score is said to be a more sensitive measure of PS , as there are more levels of function, it may be that the simpler 5-point ECOG score is a more accurate predictor as there are less options and thereby less confusing for patients. Furthermore, the patient is the best judge of their own status and therefore the test that they understand best is likely to most accurately reflect their judgement. In our study, it was also noteworthy that although physicians and patients disagreed on PS, there was no overall trend for over- or underestimation. This suggests a consistency in judgment of physical function on the part of the physicians, with no particular bias either way – although the accuracy with which they predict PS based on patients' own judgments is still poor.

There were several limitations of this study. Amongst other things, this was a small cohort (total n=86, total NSCLC=62) with a preponderance of men (64%).Furthermore, our

exclusion of those with physician-rated PS 3-4 could have precluded a more robust

interpretation of physician-patient agreement of scores. Having PS 3-4 participants would not

only have improved the interpretation of physician-patient agreement, but also enabled

correlation between PS, muscle mass and SPPB. Furthermore, the superiority of ECOG

compared with Karnofsky in predicting receipt and completion of treatment was not able to

be established. Having all ECOG PS scores of participants might have allowed more

comprehensive interpretation of this. Although most PS 3-4 patients have best supportive

care, some PS 3 patients may have systemic anticancer treatment and again, it would be

interesting to see how PS correlated with receipt and completion of treatment. Nevertheless,

we were able to collect prospective, baseline PS information in `real time' i.e. when patients

first presented to clinic. This would prevent time biases in that patients' own recording of

their PS would be the same time as that recorded by physicians, giving a truer baseline

picture.

7.5 CONCLUSION

In conclusion, our significant finding was that the current best practice tool of

physician-rated PS was tentatively predictive of receipt of chemotherapy, however it was not

predictive of receipt or completion of all modalities of MDT-planned treatment in NSCLC. To a

lesser extent, patient-rated PS may also tentatively offer some predictive value, however this

requires appropriately powered studies to further define this concept, with longitudinal PS

measurements and survival analysis.

Chapter 8: Discussion and Future Work

CHAPTER 8   DISCUSSION AND FUTURE WORK

The overall aim of the thesis was to evaluate the predictive value of muscle mass and physical performance measurements in terms of receipt and completion of planned MDT treatment, in NSCLC.

The results of the work presented in this thesis demonstrated that physical performance, as assessed by SPPB at presentation, may be predictive of completion of more cycles of palliative chemotherapy, in those planned for this treatment. It may also be able to identify those at risk of developing chemotherapy-associated toxicities, hospitalisations and delays of treatment in this group. As there is no precedent with the use of SPPB in non-curative NSCLC patients, particularly in predicting treatment-related outcomes, our results provide a tentative framework on which future work can be based.

One of our main findings was that physician-rated PS was poorly correlated with patient-rated PS, and that physician-rated PS was not consistently predictive of treatment outcomes. These are important findings, as they highlight the potential ineffectiveness of PS in predicting treatment receipt and completion. This is in keeping with previous literature that reported that some patients with lung cancer with good PS were not receiving treatment, due to declining physical function (Vinod et al., 2010). The ability to predict treatment delivery has considerable value, as treatment for lung cancer is time-consuming, arduous, and costly. In the case of chemotherapy for palliative patients, it may mean a poorer quality of life whilst on treatment, as well as a high risk of toxic side effects. Therefore, the decision to treat patients with cancer, particularly incurable NSCLC should not be taken lightly. The finding that PS is insufficient in predicting patients' ability to receive, and complete treatment is important as currently it is the only marker of patients' fitness used

within the MDT in deciding treatment allocation. Within oncology settings in older people, it

is increasingly recognised that PS is an inadequate predictor of chemotherapy toxicity. For

example, a study in 500 older adults with a range of solid tumours, there was no significant

difference in chemotherapy toxicity across the Karnofsky PS-based risk groups, in contrast to

a predictive model with geriatric assessment questions which was predictive (Hurria et al.,

2011). This suggests that objective tests of physical performance are required in order to

gauge one's fitness levels, in planning fitness for treatment, and PS remains an imperfect

measure.

Appropriate decisions regarding treatment allocation are especially crucial in patients

deemed to have borderline fitness (PS 2) and being considered for treatment with palliative

intent. In these cases, additional information which could give a better picture of the

likelihood of receipt and completion of treatment and its tolerance, and enable more frank

discussions during decision making, for both patient and physician. Our tentative finding that

patient-rated PS may have an association with completion of treatment was surprising and

may be a line of enquiry within a larger study, in an age where shared decision making is

identified as a key element in patient-centred care (Hawley and Jagsi, 2015, Levit et al., 2013).

While there is a substantial evidence base for the use of ECOG PS in predicting

mortality in patients with cancer, less is known about its efficacy at predicting treatment-

related outcomes, such as receipt and completion of treatment, and the likelihood of patients

struggling during treatment. A more objective measure of physical performance is welcome

and one that is able to predict treatment-related outcomes would be even better. Our finding

that SPPB may be able to identify the patient group which are more likely to complete

chemotherapy, compared to PS, is therefore of interest.

SPPB is a test which originated and was validated in the elderly population. The test

components reflect this, as they assess balance, lower limb strength and endurance, and gait

speed – all of which decline with age (Samson et al., 2000, Skelton et al., 1994, Balogun et al., 1994). Our observation that it seems to be predictive of completion of more cycles of chemotherapy and of adverse events, but not other treatment modalities, is interesting. It may reflect that palliative NSCLC patients, whether elderly or not, may have declines in physical performance measures, even at first presentation, and that these measures may determine how well they do with chemotherapy. Furthermore, the fact that our cohort was considered fit enough to undergo chemotherapy in the first place, but PS was not predictive of the same outcomes, underlines the fact that SPPB or similar tests of objective physical performance may be more predictive.

There is increasing interest in geriatric oncology settings to improve the predictability of physical parameter scoring systems used pre-treatment. For example, the cancer and aging research group (CARG) and chemotherapy risk assessment scale for high-risk patients (CRASH) scores were created as risk stratification schemas for vulnerability to chemotherapy toxicity (Kelly and Shahrokni, 2016). Both these scoring systems incorporated geriatric assessment parameters of physical function – the CARG used a comprehensive tool comprising activities of daily living (ADL), instrumental activities of daily living (IADL) and social activity and support survey (Hurria et al., 2011). The CRASH assessed function using IADL, cognition, and depression scales (Extermann et al., 2012). While it is very commendable that clinicians are recognising the importance of traditional geriatric assessment in cancer patients, particularly as lung cancer remains a disease predominantly of older people, our study is unique in that the SPPB has predictive ability on its own, compared with multiple assessments. Furthermore, our finding that SPPB may be predictive not only of chemotherapy adverse events, but also completion of the chemotherapy course, adds another dimension to the argument. Finally, we found the effect to be valid not only in elderly patients, but in a wider age-range of patients; while the mean age of our lung cancer

cohort was 68.2 years, a significant proportion of NSCLC participants were under the age of 65 (41.9%).

Almost half of all new cases of lung cancer diagnosed in the UK between 2012-2014 were in patients aged 75 and older (Cancer Research UK). This makes lung cancer a disease of predominantly older people (British Lung Foundation). Elderly people tend to have more co-morbidities, as well as physiological age-related declines in muscle strength and functional abilities. Having said this, the mean age of our cohort of participants planned for palliative chemotherapy was 64.4 years. This reflects the fact that we only recruited participants with PS2 and below, and it would be reasonable to expect that the younger the patient, the more likely they might be active and mobile, hence the assignation of a good to moderate PS. Our participants were younger than the average patient with NSCLC, which in the UK is 80 years (British Lung Foundation). Therefore it was intriguing to find that SPPB, which is a test validated in older people, was able to predict completion of palliative chemotherapy in this group. A comparison is made between palliative NSCLC patients and elderly patients' SPPB scores, regardless of age, but in order to clarify this, more robust analyses need to be performed controlling for age and co-morbidities.

In contrast, we did not find any association between muscle mass, specifically sarcopenia, and receipt and/or completion of MDT-planned treatment as well as chemotherapy. Perhaps the main reasons for this might be the use of BIA, rather than CT, to assess muscle mass, and a relatively small sample size. However, a consideration is that much of what we know currently about sarcopenia in NSCLC is that i) only muscle mass is measured, with no accounting for physical performance or muscle strength, and ii) outcomes are measured largely in terms of survival. Our study has shown that measuring physical performance may be a useful parameter, compared with muscle mass, particularly in predicting treatment-related outcomes in palliative chemotherapy patients. Moreover, low

muscle mass may be predictive of survival in many cancer-specific groups, including lung

cancer (Martin et al., 2013), but its ability to predict receipt and completion of treatment is

unclear. Therefore, whilst we were unable to demonstrate conclusively that muscle mass had

any relationship with receipt or completion of treatment, there may still be a case for

measuring muscle mass in NSCLC, particularly in predicting prognosis. For the present, the

role of sarcopenia in association with treatment delivery remains to be seen. Standardisation

of methods, cut-offs and diagnostic criteria for defining sarcopenia in cancer will also go a

long way to increase understanding of this important disease process.

It was also interesting that we found the biomarkers CRP and albumin, and weight

loss of 10% or more to have some significance in prediction of either receipt or completion of

treatment. However, none of these parameters showed consistent associations, and this may

have been due to small numbers of participants. Our findings in this exploratory study is in

keeping with the literature, which has reported that systemic inflammation and poor

nutritional state predicts survival (Tewari et al., 2007, Laird et al., 2013).

In terms of bringing all this together, a larger adequately powered study in which

each of these parameters are investigated, separately or in combination, with the addition of

longitudinal analyses, would be ideal to enable a risk stratification model to be created. This

concept is similar to that of targeted treatment to changes in genetic products (referred to as

signature biomarkers) in cancer-specific groups, to enable prediction of response to

treatment (Nicolaides et al., 2014). For future longitudinal analyses, it would also be

interesting to evaluate the change in SPPB, or other parameters of interest, after a first cycle

of treatment, and whether it is able to predict completion of a full course of treatment. In

addition, while others have studied systemic inflammation in cancer, and its relationship to

patient-rated measures of physical function (Laird et al., 2011), it would be of interest to

study the relationship between SPPB, as an objective measure of physical performance, and systemic inflammation over the course of chemotherapy.

The main limitation of our study was the small sample size. This meant that some significant associations may have been missed, and in a similar vein, associations found might have been overestimated. Determination of an appropriate sample size for this study was not possible at the outset as there were no relevant published data on which to base power calculations. One outcome of this exploratory study is that it will facilitate sample size calculations for future study designs with adequate robustness to make recommendations regarding measurable parameters that predict the implementation of MDT-planned treatment. With this in mind, power calculations have been performed to power a study focussing on the role of SPPB in predicting completion of 3 or more cycles of chemotherapy. It is envisaged that there will be good power to detect an effect of an estimated odds ratio of 1.7, at the 95% confidence level, with a sample size of 300 participants.

Another limitation was our inability to perform multivariate analysis, due to a small sample size. Whilst performing univariate analyses, we found multiple associations between parameters and outcome measures of interest. However, it was not possible to account for the effect of predictor variables on each other, and prove independence between variables. There might also have been relationships between the variables themselves which we failed to detect.

A further practical limitation was the fact that although we recruited 86 participants, only 62 were subsequently diagnosed with NSCLC and eligible for analysis. This was a potential inadequacy in the study design, as the data of a proportion of participants was frustratingly unused. While we were able to recruit participants prior to a confirmed diagnosis of NSCLC, and therefore capture true baseline data, the drawback of this was a loss of follow-up later of participants who did not turn out to have NSCLC. In future, this needs to

be considered at the study design stage in order to minimise participants who will be lost to follow up and definitive analysis.

Another practical limitation was that this exploratory study was undertaken in a single centre. Therefore, assessments used may not be representative of the entire population and a larger study with a wider selection of recruitment sites would give a more illustrative picture. Whilst this study was conducted in NSCLC patients, it may not be possible to extrapolate the findings may to other tumour types, for example, or indeed to NSCLC patients in different geographical contexts. Our conclusions therefore need to be considered within the context of the population studied.

Going forward, our results show that SPPB has promise as a pre-diagnostic test in the work-up to treatment in NSCLC. Our finding that SPPB may be of benefit in this process is similar to that seen with other elderly care tests such as the Comprehensive Geriatric Assessment (CGA). It has been shown in Phase III trials in NSCLC to be a have superior predictive value of chemotherapy toxicity, compared with PS and age alone (Corre et al., 2016). Other assessments in cancer patients in general, including assessment of activities of daily living and frailty have also been found to be predictive of completion of chemotherapy and mortality, regardless of PS (Hamaker et al., 2014, Hamaker et al., 2012). While a case can be made for utilising many tests in this setting, important test characteristics should be ease of use and validity for important outcomes.

The SPPB is much shorter a test than the CGA, and warrants testing in a similar context, in order to assess its worth adequately. The SPPB is reported to be predictive of survival in other cancer groups (Cesari et al., 2013, Klepin et al., 2013, Verweij et al., 2016), but not specifically in NSCLC. Understanding any associations between SPPB at baseline and prognosis will be of benefit whilst making treatment decisions within the MDT. This test needs to be validated in a larger cohort, with sequential measurements taken over time to

enable longitudinal analysis. Evaluating its worth in terms of prognosis is also desirable,

therefore future work should include whether there is any relationship between SPPB and

survival, as well as with the delivery of treatment plans recommended by the MDT. It is

hoped that such studies will make a significant contribution to advances in treatment

decision-making which enable optimisation of the benefits of treatment for lung cancer

patients.

REFERENCES

ABBOTT, J., TELENI, L., MCKAVANAGH, D., WATSON, J., MCCARTHY, A. L. & ISENRING, E. 2016. Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) is a valid screening tool in chemotherapy outpatients. *Support Care Cancer,* 24**,** 3883-7.

ADLER, I. 1912. *Primary malignant growths of the lungs and bronchi: a pathological and clinical study,* New York Longmans, Green and Co.

AGTERESCH, H. J., RIETVELD, T., KERKHOFS, L. G., VAN DEN BERG, J. W., WILSON, J. H. & DAGNELIE, P. C. 2002. Beneficial effects of adenosine triphosphate on nutritional status in advanced lung cancer patients: a randomized clinical trial. *J Clin Oncol,* 20**,** 371-8.

AJANI, J. A., IZZO, J. G. & LEE, J. S. 2009. Chemotherapy and radiotherapy resistance: complexity, reality, and promise. *J Clin Oncol,* 27**,** 162-3; author reply 163.

ALLEMANI, C., WEIR, H. K., CARREIRA, H., HAREWOOD, R., SPIKA, D., WANG, X. S., BANNON, F., AHN, J. V., JOHNSON, C. J., BONAVENTURE, A., MARCOS-GRAGERA, R., STILLER, C., AZEVEDO E SILVA, G., CHEN, W. Q., OGUNBIYI, O. J., RACHET, B., SOEBERG, M. J., YOU, H., MATSUDA, T., BIELSKA-LASOTA, M., STORM, H., TUCKER, T. C. & COLEMAN, M. P. 2015. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet,* 385**,** 977-1010.

ANDO, M., ANDO, Y., HASEGAWA, Y., SHIMOKATA, K., MINAMI, H., WAKAI, K., OHNO, Y. & SAKAI, S. 2001. Prognostic value of performance status assessed by patients themselves, nurses, and oncologists in advanced non-small cell lung cancer. *Br J Cancer,* 85**,** 1634-9.

ANKER, S. D., MORLEY, J. E. & VON HAEHLING, S. 2016. Welcome to the ICD-10 code for sarcopenia. *J Cachexia Sarcopenia Muscle,* 7**,** 512-514.

ANTOUN, S., BARACOS, V. E., BIRDSELL, L., ESCUDIER, B. & SAWYER, M. B. 2010. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. *Ann Oncol,* 21**,** 1594-8.

ARGILES, J. M., BUSQUETS, S., FELIPE, A. & LOPEZ-SORIANO, F. J. 2005a. Molecular mechanisms involved in muscle wasting in cancer and ageing: cachexia versus sarcopenia. *Int J Biochem Cell Biol,* 37**,** 1084-104.

ARGILES, J. M., BUSQUETS, S., GARCIA-MARTINEZ, C. & LOPEZ-SORIANO, F. J. 2005b. Mediators involved in the cancer anorexia-cachexia syndrome: past, present, and future. *Nutrition,* 21**,** 977-85.

ARRIETA, O., DE LA TORRE-VALLEJO, M., LOPEZ-MACIAS, D., ORTA, D., TURCOTT, J., MACEDO-PEREZ, E. O., SANCHEZ-LARA, K., RAMIREZ-TIRADO, L. A. & BARACOS, V. E. 2015. Nutritional Status, Body Surface, and Low Lean Body Mass/Body Mass Index Are Related to Dose Reduction and Severe Gastrointestinal Toxicity Induced by Afatinib in Patients With Non-Small Cell Lung Cancer. *Oncologist,* 20**,** 967-74.

ATTAIX, D. & BECHET, D. 2007. FoxO3 controls dangerous proteolytic liaisons. *Cell Metab,* 6**,** 425-7.

ATTAR, A., MALKA, D., SABATE, J. M., BONNETAIN, F., LECOMTE, T., APARICIO, T., LOCHER, C., LAHARIE, D., EZENFIS, J. & TAIEB, J. 2012. Malnutrition is high and underestimated during chemotherapy in gastrointestinal cancer: an AGEO prospective cross-sectional multicenter study. *Nutr Cancer,* 64**,** 535-42.

AUBREY, J., ESFANDIARI, N., BARACOS, V. E., BUTEAU, F. A., FRENETTE, J., PUTMAN, C. T. & MAZURAK, V. C. 2014. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. *Acta Physiol (Oxf),* 210**,** 489-97.

AUYEUNG, T. W., LEE, S. W., LEUNG, J., KWOK, T. & WOO, J. 2014. Age-associated decline of muscle mass, grip strength and gait speed: a 4-year longitudinal study of 3018 community-dwelling older Chinese. *Geriatr Gerontol Int,* 14 Suppl 1**,** 76-84.

BADE, B. C., THOMAS, D. D., SCOTT, J. B. & SILVESTRI, G. A. 2015. Increasing physical activity and exercise in lung cancer: reviewing safety, benefits, and application. *J Thorac Oncol,* 10**,** 861-71.

BALOGUN, J. A., AKINDELE, K. A., NIHINLOLA, J. O. & MARZOUK, D. K. 1994. Age-related changes in balance performance. *Disabil Rehabil,* 16**,** 58-62.

BARACOS, V. & KAZEMI-BAJESTANI, S. M. 2013. Clinical outcomes related to muscle mass in humans with cancer and catabolic illnesses. *Int J Biochem Cell Biol,* 45**,** 2302-8.

BARACOS, V. E., REIMAN, T., MOURTZAKIS, M., GIOULBASANIS, I. & ANTOUN, S. 2010. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am J Clin Nutr,* 91**,** 1133S-1137S.

BARRET, M., ANTOUN, S., DALBAN, C., MALKA, D., MANSOURBAKHT, T., ZAANAN, A., LATKO, E. & TAIEB, J. 2014. Sarcopenia is linked to treatment toxicity in patients with metastatic colorectal cancer. *Nutr Cancer,* 66**,** 583-9.

BAUMGARTNER, R. N., KOEHLER, K. M., GALLAGHER, D., ROMERO, L., HEYMSFIELD, S. B., ROSS, R. R., GARRY, P. J. & LINDEMAN, R. D. 1998. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol,* 147**,** 755-63.

BECKETT, P., WOOLHOUSE, I., STANLEY, R. & PEAKE, M. D. 2012. Exploring variations in lung cancer care across the UK--the 'story so far' for the National Lung Cancer Audit. *Clin Med,* 12**,** 14-8.

BELAND, F. & POIRIER, M. 1994. *Methods to assess DNA damage and repair : interspecies comparisons / edited by Robert G. Tardiff, Paul H. M. Lohman, Gerald N. Wogan ; prepared by Scientific Group on Methodologies for the Safety Evaluation of Chemicals (SGOMSEC),* Chichester [England] ; New York, J. Wiley.

BENNANI-BAITI, N. & WALSH, D. 2011. Animal models of the cancer anorexia-cachexia syndrome. *Support Care Cancer,* 19**,** 1451-63.

BERENSTEIN, E. G. & ORTIZ, Z. 2005. Megestrol acetate for the treatment of anorexia-cachexia syndrome. *Cochrane Database Syst Rev***,** CD004310.

BERGER, M., LUND, M. J. & BRAWLEY, O. W. 2007. Racial disparities in lung cancer. *Curr Probl Cancer,* 31**,** 202-10.

BERRINO, F., DE ANGELIS, R., SANT, M., ROSSO, S., BIELSKA-LASOTA, M., COEBERGH, J. W. & SANTAQUILANI, M. 2007. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study. *Lancet Oncol,* 8**,** 773-83.

BERRY, M. F., HANNA, J., TONG, B. C., BURFEIND, W. R., JR., HARPOLE, D. H., D'AMICO, T. A. & ONAITIS, M. W. 2009. Risk factors for morbidity after lobectomy for lung cancer in elderly patients. *Ann Thorac Surg,* 88**,** 1093-9.

BEUMER, J. H., CHU, E. & SALAMONE, S. J. 2012. Body-surface area-based chemotherapy dosing: appropriate in the 21st century? *J Clin Oncol,* 30**,** 3896-7.

BIESMA, B., WYMENGA, A. N., VINCENT, A., DALESIO, O., SMIT, H. J., STIGT, J. A., SMIT, E. F., VAN FELIUS, C. L., VAN PUTTEN, J. W., SLAETS, J. P. & GROEN, H. J. 2011. Quality of life, geriatric assessment and survival in elderly patients with non-small-cell lung cancer treated with carboplatin-gemcitabine or carboplatin-paclitaxel: NVALT-3 a phase III study. *Ann Oncol,* 22**,** 1520-7.

BLAGDEN, S. P., CHARMAN, S. C., SHARPLES, L. D., MAGEE, L. R. & GILLIGAN, D. 2003. Performance status score: do patients and their oncologists agree? *Br J Cancer,* 89**,** 1022-7.

BLAKE, G. M., NAEEM, M. & BOUTROS, M. 2006. Comparison of effective dose to children and adults from dual X-ray absorptiometry examinations. *Bone,* 38**,** 935-42.

BLUM, D., OMLIN, A., BARACOS, V. E., SOLHEIM, T. S., TAN, B. H., STONE, P., KAASA, S., FEARON, K. & STRASSER, F. 2011a. Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer. *Crit Rev Oncol Hematol,* 80**,** 114-44.

BLUM, D., OMLIN, A., BARACOS, V. E., SOLHEIM, T. S., TAN, B. H., STONE, P., KAASA, S., FEARON, K., STRASSER, F. & EUROPEAN PALLIATIVE CARE RESEARCH, C. 2011b. Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer. *Crit Rev Oncol Hematol,* 80**,** 114-44.

BOLEO-TOME, C., MONTEIRO-GRILLO, I., CAMILO, M. & RAVASCO, P. 2012. Validation of the Malnutrition Universal Screening Tool (MUST) in cancer. *Br J Nutr,* 108**,** 343-8.

BORGHAEI, H., PAZ-ARES, L., HORN, L., SPIGEL, D. R., STEINS, M., READY, N. E., CHOW, L. Q., VOKES, E. E., FELIP, E., HOLGADO, E., BARLESI, F., KOHLHAUFL, M., ARRIETA, O., BURGIO, M. A., FAYETTE, J., LENA, H., PODDUBSKAYA, E., GERBER, D. E., GETTINGER, S. N., RUDIN, C. M., RIZVI, N., CRINO, L., BLUMENSCHEIN, G. R., JR., ANTONIA, S. J., DORANGE, C., HARBISON, C. T., GRAF FINCKENSTEIN, F. & BRAHMER, J. R. 2015. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med,* 373**,** 1627-39.

BOSAEUS, I. 2008. Nutritional support in multimodal therapy for cancer cachexia. *Support Care Cancer,* 16**,** 447-51.

BOSAEUS, I., DANERYD, P., SVANBERG, E. & LUNDHOLM, K. 2001. Dietary intake and resting energy expenditure in relation to weight loss in unselected cancer patients. *Int J Cancer,* 93**,** 380-3.

BOSSOLA, M., PACELLI, F., COSTELLI, P., TORTORELLI, A., ROSA, F. & DOGLIETTO, G. B. 2008. Proteasome activities in the rectus abdominis muscle of young and older individuals. *Biogerontology,* 9**,** 261-8.

BOVIO, G., BETTAGLIO, R., BONETTI, G., MIOTTI, D. & VERNI, P. 2008. Evaluation of nutritional status and dietary intake in patients with advanced cancer on palliative care. *Minerva Gastroenterol Dietol,* 54**,** 243-50.

BRAHMER, J., RECKAMP, K. L., BAAS, P., CRINO, L., EBERHARDT, W. E., PODDUBSKAYA, E., ANTONIA, S., PLUZANSKI, A., VOKES, E. E., HOLGADO, E., WATERHOUSE, D., READY, N., GAINOR, J., AREN FRONTERA, O., HAVEL, L., STEINS, M., GARASSINO, M. C., AERTS, J. G., DOMINE, M., PAZ-ARES, L., RECK, M., BAUDELET, C., HARBISON, C. T., LESTINI, B. & SPIGEL, D. R. 2015. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med,* 373**,** 123-35.

BRAMBILLA, E., TRAVIS, W. D., COLBY, T. V., CORRIN, B. & SHIMOSATO, Y. 2001. The new World Health Organization classification of lung tumours. *Eur Respir J,* 18**,** 1059-68.

BRENNAN, P., CRISPO, A., ZARIDZE, D., SZESZENIA-DABROWSKA, N., RUDNAI, P., LISSOWSKA, J., FABIANOVA, E., MATES, D., BENCKO, V., FORETOVA, L., JANOUT, V., FLETCHER, T. & BOFFETTA, P. 2006. High cumulative risk of lung cancer death among smokers and nonsmokers in Central and Eastern Europe. *Am J Epidemiol,* 164**,** 1233-41.

BRITISH LUNG FOUNDATION. *Lung cancer statistics.* [Online]. Statistics compiled as part of the Respiratory Health of the Nation project by St George's, University of London, Nottingham University and Imperial College London. . Available: https://statistics.blf.org.uk/lung-cancer June 2017].

BROWN, D. J., MCMILLAN, D. C. & MILROY, R. 2005. The correlation between fatigue, physical function, the systemic inflammatory response, and psychological distress in patients with advanced lung cancer. *Cancer,* 103**,** 377-82.

BROWN, J. C., HARHAY, M. O. & HARHAY, M. N. 2015. Physical function as a prognostic biomarker among cancer survivors. *Br J Cancer,* 112**,** 194-8.

BROZEK, J., GRANDE, F., ANDERSON, J. T. & KEYS, A. 1963. DENSITOMETRIC ANALYSIS OF BODY COMPOSITION: REVISION OF SOME QUANTITATIVE ASSUMPTIONS. *Ann N Y Acad Sci,* 110**,** 113-40.

BRULE, S. Y., AL-BAIMANI, K., JONKER, H., ZHANG, T., NICHOLAS, G., GOSS, G., LAURIE, S. A. & WHEATLEY-PRICE, P. 2016. Palliative systemic therapy for advanced non-small cell lung cancer: Investigating disparities between patients who are treated versus those who are not. *Lung Cancer,* 97**,** 15-21.

BUCCHERI, G., FERRIGNO, D. & TAMBURINI, M. 1996. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. *Eur J Cancer,* 32A**,** 1135-41.

BUTLER, J., FOOT, C., BOMB, M., HIOM, S., COLEMAN, M., BRYANT, H., VEDSTED, P., HANSON, J. & RICHARDS, M. 2013. The International Cancer Benchmarking Partnership: an international collaboration to inform cancer policy in Australia, Canada, Denmark, Norway, Sweden and the United Kingdom. *Health Policy,* 112**,** 148-55.

CABAL-MANZANO, R., BHARGAVA, P., TORRES-DUARTE, A., MARSHALL, J., BHARGAVA, P. & WAINER, I. W. 2001. Proteolysis-inducing factor is expressed in tumours of patients with gastrointestinal cancers and correlates with weight loss. *Br J Cancer,* 84**,** 1599-601.

CALIFANO, R., ABIDIN, A. Z., PECK, R., FAIVRE-FINN, C. & LORIGAN, P. 2012. Management of small cell lung cancer: recent developments for optimal care. *Drugs,* 72**,** 471-90.

CALLE, E. E., RODRIGUEZ, C., WALKER-THURMOND, K. & THUN, M. J. 2003. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med,* 348**,** 1625-38.

CANCER RESEARCH UK. *Lung cancer incidence statistics.* [Online]. Available: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#ref-1 June 2017].

CANCER RESEARCH UK. *Lung cancer mortality statistics.* [Online]. Available: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/mortality#heading-Zero.

CANCER RESEARCH UK. *Performance status.* [Online]. Available: http://www.cancerresearchuk.org/cancer-help/about-cancer/cancer-questions/performance-status [Accessed 09/01/2014 2014].

CATARINO, P. A. & GOLDSTRAW, P. 2006. The future in diagnosis and staging of lung cancer: surgical techniques. *Respiration,* 73**,** 717-32.

CELIS-MORALES, C. A., WELSH, P., LYALL, D. M., STEELL, L., PETERMANN, F., ANDERSON, J., ILIODROMITI, S., SILLARS, A., GRAHAM, N., MACKAY, D. F., PELL, J. P., GILL, J. M. R., SATTAR, N. & GRAY, S. R. 2018. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. *BMJ,* 361**,** k1651.

CESARI, M., CERULLO, F., ZAMBONI, V., DI PALMA, R., SCAMBIA, G., BALDUCCI, L., ANTONELLI INCALZI, R., VELLAS, B. & GAMBASSI, G. 2013. Functional status and mortality in older women with gynecological cancer. *J Gerontol A Biol Sci Med Sci,* 68**,** 1129-33.

CHAMBERS, A., ROUTLEDGE, T., PILLING, J. & SCARCI, M. 2010. In elderly patients with lung cancer is resection justified in terms of morbidity, mortality and residual quality of life? *Interact Cardiovasc Thorac Surg,* 10**,** 1015-21.

CHEMAMA, S., BAYAR, M. A., LANOY, E., AMMARI, S., STOCLIN, A., GOERE, D., ELIAS, D., RAYNARD, B. & ANTOUN, S. 2016. Sarcopenia is Associated with Chemotherapy Toxicity in Patients Undergoing Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis from Colorectal Cancer. *Ann Surg Oncol,* 23**,** 3891-3898.

CHEN, L. K., LIU, L. K., WOO, J., ASSANTACHAI, P., AUYEUNG, T. W., BAHYAH, K. S., CHOU, M. Y., CHEN, L. Y., HSU, P. S., KRAIRIT, O., LEE, J. S., LEE, W. J., LEE, Y., LIANG, C. K., LIMPAWATTANA, P., LIN, C. S., PENG, L. N., SATAKE, S., SUZUKI, T., WON, C. W., WU, C. H., WU, S. N., ZHANG, T., ZENG, P., AKISHITA, M. & ARAI, H. 2014. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc,* 15**,** 95-101.

CHU, M. P., LIEFFERS, J., GHOSH, S., BELCH, A. R., CHUA, N. S., FONTAINE, A., SANGHA, R., TURNER, A. R., BARACOS, V. E. & SAWYER, M. B. 2015. Skeletal muscle radio-density is an independent predictor of response and outcomes in follicular lymphoma treated with chemoimmunotherapy. *PLoS One,* 10**,** e0127589.

CHUMLEA, W. C., GUO, S. S., KUCZMARSKI, R. J., FLEGAL, K. M., JOHNSON, C. L., HEYMSFIELD, S. B., LUKASKI, H. C., FRIEDL, K. & HUBBARD, V. S. 2002. Body composition estimates from NHANES III bioelectrical impedance data. *Int J Obes Relat Metab Disord,* 26**,** 1596-609.

CIULEANU, T., BRODOWICZ, T., ZIELINSKI, C., KIM, J. H., KRZAKOWSKI, M., LAACK, E., WU, Y. L., BOVER, I., BEGBIE, S., TZEKOVA, V., CUCEVIC, B., PEREIRA, J. R., YANG, S. H., MADHAVAN, J., SUGARMAN, K. P., PETERSON, P., JOHN, W. J., KREJCY, K. & BELANI, C. P. 2009. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet,* 374**,** 1432-40.

COLEMAN, M. P., GATTA, G., VERDECCHIA, A., ESTEVE, J., SANT, M., STORM, H., ALLEMANI, C., CICCOLALLO, L., SANTAQUILANI, M. & BERRINO, F. 2003. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. *Ann Oncol,* 14 Suppl 5**,** v128-49.

COLEMAN, R. E. 2004. Bisphosphonates: clinical experience. *Oncologist,* 9 Suppl 4**,** 14-27.

COLLINS, J., NOBLE, S., CHESTER, J., COLES, B. & BYRNE, A. 2014. The assessment and impact of sarcopenia in lung cancer: a systematic literature review. *BMJ Open,* 4.

COLLINS, J. T., NOBLE, S., CHESTER, J., DAVIES, H. E., EVANS, W. D., LESTER, J., PARRY, D., PETTIT, R. J. & BYRNE, A. 2015. Association of sarcopenia and observed physical performance with attainment of multidisciplinary team planned treatment in non-small cell lung cancer: an observational study protocol. *BMC Cancer,* 15**,** 544.

COLOMER, R., MORENO-NOGUEIRA, J. M., GARCIA-LUNA, P. P., GARCIA-PERIS, P., GARCIA-DE-LORENZO, A., ZARAZAGA, A., QUECEDO, L., DEL LLANO, J., USAN, L. & CASIMIRO, C. 2007. N-3 fatty acids, cancer and cachexia: a systematic review of the literature. *Br J Nutr,* 97**,** 823-31.

CONILL, C., VERGER, E. & SALAMERO, M. 1990. Performance status assessment in cancer patients. *Cancer,* 65**,** 1864-6.

COOK, R. M., MILLER, Y. E. & BUNN, P. A., JR. 1993. Small cell lung cancer: etiology, biology, clinical features, staging, and treatment. *Curr Probl Cancer,* 17**,** 69-141.

CORRE, R., GREILLIER, L., CAËR, H. L., AUDIGIER-VALETTE, C., BAIZE, N., BÉRARD, H., FALCHERO, L., MONNET, I., DANSIN, E., VERGNENÈGRE, A., MARCQ, M., DECROISETTE, C., AULIAC, J.-B., BOTA, S., LAMY, R., MASSUTI, B., DUJON, C., PÉROL, M., DAURÈS, J.-P., DESCOURT, R., LÉNA, H., PLASSOT, C. & CHOUAÏD, C. 2016. Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC-GECP 08-02 Study. *Journal of Clinical Oncology,* 34**,** 1476-1483.

COX, J. D. & YESNER, R. A. 1981. Causes of treatment failure and death in carcinoma of the lung. *Yale J Biol Med,* 54**,** 201-7.

CRUZ-JENTOFT, A. J., BAEYENS, J. P., BAUER, J. M., BOIRIE, Y., CEDERHOLM, T., LANDI, F., MARTIN, F. C., MICHEL, J. P., ROLLAND, Y., SCHNEIDER, S. M., TOPINKOVA, E., VANDEWOUDE, M. & ZAMBONI, M. 2010. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing,* 39**,** 412-23.

CUSHEN, S. J., POWER, D. G., TEO, M. Y., MACENEANEY, P., MAHER, M. M., MCDERMOTT, R., O'SULLIVAN, K. & RYAN, A. M. 2014. Body Composition by Computed Tomography as a Predictor of Toxicity in Patients With Renal Cell Carcinoma Treated With Sunitinib. *Am J Clin Oncol*.

DAHLBERG, S. E., SCHILLER, J. H., BONOMI, P. B., SANDLER, A. B., BRAHMER, J. R., RAMALINGAM, S. S. & JOHNSON, D. H. 2013. Body mass index and its association with clinical outcomes for advanced non-small-cell lung cancer patients enrolled on Eastern Cooperative Oncology Group clinical trials. *J Thorac Oncol,* 8**,** 1121-7.

DAJCZMAN, E., KASYMJANOVA, G., KREISMAN, H., SWINTON, N., PEPE, C. & SMALL, D. 2008. Should patient-rated performance status affect treatment decisions in advanced lung cancer? *J Thorac Oncol,* 3**,** 1133-6.

DALY, L. E., PRADO, C. M. & RYAN, A. M. 2018. A window beneath the skin: how computed tomography assessment of body composition can assist in the identification of hidden wasting conditions in oncology that profoundly impact outcomes. *Proc Nutr Soc,* 77**,** 135-151.

DAMHUIS, R. A. & SCHUTTE, P. R. 1996. Resection rates and postoperative mortality in 7,899 patients with lung cancer. *Eur Respir J,* 9**,** 7-10.

DARBY, S., HILL, D., AUVINEN, A., BARROS-DIOS, J. M., BAYSSON, H., BOCHICCHIO, F., DEO, H., FALK, R., FORASTIERE, F., HAKAMA, M., HEID, I., KREIENBROCK, L., KREUZER, M., LAGARDE, F., MAKELAINEN, I., MUIRHEAD, C., OBERAIGNER, W., PERSHAGEN, G., RUANO-RAVINA, A., RUOSTEENOJA, E., ROSARIO, A. S., TIRMARCHE, M., TOMASEK, L., WHITLEY, E., WICHMANN, H. E. & DOLL, R. 2005. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ,* 330**,** 223.

DE BLASIO, F., DI GREGORIO, A., DE BLASIO, F., BIANCO, A., BELLOFIORE, B. & SCALFI, L. 2018. Malnutrition and sarcopenia assessment in patients with chronic obstructive pulmonary disease according to international diagnostic criteria, and evaluation of raw BIA variables. *Respir Med,* 134**,** 1-5.

DE HOLLANDER, E. L., BEMELMANS, W. J. & DE GROOT, L. C. 2013. Associations between changes in anthropometric measures and mortality in old age: a role for mid-upper arm circumference? *J Am Med Dir Assoc,* 14**,** 187-93.

DEANS, D. A., WIGMORE, S. J., GILMOUR, H., TISDALE, M. J., FEARON, K. C. & ROSS, J. A. 2006. Expression of the proteolysis-inducing factor core peptide mRNA is upregulated in both tumour and adjacent normal tissue in gastro-oesophageal malignancy. *Br J Cancer,* 94**,** 731-6.

DETTERBECK, F. C., JANTZ, M. A., WALLACE, M., VANSTEENKISTE, J. & SILVESTRI, G. A. 2007. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest,* 132**,** 202S-220S.

DEWEY, A., BAUGHAN, C., DEAN, T., HIGGINS, B. & JOHNSON, I. 2007. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. *Cochrane Database Syst Rev***,** CD004597.

DEWYS, W. D., BEGG, C., LAVIN, P. T., BAND, P. R., BENNETT, J. M., BERTINO, J. R., COHEN, M. H., DOUGLASS, H. O., JR., ENGSTROM, P. F., EZDINLI, E. Z., HORTON, J., JOHNSON, G. J., MOERTEL, C. G., OKEN, M. M., PERLIA, C., ROSENBAUM, C., SILVERSTEIN, M. N.,

SKEEL, R. T., SPONZO, R. W. & TORMEY, D. C. 1980. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med,* 69**,** 491-7.

DIXON, J. B. & EGGER, G. J. 2014. A narrow view of optimal weight for health generates the obesity paradox. *Am J Clin Nutr,* 99**,** 969-70.

DODDS, L., DAVIS, S. & POLISSAR, L. 1986. A population-based study of lung cancer incidence trends by histologic type, 1974-81. *J Natl Cancer Inst,* 76**,** 21-9.

DOLL, R. & HILL, A. B. 1950. Smoking and carcinoma of the lung; preliminary report. *Br Med J,* 2**,** 739-48.

DONOHOE, C. L., RYAN, A. M. & REYNOLDS, J. V. 2011. Cancer cachexia: mechanisms and clinical implications. *Gastroenterol Res Pract,* 2011**,** 601434.

DOWNEY, R. S., SEWELL, C. W. & MANSOUR, K. A. 1989. Large cell carcinoma of the lung: a highly aggressive tumor with dismal prognosis. *Ann Thorac Surg,* 47**,** 806-8.

DUNICAN, E., UZBECK, M., CLINCE, J., TONER, S., ROYSTON, D., LOGAN, M. P., BREATHNACH, O., YOUNG, V., LINNANE, S. I. & MORGAN, R. K. 2011. Outcomes of patients presenting to a dedicated rapid access lung cancer clinic. *Ir Med J,* 104**,** 265-8.

EVANS, W. J., MORLEY, J. E., ARGILES, J., BALES, C., BARACOS, V., GUTTRIDGE, D., JATOI, A., KALANTAR-ZADEH, K., LOCHS, H., MANTOVANI, G., MARKS, D., MITCH, W. E., MUSCARITOLI, M., NAJAND, A., PONIKOWSKI, P., ROSSI FANELLI, F., SCHAMBELAN, M., SCHOLS, A., SCHUSTER, M., THOMAS, D., WOLFE, R. & ANKER, S. D. 2008. Cachexia: a new definition. *Clin Nutr,* 27**,** 793-9.

EXTERMANN, M., AAPRO, M., BERNABEI, R., COHEN, H. J., DROZ, J. P., LICHTMAN, S., MOR, V., MONFARDINI, S., REPETTO, L., SORBYE, L. & TOPINKOVA, E. 2005. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit Rev Oncol Hematol,* 55**,** 241-52.

EXTERMANN, M., BOLER, I., REICH, R. R., LYMAN, G. H., BROWN, R. H., DEFELICE, J., LEVINE, R. M., LUBINER, E. T., REYES, P., SCHREIBER, F. J. & BALDUCCI, L. 2012. Predicting the risk of chemotherapy toxicity in older patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer,* 118**,** 3377-3386.

FEARON, K., STRASSER, F., ANKER, S. D., BOSAEUS, I., BRUERA, E., FAINSINGER, R. L., JATOI, A., LOPRINZI, C., MACDONALD, N., MANTOVANI, G., DAVIS, M., MUSCARITOLI, M., OTTERY, F., RADBRUCH, L., RAVASCO, P., WALSH, D., WILCOCK, A., KAASA, S. & BARACOS, V. E. 2011. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol,* 12**,** 489-95.

FEARON, K. C., BARBER, M. D., MOSES, A. G., AHMEDZAI, S. H., TAYLOR, G. S., TISDALE, M. J. & MURRAY, G. D. 2006a. Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. *J Clin Oncol,* 24**,** 3401-7.

FEARON, K. C., VOSS, A. C. & HUSTEAD, D. S. 2006b. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *Am J Clin Nutr,* 83**,** 1345-50.

FERGUSON, M. K., IM, H. K., WATSON, S., JOHNSON, E., WIGFIELD, C. H. & VIGNESWARAN, W. T. 2014. Association of body mass index and outcomes after major lung resection. *Eur J Cardiothorac Surg,* 45**,** e94-9; discussion e99.

FERLAY, J., SHIN, H. R., BRAY, F., FORMAN, D., MATHERS, C. & PARKIN, D. M. 2010. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer,* 127**,** 2893-917.

FIELD, R. W., STECK, D. J., SMITH, B. J., BRUS, C. P., FISHER, E. F., NEUBERGER, J. S. & LYNCH, C. F. 2001. The Iowa radon lung cancer study--phase I: Residential radon gas exposure and lung cancer. *Sci Total Environ,* 272**,** 67-72.

FIORELLI, A., VICIDOMINI, G., MAZZELLA, A., MESSINA, G., MILIONE, R., DI CRESCENZO, V. G. & SANTINI, M. 2014. The influence of body mass index and weight loss on outcome of elderly patients undergoing lung cancer resection. *Thorac Cardiovasc Surg,* 62**,** 578-87.

FISCHER, B., LASSEN, U., MORTENSEN, J., LARSEN, S., LOFT, A., BERTELSEN, A., RAVN, J., CLEMENTSEN, P., HOGHOLM, A., LARSEN, K., RASMUSSEN, T., KEIDING, S., DIRKSEN, A., GERKE, O., SKOV, B., STEFFENSEN, I., HANSEN, H., VILMANN, P., JACOBSEN, G., BACKER, V., MALTBAEK, N., PEDERSEN, J., MADSEN, H., NIELSEN, H. & HOJGAARD, L. 2009. Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med,* 361**,** 32-9.

FLORES, E. A., BISTRIAN, B. R., POMPOSELLI, J. J., DINARELLO, C. A., BLACKBURN, G. L. & ISTFAN, N. W. 1989. Infusion of tumor necrosis factor/cachectin promotes muscle catabolism in the rat. A synergistic effect with interleukin 1. *J Clin Invest,* 83**,** 1614-22.

FREIBERGER, E., DE VREEDE, P., SCHOENE, D., RYDWIK, E., MUELLER, V., FRANDIN, K. & HOPMAN-ROCK, M. 2012. Performance-based physical function in older community-dwelling persons: a systematic review of instruments. *Age Ageing,* 41**,** 712-21.

FRY, W. A., PHILLIPS, J. L. & MENCK, H. R. 1999. Ten-year survey of lung cancer treatment and survival in hospitals in the United States: a national cancer data base report. *Cancer,* 86**,** 1867-76.

FUJIWARA, Y., KIURA, K., HOTTA, K., TABATA, M., TAKIGAWA, N. & TANIMOTO, M. 2007. Being overweight influences the development of hepatic dysfunction in Japanese patients with non-small-cell lung cancer undergoing cytotoxic chemotherapy. *Lung Cancer,* 55**,** 343-8.

FUNAI, K., YOKOSE, T., ISHII, G., ARAKI, K., YOSHIDA, J., NISHIMURA, M., NAGAI, K., NISHIWAKI, Y. & OCHIAI, A. 2003. Clinicopathologic characteristics of peripheral squamous cell carcinoma of the lung. *Am J Surg Pathol,* 27**,** 978-84.

GALLAGHER, I. J., STEPHENS, N. A., MACDONALD, A. J., SKIPWORTH, R. J., HUSI, H., GREIG, C. A., ROSS, J. A., TIMMONS, J. A. & FEARON, K. C. 2012. Suppression of skeletal muscle turnover in cancer cachexia: evidence from the transcriptome in sequential human muscle biopsies. *Clin Cancer Res,* 18**,** 2817-27.

GAO, G., REN, S., LI, A., XU, J., XU, Q., SU, C., GUO, J., DENG, Q. & ZHOU, C. 2012. Epidermal growth factor receptor-tyrosine kinase inhibitor therapy is effective as first-line treatment of advanced non-small-cell lung cancer with mutated EGFR: A meta-analysis from six phase III randomized controlled trials. *Int J Cancer,* 131**,** E822-9.

GAVRILOVIC, I. T. & POSNER, J. B. 2005. Brain metastases: epidemiology and pathophysiology. *J Neurooncol,* 75**,** 5-14.

GAZDAR, A. F. & BRAMBILLA, E. 2010. Preoplasia of lung cancer. *Cancer Biomark,* 9**,** 385-96.

GIOULBASANIS, I., GEORGOULIAS, P., VLACHOSTERGIOS, P. J., BARACOS, V., GHOSH, S., GIANNOUSI, Z., PAPANDREOU, C. N., MAVROUDIS, D. & GEORGOULIAS, V. 2011. Mini Nutritional Assessment (MNA) and biochemical markers of cachexia in metastatic lung cancer patients: interrelations and associations with prognosis. *Lung Cancer,* 74**,** 516-20.

GONZALEZ, M. C. & HEYMSFIELD, S. B. 2017. Bioelectrical impedance analysis for diagnosing sarcopenia and cachexia: what are we really estimating? *J Cachexia Sarcopenia Muscle*.

GONZALEZ, M. C., PASTORE, C. A., ORLANDI, S. P. & HEYMSFIELD, S. B. 2014. Obesity paradox in cancer: new insights provided by body composition. *Am J Clin Nutr,* 99**,** 999-1005.

GOODPASTER, B. H., PARK, S. W., HARRIS, T. B., KRITCHEVSKY, S. B., NEVITT, M., SCHWARTZ, A. V., SIMONSICK, E. M., TYLAVSKY, F. A., VISSER, M. & NEWMAN, A. B. 2006. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci,* 61**,** 1059-64.

GOTAY, C. C., KAWAMOTO, C. T., BOTTOMLEY, A. & EFFICACE, F. 2008. The prognostic significance of patient-reported outcomes in cancer clinical trials. *J Clin Oncol,* 26**,** 1355-63.

GRANGER, C. L., CHAO, C., MCDONALD, C. F., BERNEY, S. & DENEHY, L. 2013. Safety and feasibility of an exercise intervention for patients following lung resection: a pilot randomized controlled trial. *Integr Cancer Ther,* 12**,** 213-24.

GRANGER, C. L., CONNOLLY, B., DENEHY, L., HART, N., ANTIPPA, P., LIN, K. Y. & PARRY, S. M. 2017. Understanding factors influencing physical activity and exercise in lung cancer: a systematic review. *Support Care Cancer,* 25**,** 983-999.

GRAY, S. W., LANDRUM, M. B., LAMONT, E. B., MCNEIL, B. J., JAKLITSCH, M. T. & KEATING, N. L. 2012. Improved outcomes associated with higher surgery rates for older patients with early stage nonsmall cell lung cancer. *Cancer,* 118**,** 1404-11.

GREENHALGH, J., DWAN, K., BOLAND, A., BATES, V., VECCHIO, F., DUNDAR, Y., JAIN, P. & GREEN, J. A. 2016. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. *Cochrane Database of Systematic Reviews*.

GRIDELLI, C. 2002. Does chemotherapy have a role as palliative therapy for unfit or elderly patients with non-small-cell lung cancer? *Lung Cancer,* 38 Suppl 2**,** S45-50.

GRIDELLI, C., ARDIZZONI, A., LE CHEVALIER, T., MANEGOLD, C., PERRONE, F., THATCHER, N., VAN ZANDWIJK, N., DI MAIO, M., MARTELLI, O. & DE MARINIS, F. 2004. Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European Experts Panel. *Ann Oncol,* 15**,** 419-26.

GRIVAUX, M., DEBIEUVRE, D., HERMAN, D., LEMONNIER, C., MARCOS, J. M., CREQUIT, J., VUILLERMOZ-BLAS, S., BARRE, P., SAILLOUR, M. & MARTIN, F. 2016. Early mortality in lung cancer: French prospective multicentre observational study. *BMC Pulm Med,* 16**,** 45.

GUADAGNOLI, E., WEITBERG, A., MOR, V., SILLIMAN, R. A., GLICKSMAN, A. S. & CUMMINGS, F. J. 1990. The influence of patient age on the diagnosis and treatment of lung and colorectal cancer. *Arch Intern Med,* 150**,** 1485-90.

GUPTA, D., LAMMERSFELD, C. A., BURROWS, J. L., DAHLK, S. L., VASHI, P. G., GRUTSCH, J. F., HOFFMAN, S. & LIS, C. G. 2004. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in advanced colorectal cancer. *Am J Clin Nutr,* 80**,** 1634-8.

GURALNIK, J. M., FERRUCCI, L., PIEPER, C. F., LEVEILLE, S. G., MARKIDES, K. S., OSTIR, G. V., STUDENSKI, S., BERKMAN, L. F. & WALLACE, R. B. 2000. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci,* 55**,** M221-31.

GURALNIK, J. M., SIMONSICK, E. M., FERRUCCI, L., GLYNN, R. J., BERKMAN, L. F., BLAZER, D. G., SCHERR, P. A. & WALLACE, R. B. 1994. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol,* 49**,** M85-94.

GUSELLA, M., TOSO, S., FERRAZZI, E., FERRARI, M. & PADRINI, R. 2002. Relationships between body composition parameters and fluorouracil pharmacokinetics. *Br J Clin Pharmacol,* 54**,** 131-9.

HAIMAN, C. A., STRAM, D. O., WILKENS, L. R., PIKE, M. C., KOLONEL, L. N., HENDERSON, B. E. & LE MARCHAND, L. 2006. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med,* 354**,** 333-42.

HAMAKER, M. E., PRINS, M. C. & STAUDER, R. 2014. The relevance of a geriatric assessment for elderly patients with a haematological malignancy--a systematic review. *Leuk Res,* 38**,** 275-83.

HAMAKER, M. E., VOS, A. G., SMORENBURG, C. H., DE ROOIJ, S. E. & VAN MUNSTER, B. C. 2012. The value of geriatric assessments in predicting treatment tolerance and all-cause mortality in older patients with cancer. *Oncologist,* 17**,** 1439-49.

HAN, L., SHI, S., GONG, T., ZHANG, Z. & SUN, X. 2013. Cancer stem cells: therapeutic implications and perspectives in cancer therapy. *Acta Pharmaceutica Sinica B,* 3**,** 65-75.

HANAHAN, D. & WEINBERG, R. A. 2011. Hallmarks of cancer: the next generation. *Cell,* 144**,** 646-74.

HARVIE, M. N., CAMPBELL, I. T., THATCHER, N. & BAILDAM, A. 2003. Changes in body composition in men and women with advanced nonsmall cell lung cancer (NSCLC) undergoing chemotherapy. *J Hum Nutr Diet,* 16**,** 323-6.

HARVIE, M. N., HOWELL, A., THATCHER, N., BAILDAM, A. & CAMPBELL, I. 2005. Energy balance in patients with advanced NSCLC, metastatic melanoma and metastatic breast cancer receiving chemotherapy--a longitudinal study. *Br J Cancer,* 92**,** 673-80.

HAWLEY, S. T. & JAGSI, R. 2015. Shared decision making in cancer care: Does one size fit all? *JAMA Oncology,* 1**,** 58-59.

HECHT, S. S. 2002. Cigarette smoking and lung cancer: chemical mechanisms and approaches to prevention. *Lancet Oncol,* 3**,** 461-9.

HECHT, S. S. 2012. Lung carcinogenesis by tobacco smoke. *Int J Cancer,* 131**,** 2724-32.

HERBST, R. S., BAAS, P., KIM, D. W., FELIP, E., PEREZ-GRACIA, J. L., HAN, J. Y., MOLINA, J., KIM, J. H., ARVIS, C. D., AHN, M. J., MAJEM, M., FIDLER, M. J., DE CASTRO, G., JR., GARRIDO, M., LUBINIECKI, G. M., SHENTU, Y., IM, E., DOLLED-FILHART, M. & GARON, E. B. 2016. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet,* 387**,** 1540-50.

HESPANHOL, V., QUEIROGA, H., MAGALHAES, A., SANTOS, A. R., COELHO, M. & MARQUES, A. 1995. Survival predictors in advanced non-small cell lung cancer. *Lung Cancer,* 13**,** 253-67.

HEYMSFIELD, S. B., WANG, Z., BAUMGARTNER, R. N., DILMANIAN, F. A., MA, R. & YASUMURA, S. 1993. Body composition and aging: a study by in vivo neutron activation analysis. *J Nutr,* 123**,** 432-7.

HILSENBECK, S. G., RAUB, W. A., JR. & SRIDHAR, K. S. 1993. Prognostic factors in lung cancer based on multivariate analysis. *Am J Clin Oncol,* 16**,** 301-9.

HOFFMANN, D., HOFFMANN, I. & EL-BAYOUMY, K. 2001. The less harmful cigarette: a controversial issue. a tribute to Ernst L. Wynder. *Chem Res Toxicol,* 14**,** 767-90.

HOLMBERG, L., SANDIN, F., BRAY, F., RICHARDS, M., SPICER, J., LAMBE, M., KLINT, A., PEAKE, M., STRAND, T. E., LINKLATER, K., ROBINSON, D. & MOLLER, H. 2010. National comparisons of lung cancer survival in England, Norway and Sweden 2001-2004: differences occur early in follow-up. *Thorax,* 65**,** 436-41.

HOWLADER, N., NOONE, A. M., KRAPCHO, M., MILLER, D., BISHOP, K., ALTEKRUSE, S. F., KOSARY, C. L., YU, M., RUHL, J., TATALOVICH, Z., MARIOTTO, A., LEWIS, D. R., CHEN, H. S., FEUER, E. J. & CRONIN, K. A. E. April 2016. SEER Cancer Statistics Review, 1975-2013. Bethesda, MD

National Cancer Institute

HOWLADER, N., NOONE, A. M., M., K., N., N., R., A., W., W., S.F., A., C.L., K., J., R., Z., T., H., C., A., M., M.P., E., D.R., L., H.S., C., E.J., F. & (EDS), C. K. A. 2011. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). *In:* INSTITUTE, N. C. (ed.). Bethesda, Maryland.

HSU, B., MEROM, D., BLYTH, F. M., NAGANATHAN, V., HIRANI, V., LE COUTEUR, D. G., SEIBEL, M. J., WAITE, L. M., HANDELSMAN, D. J. & CUMMING, R. G. 2018. Total Physical Activity, Exercise Intensity, and Walking Speed as Predictors of All-Cause and Cause-Specific Mortality Over 7 Years in Older Men: The Concord Health and Aging in Men Project. *J Am Med Dir Assoc,* 19**,** 216-222.

HUGHES, V. A., FRONTERA, W. R., WOOD, M., EVANS, W. J., DALLAL, G. E., ROUBENOFF, R. & FIATARONE SINGH, M. A. 2001. Longitudinal muscle strength changes in older adults: influence of muscle mass, physical activity, and health. *J Gerontol A Biol Sci Med Sci,* 56**,** B209-17.

HUILLARD, O., MIR, O., PEYROMAURE, M., TLEMSANI, C., GIROUX, J., BOUDOU-ROUQUETTE, P., ROPERT, S., DELONGCHAMPS, N. B., ZERBIB, M. & GOLDWASSER, F. 2013. Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients. *Br J Cancer,* 108**,** 1034-41.

HURRIA, A., TOGAWA, K., MOHILE, S. G., OWUSU, C., KLEPIN, H. D., GROSS, C. P., LICHTMAN, S. M., GAJRA, A., BHATIA, S., KATHERIA, V., KLAPPER, S., HANSEN, K., RAMANI, R., LACHS, M., WONG, F. L. & TEW, W. P. 2011. Predicting Chemotherapy Toxicity in Older Adults With Cancer: A Prospective Multicenter Study. *Journal of Clinical Oncology,* 29**,** 3457-3465.

HYNES, N. E. & LANE, H. A. 2005. ERBB receptors and cancer: the complexity of targeted inhibitors. *Nat Rev Cancer,* 5**,** 341-54.

INFORMATION SERVICES DIVISION 2013. Cancer Incidence in Scotland (2011).

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 2007. Smokeless tobacco and some tobacco-specific n-nitrosamines. IARC monographs on the evaluation of the carcinogenic risks to humans. . Lyon, France: World Health Organisation, IARC.

JAFRI, S. H., SHI, R. & MILLS, G. 2013. Advance lung cancer inflammation index (ALI) at diagnosis is a prognostic marker in patients with metastatic non-small cell lung cancer (NSCLC): a retrospective review. *BMC Cancer,* 13**,** 158.

JAGOE, R. T., GOODSHIP, T. H. & GIBSON, G. J. 2001. Nutritional status of patients undergoing lung cancer operations. *Ann Thorac Surg,* 71**,** 929-35.

JAGOE, R. T., REDFERN, C. P., ROBERTS, R. G., GIBSON, G. J. & GOODSHIP, T. H. 2002. Skeletal muscle mRNA levels for cathepsin B, but not components of the ubiquitin-proteasome pathway, are increased in patients with lung cancer referred for thoracotomy. *Clin Sci (Lond),* 102**,** 353-61.

JANSSEN, I., BAUMGARTNER, R. N., ROSS, R., ROSENBERG, I. H. & ROUBENOFF, R. 2004. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. *Am J Epidemiol,* 159**,** 413-21.

JANSSEN, I., HEYMSFIELD, S. B., BAUMGARTNER, R. N. & ROSS, R. 2000. Estimation of skeletal muscle mass by bioelectrical impedance analysis. *J Appl Physiol (1985),* 89**,** 465-71.

JANSSEN, I., HEYMSFIELD, S. B. & ROSS, R. 2002. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc,* 50**,** 889-96.

JATOI, A., DALY, B. D., HUGHES, V. A., DALLAL, G. E., KEHAYIAS, J. & ROUBENOFF, R. 2001. Do patients with nonmetastatic non-small cell lung cancer demonstrate altered resting energy expenditure? *Ann Thorac Surg,* 72**,** 348-51.

JATOI, A., KUMAR, S., SLOAN, J. A. & NGUYEN, P. L. 2003. On Appetite and Its Loss. *Journal of Clinical Oncology,* 21**,** 79-81.

JOHNS, N., STEPHENS, N. A. & FEARON, K. C. 2013. Muscle wasting in cancer. *Int J Biochem Cell Biol,* 45**,** 2215-29.

JOHNSON, D. H., FEHRENBACHER, L., NOVOTNY, W. F., HERBST, R. S., NEMUNAITIS, J. J., JABLONS, D. M., LANGER, C. J., DEVORE, R. F., 3RD, GAUDREAULT, J., DAMICO, L. A., HOLMGREN, E. & KABBINAVAR, F. 2004. Randomized phase II trial comparing

bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol,* 22**,** 2184-91.

JOPPA, P., TKACOVA, R., FRANSSEN, F. M., HANSON, C., RENNARD, S. I., SILVERMAN, E. K., MCDONALD, M. L., CALVERLEY, P. M., TAL-SINGER, R., SPRUIT, M. A., KENN, K., WOUTERS, E. F. & RUTTEN, E. P. 2016. Sarcopenic Obesity, Functional Outcomes, and Systemic Inflammation in Patients With Chronic Obstructive Pulmonary Disease. *J Am Med Dir Assoc,* 17**,** 712-8.

KANISKI, F., ENEWOLD, L., THOMAS, A., MALIK, S., STEVENS, J. L. & HARLAN, L. C. 2017. Temporal patterns of care and outcomes of non-small cell lung cancer patients in the United States diagnosed in 1996, 2005, and 2010. *Lung Cancer,* 103**,** 66-74.

KARNOFSKY, D. A. & BURCHENAL, J. H. 1949. The clinical evaluation of chemotherapeutic agents in cancer. New York: Columbia University Press.

KASYMJANOVA, G., CORREA, J. A., KREISMAN, H., DAJCZMAN, E., PEPE, C., DOBSON, S., LAJEUNESSE, L., SHARMA, R. & SMALL, D. 2009. Prognostic value of the six-minute walk in advanced non-small cell lung cancer. *J Thorac Oncol,* 4**,** 602-7.

KELLY, C. M. & SHAHROKNI, A. 2016. Moving beyond Karnofsky and ECOG Performance Status Assessments with New Technologies. *Journal of Oncology,* 2016**,** 13.

KHAKWANI, A., RICH, A. L., POWELL, H. A., TATA, L. J., STANLEY, R. A., BALDWIN, D. R., DUFFY, J. P. & HUBBARD, R. B. 2013. Lung cancer survival in England: trends in non-small-cell lung cancer survival over the duration of the National Lung Cancer Audit. *Br J Cancer,* 109**,** 2058-65.

KILGOUR, R. D., CARDIFF, K., ROSENTHALL, L., LUCAR, E., TRUTSCHNIGG, B. & VIGANO, A. 2016. Use of prediction equations to determine the accuracy of whole-body fat and fat-free mass and appendicular skeletal muscle mass measurements from a single abdominal image using computed tomography in advanced cancer patients. *Appl Physiol Nutr Metab,* 41**,** 70-5.

KILGOUR, R. D., VIGANO, A., TRUTSCHNIGG, B., HORNBY, L., LUCAR, E., BACON, S. L. & MORAIS, J. A. 2010. Cancer-related fatigue: the impact of skeletal muscle mass and strength in patients with advanced cancer. *J Cachexia Sarcopenia Muscle,* 1**,** 177-185.

KILGOUR, R. D., VIGANO, A., TRUTSCHNIGG, B., LUCAR, E., BOROD, M. & MORAIS, J. A. 2013. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. *Support Care Cancer,* 21**,** 3261-70.

KIM, S. W., KIM, M. Y., LEE, Y. P., RYU, Y. J., LEE, S. J., LEE, J. H., CHANG, J. H. & SHIM, S. S. 2013. Clinical features and prognostic factors in elderly koreans with advanced non-small-cell lung cancer in a tertiary referral hospital. *Tuberc Respir Dis (Seoul),* 75**,** 52-8.

KLEPIN, H. D., GEIGER, A. M., TOOZE, J. A., KRITCHEVSKY, S. B., WILLIAMSON, J. D., PARDEE, T. S., ELLIS, L. R. & POWELL, B. L. 2013. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood,* 121**,** 4287-94.

KOCH, U., KRAUSE, M. & BAUMANN, M. 2010. Cancer stem cells at the crossroads of current cancer therapy failures--radiation oncology perspective. *Semin Cancer Biol,* 20**,** 116-24.

KOEGELENBERG, C. F., DIACON, A. H., IRANI, S. & BOLLIGER, C. T. 2008. Stair climbing in the functional assessment of lung resection candidates. *Respiration,* 75**,** 374-9.

KREWSKI, D., LUBIN, J. H., ZIELINSKI, J. M., ALAVANJA, M., CATALAN, V. S., FIELD, R. W., KLOTZ, J. B., LETOURNEAU, E. G., LYNCH, C. F., LYON, J. L., SANDLER, D. P., SCHOENBERG, J. B., STECK, D. J., STOLWIJK, J. A., WEINBERG, C. & WILCOX, H. B. 2006. A combined analysis of North American case-control studies of residential radon and lung cancer. *J Toxicol Environ Health A,* 69**,** 533-97.

KUYS, S. S., PEEL, N. M., KLEIN, K., SLATER, A. & HUBBARD, R. E. 2014. Gait speed in ambulant older people in long term care: a systematic review and meta-analysis. *J Am Med Dir Assoc,* 15**,** 194-200.

LAIRD, B. J., KAASA, S., MCMILLAN, D. C., FALLON, M. T., HJERMSTAD, M. J., FAYERS, P. & KLEPSTAD, P. 2013. Prognostic factors in patients with advanced cancer: a comparison of clinicopathological factors and the development of an inflammation-based prognostic system. *Clin Cancer Res,* 19**,** 5456-64.

LAIRD, B. J., SCOTT, A. C., COLVIN, L. A., MCKEON, A. L., MURRAY, G. D., FEARON, K. C. & FALLON, M. T. 2011. Pain, depression, and fatigue as a symptom cluster in advanced cancer. *J Pain Symptom Manage,* 42**,** 1-11.

LAM, V. K., BENTZEN, S. M., MOHINDRA, P., NICHOLS, E. M., BHOOSHAN, N., VYFHUIS, M., SCILLA, K. A., FEIGENBERG, S. J., EDELMAN, M. J. & FELICIANO, J. L. 2017. Obesity is associated with long-term improved survival in definitively treated locally advanced non-small cell lung cancer (NSCLC). *Lung Cancer,* 104**,** 52-57.

LANDI, F., LIPEROTI, R., FUSCO, D., MASTROPAOLO, S., QUATTROCIOCCHI, D., PROIA, A., TOSATO, M., BERNABEI, R. & ONDER, G. 2012. Sarcopenia and mortality among older nursing home residents. *J Am Med Dir Assoc,* 13**,** 121-6.

LANDI, F., RUSSO, A., LIPEROTI, R., PAHOR, M., TOSATO, M., CAPOLUONGO, E., BERNABEI, R. & ONDER, G. 2010. Midarm muscle circumference, physical performance and mortality: results from the aging and longevity study in the Sirente geographic area (ilSIRENTE study). *Clin Nutr,* 29**,** 441-7.

LANGER, C. J., O'BYRNE, K. J., SOCINSKI, M. A., MIKHAILOV, S. M., LESNIEWSKI-KMAK, K., SMAKAL, M., CIULEANU, T. E., ORLOV, S. V., DEDIU, M., HEIGENER, D., EISENFELD, A. J., SANDALIC, L., OLDHAM, F. B., SINGER, J. W. & ROSS, H. J. 2008. Phase III trial comparing paclitaxel poliglumex (CT-2103, PPX) in combination with carboplatin versus standard paclitaxel and carboplatin in the treatment of PS 2 patients with chemotherapy-naive advanced non-small cell lung cancer. *J Thorac Oncol,* 3**,** 623-30.

LARDINOIS, D., WEDER, W., HANY, T. F., KAMEL, E. M., KOROM, S., SEIFERT, B., VON SCHULTHESS, G. K. & STEINERT, H. C. 2003. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *N Engl J Med,* 348**,** 2500-7.

LARSSON, S. C. & WOLK, A. 2008. Excess body fatness: an important cause of most cancers. *Lancet,* 371**,** 536-7.

LASHEEN, W. & WALSH, D. 2010. The cancer anorexia-cachexia syndrome: myth or reality? *Support Care Cancer,* 18**,** 265-72.

LEE, D. S., KANG, J. H., LEE, C. G., KIM, S. J., CHOI, Y. J., LEE, K. Y. & KIM, Y. S. 2013. Predicting Survival in Patients with Advanced Non-squamous Non-small Cell Lung Cancer: Validating the Extent of Metastasis. *Cancer Res Treat,* 45**,** 95-102.

LEUENBERGER, M., KURMANN, S. & STANGA, Z. 2010. Nutritional screening tools in daily clinical practice: the focus on cancer. *Support Care Cancer,* 18 Suppl 2**,** S17-27.

LEUNG, C. C., LAM, T. H., YEW, W. W., CHAN, W. M., LAW, W. S. & TAM, C. M. 2011. Lower lung cancer mortality in obesity. *Int J Epidemiol,* 40**,** 174-82.

LEVETT, D. Z. H., JACK, S., SWART, M., CARLISLE, J., WILSON, J., SNOWDEN, C., RILEY, M., DANJOUX, G., WARD, S. A., OLDER, P. & GROCOTT, M. P. W. 2018. Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. *Br J Anaesth,* 120**,** 484-500.

LEVIT, L., BALOGH, E., NASS, S. & GANZ, P. A. 2013. Delivering high quality cancer care: charting a new course for a system in crisis. *In:* PRESS, N. A. (ed.). Washington, DC.

LIEDMAN, B., ANDERSSON, H., BOSAEUS, I., HUGOSSON, I. & LUNDELL, L. 1997. Changes in body composition after gastrectomy: results of a controlled, prospective clinical trial. *World J Surg,* 21**,** 416-20; discussion 420-1.

LLOVERA, M., GARCIA-MARTINEZ, C., AGELL, N., LOPEZ-SORIANO, F. J. & ARGILES, J. M. 1997. TNF can directly induce the expression of ubiquitin-dependent proteolytic system in rat soleus muscles. *Biochem Biophys Res Commun,* 230**,** 238-41.

LOPEZ-ENCUENTRA, A. 2002. Comorbidity in operable lung cancer: a multicenter descriptive study on 2992 patients. *Lung Cancer,* 35**,** 263-9.

LOPRINZI, C. L., LAURIE, J. A., WIEAND, H. S., KROOK, J. E., NOVOTNY, P. J., KUGLER, J. W., BARTEL, J., LAW, M., BATEMAN, M., KLATT, N. E. & ET AL. 1994. Prospective evaluation of prognostic variables from patient-completed questionnaires. North Central Cancer Treatment Group. *J Clin Oncol,* 12**,** 601-7.

LOPRINZI, C. L., SCHAID, D. J., DOSE, A. M., BURNHAM, N. L. & JENSEN, M. D. 1993. Body-composition changes in patients who gain weight while receiving megestrol acetate. *J Clin Oncol,* 11**,** 152-4.

LUBIN, J. H., BOICE, J. D., JR., EDLING, C., HORNUNG, R. W., HOWE, G. R., KUNZ, E., KUSIAK, R. A., MORRISON, H. I., RADFORD, E. P., SAMET, J. M. & ET AL. 1995. Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. *J Natl Cancer Inst,* 87**,** 817-27.

LUBIN, J. H., CAPORASO, N., WICHMANN, H. E., SCHAFFRATH-ROSARIO, A. & ALAVANJA, M. C. 2007. Cigarette smoking and lung cancer: modeling effect modification of total exposure and intensity. *Epidemiology,* 18**,** 639-48.

LUBIN, J. H. & CAPORASO, N. E. 2006. Cigarette smoking and lung cancer: modeling total exposure and intensity. *Cancer Epidemiol Biomarkers Prev,* 15**,** 517-23.

LUKASKI, H. C. 1987. Methods for the assessment of human body composition: traditional and new. *Am J Clin Nutr,* 46**,** 537-56.

LUO, J., CHEN, Y. J., NARSAVAGE, G. L. & DUCATMAN, A. 2012. Predictors of survival in patients with non-small cell lung cancer. *Oncol Nurs Forum,* 39**,** 609-16.

LYNCH, T. J., BELL, D. W., SORDELLA, R., GURUBHAGAVATULA, S., OKIMOTO, R. A., BRANNIGAN, B. W., HARRIS, P. L., HASERLAT, S. M., SUPKO, J. G., HALUSKA, F. G., LOUIS, D. N., CHRISTIANI, D. C., SETTLEMAN, J. & HABER, D. A. 2004. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med,* 350**,** 2129-39.

MACDONALD, A. J., GREIG, C. A. & BARACOS, V. 2011. The advantages and limitations of cross-sectional body composition analysis. *Curr Opin Support Palliat Care,* 5**,** 342-9.

MARCHESANI, W. 1924. "Ueber den primarien bronchieikriebs.". *Frankfurter Pathol,* 30**,** 158.

MARTIN, L., BIRDSELL, L., MACDONALD, N., REIMAN, T., CLANDININ, M. T., MCCARGAR, L. J., MURPHY, R., GHOSH, S., SAWYER, M. B. & BARACOS, V. E. 2013. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol,* 31**,** 1539-47.

MARTIN, L., SENESSE, P., GIOULBASANIS, I., ANTOUN, S., BOZZETTI, F., DEANS, C., STRASSER, F., THORESEN, L., JAGOE, R. T., CHASEN, M., LUNDHOLM, K., BOSAEUS, I., FEARON, K. H. & BARACOS, V. E. 2015. Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol,* 33**,** 90-9.

MARTINEZ-HERNANDEZ, P. L., HERNANZ-MACIAS, A., GOMEZ-CANDELA, C., GRANDE-ARAGON, C., FELIU-BATLLE, J., CASTRO-CARPENO, J., MARTINEZ-MUNOZ, I., ZURITA-ROSA, L., VILLARINO-SANZ, M., PRADOS-SANCHEZ, C. & SANCHEZ GARCIA-GIRON, J. 2012. Serum interleukin-15 levels in cancer patients with cachexia. *Oncol Rep,* 28**,** 1443-52.

MATSUNAGA, T., SUZUKI, K., IMASHIMIZU, K., BANNO, T., TAKAMOCHI, K. & OH, S. 2015. Body Mass Index as a Prognostic Factor in Resected Lung Cancer: Obesity or Underweight, Which Is the Risk Factor? *Thorac Cardiovasc Surg,* 63**,** 551-7.

MATTHYS, P., HEREMANS, H., OPDENAKKER, G. & BILLIAU, A. 1991. Anti-interferon-gamma antibody treatment, growth of Lewis lung tumours in mice and tumour-associated cachexia. *Eur J Cancer,* 27**,** 182-7.

MAY, C. H., LESTER, J. F. & LEE, S. 2012. Performance status discordance and why it matters. *Lung Cancer,* 75**,** S1-S72.

MAZZOTTA, P. & JENEY, C. M. 2009. Anorexia-cachexia syndrome: a systematic review of the role of dietary polyunsaturated Fatty acids in the management of symptoms, survival, and quality of life. *J Pain Symptom Manage,* 37**,** 1069-77.

MCMILLAN, D. C. 2009. Systemic inflammation, nutritional status and survival in patients with cancer. *Curr Opin Clin Nutr Metab Care,* 12**,** 223-6.

MCMILLAN, D. C. 2013. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat Rev,* 39**,** 534-40.

MENCK, H. R. & HENDERSON, B. E. 1982. Cancer incidence patterns in the Pacific Basin. *Natl Cancer Inst Monogr,* 62**,** 101-9.

MIJNARENDS, D. M., MEIJERS, J. M., HALFENS, R. J., TER BORG, S., LUIKING, Y. C., VERLAAN, S., SCHOBERER, D., CRUZ JENTOFT, A. J., VAN LOON, L. J. & SCHOLS, J. M. 2013. Validity and reliability of tools to measure muscle mass, strength, and physical performance in community-dwelling older people: a systematic review. *J Am Med Dir Assoc,* 14**,** 170-8.

MILLER, K. L., KOCAK, Z., KAHN, D., ZHOU, S. M., BAYDUSH, A., HOLLIS, D., FOLZ, R. J., TISCH, A., CLOUGH, R., YU, X., LIGHT, K. & MARKS, L. B. 2005. Preliminary report of the 6-minute walk test as a predictor of radiation-induced pulmonary toxicity. *Int J Radiat Oncol Biol Phys,* 62**,** 1009-13.

MIR, O., CORIAT, R., BLANCHET, B., DURAND, J. P., BOUDOU-ROUQUETTE, P., MICHELS, J., ROPERT, S., VIDAL, M., POL, S., CHAUSSADE, S. & GOLDWASSER, F. 2012. Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. *PLoS One,* 7**,** e37563.

MITSUDOMI, T., MORITA, S., YATABE, Y., NEGORO, S., OKAMOTO, I., TSURUTANI, J., SETO, T., SATOUCHI, M., TADA, H., HIRASHIMA, T., ASAMI, K., KATAKAMI, N., TAKADA, M., YOSHIOKA, H., SHIBATA, K., KUDOH, S., SHIMIZU, E., SAITO, H., TOYOOKA, S., NAKAGAWA, K. & FUKUOKA, M. 2010. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol,* 11**,** 121-8.

MOK, T. S., WU, Y. L., THONGPRASERT, S., YANG, C. H., CHU, D. T., SAIJO, N., SUNPAWERAVONG, P., HAN, B., MARGONO, B., ICHINOSE, Y., NISHIWAKI, Y., OHE, Y., YANG, J. J., CHEWASKULYONG, B., JIANG, H., DUFFIELD, E. L., WATKINS, C. L., ARMOUR, A. A. & FUKUOKA, M. 2009. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med,* 361**,** 947-57.

MOLEY, J. F., AAMODT, R., RUMBLE, W., KAYE, W. & NORTON, J. A. 1987. Body cell mass in cancer-bearing and anorexic patients. *JPEN J Parenter Enteral Nutr,* 11**,** 219-22.

MONTAZERI, A. 2009. Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008. *Health Qual Life Outcomes,* 7**,** 102.

MONTAZERI, A., MILROY, R., HOLE, D., MCEWEN, J. & GILLIS, C. R. 2001. Quality of life in lung cancer patients: as an important prognostic factor. *Lung Cancer,* 31**,** 233-40.

MONTOYA, M., FOSSELLA, F., PALMER, J. L., KAUR, G., PACE, E. A., YADAV, R., SIMMONDS, M., GILLIS, T. & BRUERA, E. 2006. Objective evaluation of physical function in patients with advanced lung cancer: a preliminary report. *J Palliat Med,* 9**,** 309-16.

MOUMTZI, D., LAMPAKI, S., ZAROGOULIDIS, P., PORPODIS, K., LAGOUDI, K., HOHENFORST-SCHMIDT, W., PATAKA, A., TSIOUDA, T., ZISSIMOPOULOS, A., LAZARIDIS, G.,

KARAVASILIS, V., TIMOTHEADOU, H., BARBETAKIS, N., PAVLIDIS, P., KONTAKIOTIS, T. & ZAROGOULIDIS, K. 2016. Prognostic factors for long term survival in patients with advanced non-small cell lung cancer. *Ann Transl Med,* 4**,** 161.

MOURTZAKIS, M., PRADO, C. M., LIEFFERS, J. R., REIMAN, T., MCCARGAR, L. J. & BARACOS, V. E. 2008. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab,* 33**,** 997-1006.

MULLEN, J. T., MOORMAN, D. W. & DAVENPORT, D. L. 2009. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. *Ann Surg,* 250**,** 166-72.

MUNGO, B., ZOGG, C. K., HOOKER, C. M., YANG, S. C., BATTAFARANO, R. J., BROCK, M. V. & MOLENA, D. 2015. Does obesity affect the outcomes of pulmonary resections for lung cancer? A National Surgical Quality Improvement Program analysis. *Surgery,* 157**,** 792-800.

MUSCARITOLI, M., ANKER, S. D., ARGILES, J., AVERSA, Z., BAUER, J. M., BIOLO, G., BOIRIE, Y., BOSAEUS, I., CEDERHOLM, T., COSTELLI, P., FEARON, K. C., LAVIANO, A., MAGGIO, M., ROSSI FANELLI, F., SCHNEIDER, S. M., SCHOLS, A. & SIEBER, C. C. 2010. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr,* 29**,** 154-9.

NATIONAL CANCER INSTITUTE 2009. Common Toxicity Criteria for Adverse Events (CTCAE) v4.03. *In:* (CTEP), N. C. I. C. T. E. P. (ed.).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE 2011. Lung Cancer: Diagnosis and Mangement. Clinical Guidance 121. *In:* THE GUIDELINE DEVELOPMENT GROUP, N. C. C. A. N. P. T. (ed.).

NHS INFORMATION CENTRE (NHSIC) 2011. National Lung Cancer Audit Report 2011. Leeds.

NICOLAIDES, N. C., O'SHANNESSY, D. J., ALBONE, E. & GRASSO, L. 2014. Co-development of diagnostic vectors to support targeted therapies and theranostics: essential tools in personalized cancer therapy. *Front Oncol,* 4**,** 141.

NON-SMALL CELL LUNG CANCER COLLABORATIVE GROUP 2010. Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. *Cochrane Database Syst Rev***,** CD007309.

NOORDIJK, E. M., VECHT, C. J., HAAXMA-REICHE, H., PADBERG, G. W., VOORMOLEN, J. H., HOEKSTRA, F. H., TANS, J. T., LAMBOOIJ, N., METSAARS, J. A., WATTENDORFF, A. R. & ET AL. 1994. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys,* 29**,** 711-7.

NORTHERN IRELAND CANCER REGISTRY 2011. Number of cases and incidence rates by sex and year of diagnosis: Trachea, bronchus and lung Northern Ireland Cancer Registry.

O'BRIEN, M. E., SOCINSKI, M. A., POPOVICH, A. Y., BONDARENKO, I. N., TOMOVA, A., BILYNSKY, B. T., HOTKO, Y. S., GANUL, V. L., KOSTINSKY, I. Y., EISENFELD, A. J., SANDALIC, L., OLDHAM, F. B., BANDSTRA, B., SANDLER, A. B. & SINGER, J. W. 2008. Randomized phase III trial comparing single-agent paclitaxel Poliglumex (CT-2103, PPX) with single-agent gemcitabine or vinorelbine for the treatment of PS 2 patients with chemotherapy-naive advanced non-small cell lung cancer. *J Thorac Oncol,* 3**,** 728-34.

O'DOWD, E. L., MCKEEVER, T. M., BALDWIN, D. R., ANWAR, S., POWELL, H. A., GIBSON, J. E., IYEN-OMOFOMAN, B. & HUBBARD, R. B. 2015. What characteristics of primary care and patients are associated with early death in patients with lung cancer in the UK? *Thorax,* 70**,** 161-8.

O'ROURKE, M. A., FEUSSNER, J. R., FEIGL, P. & LASZLO, J. 1987. Age trends of lung cancer stage at diagnosis. Implications for lung cancer screening in the elderly. *JAMA,* 258**,** 921-6.

OFFICE FOR NATIONAL STATISTICS 2010. General lifestyle survey overview: a report on the 2010 General Lifestyle Survey ONS.

OFFICE FOR NATIONAL STATISTICS 2011. Cancer survival in England: Patients diagnosed 2005-2009 and followed up to 2010 London: ONS.

OFFICE FOR NATIONAL STATISTICS 2012. Cancer incidence and mortality in the UK, 2007-2009.

OFFICE FOR NATIONAL STATISTICS 2013 Cancer Registration Statistics , England 2011. Office for National Statistics.

OFFICE FOR NATIONAL STATISTICS 2015a. Cancer survival in England: patients diagnosed between 2010 and 2014 and followed up in 2015. .

OFFICE FOR NATIONAL STATISTICS 2015b. Deaths registered in England and Wales Statistical Bulletins.: Office for National Statistics.

OKEN, M. M., CREECH, R. H., TORMEY, D. C., HORTON, J., DAVIS, T. E., MCFADDEN, E. T. & CARBONE, P. P. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol,* 5**,** 649-55.

OP DEN KAMP, C. M., DE RUYSSCHER, D. K., VAN DEN HEUVEL, M., ELFERINK, M., HOUBEN, R. M., OBERIJE, C. J., BOOTSMA, G. P., GERAEDTS, W. H., PITZ, C. C., LANGEN, R. C., WOUTERS, E. F., SCHOLS, A. M. & DINGEMANS, A. M. 2014. Early body weight loss during concurrent chemo-radiotherapy for non-small cell lung cancer. *J Cachexia Sarcopenia Muscle,* 5**,** 127-37.

OP DEN KAMP, C. M., LANGEN, R. C., MINNAARD, R., KELDERS, M. C., SNEPVANGERS, F. J., HESSELINK, M. K., DINGEMANS, A. C. & SCHOLS, A. M. 2012. Pre-cachexia in patients with stages I-III non-small cell lung cancer: systemic inflammation and functional impairment without activation of skeletal muscle ubiquitin proteasome system. *Lung Cancer,* 76**,** 112-7.

OP DEN KAMP, C. M., LANGEN, R. C., SNEPVANGERS, F. J., DE THEIJE, C. C., SCHELLEKENS, J. M., LAUGS, F., DINGEMANS, A. M. & SCHOLS, A. M. 2013. Nuclear transcription factor kappa B activation and protein turnover adaptations in skeletal muscle of patients with progressive stages of lung cancer cachexia. *Am J Clin Nutr,* 98**,** 738-48.

OWONIKOKO, T. K., RAGIN, C. C., BELANI, C. P., OTON, A. B., GOODING, W. E., TAIOLI, E. & RAMALINGAM, S. S. 2007. Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. *J Clin Oncol,* 25**,** 5570-7.

OWUSU, C., MARGEVICIUS, S., SCHLUCHTER, M., KOROUKIAN, S. M. & BERGER, N. A. 2017. Short Physical Performance Battery, usual gait speed, grip strength and Vulnerable Elders Survey each predict functional decline among older women with breast cancer. *J Geriatr Oncol,* 8**,** 356-362.

PACE, N. & RATHBUN, E. N. 1945. STUDIES ON BODY COMPOSITION: III. THE BODY WATER AND CHEMICALLY COMBINED NITROGEN CONTENT IN RELATION TO FAT CONTENT. *Journal of Biological Chemistry,* 158**,** 685-691.

PAMOUKDJIAN, F., PAILLAUD, E., ZELEK, L., LAURENT, M., LEVY, V., LANDRE, T. & SEBBANE, G. 2015. Measurement of gait speed in older adults to identify complications associated with frailty: A systematic review. *J Geriatr Oncol,* 6**,** 484-96.

PAO, W., MILLER, V., ZAKOWSKI, M., DOHERTY, J., POLITI, K., SARKARIA, I., SINGH, B., HEELAN, R., RUSCH, V., FULTON, L., MARDIS, E., KUPFER, D., WILSON, R., KRIS, M. & VARMUS, H. 2004. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A,* 101**,** 13306-11.

PARK, S., PARK, S., LEE, S. H., SUH, B., KEAM, B., KIM, T. M., KIM, D. W., KIM, Y. W. & HEO, D. S. 2016. Nutritional status in the era of target therapy: poor nutrition is a prognostic factor in non-small cell lung cancer with activating epidermal growth factor receptor mutations. *Korean J Intern Med,* 31**,** 1140-1149.

PARKIN, D. M. 2001. Global cancer statistics in the year 2000. *Lancet Oncol,* 2**,** 533-43.

PARKIN, D. M. 2011. 2. Tobacco-attributable cancer burden in the UK in 2010. *Br J Cancer,* 105 Suppl 2**,** S6-S13.

PASCUAL LOPEZ, A., ROQUE I FIGULS, M., URRUTIA CUCHI, G., BERENSTEIN, E. G., ALMENAR PASIES, B., BALCELLS ALEGRE, M. & HERDMAN, M. 2004. Systematic review of megestrol acetate in the treatment of anorexia-cachexia syndrome. *J Pain Symptom Manage,* 27**,** 360-9.

PAZ-ARES, L., DE MARINIS, F., DEDIU, M., THOMAS, M., PUJOL, J. L., BIDOLI, P., MOLINIER, O., SAHOO, T. P., LAACK, E., RECK, M., CORRAL, J., MELEMED, S., JOHN, W., CHOUAKI, N., ZIMMERMANN, A. H., VISSEREN-GRUL, C. & GRIDELLI, C. 2012. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol,* 13**,** 247-55.

PEDDLE-MCINTYRE, C. J., BELL, G., FENTON, D., MCCARGAR, L. & COURNEYA, K. S. 2012. Feasibility and preliminary efficacy of progressive resistance exercise training in lung cancer survivors. *Lung Cancer,* 75**,** 126-32.

PENNA, F., COSTAMAGNA, D., PIN, F., CAMPERI, A., FANZANI, A., CHIARPOTTO, E. M., CAVALLINI, G., BONELLI, G., BACCINO, F. M. & COSTELLI, P. 2013. Autophagic degradation contributes to muscle wasting in cancer cachexia. *Am J Pathol,* 182**,** 1367-78.

PEREZ-STABLE, E. J., HERRERA, B., JACOB, P., 3RD & BENOWITZ, N. L. 1998. Nicotine metabolism and intake in black and white smokers. *JAMA,* 280**,** 152-6.

PERFETTI, T. & RODGMAN, A. 2008. *The Chemical Components of Tobacco and Tobacco Smoke.* CRC Press.

PESSINA, P., CONTI, V., PACELLI, F., ROSA, F., DOGLIETTO, G. B., BRUNELLI, S. & BOSSOLA, M. 2010. Skeletal muscle of gastric cancer patients expresses genes involved in muscle regeneration. *Oncol Rep,* 24**,** 741-5.

PETERS, S., ADJEI, A. A., GRIDELLI, C., RECK, M., KERR, K. & FELIP, E. 2012. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol,* 23 Suppl 7**,** vii56-64.

PETO, R., LOPEZ, A., BOREHAM, J., THUN, M. & HEATH, C. 1994. *Mortality from smoking in developed countries 1950-2000: indirect estimates from national vital statistics* New York Oxford University Press

PRADO, C. M., BARACOS, V. E., MCCARGAR, L. J., REIMAN, T., MOURTZAKIS, M., TONKIN, K., MACKEY, J. R., KOSKI, S., PITUSKIN, E. & SAWYER, M. B. 2009. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res,* 15**,** 2920-6.

PRADO, C. M., LIEFFERS, J. R., MCCARGAR, L. J., REIMAN, T., SAWYER, M. B., MARTIN, L. & BARACOS, V. E. 2008. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol,* 9**,** 629-35.

PRADO, C. M., WELLS, J. C., SMITH, S. R., STEPHAN, B. C. & SIERVO, M. 2012. Sarcopenic obesity: A Critical appraisal of the current evidence. *Clin Nutr,* 31**,** 583-601.

PSUTKA, S. P., BOORJIAN, S. A., MOYNAGH, M. R., SCHMIT, G. D., FRANK, I., CARRASCO, A., STEWART, S. B., TARRELL, R., THAPA, P. & TOLLEFSON, M. K. 2015. Mortality after

radical cystectomy: impact of obesity versus adiposity after adjusting for skeletal muscle wasting. *J Urol,* 193**,** 1507-13.

PUBLIC HEALTH ENGLAND 2007. UK Radon: Overall map of radon affected areas in England and Wales Health Protection Agency and British Geological Survey

RAGUZ, S. & YAGUE, E. 2008. Resistance to chemotherapy: new treatments and novel insights into an old problem. *Br J Cancer,* 99**,** 387-91.

RAJASEKARAN, A. B., SILVEY, D., LEUNG, B., HONEYBOURNE, D., CAYTON, R. M., REYNOLDS, J., TROTTER, S. & ROLAND, M. A. 2006. Effect of a multidisciplinary lung investigation day on a rapid access lung cancer service. *Postgrad Med J,* 82**,** 414-6.

RAMI-PORTA, R., ASAMURA, H., TRAVIS, W. D. & RUSCH, V. W. 2017. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*.

RAPP, E., PATER, J. L., WILLAN, A., CORMIER, Y., MURRAY, N., EVANS, W. K., HODSON, D. I., CLARK, D. A., FELD, R., ARNOLD, A. M. & ET AL. 1988. Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer--report of a Canadian multicenter randomized trial. *J Clin Oncol,* 6**,** 633-41.

RENEHAN, A. G. 2014. The 'obesity paradox' and survival after colorectal cancer: true or false? *Cancer Causes Control,* 25**,** 1419-22.

RENEHAN, A. G., TYSON, M., EGGER, M., HELLER, R. F. & ZWAHLEN, M. 2008. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet,* 371**,** 569-78.

REYA, T., MORRISON, S. J., CLARKE, M. F. & WEISSMAN, I. L. 2001. Stem cells, cancer, and cancer stem cells. *Nature,* 414**,** 105-111.

RIAZ, S. P., LUCHTENBORG, M., JACK, R. H., COUPLAND, V. H., LINKLATER, K. M., PEAKE, M. D. & MOLLER, H. 2012. Variation in surgical resection for lung cancer in relation to survival: population-based study in England 2004-2006. *Eur J Cancer,* 48**,** 54-60.

RICHARDS, E. W., LONG, C. L., NELSON, K. M., PINKSTON, J. A., NAVARI, R. M., GEIGER, J. W., GANDY, R. E. & BLAKEMORE, W. S. 1992. Glucose metabolism in advanced lung cancer patients. *Nutrition,* 8**,** 245-51.

RIER, H. N., JAGER, A., SLEIJFER, S., MAIER, A. B. & LEVIN, M. D. 2016. The Prevalence and Prognostic Value of Low Muscle Mass in Cancer Patients: A Review of the Literature. *Oncologist*.

RIES, A., TROTTENBERG, P., ELSNER, F., STIEL, S., HAUGEN, D., KAASA, S. & RADBRUCH, L. 2012. A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: an EPCRC cachexia guidelines project. *Palliat Med,* 26**,** 294-304.

ROILA, F., LUPATTELLI, M., SASSI, M., BASURTO, C., BRACARDA, S., PICCIAFUOCO, M., BOSCHETTI, E., MILELLA, G., BALLATORI, E., TONATO, M. & ET AL. 1991. Intra and interobserver variability in cancer patients' performance status assessed according to Karnofsky and ECOG scales. *Ann Oncol,* 2**,** 437-9.

ROLLAND, Y. Evaluation of sarcopenia. 4th International Seminar on Preventive Geriatrics., 2011 Athens, Greece.

ROSELL, R., CARCERENY, E., GERVAIS, R., VERGNENEGRE, A., MASSUTI, B., FELIP, E., PALMERO, R., GARCIA-GOMEZ, R., PALLARES, C., SANCHEZ, J. M., PORTA, R., COBO, M., GARRIDO, P., LONGO, F., MORAN, T., INSA, A., DE MARINIS, F., CORRE, R., BOVER, I., ILLIANO, A., DANSIN, E., DE CASTRO, J., MILELLA, M., REGUART, N., ALTAVILLA, G., JIMENEZ, U., PROVENCIO, M., MORENO, M. A., TERRASA, J., MUNOZ-LANGA, J., VALDIVIA, J., ISLA, D., DOMINE, M., MOLINIER, O., MAZIERES, J., BAIZE, N., GARCIA-CAMPELO, R., ROBINET, G., RODRIGUEZ-ABREU, D., LOPEZ-VIVANCO, G., GEBBIA, V., FERRERA-DELGADO, L., BOMBARON, P., BERNABE, R., BEARZ, A., ARTAL, A., CORTESI, E., ROLFO, C., SANCHEZ-RONCO, M., DROZDOWSKYJ, A., QUERALT, C., DE AGUIRRE, I., RAMIREZ, J. L., SANCHEZ, J. J., MOLINA, M. A., TARON, M. & PAZ-ARES, L. 2012.

Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol,* 13**,** 239-46.

ROSELL, R., MORAN, T., QUERALT, C., PORTA, R., CARDENAL, F., CAMPS, C., MAJEM, M., LOPEZ-VIVANCO, G., ISLA, D., PROVENCIO, M., INSA, A., MASSUTI, B., GONZALEZ-LARRIBA, J. L., PAZ-ARES, L., BOVER, I., GARCIA-CAMPELO, R., MORENO, M. A., CATOT, S., ROLFO, C., REGUART, N., PALMERO, R., SANCHEZ, J. M., BASTUS, R., MAYO, C., BERTRAN-ALAMILLO, J., MOLINA, M. A., SANCHEZ, J. J. & TARON, M. 2009. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med,* 361**,** 958-67.

ROSENBERG, I. H. 1989. Summary comments. *The American Journal of Clinical Nutrition,* 50**,** 1231-1233.

ROSENBERG, I. H. 1997. Sarcopenia: origins and clinical relevance. *J Nutr,* 127**,** 990S-991S.

ROSS, P. J., ASHLEY, S., NORTON, A., PRIEST, K., WATERS, J. S., EISEN, T., SMITH, I. E. & O'BRIEN, M. E. 2004. Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? *Br J Cancer,* 90**,** 1905-11.

RUSCH, V., KLIMSTRA, D., LINKOV, I. & DMITROVSKY, E. 1995. Aberrant expression of p53 or the epidermal growth factor receptor is frequent in early bronchial neoplasia and coexpression precedes squamous cell carcinoma development. *Cancer Res,* 55**,** 1365-72.

RUSHTON, L., HUTCHINGS, S. & BROWN, T. 2008. The burden of cancer at work: estimation as the first step to prevention. *Occup Environ Med,* 65**,** 789-800.

SACHER, A. G., LE, L. W., LAU, A., EARLE, C. C. & LEIGHL, N. B. 2015. Real-world chemotherapy treatment patterns in metastatic non-small cell lung cancer: Are patients undertreated? *Cancer,* 121**,** 2562-9.

SAMET, J. M. 1991. Diseases of uranium miners and other underground miners exposed to radon. *Occup Med,* 6**,** 629-39.

SAMSON, M. M., MEEUWSEN, I. B., CROWE, A., DESSENS, J. A., DUURSMA, S. A. & VERHAAR, H. J. 2000. Relationships between physical performance measures, age, height and body weight in healthy adults. *Age Ageing,* 29**,** 235-42.

SANGHA, R. & LARA JR., P. N. 2011. *Evaluation, management and medical therapy of small cell lung cancer. ,* New York, Demos Medical Publishing.

SARHILL, N., MAHMOUD, F., WALSH, D., NELSON, K. A., KOMURCU, S., DAVIS, M., LEGRAND, S., ABDULLAH, O. & RYBICKI, L. 2003. Evaluation of nutritional status in advanced metastatic cancer. *Support Care Cancer,* 11**,** 652-9.

SCAGLIOTTI, G., HANNA, N., FOSSELLA, F., SUGARMAN, K., BLATTER, J., PETERSON, P., SIMMS, L. & SHEPHERD, F. A. 2009. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist,* 14**,** 253-63.

SCHAAP, L. A., PLUIJM, S. M., DEEG, D. J., HARRIS, T. B., KRITCHEVSKY, S. B., NEWMAN, A. B., COLBERT, L. H., PAHOR, M., RUBIN, S. M., TYLAVSKY, F. A. & VISSER, M. 2009. Higher inflammatory marker levels in older persons: associations with 5-year change in muscle mass and muscle strength. *J Gerontol A Biol Sci Med Sci,* 64**,** 1183-9.

SCHNADIG, I. D., FROMME, E. K., LOPRINZI, C. L., SLOAN, J. A., MORI, M., LI, H. & BEER, T. M. 2008. Patient-physician disagreement regarding performance status is associated with worse survivorship in patients with advanced cancer. *Cancer,* 113**,** 2205-14.

SCHULKES, K. J., HAMAKER, M. E., VAN DEN BOS, F. & VAN ELDEN, L. J. 2016. Relevance of a Geriatric Assessment for Elderly Patients With Lung Cancer-A Systematic Review. *Clin Lung Cancer,* 17**,** 341-349 e3.

SCOTT, H. R., MCMILLAN, D. C., WATSON, W. S., MILROY, R. & MCARDLE, C. S. 2001. Longitudinal study of resting energy expenditure, body cell mass and the

inflammatory response in male patients with non-small cell lung cancer. *Lung Cancer,* 32**,** 307-12.

SCOTT, W. J., HOWINGTON, J., FEIGENBERG, S., MOVSAS, B. & PISTERS, K. 2007. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest,* 132**,** 234S-242S.

SEER DATABASE. 2008. *Cancer of the Lung and Bronchus (Invasive)* [Online]. Available: http://seer.cancer.gov/csr/1975_2008/browse_csr.php?section=15&page=sect_15_table.10.html [Accessed 4th June 2013.

SEN, M., DEMIRAL, A. S., CETINGOZ, R., ALANYALI, H., AKMAN, F., SENTURK, D. & KINAY, M. 1998. Prognostic factors in lung cancer with brain metastasis. *Radiother Oncol,* 46**,** 33-8.

SHACHAR, S. S., DEAL, A. M., WEINBERG, M., NYROP, K. A., WILLIAMS, G. R., NISHIJIMA, T. F., BENBOW, J. M. & MUSS, H. B. 2017. Skeletal Muscle Measures as Predictors of Toxicity, Hospitalization, and Survival in Patients with Metastatic Breast Cancer Receiving Taxane-Based Chemotherapy. *Clin Cancer Res,* 23**,** 658-665.

SHALLWANI, S. M., SIMMONDS, M. J., KASYMJANOVA, G. & SPAHIJA, J. 2016. Quality of life, symptom status and physical performance in patients with advanced non-small cell lung cancer undergoing chemotherapy: an exploratory analysis of secondary data. *Lung Cancer,* 99**,** 69-75.

SHEN, W., PUNYANITYA, M., WANG, Z., GALLAGHER, D., ST.-ONGE, M.-P., ALBU, J., HEYMSFIELD, S. B. & HESHKA, S. 2004. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *Journal of Applied Physiology,* 97**,** 2333-2338.

SHIMIZU, K., OKITA, R., SAISHO, S., MAEDA, A., NOJIMA, Y. & NAKATA, M. 2015. Preoperative neutrophil/lymphocyte ratio and prognostic nutritional index predict survival in patients with non-small cell lung cancer. *World J Surg Oncol,* 13**,** 291.

SIEGEL, R. L., MILLER, K. D. & JEMAL, A. 2017. Cancer Statistics, 2017. *CA Cancer J Clin,* 67**,** 7-30.

SIEGELIN, M. D. & BORCZUK, A. C. 2014. Epidermal growth factor receptor mutations in lung adenocarcinoma. *Lab Invest,* 94**,** 129-37.

SIMMONS, C. P., KOINIS, F., FALLON, M. T., FEARON, K. C., BOWDEN, J., SOLHEIM, T. S., GRONBERG, B. H., MCMILLAN, D. C., GIOULBASANIS, I. & LAIRD, B. J. 2015. Prognosis in advanced lung cancer--A prospective study examining key clinicopathological factors. *Lung Cancer,* 88**,** 304-9.

SIMONS, J. P., SCHOLS, A. M., HOEFNAGELS, J. M., WESTERTERP, K. R., TEN VELDE, G. P. & WOUTERS, E. F. 1998. Effects of medroxyprogesterone acetate on food intake, body composition, and resting energy expenditure in patients with advanced, nonhormone-sensitive cancer: a randomized, placebo-controlled trial. *Cancer,* 82**,** 553-60.

SJOBLOM, B., GRONBERG, B. H., WENTZEL-LARSEN, T., BARACOS, V. E., HJERMSTAD, M. J., AASS, N., BREMNES, R. M., FLOTTEN, O., BYE, A. & JORDHOY, M. 2016. Skeletal muscle radiodensity is prognostic for survival in patients with advanced non-small cell lung cancer. *Clin Nutr,* 35**,** 1386-1393.

SKELTON, D. A., GREIG, C. A., DAVIES, J. M. & YOUNG, A. 1994. Strength, power and related functional ability of healthy people aged 65-89 years. *Age Ageing,* 23**,** 371-7.

SMITH, K. L. & TISDALE, M. J. 1993. Increased protein degradation and decreased protein synthesis in skeletal muscle during cancer cachexia. *Br J Cancer,* 67**,** 680-5.

SOMMER, M. S., TRIER, K., VIBE-PETERSEN, J., MISSEL, M., CHRISTENSEN, M., LARSEN, K. R., LANGER, S. W., HENDRIKSEN, C., CLEMENTSEN, P., PEDERSEN, J. H. & LANGBERG, H. 2014. Perioperative rehabilitation in operation for lung cancer (PROLUCA) - rationale and design. *BMC Cancer,* 14**,** 404.

SONPAVDE, G., VOGELZANG, N. J., GALSKY, M. D., RAGHAVAN, V. A. & DANIEL, S. 2012. Objective measures of physical functional capacity warrant exploration to complement or replace the subjective physician estimated performance status. *Am J Clin Oncol,* 35**,** 163-6.

SORENSEN, J. B., KLEE, M., PALSHOF, T. & HANSEN, H. H. 1993. Performance status assessment in cancer patients. An inter-observer variability study. *Br J Cancer,* 67**,** 773-5.

SPIRO, S. G. & SILVESTRI, G. A. 2005a. One hundred years of lung cancer. *Am J Respir Crit Care Med,* 172**,** 523-9.

SPIRO, S. G. & SILVESTRI, G. A. 2005b. The treatment of advanced non-small cell lung cancer. *Curr Opin Pulm Med,* 11**,** 287-91.

SRDIC, D., PLESTINA, S., SVERKO-PETERNAC, A., NIKOLAC, N., SIMUNDIC, A. M. & SAMARZIJA, M. 2016. Cancer cachexia, sarcopenia and biochemical markers in patients with advanced non-small cell lung cancer-chemotherapy toxicity and prognostic value. *Support Care Cancer,* 24**,** 4495-502.

STAYNER, L., BENA, J., SASCO, A. J., SMITH, R., STEENLAND, K., KREUZER, M. & STRAIF, K. 2007. Lung cancer risk and workplace exposure to environmental tobacco smoke. *Am J Public Health,* 97**,** 545-51.

STENHOLM, S., ALLEY, D., BANDINELLI, S., GRISWOLD, M. E., KOSKINEN, S., RANTANEN, T., GURALNIK, J. M. & FERRUCCI, L. 2009. The effect of obesity combined with low muscle strength on decline in mobility in older persons: results from the InCHIANTI study. *Int J Obes (Lond),* 33**,** 635-44.

STRAIF, K., BAAN, R., GROSSE, Y., SECRETAN, B., EL GHISSASSI, F. & COGLIANO, V. 2006. Carcinogenicity of household solid fuel combustion and of high-temperature frying. *Lancet Oncol,* 7**,** 977-8.

STRASSMANN, G., FONG, M., KENNEY, J. S. & JACOB, C. O. 1992. Evidence for the involvement of interleukin 6 in experimental cancer cachexia. *J Clin Invest,* 89**,** 1681-4.

STRATTON, R. J., HACKSTON, A., LONGMORE, D., DIXON, R., PRICE, S., STROUD, M., KING, C. & ELIA, M. 2004. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool' ('MUST') for adults. *Br J Nutr,* 92**,** 799-808.

SUGIURA, H., YAMADA, K., SUGIURA, T., HIDA, T. & MITSUDOMI, T. 2008. Predictors of survival in patients with bone metastasis of lung cancer. *Clin Orthop Relat Res,* 466**,** 729-36.

SUGIURA, S., ANDO, Y., MINAMI, H., ANDO, M., SAKAI, S. & SHIMOKATA, K. 1997. Prognostic value of pleural effusion in patients with non-small cell lung cancer. *Clin Cancer Res,* 3**,** 47-50.

SUH, S. Y., LEBLANC, T. W., SHELBY, R. A., SAMSA, G. P. & ABERNETHY, A. P. 2011. Longitudinal patient-reported performance status assessment in the cancer clinic is feasible and prognostic. *J Oncol Pract,* 7**,** 374-81.

SULLIVAN, J. P., MINNA, J. D. & SHAY, J. W. 2010. Evidence for self-renewing lung cancer stem cells and their implications in tumor initiation, progression, and targeted therapy. *Cancer Metastasis Rev,* 29**,** 61-72.

SUZUKI, Y., OKAMOTO, T., FUJISHITA, T., KATSURA, M., AKAMINE, T., TAKAMORI, S., MORODOMI, Y., TAGAWA, T., SHOJI, F. & MAEHARA, Y. 2016. Clinical implications of sarcopenia in patients undergoing complete resection for early non-small cell lung cancer. *Lung Cancer,* 101**,** 92-97.

TALMADGE, J. E. & FIDLER, I. J. 2010. AACR centennial series: the biology of cancer metastasis: historical perspective. *Cancer Res,* 70**,** 5649-69.

TAN, B. H., BRAMMER, K., RANDHAWA, N., WELCH, N. T., PARSONS, S. L., JAMES, E. J. & CATTON, J. A. 2015a. Sarcopenia is associated with toxicity in patients undergoing

neo-adjuvant chemotherapy for oesophago-gastric cancer. *Eur J Surg Oncol,* 41**,** 333-8.

TAN, C. S., READ, J. A., PHAN, V. H., BEALE, P. J., PEAT, J. K. & CLARKE, S. J. 2015b. The relationship between nutritional status, inflammatory markers and survival in patients with advanced cancer: a prospective cohort study. *Support Care Cancer,* 23**,** 385-91.

TARDIF, N., KLAUDE, M., LUNDELL, L., THORELL, A. & ROOYACKERS, O. 2013. Autophagic-lysosomal pathway is the main proteolytic system modified in the skeletal muscle of esophageal cancer patients. *Am J Clin Nutr,* 98**,** 1485-92.

TAYLOR, A. E., OLVER, I. N., SIVANTHAN, T., CHI, M. & PURNELL, C. 1999. Observer error in grading performance status in cancer patients. *Support Care Cancer,* 7**,** 332-5.

TAYLOR, R., NAJAFI, F. & DOBSON, A. 2007. Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent. *Int J Epidemiol,* 36**,** 1048-59.

TESSITORE, L., COSTELLI, P. & BACCINO, F. M. 1994. Pharmacological interference with tissue hypercatabolism in tumour-bearing rats. *Biochem J,* 299 (Pt 1)**,** 71-8.

TEWARI, N., MARTIN-UCAR, A. E., BLACK, E., BEGGS, L., BEGGS, F. D., DUFFY, J. P. & MORGAN, W. E. 2007. Nutritional status affects long term survival after lobectomy for lung cancer. *Lung Cancer,* 57**,** 389-94.

THIBAULT, R., GENTON, L. & PICHARD, C. 2012. Body composition: why, when and for who? *Clin Nutr,* 31**,** 435-47.

THOMAS, P. A., BERBIS, J., FALCOZ, P. E., LE PIMPEC-BARTHES, F., BERNARD, A., JOUGON, J., PORTE, H., ALIFANO, M. & DAHAN, M. 2014. National perioperative outcomes of pulmonary lobectomy for cancer: the influence of nutritional status. *Eur J Cardiothorac Surg,* 45**,** 652-9; discussion 659.

TIDBALL, J. G. & SPENCER, M. J. 2000. Calpains and muscular dystrophies. *Int J Biochem Cell Biol,* 32**,** 1-5.

TISDALE, M. J. 1997. Cancer cachexia: metabolic alterations and clinical manifestations. *Nutrition,* 13**,** 1-7.

TISDALE, M. J. 2009. Mechanisms of cancer cachexia. *Physiol Rev,* 89**,** 381-410.

TOLOZA, E. M., HARPOLE, L., DETTERBECK, F. & MCCRORY, D. C. 2003a. Invasive staging of non-small cell lung cancer: a review of the current evidence. *Chest,* 123**,** 157S-166S.

TOLOZA, E. M., HARPOLE, L. & MCCRORY, D. C. 2003b. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. *Chest,* 123**,** 137S-146S.

TRAVIS, W. D. 2011. Pathology of lung cancer. *Clin Chest Med,* 32**,** 669-92.

TRAVIS, W. D., BRAMBILLA, E., MULLER-HERMELINK, H. K. & HARRIS, C. C. 2004. *Pathology and genetics: tumours of the lung, pleura, thymus and heart. ,* Lyon, France.

TRUTSCHNIGG, B., KILGOUR, R. D., REINGLAS, J., ROSENTHALL, L., HORNBY, L., MORAIS, J. A. & VIGANO, A. 2008. Precision and reliability of strength (Jamar vs. Biodex handgrip) and body composition (dual-energy X-ray absorptiometry vs. bioimpedance analysis) measurements in advanced cancer patients. *Appl Physiol Nutr Metab,* 33**,** 1232-9.

US ADVISORY COMMITTEE TO THE PUBLIC HEALTH SERVICE 1964. Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, D.C.

VADELL, C., SEGUI, M. A., GIMENEZ-ARNAU, J. M., MORALES, S., CIRERA, L., BESTIT, I., BATISTE, E., BLANCO, R., JOLIS, L., BOLEDA, M. & ANTON, I. 1998. Anticachectic efficacy of megestrol acetate at different doses and versus placebo in patients with neoplastic cachexia. *Am J Clin Oncol,* 21**,** 347-51.

VAN DURME, Y. M., VERHAMME, K. M., STIJNEN, T., VAN ROOIJ, F. J., VAN POTTELBERGE, G. R., HOFMAN, A., JOOS, G. F., STRICKER, B. H. & BRUSSELLE, G. G. 2009. Prevalence, incidence, and lifetime risk for the development of COPD in the elderly: the Rotterdam study. *Chest,* 135**,** 368-77.

VEASEY RODRIGUES, H., BARACOS, V. E., WHELER, J. J., PARSONS, H. A., HONG, D. S., NAING, A., FU, S., FALCHOOCK, G., TSIMBERIDOU, A. M., PIHA-PAUL, S., CHISHOLM, G. & KURZROCK, R. 2013. Body composition and survival in the early clinical trials setting. *Eur J Cancer,* 49**,** 3068-75.

VEGLIA, F., VINEIS, P., OVERVAD, K., BOEING, H., BERGMANN, M., TRICHOPOULOU, A., TRICHOPOULOS, D., PALLI, D., KROGH, V., TUMINO, R., LINSEISEN, J., STEINDORF, K., RAASCHOU-NIELSEN, O., TJONNELAND, A., GONZALEZ, C. A., MARTINEZ, C., DORRONSORO, M., BARRICARTE, A., CIRERA, L., QUIROS, J. R., DAY, N. E., SARACCI, R. & RIBOLI, E. 2007. Occupational exposures, environmental tobacco smoke, and lung cancer. *Epidemiology,* 18**,** 769-75.

VERWEIJ, N. M., SCHIPHORST, A. H., PRONK, A., VAN DEN BOS, F. & HAMAKER, M. E. 2016. Physical performance measures for predicting outcome in cancer patients: a systematic review. *Acta Oncol,* 55**,** 1386-1391.

VINOD, S. K., O'CONNELL, D. L., SIMONELLA, L., DELANEY, G. P., BOYER, M., PETERS, M., MILLER, D., SUPRAMANIAM, R., MCCAWLEY, L. & ARMSTRONG, B. 2008. Gaps in optimal care for lung cancer. *J Thorac Oncol,* 3**,** 871-9.

VINOD, S. K., SIDHOM, M. A., GABRIEL, G. S., LEE, M. T. & DELANEY, G. P. 2010. Why do some lung cancer patients receive no anticancer treatment? *J Thorac Oncol,* 5**,** 1025-32.

VISSER, M., GOODPASTER, B. H., KRITCHEVSKY, S. B., NEWMAN, A. B., NEVITT, M., RUBIN, S. M., SIMONSICK, E. M. & HARRIS, T. B. 2005. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. *J Gerontol A Biol Sci Med Sci,* 60**,** 324-33.

VON HAEHLING, S. & ANKER, S. D. 2010. Cachexia as a major underestimated and unmet medical need: facts and numbers. *J Cachexia Sarcopenia Muscle,* 1**,** 1-5.

VRIELING, A. & KAMPMAN, E. 2010. The role of body mass index, physical activity, and diet in colorectal cancer recurrence and survival: a review of the literature. *Am J Clin Nutr,* 92**,** 471-90.

WALTERS, S., MARINGE, C., COLEMAN, M. P., PEAKE, M. D., BUTLER, J., YOUNG, N., BERGSTROM, S., HANNA, L., JAKOBSEN, E., KOLBECK, K., SUNDSTROM, S., ENGHOLM, G., GAVIN, A., GJERSTORFF, M. L., HATCHER, J., JOHANNESEN, T. B., LINKLATER, K. M., MCGAHAN, C. E., STEWARD, J., TRACEY, E., TURNER, D., RICHARDS, M. A. & RACHET, B. 2013. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. *Thorax,* 68**,** 551-64.

WANG, A., WANG, H. Y., LIU, Y., ZHAO, M. C., ZHANG, H. J., LU, Z. Y., FANG, Y. C., CHEN, X. F. & LIU, G. T. 2015. The prognostic value of PD-L1 expression for non-small cell lung cancer patients: a meta-analysis. *Eur J Surg Oncol,* 41**,** 450-6.

WARD, P., HECHT, J. R., WANG, H. J., DICHMANN, R., LIEM, A. K., CHAN, D., PATEL, R., HU, E. H., TCHEKMEDYIAN, N. S., WAINBERG, Z. A. & NAEIM, A. 2014. Physical function and quality of life in frail and/or elderly patients with metastatic colorectal cancer treated with capecitabine and bevacizumab: an exploratory analysis. *J Geriatr Oncol,* 5**,** 368-75.

WELLE, S., BHATT, K., PINKERT, C. A., TAWIL, R. & THORNTON, C. A. 2007. Muscle growth after postdevelopmental myostatin gene knockout. *Am J Physiol Endocrinol Metab,* 292**,** E985-91.

WELSH CANCER INTELLIGENCE AND SURVEILLANCE UNIT 2011. Cancer Incidence in Wales, 2007-2011. Public Health Wales.

WEST, H. J. 2013. Patients with advanced non-small-cell lung cancer and marginal performance status: walking the tight rope towards improved survival. *J Clin Oncol,* 31**,** 2841-3.

WESTMAN, G., BERGMAN, B., ALBERTSSON, M., KADAR, L., GUSTAVSSON, G., THANING, L., ANDERSSON, M., STRAUMITS, A., JEPPSON, B., LINDEN, C. J., EWERS, S. B., ANDERSSON, H., MERCKE, C., HAFSTROM, L., BIRCK, O. & ORGUM, P. 1999. Megestrol acetate in advanced, progressive, hormone-insensitive cancer. Effects on the quality of life: a placebo-controlled, randomised, multicentre trial. *Eur J Cancer,* 35**,** 586-95.

WIELAND, B. M., STEWART, G. D., SKIPWORTH, R. J., SANGSTER, K., FEARON, K. C., ROSS, J. A., REIMAN, T. J., EASAW, J., MOURTZAKIS, M., KUMAR, V., PAK, B. J., CALDER, K., FILIPPATOS, G., KREMASTINOS, D. T., PALCIC, M. & BARACOS, V. E. 2007. Is there a human homologue to the murine proteolysis-inducing factor? *Clin Cancer Res,* 13**,** 4984-92.

WIGMORE, S. J., TODOROV, P. T., BARBER, M. D., ROSS, J. A., TISDALE, M. J. & FEARON, K. C. 2000. Characteristics of patients with pancreatic cancer expressing a novel cancer cachectic factor. *Br J Surg,* 87**,** 53-8.

WIN, T., JACKSON, A., GROVES, A. M., SHARPLES, L. D., CHARMAN, S. C. & LAROCHE, C. M. 2006. Comparison of shuttle walk with measured peak oxygen consumption in patients with operable lung cancer. *Thorax,* 61**,** 57-60.

WORKING GROUP ON FUNCTIONAL OUTCOME MEASURES FOR CLINICAL TRIALS 2008. Functional outcomes for clinical trials in frail older persons: time to be moving. *J Gerontol A Biol Sci Med Sci,* 63**,** 160-4.

WORLD HEALTH ORGANISATION 1967. *Histological typing of lung tumours,* Geneva, WHO.

WORLD HEALTH ORGANISATION 1981. *Histological typing of lung tumours.,* Geneva, WHO.

WORLD HEALTH ORGANISATION 2008. WHO report on the global tobacco epidemic. Geneva, Switzerland.

WU, X., CHEN, H. & WANG, X. 2012. Can lung cancer stem cells be targeted for therapies? *Cancer Treat Rev,* 38**,** 580-8.

YAN, T. D., BLACK, D., BANNON, P. G. & MCCAUGHAN, B. C. 2009. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. *J Clin Oncol,* 27**,** 2553-62.

YANG, L., YANG, G., ZHOU, M., SMITH, M., GE, H., BOREHAM, J., HU, Y., PETO, R., WANG, J. & CHEN, Z. 2009. Body mass index and mortality from lung cancer in smokers and nonsmokers: a nationally representative prospective study of 220,000 men in China. *Int J Cancer,* 125**,** 2136-43.

YANG, R., CHEUNG, M. C., PEDROSO, F. E., BYRNE, M. M., KONIARIS, L. G. & ZIMMERS, T. A. 2011. Obesity and weight loss at presentation of lung cancer are associated with opposite effects on survival. *J Surg Res,* 170**,** e75-83.

YU, I. T., CHIU, Y. L., AU, J. S., WONG, T. W. & TANG, J. L. 2006. Dose-response relationship between cooking fumes exposures and lung cancer among Chinese nonsmoking women. *Cancer Res,* 66**,** 4961-7.

ZAKI, M. H., NEMETH, J. A. & TRIKHA, M. 2004. CNTO 328, a monoclonal antibody to IL-6, inhibits human tumor-induced cachexia in nude mice. *Int J Cancer,* 111**,** 592-5.

ZAMMIT, P. S., GOLDING, J. P., NAGATA, Y., HUDON, V., PARTRIDGE, T. A. & BEAUCHAMP, J. R. 2004. Muscle satellite cells adopt divergent fates: a mechanism for self-renewal? *J Cell Biol,* 166**,** 347-57.

ZIMMERMANN, C., BURMAN, D., BANDUKWALA, S., SECCARECCIA, D., KAYA, E., BRYSON, J., RODIN, G. & LO, C. 2010. Nurse and physician inter-rater agreement of three performance status measures in palliative care outpatients. *Support Care Cancer,* 18**,** 609-16.

ZIMMERS, T. A., DAVIES, M. V., KONIARIS, L. G., HAYNES, P., ESQUELA, A. F., TOMKINSON, K. N., MCPHERRON, A. C., WOLFMAN, N. M. & LEE, S. J. 2002. Induction of cachexia in mice by systemically administered myostatin. *Science,* 296**,** 1486-8.

ZOGG, C. K., MUNGO, B., LIDOR, A. O., STEM, M., RIOS DIAZ, A. J., HAIDER, A. H. & MOLENA, D. 2015. Influence of body mass index on outcomes after major resection for cancer. *Surgery,* 158**,** 472-85.

ZOU, W. & CHEN, L. 2008. Inhibitory B7-family molecules in the tumour microenvironment. *Nat Rev Immunol,* 8**,** 467-77.

Appendix A: Case Report Form

Participant Code Number:
Participant Initials:
Date of Study:
Form completed by:

Case Report Form

Association of Muscle Bulk and Physical Fitness Measurements with Receipt and Completion of Treatment

Screening Inclusion and Exclusion criteria

Inclusion   Age ≥ 18 years   ☐

Suspected NSCLC   ☐

Clinician scored WHO PS 0-2   ☐

Able to give informed consent   ☐

Willing to participate   ☐

Exclusion   No ICD or Pacemaker   ☐

No excessive alcohol 24 hrs prior   ☐

No strenuous exercise 24 hrs prior   ☐

No significant peripheral oedema   ☐

No physical impediment precluding participation   ☐

No neurological impediment precluding participation   ☐

Able to give informed consent with sufficient ability to communicate in English   ☐

Baseline data

Participant Code Number:
Participant Initials:
Date of Study:
Form completed by:

Demographics

Age
Gender

Weight _____ kg   Baseline Wt _____ kg
Height _____m   BMI_____ kg/m^2
Wt change _____kg, _____ % over past 3-6 mths
Acutely ill or no nutritional intake in >5 days   Y / N
MUST score (circle)   0   1   ≥2
Food and drink over last 12 hrs _____
_____

Baseline Data

Physician assessed PS   ECOG/WHO _____ Karnofsky_____
Co-morbidities (list) _____
If COPD, severity _____   NSAID/ steroid use _____
Baseline blood tests: Hb _____   Albumin _____ CRP _____

Body Composition

Predicted MM1 _____kg   DEXA performed Y / N
Appendicular MM1_____kg   DEXA MM (Subtotal) _____kg
Predicted MM2_____kg   DEXA ASM   _____kg
Appendicular MM2 _____kg   DEXA ASM index _____kg/m^2
BIA MM index_____kg/m^2
BIA ASM index _____kg/m^2

Physical Function

Participant assessed PS   ECOG/WHO _____ Karnofsky _____
SPPB: Balance _____ 0-4   Gait speed _____ 0-4   Chair stands _____ 0-4
Total SPPB _____ 0-12

Participant Code Number:

Participant Initials:

Date of Study:

Form completed by:

Longitudinal data

MDT Treatment plan _____

Receipt of MDT Treatment plan   Y / N

Date received _____

If No, what treatment was received? _____

Completion of MDT Treatment plan   Y / N

Date completed _____

Chemotherapy

Decision for chemo   Y / N   Received chemo   Y / N

If No, reason? _____

Chemotherapy type _____

Date of receipt of 1st cycle _____

No. of chemo cycles completed _____

Completion of full course Y / N

Date of completion _____

If Not completed, reason? _____

Toxicities	Frequency	CTCAE grade
Fatigue		
Nausea		
Vomiting		
Diarrhoea		
Constipation		
Sore mouth		
Hand foot skin reactions		
Neuropathy		
Fever		
Neutropenia		
Other		
Other		
Necessity of dose reduction Y / N		

Surgery

Decision for surgery   Y / N

Received surgery   Y / N

If No, reason? _____

Date of surgery _____

Radiotherapy

Decision for RT   Y / N

Received RT   Y / N

If No, reason? _____

Date of commencement of RT _____
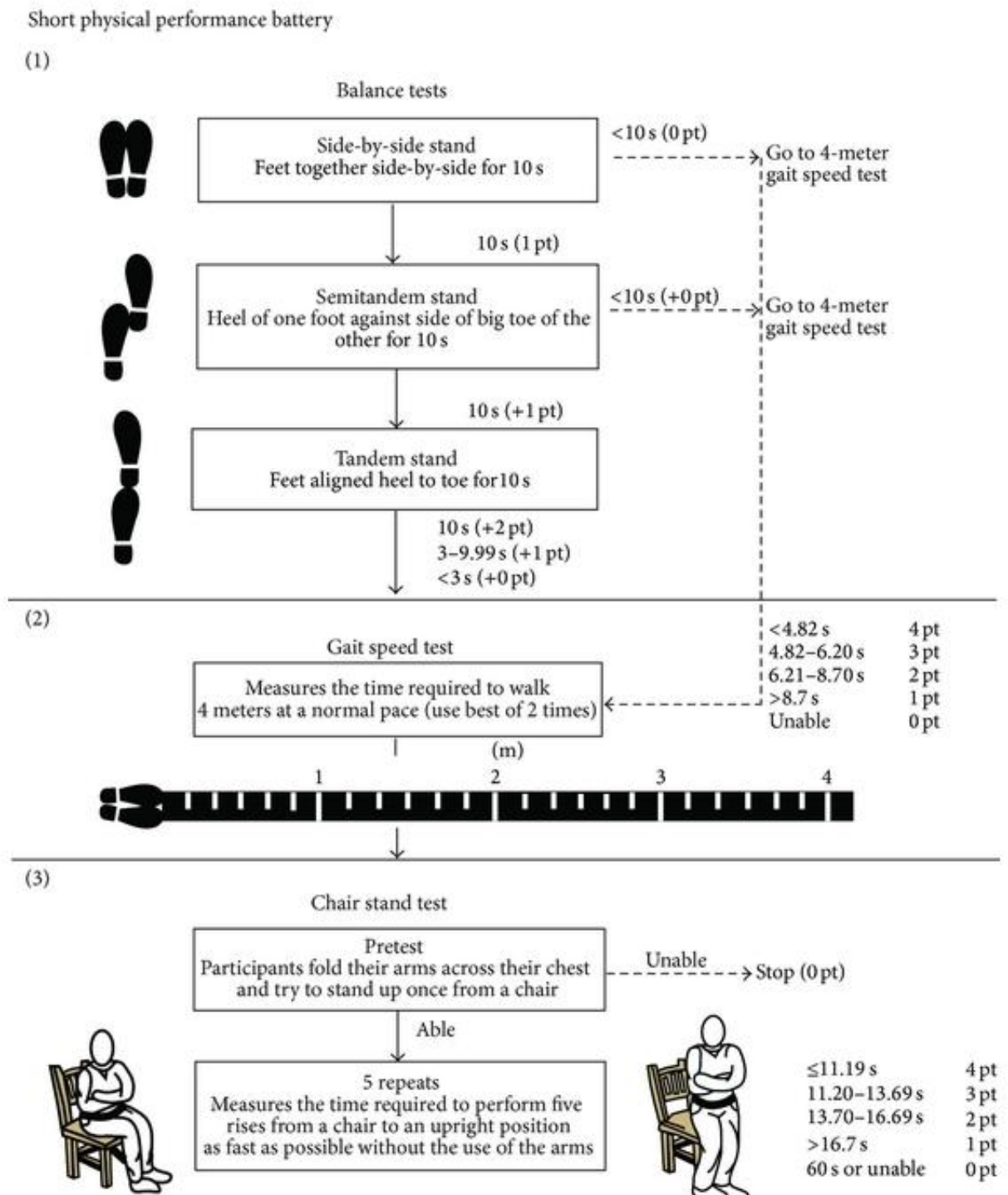
Date of completion of RT course_____

Termination / withdrawal of participation

Date _____

Reason, if any _____

Was the study completed?   Y/N

If Yes, date of completion _____

Any other observations

Appendix B: Short Physical Performance Battery score chart

Short physical performance battery

(1)

Balance tests

Side-by-side stand
Feet together side-by-side for 10 s

<10 s (0 pt) ----→ Go to 4-meter gait speed test

10 s (1 pt)

Semitandem stand
Heel of one foot against side of big toe of the other for 10 s

<10 s (+0 pt) ----→ Go to 4-meter gait speed test

10 s (+1 pt)

Tandem stand
Feet aligned heel to toe for 10 s

10 s (+2 pt)
3–9.99 s (+1 pt)
<3 s (+0 pt)

(2)

Gait speed test

Measures the time required to walk
4 meters at a normal pace (use best of 2 times)

<4.82 s   4 pt
4.82–6.20 s   3 pt
6.21–8.70 s   2 pt
>8.7 s   1 pt
Unable   0 pt

(m)

1   2   3   4

(3)

Chair stand test

Pretest
Participants fold their arms across their chest
and try to stand up once from a chair

Unable ----→ Stop (0 pt)

Able

5 repeats
Measures the time required to perform five
rises from a chair to an upright position
as fast as possible without the use of the arms

≤11.19 s   4 pt
11.20–13.69 s 3 pt
13.70–16.69 s 2 pt
>16.7 s   1 pt
60 s or unable 0 pt

From Guralnik et al (Guralnik et al., 2000)

Appendix C:

Reference Ranges for body composition healthy subjects, adapted from Chumlea et al, 2002. NHANES data for non-Hispanic Whites according to age and gender.

	Fat mass, kg, mean ± SD		Fat-free mass, kg, mean ± SD	
Age	Men	Women	Men	Women
12-13.9	10 ± 6	14 ± 8.7	41.8 ± 8.2	38.1 ± 5.6
14-15.9	14 ± 12.2	17.4 ± 6.9	54.3 ± 9.6	40.4 ± 4.8
16-17.9	13.1 ± 7.5	19.5 ± 10.1	57.8 ± 8.4	41.6 ± 5.5
18-19.9	15.1 ± 8.5	20.6 ± 10.3	58 ± 8	43.1 ± 5.6
20-29.9	17.9 ± 8.7	20.5 ± 9.6	61.3 ± 9.5	42.8 ± 5.9
30-39.9	20.4 ± 8.5	24.1 ± 12.3	63.6 ± 10.5	45 ± 6.9
40-49.9	21.3 ± 8.5	25.9 ± 10.9	64.6 ± 10.6	44.8 ± 6.9
50-59.9	22.3 ± 8.3	28.6 ± 11.6	64.6 ± 8.8	45.4 ± 6.7
60-69.9	22.7 ± 7.7	26.7 ± 9.9	62.3 ± 8.9	43.6 ± 6.3
70-79.9	20.3 ± 6.8	24.8 ± 9.3	59.1 ± 8.6	42.3 ± 6.5