COMORBIDITY IN LUNG CANCER: INFLUENCE ON TREATMENT AND SURVIVAL

by

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DEDICATION

I dedicate this thesis to my wife Pauline and to my children, Cameron and Emma, for their love and support.

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DECLARATION

I declare that all work in this thesis was performed personally unless otherwise acknowledged.

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PUBLICATIONS

The work presented in this thesis has resulted in the following publications:

Grose D, Devereux G, Brown L, Jones R, Sharma D, Selby C, Morrison DS, Docherty K, McIntosh D, Louden G, Downer P, Nicolson M, Milroy R. Variation in comorbidity and clinical management in patients newly diagnosed with lung cancer in four Scottish centres. J ThoracOncol. 2011 Mar;6(3):500-9

Grose D, Devereux G, Milroy R. Comorbidity in lung cancer: important but neglected. A review of the current literature.Clin Lung Cancer. 2011 Jul;12(4):207-11

Grose D, Milroy R. Chronic obstructive pulmonary disease: a complex comorbidity of lung cancer. Jrnl Comorbidity 2011;1:45–50

Grose D, Devereux G, Brown L, Jones R, Sharma D, Selby C, Morrison DS, Docherty K, McIntosh D, Louden G, McElhinney P, Nicolson M, McMillan DC Milroy R.Simple and objective prediction of survival in patients with lung cancer; staging the host systemic inflammatory response. Lung Ca Int 2014, Article ID 731925

Derek Grose, David S Morrison, Graham Devereux, Richard Jones, Dave Sharma, Colin Selby, Kirsty Docherty, David McIntosh, Greig Louden, Marianne Nicolson, Donald C McMillan, Robert Milroy, on behalf of the Scottish Lung Cancer Forum. Comorbidities in lung cancer: prevalence, severity and links with socioeconomic status and treatment. Postgrad Med J 2014;90:1064 305-310

Grose D, Morrison DS, Devereux G, Jones R, Sharma D, Selby C, Docherty K, McIntosh D, Nicolson M, McMillan DC, Milroy R; Scottish Lung Cancer Forum. The impact of comorbidity upon determinants of outcome in patients with lung cancer. Lung Cancer. 2015 Feb;87(2):186-92.

ABSTRACT

Lung cancer is the commonest cancer in Scotland and survival rates for patients in Scotland appear lower than in many other European countries. Although this variation in survival is usually interpreted as evidence of variation in facilities, access to care and clinical practice it is possible that the increased comorbidity and poor performance status of the Scottish population may contribute to the observed disparities in treatment and outcomes, although this has never been proven.

The overall aim of the Thesis was to examine the impact of comorbidity in lung cancer, to attempt to quantify the extent and severity of comorbidity and to explore its relationship with treatment and survival.

Between 2005 and 2008 all newly diagnosed lung cancer patients coming through the Multi-Disciplinary Teams (MDTs) in four Scottish Centres were included in the study. Patient demographics, World Health Organization/Eastern Cooperative Oncology Group performance status (PS), clinic-pathological features, stage, comorbidity, markers of systemic inflammation and proposed primary treatment modality were all recorded. Information on date of death was obtained via survival analysis undertaken by the Information Service Division (ISD) of NHS Scotland. Death records were complete until 1 June 2011, which served as the censor date for those alive.

Chapter 4 examines the variations in demographics and baseline characteristics seen between the centres and reveals significant differences between the centres such as deprivation, stage at presentation, PS and treatments offered.

Chapter 5 explores the relationship between comorbidity and the patient cohort. It shows that comorbidity can be quantified using a scoring index (the Scottish Comorbidity Scoring System (SCSS)) and that increasing

comorbidity is associated with treatment centre and socio-economic status, with the most deprived patients having increased levels of co-morbidity. It also demonstrates that comorbidity appears to have an impact on treatment offered.

Chapter 6 examines the relationship between systemic inflammation (utilizing the well established modified Glasgow Prognostic Score (mGPS)) and outcome in the patient cohort. It confirms previous work supporting the use of the mGPS in predicting lung cancer survival and also shows how it might be used to provide more objective risk stratification in patients diagnosed with lung cancer.

Chapter 7 explores the relationship between a novel comorbidity scoring system (SCSS) and the already established Charlson Comorbidity Index (CCI) and the modified Glasgow Prognostic Score (mGPS). This study aimed to determine which of these factors provided the most accurate information on survival. The novel comorbidity scoring system, the SCSS compares very favourably with the more established CCI. In addition this study demonstrates clear differences between patients having potentially radically treatable disease (NSCLC stage I – IIIa) and disease which would generally be considered incurable (NSCLC IIIb/IV and SCLC).

Chapter 8 examines the reasons for the clinician decision-making process and if these reasons do indeed mirror the individual patient's demographics, fitness and stage. In the majority of patients, both in the early and advanced stage at presentation, the treatment decision appears to be appropriate given the recorded fitness, PS and comorbidity. However in a small but significant number of patients there did appear to be discrepancies between the clinician's reasons for sub-optimal therapy and the recorded objective assessment of the patient in question.

The work presented in this thesis has demonstrated the significant extent of comorbidity in lung cancer and the important role it appears to play

(along with systemic inflammation) in determining treatment choice and survival.

CHAPTER 1: INTRODUCTION

1.1 Lung Cancer in Scotland

Lung cancer is the commonest cancer in Scotland and the second commonest in the UK (Office for National Statistics, 2006; ISD, 2009). In 2011 5,096 cases of lung cancer were recorded in Scotland. 2,601 were in males with 2,495 being in females. The incidence rate in Scotland was 97.0 per 100,000 in comparison to 68.7 per 100,000 across the UK (ISD Scotland, 2013). The incidence rates in Scotland remain amongst the highest in the world (Parkin et al., 2002) reflecting the history of high smoking prevalence.

Treatment and survival rates for patients with lung cancer in Scotland appear lower than in many other European countries. Five-year survival is quoted at 6-7% (Gregor et al., 2001) compared with 8-15% in other European countries and America (Janssen-Heijnen et al., 1998). Erridge et al showed significant differences in survival between Scotland and British Columbia with 2 yr. OS being 10% vs. 23% (Erridge et al., 2009). There also appear to be variations in treatment rates within Scotland (Gregor et al., 2001).

Although this variation in treatment and survival is usually interpreted as evidence of variation in facilities, access to care and clinical practice it is possible that the increased co-morbidity and poor performance status of the Scottish population may contribute to the observed disparities in treatment and outcomes, although this has never been proven. In a recent Lung Cancer paper Erridge et al suggesting that suboptimal treatment is not the only reason for poor outcome, even when treatment rates were taken into account, also showed a significant hazard ratio for death of 1.5.

The majority of patients with lung cancer will have smoked and will, in general, have a less favourable socio-economic status, two factors known to be associated with an increased likelihood of co-morbid conditions e.g. Chronic Obstructive Pulmonary Disease (COPD), Ischaemic Heart Disease, that influence treatment options. Co-existent comorbidities may also have an adverse effect on the rate of deterioration of performance status when lung cancer develops, with obvious consequence for treatment options and survival. The demonstration that comorbidity influences treatment and survival rates will have important implications for the targeting of health services resources, screening, interpretation of cancer statistics and the assessment and management of patients with lung cancer.

1.2 Incidence

Lung cancer incidence is strongly related to age. In the UK more than four in ten cases are in those aged 75+ (Office for National Statistics, 2013; ISD Scotland, 2013).

Male lung cancer incidence rates have gradually decreased over the last twenty years. Unfortunately the rates for females continue to rise indicating the changing frequency of smoking between the sexes (Office for National Statistics, 2013;ISD, 2013)

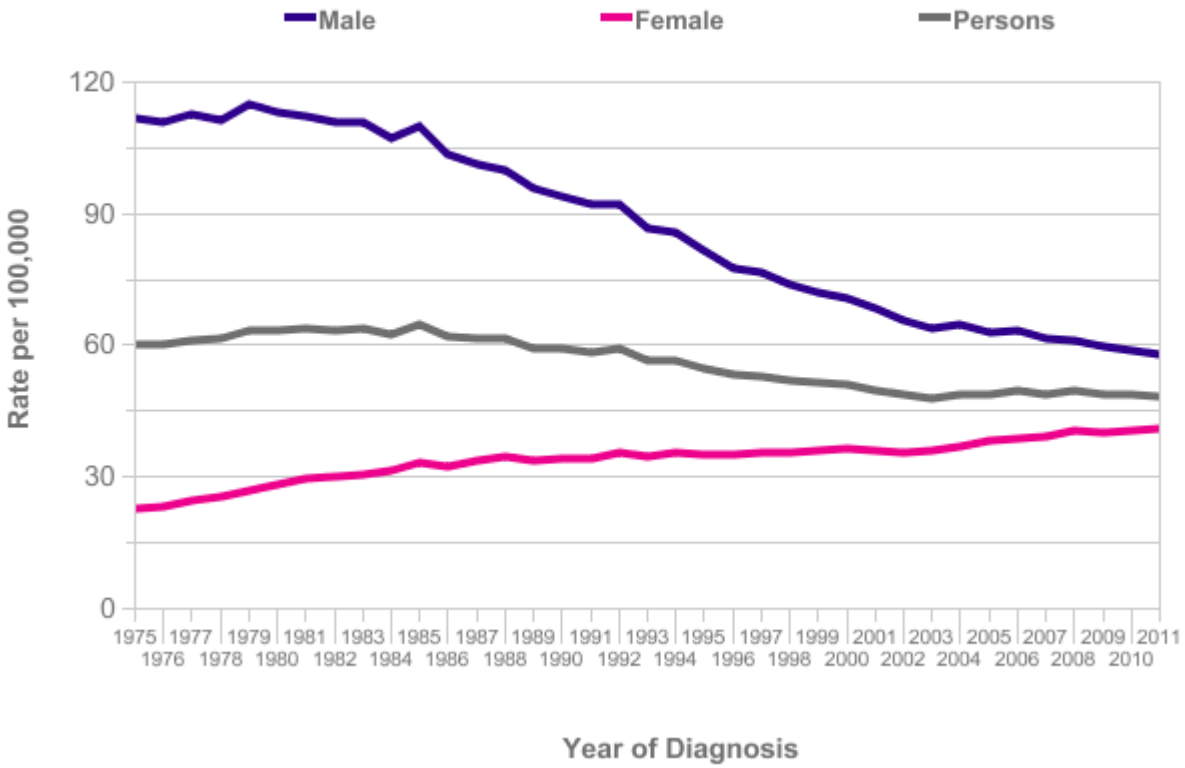

Figure 1.1 European Age-Standardised Incidence Rates per 100,000 Population, by Sex, Great Britain

There also appears to be an association between lung cancer incidence and deprivation. Data from England in 2006 -2010 shows significantly higher rates for those living in the most deprived areas compared to the least (CRUK, 2012).

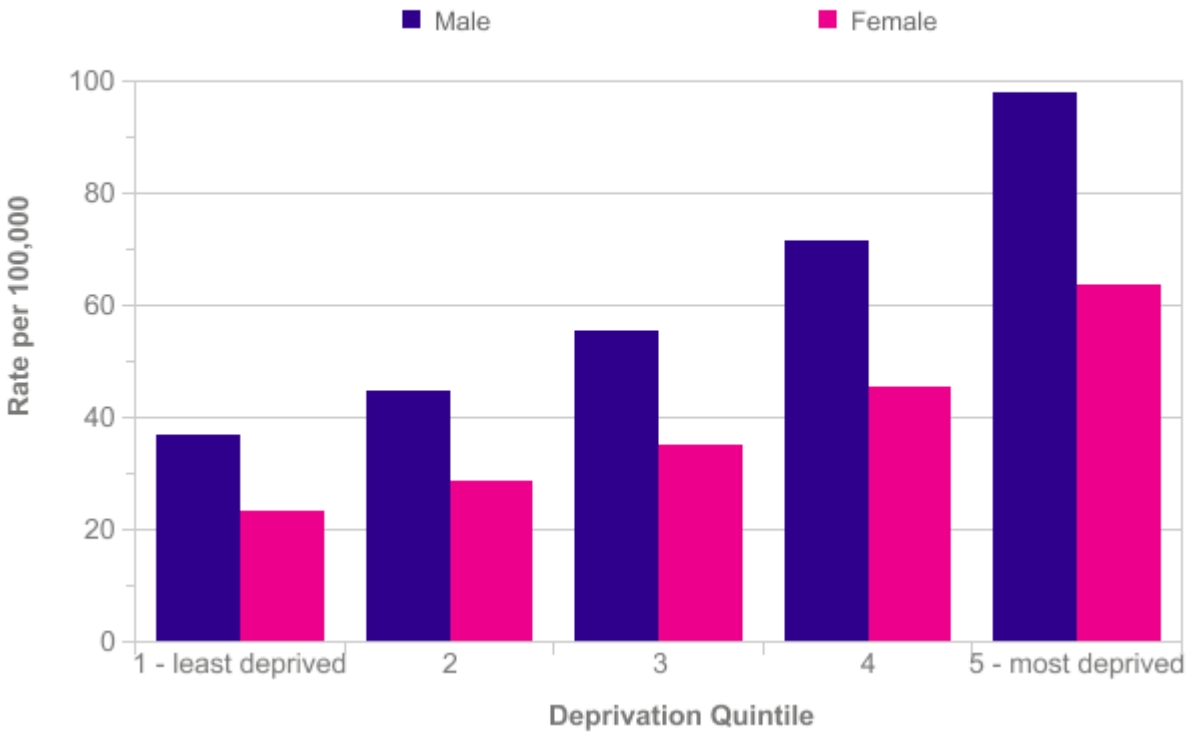

Figure 1.2 ***European Age-Standardised Incidence Rates by Deprivation Quintile, England***

1.3 Lung cancer risk factors

Smoking remains the commonest cause of lung cancer with an estimated 86% of lung cancer deaths in the UK being caused by tobacco smoking (Parkin et al., 2011). In addition lung cancer death risk is around 15 times higher in current smokers compared with never-smokers. (Doll et al., 2005)

An estimated 0.5% of lung cancer in the UK is linked to radon gas exposure. (Parkin et al., 2011). Approximately 1% of the total is linked to previous radiation exposure (either radiotherapy or diagnostic radiation) (Parkin et al., 2011)

A number of occupational exposures are classified as causes of lung cancer. This is seen in an estimated 21% of men with lung cancer and 5% of women. This is commonest in occupations linked to asbestos exposure (typically construction and shipyard workers) with an estimated 6-8% of all lung cancer in the UK being associated with asbestos exposure. (Brown et al., 2012).

Lung cancer risk is increased in survivors of several cancers. In particularly previous breast cancer (Lorigan et al., 2010; Maddams et al 2011) and Hodgkin's lymphoma (Ibrahim et al., 2013). This risk is related to previous thoracic radiotherapy.

1.4 Presentation

Lung cancer often produces very few symptoms until the disease is well advanced (over 50% will have incurable disease at diagnosis (NLCA, 2013). In addition lung cancer can present as an incidental finding on chest radiological imaging undertaken for other reasons. (Spiro et al., 2007). When lung cancer presents in this way it is more often diagnosed at an early and potentially curable stage).

Cough is the most commonly reported symptom along with dyspnoea, chest pain and haempotysis due to chest disease. Non-specific symptoms such as weight loss, fatigue and cachexia are commonly seen due to metastatic disease. Specific symptoms due to site of metastatic spread such as headaches with intracranial deposits and localised pain due to bone metastasis are also commonly seen.

1.5 Diagnosis

A chest x-ray is the first investigation for all patients being investigated for the possibility of lung cancer (Detterbeck et al., 2001). A contrast enhanced CT scan of the chest and abdomen is recommended in all suspected lung cancer cases, regardless of CXR findings (SIGN 137). Results from CT scanning are variable but a high sensitivity and relatively lower specificity is the norm (Yankelevitz et al., 1999). This should be performed prior to further diagnostic investigation, including bronchoscopy, as the result of the CT scan is likely to help guide the investigation most likely to provide a diagnosis (Laroche et al., 2000).

If not contraindicated either by patient fitness or wishes then a tissue diagnosis should be obtained both to confirm diagnosis and help determine

most appropriate treatment (SIGN 137). Bronchoscopy has a good diagnostic sensitivity for central lesions (Schreiber et al., 2003). However this is lower for peripheral lesions (Schreiber et al., 2003) in which case percutaneous biopsy should be considered (Detterbeck et al., 2001).

All pathological samples should be, if possible, classified as Small Cell Lung Cancer (SCLC) or Non Small Cell Lung Cancer (NSCLC). NSCLC tumours should then be subtyped and genetic mutations for EGFR and ALK examined for (SIGN 137).

1.6 Staging

Lung cancer is currently staged using the 7th edition of TNM staging system, which covers NSCLC and SCLC. At the time of data collection of this research the 6th edition of TNM was the current version and for all future references during this work it will be the 6thedition, which will be used. It is to be acknowledged that the TNM staging update, in particular the refined use of tumour size, may make a potential difference to interpretation of the results. However the data recorded would not allow for formal “restaging” of patients.

Table 1.1 International Lung Cancer Staging (6th edition)

T1	≤3cm, surrounded by lung or visceral pleura, without bronchscopic evidence of invasion of more proximal than lobar bronchus
T2	Any of the following features: ≥3cm involves main bronchus, 2cm or more distal to the carina invades visceral pleura associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3	Tumour of any size that directly invades any of the following: chest wall diaphragm mediastinal pleura parietal pericardium tumour in main bronchus <2cm distal to carina associated with atelectasis or obstructive pneumonitis that involves the entire lung
T4	Tumour of any size that invades any of the following: mediastinum heart great vessels trachea oesophagus vertebral bod carina Or separate tumour nodules in the same lobe Or tumour with malignant pleural effusion
N0	No involved lymph nodes.
N1	Involved ipsilateralhilar lymph nodes.
N2	Involved mediastinal lymph nodes.
N3	Involved contralateral lymph nodes.
M1	Distant metastasis present

T = Primary tumour, N = Regional Lymph Nodes, M = Distant Metastasis

Table 1.2 Stage Grouping

Stage	T N M
Ia	T1
Ib	T2
IIa	T1 N1
IIb	T2 N1 or T3 N0
IIIa	T1 N2, T2 N2, T3 N1 or T3 N2
IIIb	Any T4 or any N3
IV	Any M1

CT scanning is poor at predicting more advanced T staging e.g. T3/4 (Detterbeck et al., 2001). FDG PET-CT is more accurate in detecting mediastinal nodal metastases in patients with NSCLC (De Leyn et al., 2007). In addition FDG PET-CT has been shown to identify unsuspected metastases in 10-15% of patients with NSCLC (Pieterman et al., 2000). As such, all patients with NSCLC being considered for radical treatment should have a staging FDG PET-CT.

The majority of patients have advanced stage disease (NSCLC IIIb/IV or SCLC) at time of diagnosis (national lung cancer audit report 2012). In the most recent national lung cancer audit 12% of new lung cancer cases were classified as SCLC. The remaining cases were either NSCLC (87%) or carcinoid (1%). Of the different subtypes of NSCLC squamous (35%) and adenocarcinoma (30-40%) are the most common.

1.7 Treatment of NSCLC

Treatment options are dependent upon pathology, TNM staging, patient fitness and choice. Radical (i.e. potentially curable) treatment options are surgery or radical radiotherapy (+/- chemotherapy).

Surgery

Patients with Stage I + II NSCLC should be considered for curative surgery whenever possible as it confers the highest chance of cure. 5 Year survival of 54-80% for patients with St 1a and 38-65% for patients with Stage 1b has been reported (Suzuki et al., 1999; Makitaro et al., 2002; Inoue et al., 1998). In patients with good performance status (PS 0/1) that have completely resected NSCLC (stage II to IIIa) should be offered platinum based postoperative systemic anticancer therapy (NSCLC Meta-analyses Collaborative Group. 2010).

Radical Radiotherapy

In patients with localized NSCLC not fit / suitable for surgery, radical radiotherapy (+/- chemotherapy) is an appropriate option. Meta-analysis of retrospective studies in patients with Stage I/II has shown overall survival from 50-93% at one year and 0-42% at 5 years (Rowell et al., 2004). In recent years the option of Stereotactic Ablative Radiotherapy has become a very reasonable alternative for those with early stage disease and in many institutions has replaced conventional radiotherapy in this setting. (Palma et al., 2011; Lagerwald FJ., 2012)

Palliative Chemotherapy

In patients with advanced disease and a PS <2 then systemic chemotherapy with a platinum based doublet has been shown to confer a survival benefit of approximately 2 – 4 months (Goffin et al., 2010). Recent advances including tyrosine kinase inhibitors (in those with an EGFR mutation) (Rosell et al., 2012) and pemetrexed/platinum doublets in adenocarcinoma (Scagliotti et al., 2008) have shown further improvement in survival but these treatments were not routinely available at the time of this research.

Symptomatic Therapy

Palliative radiotherapy to areas causing symptoms such as pain is very effective at reducing such symptoms. In addition all patients should be considered for referral to specialist palliative care services (SIGN 137). There has also been some suggestion of a modest improvement in survival with early integrated palliative care input (Temel et al., 2010)

1.8 Treatment of SCLC

Limited disease SCLC

Systemic chemotherapy with a platinum based doublet in patients of good PS has been shown to confer a survival benefit over single agent therapy (Simon et al., 2003). Radiotherapy delivered either concurrently or sequentially to the primary site appears to derive a benefit in survival, although absolute figures are difficult to quantify (De Ruysscher et al., 2000). In patients who have achieved remission after systemic chemotherapy, prophylactic cranial irradiation should be considered as it has been shown to confer a survival benefit (Arrigada et al., 2002; Auperin et al., 1999).

However even with optimal combination therapy two year survival is only around 25% (SIGN)

Extensive disease SCLC

Durable responses to chemotherapy are seldom seen. However there is often a useful symptomatic response (Girling. 1996).

1.9 Mortality

Lung cancer accounts for 6% of all deaths in the UK and is also the commonest cause of cancer death in the UK (2011), accounting for 22% of all cancer deaths. It is the commonest cause of death for both males (23%) and females (21%). Lung cancer is also the most common cause of cancer death worldwide, with around 1,590,000 deaths from lung cancer in 2012 (19% total) (Office for National statistics, 2012).

In Scotland there were 4,178 deaths due to lung cancer in 2011. 2,200 deaths were in males with 1,978 in females. The European age-standardised mortality rates (AS rates) are significantly higher in Scotland compared with the remainder of the UK. In Scotland they are 53.1 / 100,000 compared to 38.2 / 100,000 for the UK (ISD Scotland, 2013).

Data from the UK also appears to show an association between mortality and deprivation with European AS rates being approximately 170% higher in those living in the most deprived areas compared to the least deprived (CRUK, 2013).

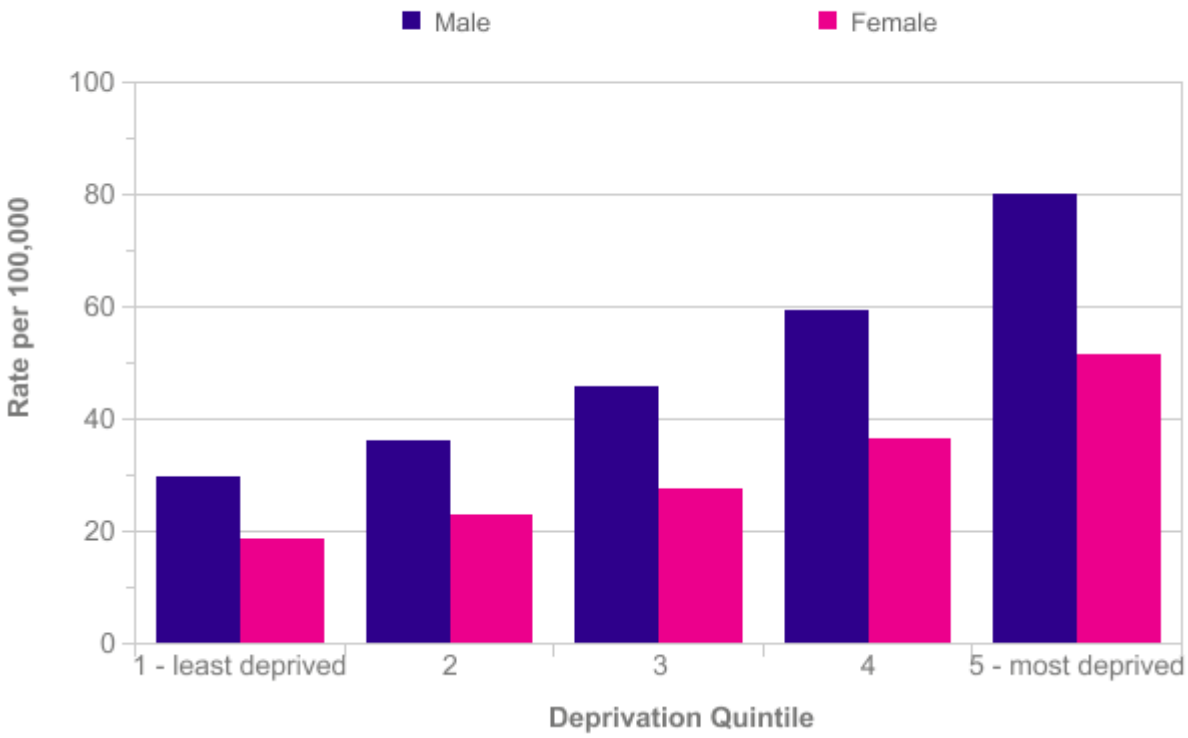

Figure 1.3 ***European Age-Standardised Mortality Rates by Deprivation Quintile, England***

1.10 Survival

Lung cancer has one of the lowest survival outcomes of any cancer because the majority of patients are diagnosed when the disease is already advanced and there is no curative option. In addition, the majority of patients are older (approx. 70 years) and have high incidence of co morbidities (NLCA Report, 2005).

Current 1 year survival in England is 29.4% for men and 33% in woman. This falls to 7.8% for men and 9.3% at 5 years respectively (Office National Statistics, 2010; ISD, 2011).

Table 1.3 Age-Standardised One, Five and Ten Year Relative Survival Rates, Adults Aged 15-99, England 2005-2009, England and Wales 2007

	Relative Survival (%)		
	1 Year	**5 Year**	**10 Year**
Sex	**2005-2009**	**2005-2009***	**2007****
Male	29.4	7.8	4.9
Female	33	9.3	5.9

By age

Lung cancer survival has been show to worsen as age increases for both men and women. For example five-year relative survival rates for men in England during 2005-2009 ranged from 35% in those diagnosed before 40 to 3% in those over 80.

By Stage

The majority of patients are diagnosed at an advanced stage with two thirds of NSCLC having either stage IIIb / IV (ISD Scotland). One and five year survival is strongly linked to stage at diagnosis. In NSCLC the one year survival varied from 71% in patients with stage I to 14% in those with stage IV. Five year survival was 35% and 1% respectively.

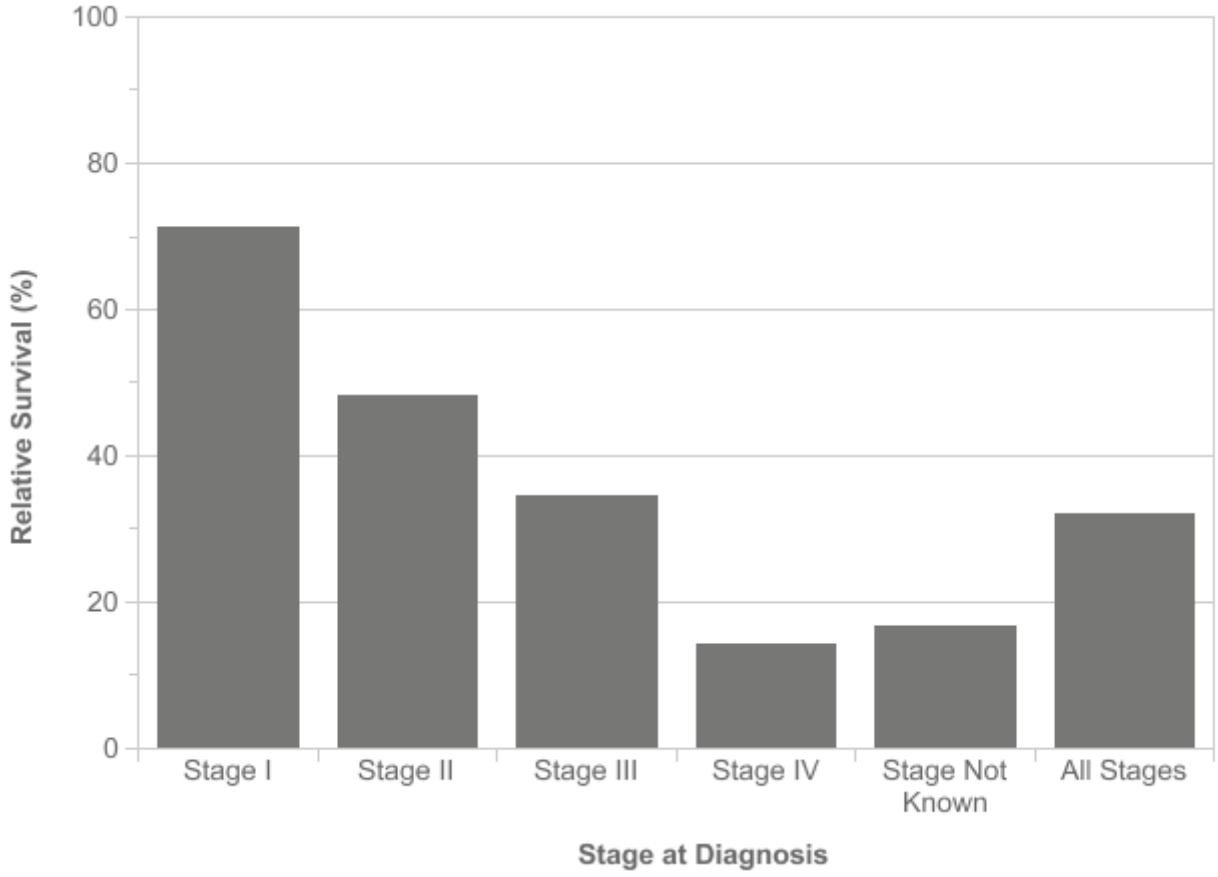

Figure 1.4 ***One-Year Relative Survival (%) by Stage, Adults 15-99, Former Anglia Cancer Network***

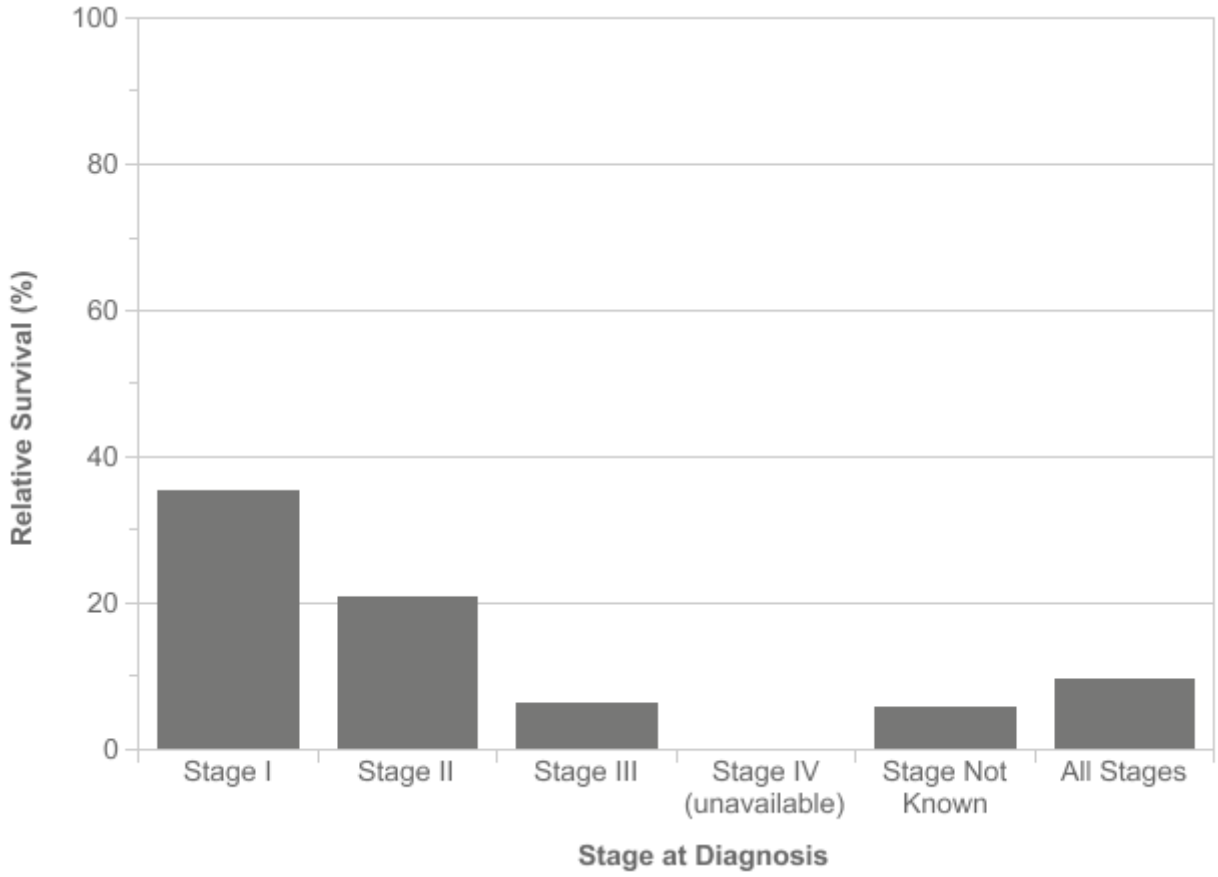

Figure 1.5 ***Five-Year Relative Survival (%) by Stage, Adults 15-99, Former Anglia Cancer Network***

By Deprivation

Analyses of lung cancer survival rates by socio-economic status in England and Wales in the late 1990s has shown a small but significant difference of 1.4% between men in the most and least affluent groups (Coleman et al., 2004).

Lung cancer is the commonest cancer in Scotland and survival rates for patients in Scotland appear lower than in many other European countries. Although this variation in survival is usually interpreted as evidence of variation in facilities, access to care and clinical practice it is possible that the increased comorbidity and poor performance status of the Scottish population may contribute to the observed disparities in treatment and outcomes, although this has never been proven.

The overall aim of the Thesis was to examine the impact of comorbidity in lung cancer, to attempt to quantify the extent and severity of comorbidity and to explore its relationship with treatment and survival.

CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Materials and Methods

Literature searches were undertaken via PubMed and Google Scholar using various arrays of the following keywords; Cancer, Comorbidity, Lung Cancer, Performance Status, Survival and Tools. The search was limited to published articles in peer-review journals with English as the language. No Abstract or posters were included in the review. Results were separated into several sections. Tools available to assess comorbidity, association between comorbidity and outcome and finally the impact upon survival. The search was completed in March 2010. An extension of the literature review to include up until December 2015 and how recent papers relate to the work in this thesis is presented in Chapter 9.

2.2 Tools available to assess co-morbidity in cancer

The evaluation of comorbidity in Lung Cancer is a relatively new area of research. In recent years a number of studies have attempted to assess the impact of comorbidity, performance status and age on treatment and survival in lung cancer. A variety of tools have been used to quantify co-morbidity primarily in breast and prostate cancer (Extermann. 2000) although none of these have been validated in lung cancer. In addition the majority of lung cancer patients are from lower socio-economic classes with significant factors which may influence ability to deliver curative treatment e.g. Chronic Obstructive Pulmonary Disease and Ischaemic Heart Disease. The biology of lung cancer is obviously significantly different from the afore-mentioned tumour types in terms of treatment options, stage at time of presentation and median survival.

Extermann reviewed 4 tools currently in place. Although these have all been validated against cancer outcomes, none have been specifically validated in lung cancer.

The most widely quoted tool is the Charlson Comorbidity Index (Charlson et al., 1987) (CCI). This was designed in 1987 and assigned 19 conditions with a weighting index of 1 – 6 in attempt to quantify the likelihood of impact upon survival. Data was acquired via patients being admitted with medical conditions to a Washington Hospital. This tool was initially validated in breast cancer patients with 10-year mortality as an endpoint. It has also been validated in predicting progression-free survival (Chen et al., 1999) in a variety of diseases such as breast and prostate cancer. However limitations with using this tool for lung cancer patients include absence of some potentially relevant diseases such as pulmonary fibrosis, the weighting of HIV is probably now less significant due to improved treatment and the lack of grading of severity of the specific disease(s).

The second method reviewed was the Cumulative Illness Rating Scale (CIRS). Designed in 1968 by Linn et al, this scale scores 14 organ systems with severity between 0-4. Since its conception it has been modified on a number of occasions and recently modified to cirs-geriatric that is specifically designed to assess geriatric oncology patients. It has been validated previously in elderly cancer patients using mortality rates as an end-point. Due to the large number of comorbidities it becomes more unwieldy and therefore has not been used widely in clinical practice. There is no published validation of the CIRS in lung cancer.

The Index of Coexistent Disease (ICED) was developed by Greenfield et al in 1987. Two subscales attempt to measure physical and functional co-morbid status. The physical subscale incorporates 14 categories with grade of severity 0-4. The functional subscale has 12 domains each rated 0-2. Overall severity is then summarised 0-3. This is the first such system to attempt to gain an understanding of the functional impact of comorbidity

rather than relying on physiological results and as such has much to recommend it. The ICED has been used in cancer studies with good validation but not in lung cancer (Bennett et al., 1991; Guadagnoli et al., 1997) In addition this is a very complicated system and it is unlikely that the information could easily be collected at the time of the decision making process. Thus its greatest attribute is possibly its major failing.

The Kaplan-Feinstein Index (Kaplan et al., 1974) was developed in 1974 and comprises 12 categories graded 0-3. It has been shown to be predictive of outcome in prostate and head and neck cancer (Clemens et al., 1986; Piccirillo, 1995) but not validated in lung cancer.

A more recent tool validated in head and neck cancer patients was the Adult Co-morbidity Evaluation 27 (ACE-27) (Piccirillo et al., 2004). This graded 27 specific conditions from mild to severe. A prospective cohort study including over 17,000 patients with all major cancer types was undertaken. This showed that worsening comorbidity significantly impacted negatively on survival. Unfortunately sub-group analysis identified comorbidity as having least prognostic information in lung cancer patients. A clear reason for this was not identified. It may be related to the finding that comorbidity had greatest impact on survival in indolent cancers with long survival time. This is an interesting view point but fails to address the affect that comorbidity has upon ability to deliver radical treatment.

The simplest tool, superficially at least, is the American Society of Anesthesiologists (ASA), which initially used a five-category physical status classification system; a sixth category was later added (ASA Relative value Guide. 2002). This system was used for assessing the fitness of a patient prior to surgery. It ranged from a healthy patient with no systemic illness to a moribund state. It has been used in assessing comorbidity and is simple to use (Riechelmann et al., 2006). Limitations of the system include the transferability of a fitness for surgery scale to patients with lung

cancer, for the majority of whom surgery is not a therapeutic option. In addition there is a well documented inter-user variability and lack of clear guidance for how to score a variety of significant diseases (Haynes et al., 1995)

None of the available tools for assessing comorbidity have been designed with lung cancer as the main focus of data collection. Thus researchers are faced with difficulty in identifying which system to use in studies of comorbidity in lung cancer patients.

2.3 Tools available to assess comorbidity specifically in lung cancer

Currently, there is only one tool that has been validated in lung cancer. Colinet et al in 2005 studied the outcome in Non Small Cell Lung Cancer (NSCLC) within 5 French territorial divisions. A prospective study of 735 consecutive patients between 1998–2003 evaluated treatment and prognosis. They used a Simplified Comorbidity Score (SCS) and also assessed Performance Status (PS), weight loss, age and the Charlson Comorbidity Index (CCI). It was shown that worsening stage, PS and SCS (>9) or CCI (>5) were independent adverse prognostic factors in terms of survival. Hazard ratio was 1.36 [1.09–1.69] Criticisms of this tool include the fact that SCS does not give any grading of disease severity or allow for more than one disease within a group e.g. a patient with both a stroke and ischaemic heart disease. In addition the reason for the extremely high weighting given to diabetes mellitus and smoking in comparison to respiratory and cardiac comorbidity is not made clear by the authors. Our own (published in abstract only) work (Milroy et al., 2005; Milroy et al., 2009) suggests that diabetes mellitus has minimal if any impact on the treatment of patients with lung cancer. However it is certainly a straightforward tool to use in clinical practice.

2.4 Association between comorbidity and cancer survival

The possible prognostic impact of comorbidity on cancer patient survival was previously studied by Read et al (Read et al., 2004). A prospective cohort study was undertaken using the local cancer registry and 11,558 patients with a variety of cancers were identified. The severity of patient comorbidity was assessed using the Adult Co-morbidity Evaluation 27 (Piccirillo. 1995). The 1 year survival was determined for each tumour site and stage combination. The results suggested that the impact of comorbidity was greatest among tumour types with the longest survival i.e. those with the most indolent course such as prostate cancer. This suggests that comorbidity should have less effect on treatment or survival in aggressive tumour types such as lung cancer.

These findings are not to be questioned. However this study was primarily evaluating inter-tumour type variations in survival. It did not compare survival within a heterogeneous group of lung cancer patients or attempt to identify causes for such variations.

2.5 Association between comorbidity and lung cancer outcome

In most cancer trials significant comorbidity is an exclusion criteria. Consequently trial data may be of limited relevance to every day clinical practice with patients, the majority of whom will have co-existing comorbidities, and would therefore have been excluded from the original trial upon which their proposed treatment may be based. It is therefore essential to assess what, if any, relationship has been shown in the literature between comorbidity and outcome in lung cancer. Although sparse, a number of studies have suggested that comorbidity has a significant impact on both treatment and outcome in lung cancer. However these studies suffer from a number of limitations.

Potosky et al (Potosky et al., 2004) retrospectively evaluated 898 patients with Non-small Cell Lung Cancer (NSCLC) and variations in initial treatment. Using National Guidelines, recommended treatment strategies were determined. Information that might influence treatment was recorded. This included stage, age, and comorbidity (using the Charlson Comorbidity Index, smoking status and race. Overall only 52% of patients received recommended therapy. The use of recommended therapy declined with increasing age and tumour stage. There was also a reported detrimental association with increasing comorbidity. This would be in keeping with most general clinical experience although there has been criticism of the effect of co-morbidity upon treatment in at least one previous article (Janssen-Heijnen et al., 2004) which is described in the next section

A previous study by Earle (Earle et al., 2000) evaluated chemotherapy utilisation for patients with stage IV NSCLC and demonstrated that younger patients and those with fewer comorbid conditions were more likely to receive chemotherapy. It was however a retrospective analysis.

An analysis from Wisconsin, USA(Firat et al., 2002) showed that KPS and comorbidity (recorded yes/no) were important independent prognostic factors in Stage III NSCLC. The limitations of this study include the focus on one tumour stage, and the fact it was a retrospective analysis of four Radiation Therapy Oncology Group studies evaluating survival benefit with radiotherapy alone. It was not a prospective study and did not have comorbidity as a primary explanatory variable.

Kates et al (2009) recently retrospectively reviewed their localised lung cancer patients (Stage I – IIIA) and attempted to predict those likely to suffer from perioperative mortality (POM). It was shown that risk of death was significantly increased with a Charlson Comorbidity Index Score of greater than 4. Acute Myocardial Infarction, perhaps not surprisingly, had

the strongest association. Other factors associated with increased POM included increasing age, male gender and extent of surgical resection.

Thus there is an indication that comorbidity has a relevance to management decisions in lung cancer. However, these studies did not explore actual survival.

2.6 Studies comparing comorbidity and survival in lung cancer

A number of articles have attempted to clarify the impact of comorbidity on lung cancer survival.

Tammemagi et al (2004) evaluated comorbidity and its association with smoking on lung cancer survival. One thousand one hundred and fifty five patients who were diagnosed with lung cancer between 1995 and 1998 were identified and retrospective analysis was performed to assess the impact of smoking on survival. It was shown that current smokers' hazard ratio for death was significantly increased compared to former/never smokers 1.37 (95% confidence interval 1.18-1.59; $p<0.001$). Sixteen significant comorbid conditions were recorded. Sub-group analysis of these was also performed. A number of these comorbid factors were found to be independent predictors of survival. However, it should be noted that this was not the primary aim of the study and it was retrospective.

Janssen-Heijnen (Janssen-Heijnen et al., 2004) evaluated 4072 patients with NSCLC. The authors assessed a number of comorbidities using a very slightly adapted version of the Charlson Comorbidity Index along with age, tumour size and proposed treatment. This study was, however, retrospective and used a comorbidity index not validated in lung cancer. Univariate and multivariate analyses of survival were performed. One year survival decreased significantly with age ($p<0.0001$). Comorbidity was not

found to have any influence on survival; however comorbidity was recorded as actual number of diseases ranging from 0 to 2 with no attempt to quantify the severity of comorbidity.

Birim et al (2005) reported the assessment of the impact of the Charlson Comorbidity Index (CCI) in patients with NSCLC treated with surgery and the impact of the CCI score on survival. With multivariate analysis it was shown that for a CCI score >3 the relative risk of death was 2.2 (95% CI 1.5–3.1). However with a score of 1 or 2 the relative risk was 1.4 (95% CI1.0–1.8). This showed a significant negative correlation on overall survival, which is decreased with increasing CCI score, suggesting that worsening comorbidity did impact negatively on survival. Limitations of this study include the absence of a grade of disease severity and that the study period was rather prolonged. In addition the authors failed to assess early stage NSCLC patients deemed ineligible for surgery.

Imperatori et al (2006) compared management and survival between Teeside (UK), which has very similar population demographics to Scotland, and Varese (Italy), which does not. Data were recorded prospectively. The study revealed that Teeside had statistically significantly more advanced disease, higher comorbidity at presentation and lower survival rates. Comorbidity was recorded simply as yes/no with no grading of severity. It did not show any impact on survival. Only surgical resection was shown in multivariate analysis to be a positive predictor of survival (HR 0.46; p= 0.0016). The overall 2 year survival was 14% for Italy and 7% in Teeside (p< 0.001). Interestingly survival was relatively low by any European standard in both Italy and England (Janssen-Heijnen et al., 1998)

Asmis et al (2008) retrospectively assessed two other studies recently undertaken by the National Cancer Institute of Canada Clinical Trials Group. The paper by Asmis evaluated age, comorbidity and performance status as factors that might influence survival. The Charlson Comorbidity Index assessed comorbidity.A CCI score of 1 was associated with a poorer

overall survival compared to 0 (hazard ratio [HR 1.28; 95% CI 1.09-1.5; p= 0.003). For a CCI >1 there was no additional effect seen. It must be noted that very few patients fell into the category of having CCI>1. Age was not shown to be an independent factor. As with most clinical trials these did not include unfit, poor performance status patients. It must also be noted that the comorbidity data was collected retrospectively. This was a highly selected group of patients as only relatively fit, good performance status patients were eligible for trial enrolment. In addition previous studies have shown that higher social class patients are more likely to be offered trial enrolment (Mosenifar et al., 2007). It would, therefore, be inappropriate to make significant judgement about the impact of comorbidity based on this report alone.

2.7 Conclusion

Lung cancer is a major cause of death and imposes a significant burden on health care systems throughout the developed world. Nearly 40,000 new cases were reported in 2008 in the UK (Ferlay et al., 2007). Furthermore, with the increase in smoking and increasing life expectancy in the developing world, lung cancer is likely to place an increasing burden on the health services of developing countries in the future.

Factors such as age, performance status and social class are often seen as correlates for comorbidity. Therefore any attempts to both evaluate and quantify comorbidity will require taking into account these additional factors if we are to determine the underlying reasons for the poor prognosis in lung cancer and regional variations in survival.

At present there is little published work in the field of comorbidity in lung cancer. None of the previous comorbidity tools were designed specifically for lung cancer, with the exception of the study by Colinet et al and most have been adapted from other uses. No published studies have definitively demonstrated and prospectively quantified the impact of comorbidity on treatment decision making and on overall survival. There is a clear need for further prospective studies to attempt to clarify further the impact of comorbidity in lung cancer patients. Finally a specific tool designed for, and validated in the lung cancer setting will be essential if we are to truly understand the multi-factorial nature of variations in treatment and survival within the lung cancer population.

CHAPTER 3: METHODS

3.1 Introduction

Four Scottish centres were included in the study. These non-tertiary centres routinely investigate, diagnose and treat patients with lung cancer who live in demographically contrasting areas of Scotland (Grose et al., 2011). Healthcare coverage in Scotland is universal, free at the point of need and highly centralised. National guidelines state that all newly diagnosed lung cancer patients should be referred to a Respiratory Physician and discussed at a Multi-Disciplinary Meeting (MDT) (SIGN, 2005). All four centres involved in this study adhere to this with a greater than 90% success (Managed Clinical Network audit report, WOSCAN, 2011) with the majority of referrals being made by General Practitioners or via unscheduled acute hospital admission with a minority from radiologists and surgeons. This ensured that patients included in the study would be representative of the underlying lung cancer population. Consecutive patients diagnosed with lung cancer were included in the study but because of local factors the centres did not recruit for the same periods of time. The study periods for each centre were Aberdeen, October 2005 to February 2007; Stobhill, December 2005 to April 2008; Inverclyde, October 2005 to December 2007 and Dunfermline, June 2007 to April 2008. All newly diagnosed lung cancer patients, whose care was discussed at the Multi-Disciplinary Team (MDT) meeting, were included in the study.

3.2 Data Collection

At the time of the patient's case being discussed at the MDT, anoymised details were entered into a specifically designed Microsoft Access database (The proforma is presented in Appendix 1). Patient demographics and baseline characteristics (age, sex, postcode and smoking history), PS, weight loss, laboratory parameters (C-reactive protein, albumin, creatinine and ventilatory function, wherever possible this was based on

full lung function testing, if unavailable spirometry was used), comorbidites (including severity), tumour stage (Detterbeck et al., 2009) and histology and primary treatment proposed by the MDT were all recorded.

Those team members involved in the decision-making processes were also recorded. The doctor delivering the treatment (e.g. thoracic surgeon or clinical oncologist) would have the final say on treatment, thus limiting any potential discrepancy between recommended and delivered treatment. If the primary treatment decision differed from that recommended by the 2005 Scottish Intercollegiate Guidelines Network (SIGN) guidelines on the management of patients with lung cancer (SIGN, 2005) the reason(s) were recorded (for example age, poor performance status, comorbidity, patient choice). If a histological diagnosis was not achieved this was recorded with reason(s) (for example failed procedure, age, poor performance status, comorbidity, non-diagnostic investigations, patient choice). All investigations attempted, clinical/radiological stage and primary treatment plan were itemised.

All four MDTs had input from both a clinical oncologist and thoracic surgeon. Assesment of patient including PS was made by a Respiratory Physician at point of diagnosis prior to MDT treatment plan. All data was recorded in real time at the MDT and at first clinic attendance by one of the clinical staff (either a respiratory physician or clinical nurse specialist), taking on average 2 -3 minutes to enter the data.

3.3 Socioeconomic Status

Information on patients' individual educational or occupational social class was not available, and we therefore used their postcode of residence as a proxy indicator of their socioeconomic status. Using the 2006 Scottish

Index of Multiple Deprivation (SIMD) ranking (Office of Chief Statistician, 2006) (see box 1) the postcode enabled us to group patients into one of 5 quintiles.

Box 1 – Scottish Index of Multiple Deprivation (SIMD)

The 2006 SIMD is a validated area-based index that uses 37 indicators in seven domains to rank 6505 small geographic areas in Scotland (data zones) from 1 (most deprived) to 6505 (least deprived). These can be subsequently grouped into quintiles. These split up the datazones into 5 groups, each containing 20% of Scotland's datazones. The first quintile contains the 20% most deprived datazones with the fifth representing the 20% least deprived.

3.4 Comorbidities and Severity Scores

Comorbidities present in each patient, with severity of each graded on a four point scale (0, 1, 2, 3) using a novel severity scales (Table 3.1) were recorded, in real time, by a clinician at time of review. The severity index was developed using, where possible, previously validated scoring systems (GOLD Guidelines, 2004; Little et al., 1994; Lyden et al., 2001; Morris, 1993;). This included use of the British Thoracic Society guidelines for Chronic Obstructive Pulmonary Disease, the Canadian Cardiovascular Society Classification for Ischaemic Heart Disease, the New York Heart Association classification for Heart Failure, the National Institutes of Health Stroke Scale for Cerebrovascular disease and the Clinical Dementia Rating. For comorbidities without a validated severity scale we used a scale based on local discussion with eminent regional experts in that particular field.

Table 3.1 Comorbidities and severity scales assessed for each subject in the study

Comorbidity	Severity scale	Severity Score			
		0	1	2	3
COPD	BTS/GOLD guidelines	No disease	FEV1 > 60%	FEV1 40-60%	FEV1 < 40%
Ischaemic heart disease	Canadian CV Society Classification	No disease	Angina with strenuous/ prolonged exertion	Angina after walking 200 hundred yards flat/flight stairs	Inability to carry out any level of exertion/angina at rest
Heart failure	NYHA classification	No disease	Slight limitation of physical activity due to dyspnoea	Comfortable at rest, less than ordinary activity causes dyspnoea	Dyspnoea at rest
Cerebrovascular disease	National Institutes of Health Stroke Scale	No detectable weakness/ sensory (incl visual/speech) impairment	Mild weakness/ deficit	Moderate weakness/ deficit	Severe weakness/ deficit
Dementia	Clinical Dementia Rating	No disease	Mild, able to carry out normal activity	Moderate, requires assistance in activities	Severe, unable to manage any activity. Full time care
Diabetes mellitus		No disease	HbA1C < 7	HbA1C 7.1 - 10	HbA1C> 10
Renal function		eGFR> 90ml/min	eGFR 60-89 ml/min	eGFR 30-59 ml/min	eGFR <30ml/min or dialysis
Previous malignancy		No disease or Basal Cell Carcinoma	Previous cancer, no evidence active disease	Active, unlikely to cause death	Active, likely to cause death before lung cancer
Peripheral Vascular Disease		None	Claudication at > 200 yards	Claudication at < 200 yards	Rest pain
Alcohol		<25 Units/week	25-50 units/week	>50 units/week	Establishd alcohol related illness or end organ failure

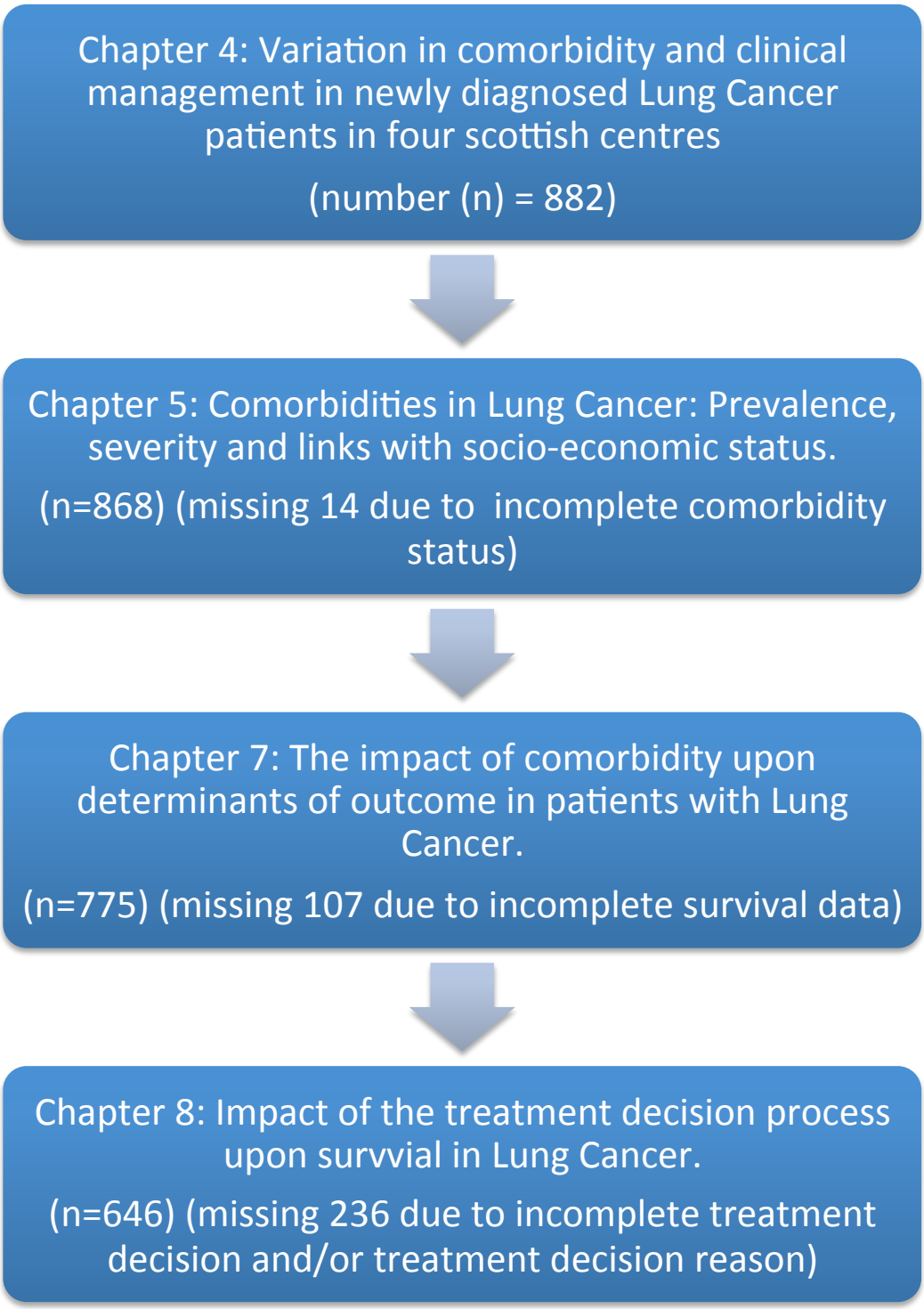

Figure 3.1: Flowchart of patient numbers in study

3.5 Survival data

Information on date of death was obtained via survival analysis undertaken by the Information Service Division (ISD) of NHS Scotland. Death records were complete until 1 June 2011, which served as the censor date for those alive.

3.6 Ethics

The audit was discussed with the local ethics department and as it was health service clinical practice audit formal ethical approval was deemed not to be necessary.

CHAPTER 4: VARIATION IN COMORBIDITY AND CLINICAL MANAGEMENT IN NEWLY DIAGNOSED LUNG CANCER PATIENTS IN FOUR SCOTTISH CENTRES

4.1 Introduction

Lung cancer is the commonest cause of cancer death for both men and women in Scotland (Office for National Statistics, 2006; ISD, 2009). Although survival has improved over the past decade, it remains significantly poorer in Scotland than in comparable Western European countries or the USA, with 5-year relative survivals of 8.0%, 10.2% and 16.3%, respectively. Variations in treatment may explain some of the observed differences in lung cancer survival between countries (Berrino et al., 2007; Horner et al., 2009). Surgical resection rates in the United Kingdom (≤10%) are consistently reported to be lower than those in Europe and North America, which are in excess of 20% (Fry et al., 1999; Laroche et al., 1998; Cartman et al., 2002; Damhuis et al., 1996). There also appear to be variations in treatment rates between healthcare sites within Scotlandthat might give insights into inequalities in survival (Gregor et al., 2001; Janssen-Heijnen et al., 1998). However, variations in treatment do not wholly explain survival differences between countries and other patient characteristics, including comorbidities, may need to be considered. A number of studies have indicated that comorbid factors influence both choice of therapy, as well as directly affecting survival (Potosky et al., 2004; Earle et al., 2000; Extermann, 2000; Charlson et al., 1987; Tammemagi et al., 2004; Janssen-Heijnen et al., 2004; Colinet et al., 2005; Birim et al., 2005; Imperatori et al., 2006; Asmis et al., 2008; Erridge et al., 2009). However, the investigation of comorbidities has not been the primary aim of any of these studies and the quantification of comorbidities has lacked precision, having been either dichotomised into yes/no categories or expressed as the crude number of co-existent diseases.

To date, no study of lung cancer has attempted to investigate specifically the association between inter-hospital variations in investigation and treatment, and the type and severity of comorbidities. In a pilot study we screened 50 newly diagnosed lung cancer patients presenting sequentially to the Lung Cancer Service at Stobhill General Hospital, Glasgow (Milroy et al., 2005). This pilot study suggested a relationship between increasing comorbidity, worsening performance status and clinicians' inability to offer either potentially curative treatment or optimal palliative treatment. Building on the results of the pilot study we have conducted a study in four Scottish centres to identify prospectively any difference in the investigation and treatment of patients diagnosed with lung cancer. In addition we have quantified the number and severity of co-morbid conditions to investigate how different comorbidity contributes to observed variation in clinical management.

4.2 **Methods**

Previously described in chapter 3

Statistical methods

Statistical analyses were performed using SPSS v17.0 (SPSS Inc., Chicago, USA). The primary outcome variable of interest was the primary treatment option decided by the MDT. Univariable analyses using χ^2, t-tests and ANOVA were used to explore the associations between treatment options and potential explanatory variables such as tumour stage, performance status, age, sex, SIMD, co-morbidities (expressed as ordinal scores) and FEV1. Potential explanatory variables with $p<0.1$ on univariable testing were included in a multiple logistic regression model to identify associations between treatment options and co-morbidities after adjustment for other potentially influential factors.

4.3 Results

Between Centre Differences

In total 882 patients were included in the study, comprising 297 from Aberdeen, 136 from Dunfermline, 285 from Glasgow and 164 from Inverclyde. The mean age of participants was 70.4 years and 55.2% were male. There were marked differences between centres in the socio-economic status profiles of the patients with the majority of patients at Glasgow, but none in Dunfermline, living in the most deprived circumstances, and less marked, but significant differences in age, sex and smoking history profiles (Table 4.1). There were clear differences in the comorbidity severity score profiles between centres for COPD (Fig 4.1a), ischaemic heart disease (Fig 4.1b), congestive cardiac failure (χ^2,$p<0.001$), dementia (χ^2,$p=0.008$), diabetes mellitus (χ^2,$p=0.001$), renal function (χ^2,$p<0.001$), weight loss (χ^2,$p<0.001$), alcohol intake (χ^2,$p<0.001$), but there were no significant between centre differences in the severity score profiles for cerebrovascular disease, previous malignancies or peripheral vascular disease. Performance status also varied between centres (Table 4.1), as did rate of deterioration in performance status. There was suggestion of between centre differences in the proportion of patients diagnosed with small cell cancer, with no differences in the stage profile (Table 4.1).

Table 4.1 Between centre differences in patient profile

	All centres n=882	Aberdeen n=297	Dunfermline n=136	Glasgow n=297	Inverclyde n=164	p value* (between centres)
Age Mean (95% CI)	70 (70-71)	69 (68-70)	71 (69-73)	71 (69-72)	73 (71-74)	0.001
% male	55%	60%	58%	49%	54%	0.049
Ever smoked	94%	94%	97%	93%	94%	0.35
Mean pack year consumption (95% CI)	44 (42-46)	46 (42-49)	38 (35-41)	44 (41-47)	44 (39-49)	0.023
Socio-economic status % in most deprived quintile of SIMD	30%	5%	0	64%	42%	<0.001
Socio-economic status % in most affluent quintile of SIMD	7%	19%	0	0	4%	<0.001
% Performance status 0/1 6 months prior to presentation	79%	81%	82%	76%	78%	0.47
% Performance status 0/1 at presentation	47%	58%	53%	43%	28%	<0.001
% Performance status fell from 0/1 to 2/3/4 in 6 months prior to presentation	41%	28%	36%	44%	65%	<0.001
FEV1 % predicted Mean (95% CI)	64% (62-65)	62% (60-65)	65% (61-69)	67% (64-69)	59% (55-63)	0.018
Serum creatinine Mean (95% CI) nmol/l	93 (90-96)	93 (89-97)	100 (92-107)	87 (83-91)	97 (89-105)	0.008
Serum albumin Mean (95% CI) g/l	37 (36-37)	40 (39-41)	36 (35-37)	33 (32-34)	37 (36-37)	<0.001
CRP mg/l Mean (95% CI)	48 (44-53)	46 (39-53)	62 (39-74)	45 (38-52)	56 (45-67)	0.21
% Non Small Cell	62%	58%	60%	59%	76%	0.001
% Small Cell	13%	15%	7%	16%	12%	0.077
% Small Cell Limited Disease	29% (33/115)	22% (10/45)	20% (2/10)	34% (14/41)	37% (7/19)	0.47
% Non Small Cell Stage I or II	21% (109/531)	27% (47/173)	22% (18/81)	18% (27/153)	14% (17/124)	0.028
% No histology Stage I or II	18% (31/173)	12% (6/50)	20% (8/41)	21% (17/81)	0% (0/1)	0.57

*ANOVA, χ^2 tests of statistical significance

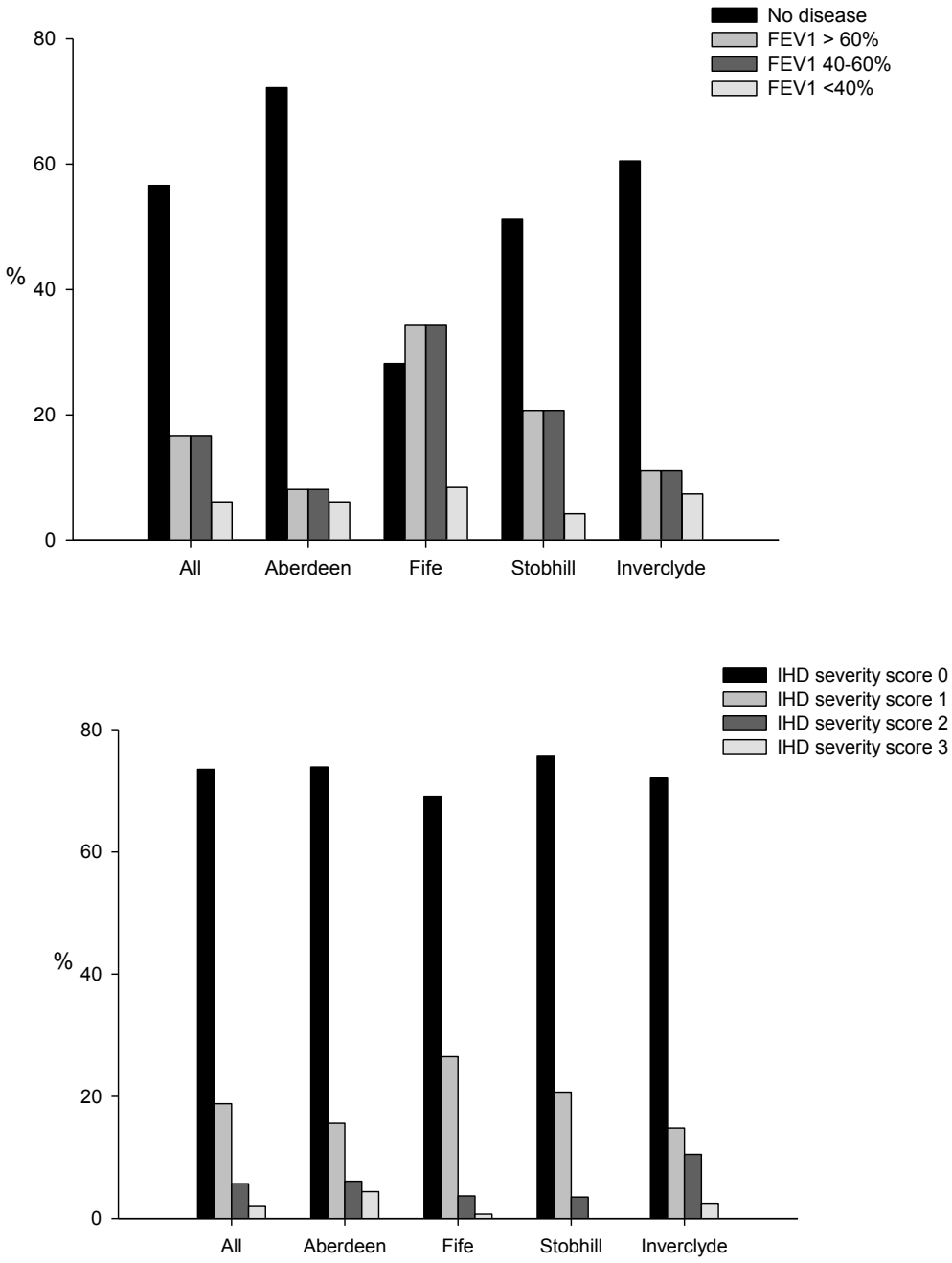

Figure 4.1 Bar chart illustrating between centre differences in severity scores for (a) chronic obstructive pulmonary disease (COPD) and (b) ischaemic heart disease (IHD). Between centre p values 0.017 for COPD and <0.001 for IHD,

There were marked differences between centres in the investigations performed to stage and characterise lung cancer. In Dunfermline, for local reasons, measurement of CRP was about a third that of other sites (χ^2,p<0.001) and histological diagnosis was lower (χ^2,p<0.001) (Table 4.1). The majority of the patients had NSCLC (62.0%), 13.4% had SCLC and the remainder of patients had no pathological confirmation. There was variation in non-small cell stage at presentation between centres with the incidence of stage I or II disease ranging from 13.7% of patients at Inverclyde to 27.2% of patients in Aberdeen (χ^2,p= 0.028) (Table 4.1). This is clinically important, as stage at presentation is one of the most important factors in determining treatment and survival (Mountain, 1986). The proportion of patients presenting with limited stage SCLC varied between centres from 36.8% at Inverclyde to 20.0% in Dunfermline, but probably because of low numbers this difference was not statistically significant (Table 4.1).

Between centre differences were observed in the rates of radical radiotherapy, the proportion of patients with locally advanced/metastatic NSCLC having chemotherapy and the proportion of patients for who best supportive care with no surgical/oncological intervention was recommended. The differences between sites in proportions of patients referred for surgical resection were small and not statistically significant (Table 4.2).

Table 4.2 Between centre differences in investigation and treatment

	All centres n=882	Aberdeen n=297	Dunfermline n=136	Glasgow n=297	Inverclyde n=164	p value* (between centres)
Measurement of CRP	86.3%	96.6%	37.5%	94.7%	93.3%	<0.001
Obtained histological diagnosis	75.5%	73.4%	66.9%	74.9%	87.2%	<0.001
Surgical resection	6.3%	7.4%	6.6%	5.6%	5.5%	0.79
Radical Radiotherapy	4.0%	4.0%	8.8%	3.1%	0.6%	0.004
Chemotherapy NSCLC stage IIIb/IV	4.0%	9.8%	0%	2.8%	0%	<0.001
No surgery/chemo/radiotherapy	20.6%	10.8%	36.8%	22.5%	22.0%	<0.001

*χ^2 or Fishers exact tests of statistical significance

Associations with Performance Status

Of the 882 patients 46.8% (413) had a performance status of 0 or 1 at time of diagnosis. Univariable analysis demonstrated that a performance status of 0/1 was associated with centre (Aberdeen 58.2%, Fife 52.9%, Stobhill 42.8%, Inverclyde 28.0%, Table 4.3 model 1, χ^2,p<0.001), younger age (67.6 years 95% CI 66.5-68.7 vs. 72.4 (71.2-73.5), t test, p<0.001), those in more affluent areas as defined by SIMD, (highest quintile of affluence 62.9% PS 0/1 vs. lowest quintile 40.4%, χ^2,p<0.001) and those with a confirmed pathological *(i.e. either cytological or histological)* diagnosis (SCLC 48.7%, NSCLC 53.3%, no histology 32.4%, χ^2,p<0.001). Univariable analysis demonstrated that performance status was adversely associated with increasing severity of the comorbidities: COPD, IHD, CCF, cerebrovascular disease, dementia, renal impairment, weight loss, peripheral vascular disease and alcohol history. There were no associations with sex, or severity of diabetes mellitus. Multivariable modeling demonstrated that a performance status of 0/1 was less likely with increasing age, some centres (Glasgow and Inverclyde), and increasing

severity of the comorbidities COPD, CCF, cerebrovascular disease and dementia (Table 4.3). Reduced performance status at presentation (PS 2/3/4) was associated with NSCLC stage IV, extensive SCLC and failure to achieving positive tumour histology. The predictive power of the final logistic regression model to identify correctly individuals with a performance status of 0/1 was assessed using receiver operating characteristic (ROC) curve analysis. The area under the ROC curve for the final logistic model was 0.79 indicating fair to good discrimination (although as this was tested on the same cohort of patients from which it was derived this may appear artificially good).

Table 4.3 Results of univariable analysis relating performance status 0/1 to centre (model 1). Model 2 is the results of multiple logistic regression modeling relating performance status 0/1 to centre, age, comorbidity scores (for COPD, CCF, cerebrovascular disease, dementia, weight loss), and tumour stage, and histology,

	Model 1		Model 2	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Aberdeen (n=173)	1		1	
Dunfermline (n=72)	0.87 (0.54-1.21)	0.30	1.50 (0.90-2.49)	0.12
Glasgow (n=122)	0.54 (0.39-0.75)	<0.001	0.47 (0.32-0.71)	<0.001
Inverclyde (n=46)	0.28 (0.19-0.42)	<0.001	0.29 (0.18-0.46)	<0.001
Age (years)				
<60 (n=80)			1	<0.001*
60-70 (n=142)			0.85 (0.51-1.41)	
70-80 (n=149)			0.58 (0.35-0.95)	
>80 (n=42)			0.25 (0.14-0.45)	
COPD (FEV_1 % predicted)				
>80% (n=252)			1	<0.001*
60-80% (n=80)			0.93 (0.59-1.48)	
40-60% (n=64)			0.54 (0.35-0.83)	
<40% (n=42)			0.22 (0.10-0.48)	
CCF (severity score)				
0 (n=369)			1	0.002*
1 (n=35)			0.67 (0.38-1.17)	
2 (n=6)			0.21 (0.08-0.59)	
3 (n=1)			0.33 (0.03-3.63)	
Cerebrovascular disease (severity score)				
0 (n=800)			1	<0.001*
1 (n=52)			0.58 (0.29-1.16)	
2 (n=18)			0.12 (0.02-0.62)	
3 (n=8)			0.00 (0.00-)+	
Dementia (severity score)				
0 (n=827)			1	0.002*
1 (n=24)			0.59 (0.19-1.86)	
2 (n=14)			0.34 (0.08-1.50)	
3 (n=1)			0.00 (0.00-)+	
Weight loss				
None (n=416)			1	<0.001*
<5% (n=131)			0.47 (0.28-0.78)	
5-10% (n=74)			0.49 (0.27-0.91)	
>10% (n=258)			0.20 (0.14-0.30)	
NSCLC stage I/II (n=136)			1	
NSCLC stage III (n=233)			0.67 (0.40-1.13)	0.13
NSCLC stage IV (n=311)			0.37 (0.22-0.62)	<0.001
SCLC limited (n=33)			0.52 (0.22-1.28)	0.15
SCLC extensive (n=82)			0.47 (0.25-0.91)	0.026
No histology (n=26)			0.42 (0.20-0.89)	0.023

*: p value for trend across categories

+: upper 95 CI not computable

Predictors of decline in performance status.

Of the 694 patients with a retrospectively estimated performance status of 0 or 1 six months prior to diagnosis, 40.9% had declined by the time of presentation. Univariable analysis demonstrated that a decline in performance status from 0/1 to 2/3/4 in the 6 months prior to presentation was associated with centre (Aberdeen 28.2%, Dunfermline 35.5%, Glasgow 43.8%, Inverclyde 65.1%, χ^2,$p<0.001$, Table 4.4 model 1), increasing age, increasing deprivation (highest quintile of affluence 18.8%, lowest quintile of affluence 46.8%), COPD, IHD, CCF, cerebrovascular disease, dementia, tumour histology and stage. Multivariable modeling (Table 4.4 model 2) demonstrated that a decline in performance status from 0/1 to 2/3/4 in the 6 months prior to presentation was associated with centre (more likely in Inverclyde), increasing age, decreasing affluence, COPD, CCF, cerebrovascular disease, tumour stage and tumour histology.

Table 4.4: Results of univariable analysis relating decline in performance status from 0/1 to 2/3/4 in the 6 months prior to presentation to centre (model 1). Model 2 is the results of multiple logistic regression modeling relating decline in performance status to centre, age, SIMD, and comorbidity scores (for COPD, CCF, cerebrovascular disease), and tumour stage and histology.

	Model 1		Model 2	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Aberdeen (n=68)	1		1	
Dunfermline (n=39)	1.40 (0.86-2.26)	0.17	1.07(0.62-1.83)	0.82
Glasgow (n=95)	1.98 (1.34-2.92)	0.001	1.48 (0.87-2.52)	0.15
Inverclyde (n=82)	4.74 (2.99-7.52)	<0.001	3.87 (2.27-6.60)	<0.001
Age (years)				
<60 (n=36)			1	<0.001*
60-70 (n=77)			1.15 (0.68-1.97)	
70-80 (n=102)			1.47 (0.87-2.49)	
>80 (n=69)			3.33 (1.77-6.28)	
Quintile affluence (SIMD)				
Q1: Least affluent(n=94)			1	0.047*
Q2(n=49)			1.39 (0.76-2.55)	
Q3 (n=90)			1.06 (0.65-1.73)	
Q4 (n=42)			0.77 (0.41-1.47)	
Q5: most affluent (n=9)			0.34 (0.13-0.88)	
COPD (FEV_1 % predicted)				
>80% (n=154)			1	<0.001*
60-80% (n=44)			1.03 (0.62-1.70)	
40-60% (n=63)			1.71 (1.07-2.73)	
<40% (n=22)			4.12 (1.80-9.45)	
CCF (severity score)				
0 (n=243)			1	0.008*
1 (n=31)			1.97 (1.08-3.59)	
2 (n=8)			3.46 (1.01-11.9)	
3 (n=1)			2.76 (0.16-46.8)	
Cerebrovascular disease (severity score)				
0 (n=257)			1	0.007*
1 (n=20)			1.84 (0.85-3.99)	
2 (n=6)			7.70 (1.27-46.9)	
3 (n=0)			++	
NSCLC stage I/II (n=21)			1	
NSCLC stage III (n=72)			2.63 (1.43-4.84)	0.002
NSCLC stage IV (n=119)			5.60 (3.09-10.1)	<0.001
SCLC limited (n=11)			3.22 (1.22-8.47)	0.018
SCLC extensive (n=28)			3.98 (1.90-8.32)	<0.001
No histology (n=23)			4.37 (1.94-9.87)	<0.001

*: p value for trend across categories

++: OR not computable (too few subjects in category)

Associations with surgical resection for NSCLC

The surgical resection rates for confirmed NSCLC were 12.7% (Aberdeen), 11.1% (Dunfermline), 10.5% (Glasgow) and 7.3% (Inverclyde) but the differences were not statistically significant. Given the differences in the patient profiles between centres, multivariable modeling was performed and the results are outlined in Table 4.5 as model 1. After adjustment, there were the expected associations between surgical resection, performance status and tumour stage. Female sex and increasing age were associated with a reduced likelihood of surgical resection. The only co-morbidity significantly associated with the reduced chance of surgical resection was COPD. The multivariable analysis indicated that after adjustment for performance status, tumour stage, age, sex and COPD, patients in Inverclyde were more than five times likely to be operated on for NSCLC than patients from Aberdeen. It was also noted however that the number of patients with Stage 1 and II NSCLC who declined surgical treatment differed between centres: 25% (Aberdeen 3/12), 50% (Dunfermline 5/10), 0% Glasgow (0/7) and Inverclyde (0/8) (χ^2,p=0.009) and that women were more likely to decline surgical treatment than men (21.7% vs. 11.5%) although this difference was not statistically significant. Patient refusal was not associated with socio-economic status. If the patients with Stage I or Stage II NSCLC who declined surgery had actually been operated on (Table 4.5 model 2) the sex and age associations with surgical resection were not significant and patients in Dunfermline were more likely to undergo surgical resection.

Table 4.5 Results of multiple logistic regression relating decision to treat non-small cell lung cancer by surgical resection to centre, sex, age, comorbidity, performance status, and tumour stage. Model 1: subjects who declined surgical intervention coded as no surgery, Model 2: subjects who declined surgical intervention coded as surgical intervention.

	Model 1		Model 2	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Aberdeen (n=22)	1		1	
Dunfermline (n=9)	1.19 (0.28-5.00)	0.81	4.39(1.14-16.9)	0.032
Glasgow (n=16)	2.49 (0.83-7.46)	0.10	1.57(0.55-4.41)	0.40
Inverclyde (n=9)	5.84 (1.50-22.7)	0.011	2.77(0.77-10.0)	0.12
Female sex (n=22)	0.39 (0.16-0.96)	0.041	0.53(0.22-1.31)	0.21
Age (years)				
<60 (n=9)	1	0.007*	1	0.051*
60-70 (n=25)	0.56 (0.13-2.47)		1.03(0.22-4.90)	
70-80 (n=21)	0.37 (0.08-1.66)		0.60(0.13-2.82)	
>80 (n=1)	0.02(0.001-0.29)		0.10(0.01-0.79)	
COPD(FEV_1% predicted)				
>80% (n=32)	1	0.008*	1	0.012*
60-80% (n=17)	0.36 (0.12-1.13)		0.37(0.13-1.08)	
40-60% (n=6)	0.26 (0.07-1.03)		0.29(0.08-0.99)	
<40% (n=1)	0.10 (0.01-1.18)		0.14(0.02-1.21)	
Performance status				
0 (n=21)	1	0.002*	1	0.018*
1 (n=27)	0.24 (0.07-0.88)		0.31(0.09-1.09)	
2 (n=6)	0.08 (0.02-0.38)		0.18(0.04-0.76)	
3 (n=2)	0.04 (0.01-0.53)		0.07(0.06-0.71)	
4 (n=0)	0.00 (0.00-)+		0.00(0.00-)+	
Tumour stage				
I (n=38)	1	<0.001*	1	<0.001*
II (n=14)	0.48 (0.18-1.30)		0.65(0.25-1.66)	
IIIa (n=4)	0.03 (0.01-0.14)		0.03(0.07-0.11)	
IIIb (n=0)	0.00 (0.00-)+		0.00(0.00-)+	
IV (n=0)	0.00 (0.00-)+		0.00(0.00-)+	

*: p value for trend across categories

+: upper 95 CI not computable

Associations with radical radiotherapy for NSCLC

There were clear between centre differences in the rates of radical radiotherapy (definition as per SIGN guidelines[23]) for NSCLC (Tables 4.2, 4.6) that persisted after adjustment for factors found to be associated with radical radiotherapy for NSCLC on univariable analysis. Multivariable modeling also indicated that the decision to treat NSCLC with radical radiotherapy was more likely if the patient was a woman and in patients with COPD. There was a non-significant association between the decision to treat with radical radiotherapy and alcohol associated comorbidity.

Table 4.6 Results of univariable analysis relating decision to treat non-small cell lung cancer by high dose radical radiotherapy to centre (model 1). Model 2 outlines the results of multiple logistic regression modeling relating decision to treat by high dose radical radiotherapy to centre, sex, comorbidity (COPD, alcohol) and tumour stage.

	Model 1		Model 2	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Aberdeen (n=31)	6.75 (0.84-54.0)	0.072	8.52 (0.98-74.3)	0.052
Dunfermline (n=19)	13.5 (1.65-110)	0.015	14.6 (1.54-137)	0.019
Glasgow (n=28)	8.60 (1.09-68.1)	0.042	9.84 (1.14-84.9)	0.038
Inverclyde (n=4)	1		1	
Female sex (n=41)			2.56 (1.05-6.26)	0.040
COPD (FEV_1% predicted)				
>80% (n=41)			1	0.023*
60-80% (n=19)			3.79 (1.22-11.8)	
40-60% (n=19)			5.41 (1.62-18.0)	
<40% (n=3)			3.68 (0.56-24.2)	
Alcohol (severity score)				
0 (n=69)			1	0.063*
1 (n=7)			0.48 (0.09-2.70)	
2 (n=3)			12.2 (0.84-178)	
3 (n=2)			12.2 (0.89-168)	
NSCLC stage I/II (n=24)			1	
NSCLC stage III (n=55)			0.24 (0.09-0.61)	0.003
NSCLC stage IV (n=0)			++	

*: p value for trend across categories

++: OR not computable (too few subjects in category)

Associations with optimal treatment of SCLC

In total 13.4% of the patients were diagnosed with SCLC, with 28.7% staged as limited disease. Optimal treatment for limited stage SCLC was defined as chemotherapy with a platinum doublet along with consolidation radiotherapy to mediastinum (conventionally defined as at least 30Gy (SIGN, 2005) and brain, either sequentially or concurrently (SIGN, 2005). There was evidence of between centre differences in the incidence of SCLC, with Aberdeen highest and Dunfermline lowest (15.2 versus 7.4% of patients respectively) but probably because of small numbers these differences did not reach statistical significance (χ^2,p=0.077) (Table 4.2). However, multivariable modeling suggested that after adjustment there were between centre differences in the decision to treat SCLC with optimal therapy, furthermore there were associations between optimal treatment and performance status, alcohol associated comorbidity and IHD comorbidity. (Table 4.7)

Table 4.7 Results of univariable analysis decision to treat small cell lung cancer with combination chemotherapy or concurrent chemoradiotherapy to centre (model 1). Model 2 outlines the results of multiple logistic regression modeling relating decision to treat small cell lung cancer with combination chemotherapy or concurrent chemoradiotherapy to centre to centre, comorbidity (alcohol, COPD), and performance status.

	Model 1		Model 2	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Aberdeen (n=5)	1.07 (0.28-4.00)	0.92	0.24 (0.03-1.67)	0.15
Dunfermline (n=1)	0.27 (0.05-1.40)	0.12	0.05 (0.04-0.56)	0.016
Glasgow (n=12)	0.83 (0.22-3.07)	0.78	0.30 (0.05-1.95)	0.21
Inverclyde (n=5)	1		1	
Ischaemic heart disease (severity score)				
0 (n=14)			1	0.037*
1 (n=2)			0.48 (0.10-2.24)	
2 (n=4)			0.06 (0.01-0.54)	
3 (n=2)			1.14 (0.02-62.1)	
Alcohol (severity score)				
0 (n=12)			1	
1 (n=3)			0.37 (0.01-17.7)	0.010*
2 (n=2)			0.02 (0.01-0.39)	
3 (n=1)			0.12 (0.01-2.09)	
COPD(FEV_1% predicted)				
>80% (n=14)			1	0.090*
60-80% (n=5)			0.09 (0.01-1.15)	
40-60% (n=3)			0.39 (0.04-3.54)	
<40% (n=1)			0.51 (0.01-2.18)	
Performance status				
0 (n=3)			1	<0.001*
1 (n=11)			1.56 (0.11-23.2)	
2 (n=9)			0.39 (0.03-4.64)	
3 (n=0)			0.00 (0.00-)+	
4 (n=0)			0.00(0.00-)+	

*: p value for trend across categories

+: upper 95 CI not computable

Associations with best supportive/palliative care

For 182 patients (20.6%) the treatment option was best supportive care and/or referral to specialist palliative care i.e. no primary surgery, radiotherapy, or chemotherapy. There were significant (χ^2,p<0.001) between centre differences in the frequency of supportive/palliative care only with 10.8% (32/265) of patients in Aberdeen, 36.8% (50/136) in Dunfermline, 22.5% (64/285) in Glasgow and 22.0% (36/164) patients in Inverclyde receiving supportive/palliative supportive care (Table 4.8 model 1). Univariable analyses revealed that the likelihood of supportive/palliative care was increased by increasing age (mean 75.1 years 95%CI 73.8-76.4 vs. 69.1 (68.4-69.9), t test p<0.001), a failure to make a histological diagnosis (SCLC 7.8%, NSCLC 13.7%, no histological diagnosis 45.9%), decreasing performance status (active supportive care for PS 0/1 7.0% vs. 32.9% for PS 2/3/4, χ^2,p<0.001), increasing serum CRP and creatinine, decreasing albumin and increasing severity scores for congestive cardiac failure, cerebrovascular disease, dementia, renal impairment, and peripheral vascular disease. The decision to manage a patient with best supportive/palliative care was not associated with sex, socio-economic status, COPD, IHD, diabetes nor alcohol history. Multivariable modeling demonstrated that even after adjustment for multiple factors, between centre differences persisted (but not between Inverclyde and Aberdeen) and in each centre the decision to treat with best supportive/palliative care was associated with age, performance status, dementia severity, and extensive small cell lung cancer (Table 4.8, model 2).

Table 4.8 Results of univariable analysis relating decision to treat by best supportive/palliative care to centre (model 1). Model 2 outlines the results of multiple logistic regression modeling relating decision to treat by best supportive/palliative care to centre, age, dementia comorbidity score, performance status, tumour stage, and tumour histology.

	Model 1		Model 2	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Aberdeen (n=32)	1		1	
Dunfermline (n=50)	4.82 (2.90-7.99)	<0.001	3.66(1.97-6.78)	<0.001
Glasgow (n=64)	2.40 (1.51-3.80)	<0.001	1.79(1.04-3.09)	0.036
Inverclyde (n=36)	2.33 (1.38-3.92)	0.001	1.20(0.66-2.18)	0.55
Age (years)				
<60 (n=19)			1	<0.001*
60-70 (n=37)			1.24(0.54-2.83)	
70-80 (n=100)			2.14(0.99-4.61)	
>80 (n=72)			3.91(1.73-8.82)	
Dementia (severity score)				
0 (n=192)			1	0.003*
1 (n=16)			4.04(1.50-10.9)	
2 (n=10)			3.92(1.05-14.6)	
3 (n=10)			3.38(0.77-14.8)	
Performance status				
0 (n=12)			1	<0.001*
1 (n=39)			2.07(0.67-6.38)	
2 (n=62)			4.40(1.44-13.4)	
3 (n=89)			19.2 (6.2-58.8)	
4 (n=26)			60.4 (14.1-259)	
NSCLC stage I/II (n=26)			1	
NSCLC stage III (n=50)			0.65 (0.33-1.28)	0.21
NSCLC stage IV(n=122)			1.23 (0.65-2.30)	0.53
SCLC limited (n=4)			0.44 (0.11-1.79)	0.25
SCLC extensive (n=8)			0.32 (0.11-0.91)	0.032
No histology (n=9)			0.77 (0.29-1.99)	0.58

*: p value for trend across categories

4.4 Discussion

In this study we have prospectively collected data from 882 patients newly diagnosed with lung cancer in four Scottish centres. Within each centre the patients were consecutive and thus representative of the local population and medical practice. Our hypothesis was that variations in population demographics such as socio-economic status, performance status, stage at presentation, comorbidity and age determined the ability to deliver optimal standard therapy. The aim was to assess variations in practice between the four Scottish centres and possible causes for this such as demographics, age and comorbidity. A number of differences were identified between centres. These included investigation, treatment (surgical rates), patient age, tumour histology, stage, smoking history, socio-economic profile, ventilatory function and performance status. These differences may, in some part, explain the variations in practice seen in Scotland and we have attempted to characterise the very complex relationship between them.

Much of the variation in the initial treatments delivered may be accounted for by differences in comorbidity and patient choice. This is especially the case for those who decline surgical intervention. For supportive/ palliative care (the decision not to offer active anti-cancer therapy) between centre differences persisted after adjustment for tumour factors, demographics and comorbidities. The treatment rates shown in this chapter are generally unexpectedly low with surgical resection rates under 8% and palliative chemotherapy less than 10%. This was noted at the time of this aspect of the work and the data reanalyzed. These rates are inaccurately low due to coding errors, which are rectified in later chapters of the thesis.

Declining PS has been shown to correlate well with poorer survival (Radzikowska et al., 2002; Ludbrook et al., 2003). It is difficult to assess if comorbidity represents a separate predictive entity for treatment choice

or is simply a surrogate for performance status. The multivariable modeling indicated that whilst performance status is strongly associated with treatment delivered, the presence of co-existing comorbidities was additionally associated with treatment differences. Thus co-morbidities not only contribute to performance status but also have additional associations with treatment selection. In our study, predictors of declining performance status included increasing severity of a number of comorbidities, age, lower socio-economic status and specific geography (primarily Glasgow and Inverclyde).

The rate of decline in PS has never previously been explored. In multivariable analysis this rate has been shown to be related to increasing age, lower socio-economic group, several comorbid factors and tumour stage. However this assessment was retrospective and it has not been validated. The decline in PS, independently associated with socio-economic status within individual cities, probably reflects social trends in psychosocial factors influencing health e.g. diet, housing and social support. This decline in performance status also highlights the need for patients, particularly in lower socio-economic classes, to be seen and assessed early on in their disease before they deteriorate to a level where radical treatment is inappropriate. The results of this study suggest that the striking differences in deprivation seen between centres and generally within Scotland, in comparison to the remainder of the United Kingdom (Office for National Statistics, 2006; ISD, 2009; Gregor et al., 2001; Janssen-Heijnen et al., 1998) may be a contributory factor to the observation that Scottish patients with lung cancer have a poorer outcome in a global setting.

Surgical resection rates are closely associated with cure for NSCLC (SIGN, 2005), and the identification of factors influencing this, especially co-morbidities, were a primary study aim. The mean surgical resection rate in this study was 6.3% with a range from 5.5% to 7.4%, these figures are similar to those reported by a Cancer Registry in the South East of England

that reported a median resection rate of 6% with a range of 4 – 10% (Jack et al., 2003). In the present study socio-economic status was not associated with the likelihood of patients declining surgery. This contrasts with published studies that suggest lower socio-economic status patients are more likely to decline surgery (Mitchell et al., 2003). COPD was the only comorbid factor to persist once multi-variable analysis, including performance status, had been performed. The available literature supports the assertion that comorbidity is detrimental to outcome. However these studies have not assessed comorbidity in any significant detail (Birim et al., 2005; Imperatori et al., 2006)

The decision to offer best supportive/palliative care rather than active anticancer therapy clearly differed between centres, even after multivariable analysis. This is likely to reflect physician's choice using different criteria to determine treatment choice for a patient and it is notable that in this study the centre with the lowest rate of initial decision to offer best supportive/palliative care had the highest rate of chemotherapy for locally advanced/metastatic NSCLC. The present study is consistent with previous studies suggesting that comorbidity appears to influence treatment choice and potentially affect outcome, but adds to the literature by identifying relevant individual comorbidities and demonstrating dose response associations (Potosky et al., 2004; Earle et al., 2000; Extermann, 2000; Charlson et al., 1987; Tammemagi et al., 2004; Janssen-Heijnen et al., 2004; Colinet et al., 2005).

In an attempt to try to assess the reasons for differences in treatment and outcome within lung cancer in Scotland, this early data has shown some interesting differences between centres in relation to patient characteristics and treatment. We believe that one of the strengths of this study is that the study population is representative of the local population of people presenting with lung cancer because the centralised system of free universal healthcare in Scotland ensures that most people with suspected lung cancer are referred directly to Respiratory Physicians, in

addition comparisons of data submitted centrally from lung cancer MDTs with Cancer Registry data confirms that Respiratory Physicians investigate in excess of 90% of people with lung cancer in Scotland (MCN, Personal Communication). We suspect that the 10% of patients not investigated by Respiratory Physicians are relatively elderly, frail with advanced cancer diagnosed and managed at home by General Practitioners and those diagnosed at post-mortem. The primary outcome of interest was the initial treatment option decided by the MDT and given that, the clinician responsible for instigating the treatment agrees upon this decision, then it is almost certain that the treatment option was initiated. A limitation of this study is that because of relative small patient numbers it was not possible to analyse the factors influencing some of the more complex combined modality treatment decisions e.g. neo-adjuvant chemotherapy, sequential chemotherapy and radical radiotherapy, furthermore for pragmatic reasons it was not possible to ascertain whether the second part of these treatment options were actually commenced and if not why not. Such considerations may have contributed to the low rates of radical radiotherapy reported. A further limitation of this study is that we do not yet have survival data on the subjects and therefore cannot relate our observations on comorbidity to survival. We are currently investigating the possibility of using centrally collected data to address this.

The important message of this study is that is scientifically unsound to compare crude data from centres or countries and conclude that variations entirely reflect differences in practice. Whilst it is common practice to adjust such comparative data for sex, age, tumour and in some instances indirect measures of comorbidity (days in hospital in previous five years) our study highlights the need to adjust for other factors such as patient choice, comorbidity and performance status. The present study suggests that adjustment of comparative data for variation in performance status is insufficient and further adjustment for specific and quantified co-morbidities should be carried out, as comorbidity appears to have an independent impact upon between centre differences. Even so, whilst the

present study highlights the importance of variation in comorbidity, performance status, and tumour stage there is still evidence of between centre differences in practice suggesting variation in clinical practice.

Previous studies have shown that Scotland (in particular the West of Scotland) suffers from significantly higher rates of many comorbid diseases such as Ischaemic Heart Disease (Mitchell et al., 2005), COPD (Thorax, 2004) and Alcoholism (Emslie et al., 2009). The present study suggests that the combination of these comorbidities and social deprivation is especially disadvantageous, not only influencing the rate at which performance status deteriorates in the six months prior to presentation, but additionally affecting the treatment options available to the assessing physician. The particularly adverse combination of chronic ill-health and social deprivation might explain the significantly poorer performance status, lower active treatment rates and poorer survival seen for certain centres in Scotland.

This study has identified many significant between centre differences within Scotland. We believe this to be the first study to identify non-tumour factors independent of performance status that together limit the ability to deliver radical, possibly curative, therapy to our lung cancer population. It is only by identifying such factors that we can hope to address the significant health inequalities seen across the four centres and in the wider population and begin to improve upon the relatively poor outlook for the majority of Scottish lung cancer patients.

CHAPTER 5: COMORBIDITIES IN LUNG CANCER: PREVALENCE, SEVERITY AND LINKS WITH SOCIO-ECONOMIC STATUS AND TREATMENT.

5.1 Introduction

Lung cancer remains the commonest cause of cancer related death in Scotland (Gregor et al., 2001). Survival lags significantly behind much of Western Europe and the United States (Gregor et al., 2001; Janssen-Heijnen et al., 1998). Many causes for this have been suggested including late presentation, the impact of comorbidity and lower treatment rates (Berrino et al., 2007; Horner et al., 2009). Surgical resection rates within Scotland are around 12% compared to figures often quoted as above 20% within Europe and the USA (Fry et al., 1999; Laroche et al., 1998; Cartman et al., 2002; Damhuis et al, 1996). Scotland frequently has lower recorded rates for both chemotherapy and radiotherapy. Patients in Scotland often present late (around 40 -50% will present with stage IV disease (Birring et al., 2005) and have significant comorbidity.

In our own previously published work, the prevalence of comorbidity was significant with 44% of patients having Chronic Obstructive Pulmonary Disease and 27% Ischaemic Heart Disease (Grose et al., 2011). Comorbidity has previously been shown to have an adverse impact upon available treatment options and subsequent outcome both in cancer in general and specifically within lung cancer (Potosky et al., 2004; Earle et al., 2000; Extermann, 2000; Charlson et al., 1987; Tammemagi et al., 2004; Janssen-Heijnen et al., 2004; Colinet et al., 2005; Birim et al., 2005; Imperatori et al., 2006; Asmis et al., 2008; Erridge et al., 2009; Grose et al., 2011) and it is likely that poorer outcomes in Scotland are due to a complex mixture of these factors.

There are few studies on the impact of comorbidity in lung cancer (Grose et al., 2011). Of these only one study used a tool specifically designed for lung cancer(Colinet et al., 2005). Most studies use the Charlson Co-morbidity Index, which was designed to assess comorbidity in patients with breast cancer (Charlson et al., 1987). In none of these studies is the grade or severity of disease fully assessed and, because of improved treatment options for some of the comorbid conditions (e.g. HIV/AIDS), the weightings given to these comorbidities may be out dated. Potential selection bias is also an issue as some of these studies only deal with operable patients. In addition, information on comorbidities is poorly recorded in routinely collected audit and cancer registry data and thus little is known about its characteristics among lung cancer patients in Scotland.

We know that treatments offered to patients with lung cancer in Scotland show inter-centre variability(Grose et al., 2011) (Tables4.1+4.2). However we do not know the reason(s) for this. The aim of our study was to prospectively describe the prevalence and severity of comorbidities in patients newly diagnosed with lung cancer. In addition we wished to assess the relationship between presence and severity of comorbidity with patient demographics, including a proxy for socioeconomic status, and the treatment offered.

5.2 Methods

Previously described in chapter 3

5.3 Statistical Analysis

All statistical testing was conducted at the 5% level. Unless otherwise stated, medians and interquartile range (IQR) are used. Where appropriate the chi-squared test for trend was used to assess for statistically significant differences, otherwise the Pearson chi-squared test was used. Statistically significant differences were set at $p \leq 0.05$.

Statistical analyses were performed using SPSS v19.0 (SPSS Inc., Chicago, IL)

5.4 Results

Demographics

882 patients were included in the study, comprising 297 from Aberdeen, 136 from Dunfermline, 285 from Glasgow, and 164 from Inverclyde. The ages ranged from 31 to 94 (median 72) and 487 (55%) were male. Baseline characteristics are previously described in Chapter 4.

24.5% of patients were diagnosed on the basis of clinical examination and radiological investigations alone, without histological evidence. This compares favourably with the National Lung Cancer Audit data, which had a median rate of 37% (Rich et al., 2011) of patients who did not have histological confirmation of lung cancer. We did not look at sub-groups of NSCLC histology.

Comorbidity

In total 868 patients had their full comorbidity recorded. Comorbidities were found in 758 (87.3%) of patients at the time of diagnosis with lung cancer (Table 5.2). Only 110 (12.7%) patients had no comorbidity. Two or more comorbidities were found in 557 (64.2%) patients; 347 (40.0%) had three or more comorbidities and 4 (0.5%) had as many as 8 (Figure 5.1). The most frequent and most severe comorbidity was weight loss, which occurred in 53% of patients and had a mean score of 1.20.COPD was the next commonest comorbidity, present in 43% of patients and with a mean severity score of 0.76, followed by renal impairment (28%, mean 0.40) and IHD (27%, mean 0.36) (Table 5.1). The cumulative severity score in those with comorbidities ranged from 1-15 (mean 3.8 and median 3.0)

The most common co-existing diseases were weight loss and COPD (215 cases, 24% of 882 patients), weight loss with renal impairment (164 cases, 19%), COPD with renal impairment (154 cases, 17%), weight loss with IHD

(144 cases, 16%) and COPD with IHD (124 cases, 14%). The numbers of patients with aetiologically similar cardiovascular morbidities was low, with IHD and CVA concurring in 32 cases (4%), IHD and PVD in 37 cases (4%) and PVD and CVA in 14 cases (2%).The commonest co-existing diseases which both had grade 3 severity were severe weight loss with severe COPD (20 cases, 2%), severe renal impairment (9 cases, 1%) or severe IHD (9 cases, 1%) (Table 5.2).

Table 5.1. Distribution of comorbidities among 868 newly diagnosed lung cancer patients.

	Severity n (%)				
Comorbidity (missing data / %)	0	1	2	3	Mean
Weight loss (3/ 0.3%)	416 (47%)	131 (15%)	74 (8%)	258 (29%)	1.20
COPD (9/ 1%)	494 (57%)	146 (17%)	180 (21%)	53 (6%)	0.76
Renal impairment (7/ 0.8%)	634 (72%)	145 (17%)	79 (9%)	17 (2%)	0.40
IHD (4/ 0.5%)	645 (73%)	165 (19%)	50 (6%)	18 (2%)	0.36
CCF (4/ 0.5%)	759 (86%)	84 (10%)	31 (4%)	4 (0.5%)	0.18
Other Malignancy (3/ 0.3%)	755 (86%)	95 (11%)	28 (3%)	1 (0.1%)	0.18
Alcohol xs (5/ 0.6%)	774 (88%)	65 (7%)	20 (2%)	18 (2%)	0.18
Diabetes (5/ 0.6%)	776 (88%)	66 (8%)	32 (4%)	3 (0.3%)	0.16
CVA (4/ 0.5%)	800 (91%)	52 (6%)	18 (2%)	8 (1%)	0.13
PVD (4/ 0.5%)	800 (91%)	45 (5%)	27 (3%)	6 (0.7%)	0.13
Dementia (4/ 0,5%)	827 (94%)	24 (3%)	14 (2%)	13 (1%)	0.10

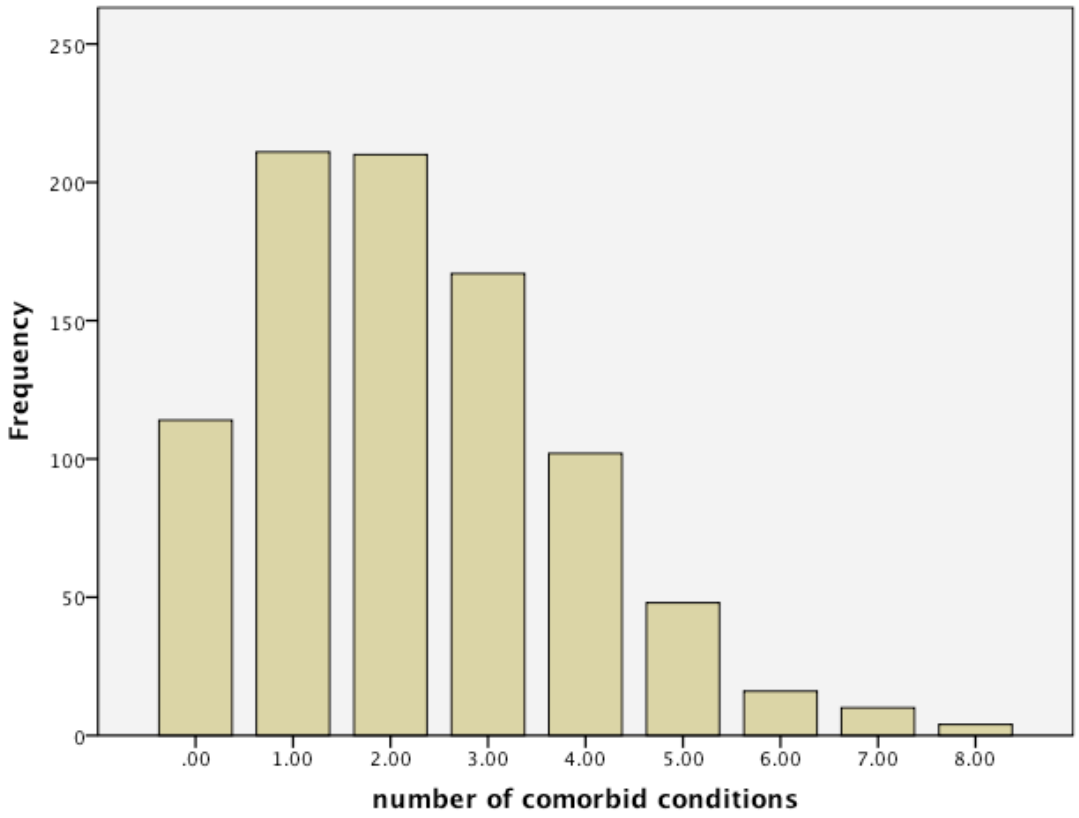

Figure 5.1. Histogram showing number of comorbid conditions per patient. 868 lung cancer patients in 4 Scottish centres, 2005-08.

Table 5.2. Concurrence between individual comorbid conditions. 868 lung cancer patients in 4 Scottish centres, 2005-08.

(Left of diagonal for any grade. Right of diagonal for grade 3 of both conditions)

Comorbidity	Comorbidity										
	Weight loss	COPD	Renal impairment	IHD	CCF	Other malignancy	Alcohol XS	Diabetes	CVA	PVD	Dementi
Weight loss		20	9	9	2	0	5	0	4	2	4
COPD	215		0	0	0	0	1	0	0	0	0
Renal impairment	164	154		0	0	0	0	0	0	0	0
IHD	144	124	83		3	0	0	0	0	0	0
CCF	76	62	43	90		0	0	0	0	0	0
Other malignancy	73	61	46	39	22		0	0	0	0	0
Alcohol xs	64	66	61	25	18	18		0	0	0	1
Diabetes	56	47	47	44	26	24	24		0	0	0
CVA	50	37	32	32	17	14	13	13		0	0
PVD	43	46	35	37	20	16	16	18	14		0
Dementia	42	33	33	24	12	12	17	15	18	10	

Using the cumulative comorbidity scoring index (Table 5.3) we found that 411 (47.4%) of patients with lung cancer had moderate (278 (32.0%) or severe comorbidities (133 (15.3%).

Table 5.3. Cumulative comorbidity scoring index. 868 lung cancer patients in 4 Scottish centres, 2005-08.

Range of cumulative comorbidity score	Group	Number of patients	Percentage of patients
0	Nil	110	12.7%
1-3	Low	347	40.0%
4-6	Moderate	278	32.0%
≥ 7	Severe	133	15.3%

Relationship between demographics and comorbidity (Table 5.4)

The presence of comorbidity in patients with lung cancer varied significantly between the 4 centres. The prevalence of severe co-morbidity (index score of 3) was three times higher in patients treated in Dunfermline than the other three centres ($p < 0.001$ Pearson chi-squared test)

Relationship between socio-economic status and comorbidity (Table 5.4)

Significant variations in the level of co-morbidity between the relative socio-economic groups were seen. The most deprived patients had increased levels of comorbidity in comparison with those from more affluent backgrounds ($p=0.026$ Pearson chi-squared test)

Relationship between cancer stage and comorbidity (Table 5.5)

The presence of comorbidity did not appear to be associated with stage of disease for either NSCLC ($p=0.406$) or SCLC ($p=0.348$)

Relationship between treatments offered for NSCLC patients and comorbidity (Table 5.4)

Among patients with NSCLC, there were significant associations between comorbidities and treatment. For NSCLC with early stage disease disease, patients offered surgery had lowest comorbidities scores, indicating fewer and less severe comorbidities, while those not offered curative treatment had most severe comorbidity scores ($p = 0.006$ Chi-square test for trend). Similarly, the least active palliative treatments were offered to those patients with most severe comorbidities ($p<0.001$ Pearson chi-squared test).

Table 5.4. The relationship between comorbidity grouping, demographics, socio-economic status, stage and treatment.

	Comorbid group % (n)			
	Nil	Low	Moderate	Severe
Centre (n = 882) (p<0.001)				
Aberdeen (297)	21%	41%	27%	11%
Glasgow (285)	8%	44%	35%	13%
Inverclyde (164)	14%	44%	30%	12%
Dunfermline (136)	3%	21%	41%	35%
Socio-economic status (quintile) (n=868) (p=0.026)				
1 (Most deprived) (265)	11%	42%	33%	14%
2 (126)	14%	33%	36%	17%
3 (248)	8%	43%	34%	15%
4 (169)	18%	35%	31%	16%
5 (60)	22%	48%	18%	12%
Stage NSCLC (n = 525) (p=0.406)				
I (65)	17%	49%	26%	8%
II (43)	7%	44%	33%	16%
IIIa (48)	6%	48%	35%	11%
IIIb (138)	14%	46%	31%	9%
IV (231)	15%	44%	25%	16%
Stage SCLC (n = 115) (p=0.348)				
Limited (33)	25%	39%	21%	15%
Extensive (82)	15%	32%	35%	18%
Early Stage NSCLC (n=156) (p=0.006)				
Surgery (55)	18%	49%	29%	4%
Radical Radiotherapy (32)	9%	47%	34%	10%
No curative Option (69)	6%	46%	30%	18%
Advanced Stage NSCLC (n = 362) (p=0.001)				
Palliative Chemotherapy (176)	18%	52%	25%	5%
Palliative radiotherapy (88)	9%	36%	36%	19%
Supportive care (98)	11%	39%	24%	26%

5.5 Discussion

We have found a high prevalence of comorbidity at presentation in patients with lung cancer. Comorbidities most frequently identified are weight loss (which was found in over 50% of patients), COPD, renal impairment and IHD. Most patients have at least one comorbidity and two thirds had two or more Given that most patients were current or ex smokers, fewer than expected had cardiovascular comorbidities. However, our findings are consistent with recent British Heart Foundation reports (British Heart Foundation, 2009). The overall severity of comorbidity was associated with socio-economic status and treatment centre. Importantly comorbidity status at presentation was associated with the treatment offered.

Treatment options for lung cancer, in particularly for advanced NSCLC, have significantly increased over the past decade (NICE 121, 2011) with a resultant improvement in survival. The trial data to support the use of such treatments is based on patients with good performance status. Significant comorbidity usually excludes a patient from enrolment into therapeutic clinical trials. We have demonstrated that worsening comorbidity detrimentally affects the likelihood of a patient being offered active treatment. It would seem logical to suggest that this is highly likely to have a negative impact upon survival.

We are not aware of any published studies that combine both the number and severity of comorbidities into a simple index. In addition no similar work has so clearly demonstrated a link between comorbidity, socioeconomic status and treatment offered. A recent study by Wang et al (2012) using the Charlson Comorbidity Index suggested that age rather than comorbidity was the most significant negative predictor of treatment. It did not look at outcomes or survival. The Adult Comorbidity Evaluation 27 (ACE-27) tool, initially validated in head and neck cancer was used in a prospective study including over 17,000 patients a large

cohort of whom had lung cancer (Piccirillo et al., 2004). This showed that worsening co-morbidity significantly impacted negatively on survival, however sub-group analysis identified comorbidity as having the least prognostic information in lung cancer patients.

The major limitation of this study is the lack of survival data currently available. Although the cumulative comorbidity index was found to be associated with, centre, socio-economic status and active treatment rates, suggesting it has some validity, clearly significantly more work will be required to demonstrate a formal link with survival. This work is currently underway.

The important role that comorbidity has in affecting outcomes in lung cancer is beginning to be noted and the inclusion of basic data within the English National Lung Cancer Audit (NLCA) is welcomed. However we believe that more detailed recording is imperative to improve the understanding we have for comorbidity and the impact it has on lung cancer outcomes. Our study goes someway towards addressing this, currently unmet, need.

CHAPTER 6: SIMPLE AND OBJECTIVE PREDICTION OF SURVIVAL IN PATIENTS WITH LUNG CANCER; STAGING THE HOST SYSTEMIC INFLAMMATORY RESPONSE.

6.1 Introduction

Within Scotland lung cancer remains the commonest cause of cancer related death (Berino et al., 2007). The prognosis is bleak with the median survival in advanced disease around four months from diagnosis (Berino et al., 2007). Survival compares unfavourably with other European countries and USA (Berino et al., 2007; Janssen-Heijnen et al. 1998). It has often been felt that the Scottish lung cancer population has more comorbidity with poorer performance status thus presenting fewer tolerable therapeutic options.

It is difficult to quantify the complex nature of patient frailty to provide a degree of objective assessment of fitness (Maltoni et al., 2005) and as a result prediction of survival in patients diagnosed with lung cancer remains problematical. Currently, prognosis is based upon a combination of stage of disease and performance status although other factors such as weight loss have been identified in the advanced cancer setting (Martin et al., 2010; Glare et al., 2004; Gripp et al., 2007). However, these host factors (weight loss and performance status) included in clinical decisions are recognized to be subjective in nature.

Recent work shows that the effect of systemic inflammation is detrimental in terms of outcome in cancer in general (McMillan, 2009; Proctor et al., 2011) and in lung cancer specifically (Wilop et al., 2006; Kock et al., 2009; Gagnon et al., 2010; Arrieta et al., 2010; Forrest et al., 2004; Forrest et al., 2005; Brown et al., 2007; Leung et al., 2012). The combination of C reactive protein and albumin when combined to calculate the modified

Glasgow Prognostic Score (Table 6.1) has been previously been validated as an independent predictor of survival (McMillan. 2014).

The aim of the present study was to examine the clinical utility of this established objective marker of the systemic inflammatory response, the modified Glasgow Prognostic Score (mGPS), as the basis of risk stratification in patients with lung cancer.

Table 6.1 The Glasgow Prognostic Scores

	Score
Glasgow Prognostic score (GPS)	
CRP ≤ 10mg/l and albumin ≥ 35g/l	0
CRP > 10mg/l or albumin < 35g/l	1
CRP > 10mg/l and albumin < 35g/l	2
modified Glasgow Prognostic Score (mGPS)	
CRP ≤ 10mg/l and albumin ≥ 35g/l	0
CRP ≤ 10mg/l and albumin < 35g/l	0
CRP > 10mg/l	1
CRP > 10mg/l and albumin < 35g/l	2

6.2 Methods

Previously discussed in chapter 3

Survival data

Information on date of death was obtained via survival analysis undertaken by the Information Service Division (ISD) of NHS Scotland. Death records were complete until 1 June 2011, which served as the censor date for those alive.

GPS/ mGPS

A venous blood sample was obtained at diagnosis for measurement of CRP concentration and albumin. The coefficient of variation for these methods over the range of measurement was less than 5%, as established by routine quality control procedures. The GPS was constructed as previously described (Table 6.1) (Forrest et al., 2003; McMillan et al., 2007). In brief, CRP more than 10 mg/L and albumin less than 35 g/dl were each given a score of 1. The GPS was calculated as 0, 1, or 2. Since hypoalbuminaemia alone in the absence of an increased CRP level did not confer a poorer cancer-specific survival in all patients with cancer (McMillan et al., 2007), the GPS was modified to assign a score of 0 in patients with hypoalbuminaemia alone (Table 6.1) (Crumley et al., 2008).

A number of recent studies have supported the use of mGPS in predicting outcome both in lung cancer and other tumour types (Wilop et al., 2006; Kock et al., 2009; Gagnon et al., 2010; Arrieta et al., 2010; Forrest et al., 2004; Forrest et al., 2005; Brown et al., 2007; Leung et al., 2012). It was our intention to stratify the group by mGPS and then analyse the impact of more conventional staging methods such as TNM stage and performance status.

6.3 Statistics

All statistical testing was conducted at the 5% level so 95% confidence intervals (CI) are reported throughout. Unless otherwise stated, medians and interquartile range (IQR) are used. The survival time defined as the number of months from study entry until death or if alive at follow-up date, was calculated. Univariate survival analysis was carried out using Kaplan-Meier method and the log rank test. Survival analysis was carried out using the Cox's proportional-hazards model and hazard ratios (HR) were calculated. Multivariate survival analysis was performed using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival. To remove a variable from the model, the corresponding P-value had to be >0.10.

Statistical analyses were performed using SPSS v19.0 (SPSS Inc., Chicago, IL).

6.4 Results

In total, 882 patients from a number of different treatment groups were included in the study, comprising 297 from Aberdeen, 136 from Dunfermline, 285 from Glasgow, and 164 from Inverclyde composing; 59 patients were excluded from the study due to missing survival data (Figure 6.1). Baseline characteristics are previously described in chapter 4. The median age of participants was 72 years old. The majority was male, current or ex-smokers, of good performance status with advanced disease and had treatment with palliative intent.

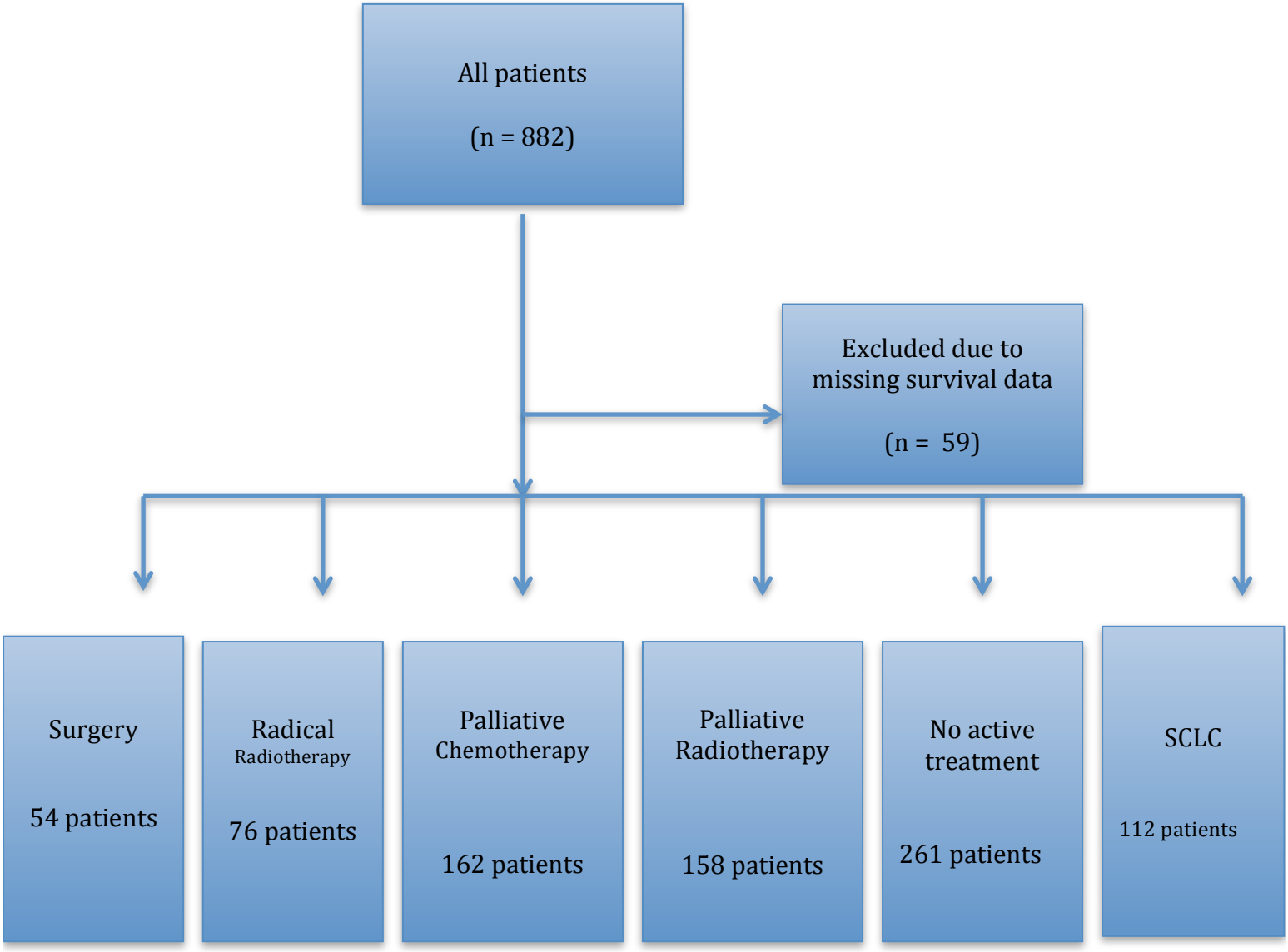

Figure 6.1 Flow chart of patient selection process

Most had an elevated mGPS. The median follow up for survivors was 24.5 months (4.6 – 40.8). The median overall survival was 5.6 months (4.8 – 6.5). The 12-month survival rate was 30% (SE 2%).

Survival analysis using both GPS and mGPS was undertaken (Figures 6.2 + 6.3). Both were highly significantly associated with survival. Since the mGPS has been most extensively validated and readily extrapolated from previous work using C-reactive protein alone (McMillan et al., 2009; McMillan, 2014) it was used in the remainder of the analysis and to stratify the three groups.

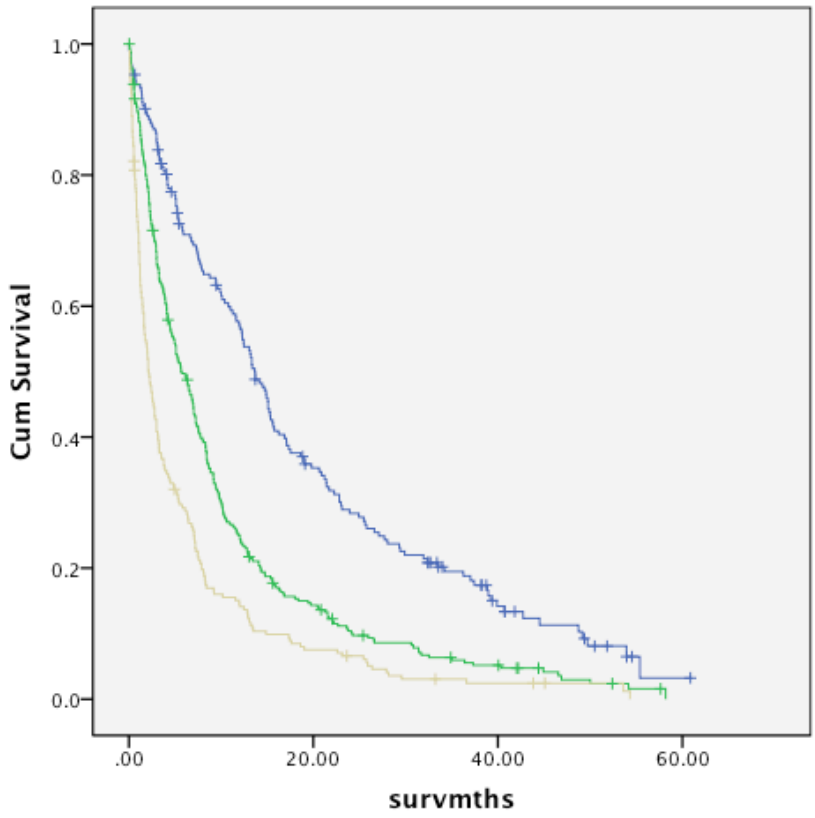

Figure 6.2 – The relationship between the Glasgow Prognostic Score (GPS) (0 – 2, from top to bottom) and survival. GPS 0 vs. 1 (log rank p<0.001), GPS 1 vs. 2 (log rank p<0.001)

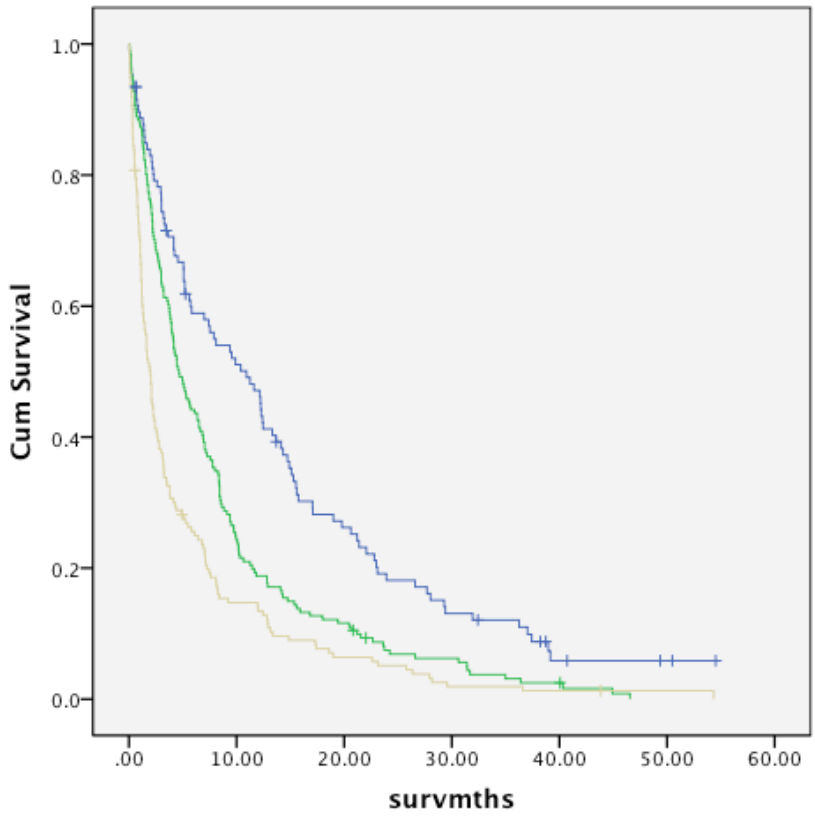

Figure 6.3 – The relationship between the modified Glasgow Prognostic Score (mGPS) (0 – 2, from top to bottom) and survival. mGPS 0 vs 1(log rank p<0.001), mGPS 1 vs 2 (log rank p<0.001)

The relationship between the mGPS and clinicopathological characteristics is shown in Table 6.2. There were 213 patients in the mGPS score of 0 group, 290 patients in the mGPS score of 1 group and 218 patients in the mGPS score of 2 group. The mGPS was associated with increasing deprivation ($p<0.001$), pack years smoking ($p<0.001$), poorer performance status ($p<0.001$), more weight loss ($p<0.001$), more advanced disease ($p<0.001$), less radical treatment ($p<0.001$) and poorer survival ($p<0.001$).

Table 6.2 The relationship between the mGPS and clinicopathological characteristics in patients with lung cancer

Demographic	mGPS			P value (chi-square test)
	0 (n= 213)	1 (n= 290)	2 (n= 218)	
Age (<60/60-69/70-79/≥80 years)	33/71/89/28	44/87/119/54	34/57/91/49	0.064
Sex Male/Female	115/108	174/130	133/98	0.201
Centre Aber/Dunf/Gla/Inver	98/10/77/38	146/25/66/67	43/16/126/46	<0.001
Deprivation Most – Least (quintile)	68/24/71/39/21	75/47/75/77/30	111/21/70/20/9	<0.001
Smoke (pack years) NS/<20/20-60/>60	21/24/126/37	11/33/177/69	13/21/128/57	0.014
Performance Status 0/1/2/3/4	42/96/60/22/3	26/130/105/40/3	5/51/88/66/21	<0.001
Weight loss (%) 0/<5/5-10/>10	147/24/12/38	146/36/13/109	79/45/33/73	<0.001
FEV1 (%) <80/61-80/40-60/<40	138/31/45/7	181/48/53/22	130/33/47/17	0.126
Local Symptoms No /Yes	36/127	18/222	29/137	0.246
Tumour Stage NSCLC I/II/IIIa/IIIb/IV	32/11/7/38/38	15/19/20/56/84	7/5/12/36/79	<0.001
Tumour Stage SCLC Limited/Extensive	13/21	10/32	8/18	0.471
Treatment				
Early Stage (Surgery/RT/no active)	26/9/38	17/15/43	4/2/18	<0.001
Advanced Stage (Chemo/RT/No active)	63/27/49	107/58/55	50/49/75	<0.001
Survival				
Alive/dead	34/181	16/274	8/211	0.003
12 month survival % (SE)	46 (4)	16 (2)	14 (3)	<0.001

The relationship between the clinico-pathological characteristics and survival in patients with an mGPS of 0 is shown in Table 6.3. The median survival was 13.2 (11.2 – 18.9) months. On univariate survival analysis, performance status ($p<0.001$), weight loss ($p<0.01$), stage of NSCLC ($p<0.001$), radical treatment offered ($p<0.01$) and palliative treatment offered ($p<0.05$) were all significantly associated with survival. On multivariate analysis, performance status (HR 1.69, 95% CI 1.39-2.06, $p<0.001$), weight loss (HR 1.18, 95% CI 1.04-1.33, $p=0.009$), stage of NSCLC (HR 1.06, 95% CI 1.01-1.23, $p=0.017$) and palliative treatment offered (HR 1.30, 95% CI 1.08-1.55, $p=0.004$) were independently associated with survival.

Table 6.3 The relationship between parameters and survival in patients with mGPS = 0 (n=213)

Parameter	Patients	Univariate		Multivariate	
	N	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (<60/ 60-69/70-79/≥80 years)	33/71/89/28	1.16(0.98-1.37)	0.077		
Sex Male	115	1			
Female	108	0.81(0.61-1.09)	0.169		
Centre Aberdeen	98	1	0.068		
Dunfermline	10	2.72(1.40-5.29)			
Glasgow	77	1.00(0.72-1.41)			
Inverclyde	38	1.13(0.75-1.70)			
Deprivation (Most deprived = 1, Least Deprived = 5) 1/2/3/4/5	68/24/71/39/21	0.94(0.85-1.05)	0.299		
Smoking history (NS = never smoker, otherwise pack years)					
NS/<20/20-60/>60	21/24/126/37	0.93(0.77-1.12)	0.467		
Performance Status					
0/1/2/3/4	42/96/60/22/3	1.76(1.47-2.11)	<0.001	1.69(1.39-2.06)	<0.001
Weight loss (%Body weight)					
0/<5/5-10/>10	147/24/12/38	1.21(1.08-1.37)	0.002	1.18(1.04-1.33)	0.009
FEV1 (%)					
>80/80-60/59-40/<40	138/31/45/7	0.94(0.80-1.12)	0.515		
Local Symptoms					
No/Yes	36/127	1.38(0.91-2.09)	0.124		
Stage					
NSCLC I/II/IIIa/IIIb/IV	32/11/7/38/38	1.38(1.25-1.53)	<0.001	1.06(1.01-1.23)	0.017
SCLC Limited/Extensive	13/21	1.05(0.97-1.14)	0.228		
Treatment					
Early Stage BSC/Surgery/RT	37/26/8	0.61(0.48-0.78)	0.001		
Advanced Stage Chemo/RT/BSC	59/27/47	1.22(1.01-1.46)	0.039	1.30(1.08-1.55)	0.004

The relationship between the clinico-pathological characteristics and survival in patients with an mGPS of 1 is shown in Table 6.4. The median survival was 6.1 (4.9 – 7.3) months. On univariate survival analysis, decreased age ($p<0.01$), performance status ($p<0.001$), weight loss ($p<0.01$), stage of NSCLC ($p<0.001$) and radical treatment offered ($p<0.001$) were significantly associated with survival. On multivariate analysis, performance status (HR 1.81, 95% CI 1.55-2.13, $p<0.001$), stage of NSCLC (HR 1.08, 95% CI 1.03-1.13, $p<0.01$) and radical treatment offered (HR 0.70, 95% CI 0.52-0.94, $p<0.05$) were independently associated with survival.

Table 6.4 The relationship between parameters and survival in patients with mGPS = 1 (n=290)

Parameter	Patients	Univariate		Multivariate	
	N	HR (95%CI)	p-value	HR (95%CI)	p-value
Age					
<60/ 60-69/70-79/≥80	33/71/89/28	1.24(1.09-1.40)	0.001		
Sex					
Male	174	1	0.171		
Female	130	0.84(0.66-1.08)			
Centre					
Aberdeen	145	1	0.425		
Dunfermline	23	0.89(0.55-1.43)			
Glasgow	55	0.99(0.72-1.36)			
Inverclyde	67	1.23(0.92-1.66)			
Deprivation(Quintile) (Most deprived = 1, Least Deprived = 5)					
1/2/3/4/5	75/47/75/77/30	0.99(0.90-1.08)	0.777		
Smoking history (NS = never smoker, otherwise pack years)					
NS/<20/20-60/>60	11/33/177/69	1.02(0.86-1.22)	0.792		
Performance Status					
0/1/2/3/4	26/130/105/40/3	1.83(1.57-2.14)	<0.001	1.81(1.55-2.13)	<0.001
Weight loss (%Body weight)					
0/<5/5-10/>10	181/48/53/22	1.15(1.06-1.25)	0.001		
FEV1 (%)					
>80/80-60/59-40/<40	138/31/45/7	0.94(0.83-1.06)	0.313		
Local Symptoms					
No/Yes	18/222	1.60(0.91-2.80)	0.105		
Stage					
NSCLC I/II/IIIa/IIIb/IV	15/19/20/56/84	1.31(1.19-1.45)	<0.001	1.08(1.03-1.13)	0.002
SCLC Limited/Extensive	10/32	0.51(0.23-1.11)	0.091		
Treatment					
Early Stage Best Supportive Care (BSC)/Surgery/RT	43/17/15	0.55(0.41-0.72)	<0.001	0.70(0.52-0.94)	0.017
Advanced Stage Chemo/RT/BSC	107/58/55	1.07(0.90-1.26)	0.436		

The relationship between the clinico-pathological characteristics and survival in patients with an mGPS of 2 is shown in Table 6.5. The median survival was 2.1 (1.5 – 2.7) months. On univariate survival analysis, centre ($p<0.01$), performance status ($p<0.001$), weight loss ($p<0.001$), stage of NSCLC ($p<0.001$) and radical treatment offered ($p<0.01$) were significantly associated with survival. On multivariate analysis, only performance status (HR 1.44, 95% CI 1.21-1.71, $p<0.001$) and weight loss (HR 1.13, 95% CI 1.00-1.28, $p<0.05$) were independently associated with survival.

Table 6.5 The relationship between parameters and survival in patients with mGPS = 2 (n=218)

Parameter	Patients	Univariate		Multivariate	
	N	HR (95%CI)	p-value	HR (95%CI)	p-value
Age					
<60/60-69/70-79/≥80	34/57/91/49	1.13(0.98-1.30)	0.084		
Sex					
Male	133	1	0.136		
Female	98	0.81(0.61-1.07)			
Centre					
Aberdeen	43	1	0.002		
Dunfermline	16	1.71(0.95-3.06)			
Glasgow	114	0.64(0.45-0.92)			
Inverclyde	45	0.88(0.57-1.35)			
Deprivation(Quintile) (Most deprived = 1, Least Deprived = 5)					
1/2/3/4/5	111/21/70/20/9	1.05(0.94-1.17)	0.408		
Smoking history (NS = never smoker, otherwise pack years)					
NS/<20/20-60/>60	13/21/128/57	0.83(0.69-1.00)	0.062		
Performance Status					
0/1/2/3/4	5/51/88/66/21	1.51(1.30-1.76)	<0.001	1.44(1.21-1.71)	<0.001
Weight loss (%Body weight)					
0/<5/5-10/>10	79/45/33/73	1.25(1.11-1.40)	<0.001	1.13(1.00-1.28)	0.047
FEV1 (%)					
>80/80-60/59-40/<40	130/33/47/17	0.88(0.77-1.01)	0.073		
Local Symptoms					
No/Yes	29/137	1.51(0.98-2.33)	0.063		
Stage					
NSCLC I/II/IIIa/IIIb/IV	7/5/12/36/79	1.32(1.15-1.50)	<0.001		
SCLC Limited/Extensive	8/18	1.01(0.91-1.12)	0.826		
Treatment					
Early Stage BSC/Surgery/RT	18/2/4	0.52(0.33-0.83)	0.006		
Advanced Stage Chemo/RT/BSC	50/49/75	0.92(0.78-1.10)	0.364		

The relationship between mGPS, Performance status and survival at 1 year is shown in Table 6.6. When used in combination survival at 1 year varied from 72% (mGPS 0, PS 0) to 6% (mGPS 2, PS 3). The numbers in the PS 4 subgroup were too small to calculate accurately a survival rate.

Table 6.6 The relationship between mGPS and PS and 12 month survival rate (%, SE).

	mGPS			Total number of patients
PS	0	1	2	
0	72% (7)	50% (10)	20% (18)	71
1	65% (5)	31% (4)	30% (7)	259
2	49% (7)	19% (4)	16% (4)	245
3	9% (6)	5% (4)	6% (3)	122
4	NC	NC	NC	20
Total number of patients	212	290	218	

NC not calculated where N<10.

The relationship between mGPS, TNM stage (NSCLC patients only) and survival at 1 year is shown in Table 6.7. Survival varied from 69% (mGPS 0, Stage I NSCLC) to 2% (mGPS 2, Stage IV NSCLC).

Table 6.7 The relationship between mGPS and TNM Stage (NSCLC only) and 12 month survival rate (%, SE).

	mGPS			Total number of patients
Stage	0	1	2	
I	69% (19)	28% (12)	NC	62
II	37% (14)	17% (9)	NC	47
IIIa	20% (13)	42% (10)	0%	53
IIIb	20% (6)	6% (3)	14% (5)	154
IV	5% (3)	4% (2)	2% (2)	261
Total number of patients	153	225	173	

NC not calculated where N<10.

To stratify for stage, the relationship between mGPS and PS and survival at 3 months for those patients with advanced NSCLC (stage IIIb/IV) is shown in Table 6.8. Survival varied from 100% (mGPS 0, PS 0) to 23% (mGPS 2, PS3). The number of patients in the PS 4 group was too small to accurately calculate survival.

Table 6.8. The Relationship between mGPS and PS and 3 month survival rate (%, SE) in patients with TNM stage IIIb/IV NSCLC (n = 374).

	mGPS			Total number of patients
PS	0	1	2	
0	100% (0)	92% (8)	100% (0)	28
1	94% (4)	73% (6)	55% (9)	119
2	65% (11)	62% (7)	43% (8)	105
3	NC	29% (11)	23% (8)	55
4	NC	NC	NC	7
Total number of patients	61	134	111	

NC not calculated when N <10

This group was then further stratified to take into account the treatment offered. The relationship between mGPS and PS at 3 months for those patients with advanced NSCLC (stage IIIb/IV) undergoing palliative chemotherapy is shown in Table 6.9. Survival varied from 92% (mGPS 0, PS 1) to 50% (mGPS 2, PS 2). The numbers of patients in the PS 0 and 4 groups were too small to accurately calculate survival.

Table 6.9. The Relationship between mGPS and PS and 3 month survival rate (%, SE) in patients with TNM stage IIIb/IV NSCLC and receiving palliative chemotherapy (n = 138).

	mGPS			Total number of patients
PS	0	1	2	
0	NC	NC	NC	13
1	92% (7)	74% (8)	54% (14)	60
2	NC	69% (12)	50% (16)	33
3	NC	NC	NC	12
4	NC	NC	NC	0
Total number of patients	27	61	30	

NC not calculated when N <10

6.5 Discussion

The results of the present study show for the first time that, in a large cohort of patients with lung cancer and using the mGPS as an objective basis for the prediction of survival, significant factors associated with survival varied significantly. Only performance status and to a lesser extent tumour stage were consistently shown to have independent prognostic value. Furthermore, the combination of the mGPS with either performance status or tumour stage effectively stratified the likely outcome in these patients. Therefore, this simple scheme based on objective criteria provides a new readily applicable approach to the routine clinical evaluation of patients with lung cancer.

In the present study it was of interest that weight loss, a well recognised poor prognostic factor, was inconsistently prognostic when included in the analysis with mGPS and performance status. This may suggest that much of the prognostic value of weight loss is attributable to the activation of the systemic inflammatory response and to the progressive loss of lean tissue leading to nutritional and functional decline (McMillan, 2009). Indeed, activation of the systemic inflammatory response resulted in a marked reduction in median survival of 13 months (mGPS 0) to 2 months (mGPS 2) independent of treatment received. This would suggest that the allocation of treatment was suboptimal and it may be that treatment allocated on a more objective scheme as proposed above will result in improved outcomes in all patients. For example, in those patients with mGPS of 2, neither stage nor treatment had independent prognostic value and therefore it would appear that such poor prognosis patients derive little benefit from standard anti-cancer. In particular a very honest appraisal of both benefits and toxicities of any treatment should be made with the patient irrespective of their tumour stage (MacDonald, 2012). However it must be noted that the very small numbers of patients in these groups (e.g. only 2 patients underwent surgery and 4 underwent radical

radiotherapy) makes it very difficult to interpret and further studies looking only at radically treatable patients are advised.

The relationship between poor survival and systemic inflammation (the mGPS) remains poorly understood but it is likely to represent an objective marker of the chronic activation of the innate immune response with the consequent up-regulation of pro-inflammatory cytokines and growth factors and the resultant cancer cachexia (Scagliotti et al., 2008; Du Clos et al., 2004; Nozoe et al., 2000; Coussens et al., 2002; Abramovitch et al., 1999; Canna et al., 2008).

It is clear that, in Scotland, lung cancer continues to confer a very poor outcome with a median life expectancy of approximately 5 months. Even in early disease (TNM stage I/II NSCLC), with patients undergoing radical treatment with an expectation of cure (10 -15% of total number of patients within Scotland (Edge et al., 2009)) the 5-year survival is only around 30-60% (Edge et al., 2009). The advent of more advanced imaging modalities such as PET-CT (SIGN, 2005) has improved detection of occult metastasis leading to stage migration and less patients undergoing futile radical local treatment. Nevertheless, the present results highlight the importance of also staging the host systemic inflammatory response. The mGPS is a simple, cheap, and reproducible prognostic tool that has been shown to be a rational starting point for such work.

Since the initial work, a decade ago the combination of C-reactive protein and albumin, the Glasgow Prognostic Score (GPS/ mGPS), has been shown to have independent prognostic value in more than 60 studies (>30,000 patients with cancer). This prognostic value has been demonstrated in a variety of clinical scenarios, in particular primary operable cancer (McMillan, 2014)

More recently in approximately 2,500 patients (Laird et al., 2013) and this present study have demonstrated that the mGPS has also clinical utility, together with performance status, in patients with advanced cancer.

In conclusion, the results of the present study confirm the independent prognostic value of the mGPS. In addition, it demonstrates the clinical utility of the mGPS combined with performance status to provide more objective risk stratification in patients diagnosed with lung cancer.

CHAPTER 7: THE IMPACT OF COMORBIDITY UPON DETERMINANTS OF OUTCOME IN PATIENTS WITH LUNG CANCER.

7.1 Introduction

Within Scotland lung cancer remains the commonest cause of cancer related death (Gregor et al., 2001). Survival lags significantly behind much of Western Europe and the United States (Gregor et al., 2001; Janssen-Heijnen et al., 1998). The cause(s) for this are not fully understood but are likely to include late presentation, the impact of comorbidity and lower treatment rates (Berrino et al., 2007; Horner et al., 2009; Fry et al., 1999; Laroche et al., 1998; Cartman et al., 2002; Damhuis et al., 1996; Birring et al., 2005). Our own, previously published, work has identified very high levels of comorbidity within an unselected lung cancer population within Scotland (Grose et al., 2011). It has also indicated that such comorbidity may play an important part in the decision to offer active treatment both in the radical and palliative setting (Grose et al., 2014). These findings have been supported by a number of studies, which have demonstrated the prognostic significance of comorbidities in many different types of cancer (Potosky et al., 2004; Earle et al. 2000; Extermann, 2000; Charlson et al., 1987; Tammemagi et al., 2004; Janssen-Heijnen et al., 2004; Colinet et al., 2005; Birim et al., 2005; Imperatori et al., 2006; Asmis et al., 2008; Erridge et al., 2009; Grose et al., 2011). However the mechanism of comorbidity upon cancer outcome is not clear. In addition there are often significant differences between the methods used to document and grade the severity of comorbidity (Grose et al., 2011)

The most widely quoted tool to assess comorbidity is the Charlson Comorbidity Index (Charlson et al., 1987) (CCI). This was designed in 1987

and assigned 19 conditions with a weighting index of 1 – 6 in attempt to quantify the likelihood of impact upon survival. Data was acquired via patients being admitted with medical conditions to a Washington Hospital, USA. This tool was initially validated in breast cancer patients with 10-year mortality as an endpoint. It has also been validated in predicting progression-free survival (Charlson et al., 1987) in a variety of diseases such as breast and prostate cancer. However limitations with using this tool for lung cancer patients include absence of some potentially relevant diseases such as pulmonary fibrosis, the weighting of HIV is probably now less significant due to improved treatment and the lack of grading of severity of the specific disease(s) (Charlson et al., 1987; Grose et al., 2011)

In addition to stage of disease (Detterbeck et al., 2009) it is clear that the prognosis in lung cancer is determined by more than just comorbidity. Performance status is widely recognised as a very accurate predictor of survival in cancer patient (Martin et al., 2010; Mor et al., 1984; Yates et al., 1980). Recent work shows that the effect of systemic inflammation is detrimental in terms of outcome in cancer in general (McMillan, 2009; Proctor et al., 2011) and in lung cancer specifically (Wilop et al.; Koch et al., 2009; Gagnon et al., 2010; Arrietta et al., 2010; Forrest et al., 2004; Forrest et al., 2005; Brown et al., 2007; Leung et al., 2012). The combination of C reactive protein and albumin when combined to calculate the modified Glasgow Prognostic Score has previously been validated as an independent predictor of survival (McMillan, 2013). Two recent publications by *Laird et al., 2013* and *Bozzetti et al, 2014* have demonstrated that a combination of mGPS and PS is predictive in determining survival in advanced cancer patients and it is likely that a common pathophysiological association between all these factors determines outcome.

We prospectively investigated the survival of a large unselected lung cancer population assessing the impact of comorbidity along with more standard prognostic determinants. The goal of this study was to determine the role of a novel comorbidity scoring system (SCSS) and to compare it with the already established Charlson Comorbidity Index and the modified Glasgow Prognostic Score (mGPS). We also wished to explore the relationship between comorbidity, mGPS and PS. In addition we investigated a number of standard prognostic markers and demographics. This study aimed to determine which of these factors provided the most accurate information on survival.

7.2 Methods

Previously discussed in chapter 3

7.3 Statistics

All statistical testing was conducted at the 5% level so 95% confidence intervals (CI) are reported throughout. Unless otherwise stated, medians and interquartile range (IQR) are used. The survival time defined as the number of months from study entry until death or if alive at follow-up date, was calculated. Univariate survival analysis was carried out using Kaplan-Meier method and the log rank test. Survival analysis was carried out using the Cox's proportional-hazards model and hazard ratios (HR) were calculated. Multivariate survival analysis was performed using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival. To remove a variable from the multivariate model, the corresponding P-value had to be >0.20.

Statistical analyses were performed using SPSS v21.0 (SPSS Inc., Chicago, IL).

7.4 Results

In total, 882 patients from a number of different treatment groups were initially included in the study, comprising 297 from Aberdeen, 136 from Dunfermline, 285 from Glasgow, and 164 from Inverclyde. Baseline characteristics are previously described in chapter 4. The median age of participants was 72 years old. The majority of patients were male, current or ex-smokers, of good performance status with advanced disease and had treatment with palliative intent.

The median follow up for survivors was 24.5 months (4.6 – 40.8). The median overall survival was 5.6 months (4.8 – 6.5). The 12-month survival rate was 30% (SE 2%).

Impact of Comorbidity

The cumulative comorbidity score, SCSS, was highly significant ($p<0.001$). Survival with low levels of comorbidity had a hazard ratio of 1.29 (1.02-1.6) while for high levels of comorbidity it was 2.05 (1.55-2.70). The survival varied at 6 months from 60.2% for those patients with no comorbidity to 32.9% in those patients with high levels of comorbidity, while at 24 months the survival varied from 22.2% to 6.4%. In addition, the cumulative comorbidity score clearly increased as both PS and mGPS increased. These relationships are shown in Table 7.1 for the Early Stage group and Table 7.2 for the Advanced Stage group.

Table 7.1 – Median Cumulative Comorbidity Score (Range) as determined by PS and mGPS in the Early Stage group (Stage I-IIIa NSCLC). ***(no of patients). Missing data = 30 patients***

PS	mGPS		
	0	1	2
0	1(5) *14 patients*	2.5 (3) *6 patients*	3.5 (5) *2 patients*
1	3 (5) *23 patients*	3 (9) *26 patients*	2 (4) *9 patients*
2	3.5 (8) *12 patients*	4 (9) *18 patients*	3 (4) *10 patients*
3	-	3.5 (6) *4 patients*	7 (0) *2 patients*
4	-	-	9 (0) *1 patients*

Table 7.2 – Median Cumulative Comorbidity Score (Range) as determined by PS and mGPS in the Advanced Stage group. *(no of patients). Missing data = 135 patients*

PS	mGPS		
	0	1	2
0	1(10) *27 patients*	1 (9) *19 patients*	2 (1) *3 patients*
1	2 (7) *63 patients*	3 (9) *95 patients*	3 (10) *36 patients*
2	3 (9) *42 patients*	4 (14) *82 patients*	5 (13) *70 patients*
3	4 (10) *17 patients*	4 (15) *35 patients*	4 (12) *52 patients*
4	1 (5) *3 patients*	3 (6) *3 patients*	6 (13) *17 patients*

Early Stage group

The relationship between the clinico-pathological characteristics and survival in patients with a Early Stage cancer is shown in Table 7.3. This group included patients with NSCLC Stage I – IIIa , the intention in such patients is for potential cure of cancer. Patients who were not offered a curative treatment were still included in this group. The median survival was 16.2 (11.7-20.7) months. On univariate survival analysis, age ($p=0.009$), sex ($p<0.001$), Performance status ($p<0.001$), SCSS ($p=0.017$), mGPS ($p<0.001$) and treatment ($p<0.001$) were significantly associated with survival. On multivariate analysis, only sex ($p<0.001$), SCSS ($p=0.002$), mGPS ($p<0.001$) and treatment ($p<0.001$) were independently associated with survival.

Table 7.3 – The relationship between parameters and survival in the Early Stage group (Stage I, II and IIIa NSCLC) *(missing data refers to those without a survival endpoint)*

Parameter	Patients	Univariate		Multivariate	
	N	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (missing data = 10) Overall p =0.009					
<60	13	1			
60-69	56	1.54(0.79-2.99)	0.205		
70-79	60	2.09(1.09-4.00)	0.026		
≥80	18	3.23(1.62-6.43)	<0.001		
Sex (missing data =9)					
Male	87	1	<0.001		<0.001
Female	61	0.55(0.39-0.77)		0.32 (0.20-0.52)	
Centre (missing = 12) overall p=0.559					
Aberdeen	59	1			
Dunfermline	27	1.22(0.77-1.96)	0.397		
Glasgow	39	1.31(0.89-1.94)	0.175		
Inverclyde	23	1.24(0.75-2.05)	0.395		
Deprivation (Quintile) (missing =9) p =0.584					
Most	38	1			
2	25	0.69(0.42-1.15)	0.154		
3	43	0.76(0.49-1.16)	0.208		
4	31	0.76(0.47-1.20)	0.240		
Least	11	0.72(0.36-1.42)	0.341		
Smoking history (missing = 15) p=0.545					
NS	4	1			
<20	19	0.61(0.24-1.53)	0.290		
20-60	87	0.53(0.23-1.22)	0.135		
>60	32	0.59(0.25-1.43)	0.247		
Performance Status (missing 9) p<0.001					
0	33	1			
1	62	1.38(0.84-2.28)	0.207		
2	44	1.71(1.02-2.85)	0.041		
3	8	4.38(2.29-8.40)	<0.001		
4	1	21.1(2.67-167)	0.004		
Scottish Comorbidity Score (missing = 10) p=0.017					
Nil	17	1			0.005
Low (1-6)	113	1.89(0.92-3.92)	0.084	1.66 (0.73-3.78)	0.227
High(7+)	17	3.66(1.54-8.66)	0.001	5.10 (1.84-14.1)	0.002
Charleson Comorbidity Index missing =10 Overall p =0.341					
Nil	38	1			
Low (1-2)	83	1.21(0.79-1.85)	0.391		
Mod (3-4)	23	1.45(0.87-2.41)	0.153		
High (>5)	3	2.01(0.83-4.88)	0.121		
mGPS (missing =37) Overall p <0.001					
0	50	1			0.002
1	49	1.70(1.12-2.58)	0.013	1.53 (0.92-2.54)	0.102
2	21	2.82(1.60-4.99)	<0.001	3.24 (1.70-6.15)	<0.001
Treatment (missing 9) Overall p <0.001					
Surgery	54	1			0.002
Radical RT	29	1.61(0.92-2.81)	0.094	1.36 (0.70-2.66)	0.361
Pall Chemo	9	1.93(0.91-4.11)	0.086	1.34 (0.58-3.08)	0.486
Pall RT	18	3.86(2.06-7.23)	<0.001	3.55 (1.77-7.10)	<0.001
BSC	38	2.43(1.44-4.09)	0.001	2.90 (1.49-5.66)	0.002

Advanced Stage group

The relationship between the clinico-pathological characteristics and survival in patients with an Advanced Stage cancer is shown in Table 7.4. This group included patients with advanced NSCLC (Stage IIIB/IV) and SCLC where the intention of treatment is almost always palliative. The median survival was 4.1 (3.5-4.8) months. On univariate survival analysis, age ($p<0.001$), centre ($p=0.003$), PS ($p<0.001$), SCSS ($p<0.001$), mGPS ($p<0.001$), and treatment ($p<0.001$) were significantly associated with survival. On multivariate analysis, only PS ($p<0.001$) and mGPS ($p<0.001$) were independently associated with survival.

Table 7.4 - The relationship between parameters and survival in the Advanced Stage group (Stage IIIb/IV NSCLC, SCLC and not staged) *(missing data refers to those without a survival endpoint)*

Parameter	Patients	Univariate		Multivariate	
	N	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (missing data = 25) Overall p <0.001					
<60	105	1			
60-69	171	1.27(0.98-1.63)	0.067		
70-79	238	1.39(1.09-1.77)	0.008		
≥80	114	1.79(1.36-2.36)	<0.001		
Sex (missing data=24)					
Male	353	1	0.370		
Female	276	0.93(0.79-1.09)			
Centre (miss = 24) overall p=0.003					
Aberdeen	225	1			
Dunfermline	92	1.52(1.18-1.94)	0.001		
Glasgow	172	0.99(0.81-1.22)	0.938		
Inverclyde	140	1.25(1.00-1.55)	0.046		
Deprivation (Quintile) (missing =24) p =0.545					
Most	184	1			
2	91	1.03(0.80-1.33)	0.820		
3	175	0.96(0.76-1.21)	0.633		
4	129	0.89(0.76-1.21)	0.737		
Least	50	0.80(0.58-1.11)	0.182		
Smoking history (missing = 61) p=0.902					
NS	37	1			
<20	60	1.11(0.73-1.69)	0.617		
20-60	359	1.00(0.71-1.41)	0.984		
>60	136	1.04(0.72-1.51)	0.824		
Performance Status (missing 24) p<0.001					
0	60	1		1	<0.001
1	211	1.57(1.15-2.14)	0.004	1.70 (1.19-2.42)	0.004
2	212	2.55(1.87-3.48)	<0.001	2.57 (1.78-3.71)	<0.001
3	119	5.32(3.80-7.45)	<0.001	5.03 (3.34-7.58)	<0.001
4	27	9.08(5.66-14.56)	<0.001	8.71 (4.86-15.6)	<0.001
Scottish Comorbidity Score (missing = 35) p<0.001					
Nil	79	1			
Low (1-6)	430	1.33(1.03-1.72)	0.028		
High(7+)	109	1.93(1.43-2.62)	<0.001		
Charleson Comorbidity Index missing =30. Overall p =0.271					
Nil	219	1			
Low (1-2)	294	0.99(0.83-1.19)	0.933		
Mod (3-4)	92	1.02(0.79-1.30)	0.901		
High (>5)	18	1.66(1.03-2.69)	0.039		
mGPS (missing =103) Overall p <0.001					
0	148	1		1	<0.001
1	227	1.60(1.28-1.98)	<0.001	1.51 (1.21-1.89)	<0.001
2	175	2.39(1.90-3.01)	<0.001	1.54 (1.20-1.99)	0.001
Treatment (missing 24) Overall p <0.001					
Radical RT	41	1			
Pall Chemo	224	1.65(1.15-2.36)	0.006		
Pall RT	143	2.58(1.78-3.76)	<0.001		
BSC	221	2.18(1.52-3.12)	<0.001		

6.5 DISCUSSION

This large unselected population based cohort study of lung cancer patients has demonstrated that a number of important factors have significant impact in terms of survival. It has gone further by showing that the factors, which influence survival, are different, depending upon the stage of cancer at diagnosis and the potential treatment strategy. The novel comorbidity scoring system, the SCSS has compared very favourably with the more established CCI. In addition, it has confirmed the very poor, general outlook for lung cancer patients with a median survival of only 5.6 months.

Our results have shown that in those patients whose cancers can be considered radically treatable female sex, a normal mGPS, low levels of comorbidity based upon the SCSS and being offered surgery were all associated with better survival. Female sex and being offered surgery have both previously been demonstrated to improve outcome in localized NSCLC (Rich et al., 2011; NICE, 2011). Since the initial work, a decade ago the combination of C-reactive protein and albumin, the Glasgow Prognostic Score (GPS/ mGPS), has been shown to have independent prognostic value in more than 60 studies (>30,000 patients with cancer). This prognostic value has been demonstrated in a variety of clinical scenarios, in particular primary operable cancer (McMillan, 2013; Grose et al., 2014). Comorbidity has often been identified as a cause of poor survival in lung cancer and the finding of the high levels of comorbidity and the impact upon survival of the SCSS is supported by many previous studies (Deleuran et al., 2013; Luchtenborg et al., 2012; Ahn et al., 2013).

In those patients whose cancer was suitable only for palliative treatment options only a higher PS and elevated mGPS, indicating systemic inflammation, were associated with poorer outcome. Both of these have been demonstrated previously to have a significant impact upon outcome

(Laird et al., 2013; Grose et al., 2014). The very poor outcome of the palliative patients, with a median survival of only 4.1 months, may be the reason why factors such as comorbidity did not appear to associated with survival. Even active palliative treatment such as chemotherapy did not appear to benefit survival across the population when other factors were accounted for in the multivariate analysis. Although chemotherapy has been shown to confer a survival benefit in large randomized trials (SIGN, 2005; NICE, 2011), this is obviously in good PS patients with low levels of comorbidity and this paper supports most clinicians assertions that palliative chemotherapy should only be offered to the fitter group of patients with advanced lung cancer.

It is perhaps surprising that the CCI was not associated with survival in either cohort. However several recent studies have also found no or little relationship (Wang et al., 2012; Ganti et al., 2011; Girones et al., 2011). The reason(s) for this are not particularly clear. However it is important to note that the CCI is now nearly 30 years old and its validation came primarily in a North American breast cancer cohort and thus may not be relevant to the Scottish lung cancer population. The weighting of some diseases e.g. AIDS, indicating the previous lack of treatment and poor survival, have significantly changed and it may be that novel scoring systems such as the one described above may have more validity in the current setting.

In addition we have demonstrated a clear trend in rising comorbidity score as both PS and mGPS rise. As demonstrated above all three of these factors appear to be determinants in patient survival. This suggests that there is a complex relationship between such factors and to the best of our knowledge this relationship has not previously been demonstrated in the literature. One limitation of this current study is the lack of reason for the treatment offered. However we intend to address this in a future paper.

In conclusion we have identified that a variety of factors are independent prognostic determinants of outcome in lung cancer. There appear to be clear differences between the radical and palliative groups. Especially in the select group of patients in whom cure of cancer is being attempted it is clear that a more detailed assessment of fitness including comorbidity and evidence of systemic inflammation is required before embarking upon a treatment plan. As the percentage of elderly patients who by definition may have more comorbidity increases then this will become even more important in the future.

CHAPTER 8: IMPACT OF THE TREATMENT DECISION PROCESS UPON SURVIVAL IN LUNG CANCER

8.1 Introduction

Lung cancer is the commonest cancer in Scotland and the second commonest in the UK (Office for National Statistics, 2006; ISD, 2009). Although one and two year survival has improved over the past decade, five year survival remains significantly poorer in Scotland than in comparable Western European countries or the USA, with 5-year relative survivals of 8.0%, 10.2% and 16.3%, respectively. Variations in treatment may explain some of the observed differences in lung cancer survival between countries (Berrino et al., 2007; Horner et al., 2009).

Treatment options are dependent upon pathology, TNM staging, patient fitness and choice. Radical (i.e. potentially curable) treatment options are surgery or radical radiotherapy (+/- chemotherapy). Patients with Stage I + II Non Small Cell Lung Cancer (NSCLC) should be considered for curative surgery whenever possible as it confers the highest chance of cure. 5 Year survival of 54-80% for patients with St 1a and 38-65% for patients with Stage 1b has been reported (Suzuki et al., 1999; Makitaro et al., 2002; Inoue et al., 1998). In patients with localized NSCLC not suitable for surgery then radical radiotherapy (+/- chemotherapy) is an appropriate option. Meta-analysis of retrospective studies in patients with Stage I/II has shown overall survival from 50-93% at one year and 0-42% at 5 years (Rowell et al., 2004). In recent years the option of Stereotactic Ablative Radiotherapy (SABR) has become a very reasonable alternative for those with early stage disease and in many centers' has replaced conventional radiotherapy in this setting. (Palma et al., 2011; Lagerwald FJ, 2012)

In patients with advanced disease and a Performance Status (PS) <2 then systemic chemotherapy with a platinum based doublet has been shown to confer a survival benefit of approximately 2 – 4 months (Goffin et al.,

2010). Recent therapeutic advances including tyrosine kinase inhibitors (in those with an EGFR mutation) (Rosell et al., 2012) and pemetrexed/platinum doublets in Adenocarcinoma (Scagliotti et al., 2008) have conferred further improvement in survival but these treatments were not available at the time of this study.

A significant proportion of lung cancer patients are not suitable for more aggressive therapies such as resection or radical radiotherapy in localized disease or indeed palliative chemotherapy in the more advanced setting (Grose et al., 2014; Grose et al., 2015; Havlik et al., 1994; NLCA 2013). Clearly this will significantly impact upon survival. Guidelines such as the National Institute for Clinical Excellence (NICE Guideline 121) and the Scottish Intercollegiate Guidelines Network (SIGN Guideline 137) have stated that a patient's suitability for a particular treatment option should be based upon an assessment including fitness, comorbidity and PS and that options such as surgery or radical radiotherapy in the curative setting or chemotherapy in the palliative setting are only suitable for those with an adequate level of fitness and PS.

Previous work undertaken by this group has supported the available guidelines in suggesting that PS, comorbidity and late stage at time of presentation all significantly impact upon survival (Grose et al., 2014; Grose et al., 2015).

The purpose of this study was to determine the reasons for clinician's decision-making process and if these reasons did indeed mirror the individual patient's demographics, fitness and stage. We therefore evaluated demographics, PS and comorbidity in both the palliative and radically treatable patient groups. Our aim was to determine if treatment offered and the evidence available substantiated the reason for that treatment being offered.

8.2 Methods

Previously discussed in chapter 3

8.3 Statistics

All statistical testing was conducted at the 5% level so 95% confidence intervals (CI) are reported throughout. Unless otherwise stated, medians and interquartile range (IQR) are used. The survival time defined as the number of months from study entry until death or if alive at follow-up date, was calculated. Univariate survival analysis was carried out using Kaplan-Meier method and the log rank test.

Statistical analyses were performed using SPSS v21.0 (SPSS Inc., Chicago, IL).

8.4 Results

In total, 646 patients from a number of different treatment groups were initially included in the study, comprising 218 from Aberdeen, 91 from Dunfermline, 194 from Glasgow, and 143 from Inverclyde. Baseline characteristics are shown in Table 8.1. The median age of participants was 70 years old. The majority of patients were male, current or ex-smokers, of good performance status with advanced disease and had treatment with palliative intent.

The median duration of follow up of survivors was 52.6 months (43.2 – 58.9). The median overall survival was 6.1 months (95% CI 5.3 – 7.0). The 12 months survival was 32% (SE 2). The median duration of follow up of survivors is significantly increase compared to in previous chapters due to updating of the survival data.

Table 8.1 Baseline characteristics of patients with lung cancer (n=646)

Parameter	
Age (years)	Median 70.0 years (range 31-92)
Sex Male Female	377 (58.4%) 269 (41.6%)
Smoking (missing = 30) Never smoker <20 Pack Years 20-60 Pack Years > 60 Pack Years	 34 (5.3%) 68 (10.5%) 378 (58.5%) 136 (21.1%)
Centre	
Aberdeen	218 (33.7 %)
Dunfermline	91 (14.1%)
Glasgow	194 (30.0%)
Inverclyde	143 (22.1%)
Deprivation (Quintile)	
Most deprived	197 (30.5%)
2.00	94 (14.6%)
3.00	183 (28.3%)
4.00	132 (20.4%)
Most affluent	40 (6.2%)
Performance Status	
0	87 (13.5%)
1	252 (39%)
2	204 (31.6%)
3	91 (14.1%)
4	12 (1.9%)
Co morbidity Score (missing = 6) Nil Low High	 83 (12.8%) 466 (72.1%) 91 (14.1%)
Staging	
NSCLC I	66 (10.2%)
NSCLC II	43 (6.7%)
NSCLC IIIa	48 (7.4%)
NSCLC IIIb	140 (21.7%)
NSCLC IV	234 (36.2%)
SCLC Limited	33 (5.1%)
SCLC Extensive	82 (12.7%)
Treatment	
Surgery Radical Radiotherapy Palliative Chemotherapy Palliative Radiotherapy + BSC Best Supportive Care (BSC)	56 (8.7%) 74 (11.5%) 232 (35.9%) 123 (19.0%) 161 (24.9%)

Stage I –IIIa NSCLC

156 patients in total were included in this group of whom a treatment decision is available for 148. 88 patients were offered radical treatment with either surgery or radical radiotherapy and 68 were deemed suitable for palliative treatment, which included chemotherapy, palliative radiotherapy and/or best supportive care (bsc). The median survival was 29.9 months (95% CI 18.2-41.6) and 11.3 months (95% CI 5.9-16.6) respectively (P<0.001).

For those patients not undergoing radical treatment the reasons as recorded at the MDT were assessed. These were then compared with the actual results, for example, in whom the PS was recorded as the reason for suboptimal therapy the actual breakdown of PS was shown. Some patients may have more than one reason recorded.

In the group in which age was a determining factor all were over 70 with the vast majority (69.2%) being 80 or over. In the group in which PS was a factor only 11.1 % had a PS of 1, of the remainder 70.4% had a PS of 2 with 22.5% being PS 3/4. In the group in who comorbidity was a determining factor 77.5% had low levels of comorbidity while 22.5% had high levels. In 7 patients radical therapy was refused (Table 8.2).

Table 8.2 Breakdown of determining factors for sub-optimal therapy in Stage I-IIIa NSCLC.

Note – Patients may have more than one reason for sub-optimal therapy.

Reason given for Sub-optimal treatment	Number	Actual	Grouping	Number (%)
Age	13	Age	70 - 79	4 (30.8%)
			> 79	9 (69.2%)
PS	27	PS	1	3 (11.1%)
			2	19 (70.4%)
			3	4 (18.8%)
			4	1 (3.7%)
Comorbidity	40	Comorbidity	Low	31 (77.5%)
			High	9 (22.5%)
Patient refusal	7			

There was a statistically significant difference in age ($p < 0.001$), PS ($p < 0.001$) and comorbidity ($p = 0.006$) between the group offered radical treatment and those offered palliative therapy with the palliative group being older, having a higher PS and more comorbidity (Table 8.3). Deprivation, as based upon the SIMD quintile, was not statistically significant ($p = 0.379$).

Table 8.3 Comparison of factors between those being offered radical and palliative therapy in Stage I-IIIa NSCLC. (n =156)

	Radical Treatment offered (N=88)	Palliative treatment offered (N=68)	P value
Age group (%) missing=1			<0.001
<60	10 (11.4%)	4 (5.9%)	
60-69	38 (43.2%)	19 (27.9%)	
70-79	37 (42%)	28 (41.2%)	
>80	3 (3.4%)	17 (25%)	
PS (%)			<0.001
0	27 (30.7%)	7 (10.1%)	
1	48 (54.5%)	19 (27.5%)	
2	11 (12.5%)	36 (52.2%)	
3	2 (2.3%)	6 (8,7%)	
4	0	1 (1.4%)	
Comorbidity (%) missing = 1			0.006
nil	13 (14.9%)	4 (5.8%)	
low	69 (79.3%)	53 (76.8%)	
high	5 (5.7%)	12 (17.4%)	

Stage IIIb/IV NSCLC + SCLC

447 patients were included in this group. 447 patients had a treatment decision available. 222 patients were offered chemotherapy while 225 were offered best supportive care (bsc) +/- palliative radiotherapy. The median survival was 6.4 months (95% CI 5.2-7.5) and 2.4 months (95% CI 2.0 -2.9) respectively (P<0.001).

In those patients who were deemed inappropriate for chemotherapy due to age the vast majority were over 80 (65.7%). In the group in which PS was a factor 55.2% had a PS of 3 or 4, 39.2% had a PS of 2 while 5.6% had a PS of 1. No patient had a PS of 0. For those patients in whom comorbidity was a determining factor 4.6% had no recorded comorbidity, 59.3% had low levels of co morbidity identified as a reason and 36.1% had high levels. 16 patients refused palliative chemotherapy. (Table 8.4)

Table 8.4 Breakdown of determining factors for sub-optimal therapy in Stage IIIb/IV NSCLC + SCLC

Note – Patients may have more than one reason for sub-optimal therapy.

Reason given for Sub-optimal treatment	Number	Actual	Grouping	Number (%)
Age	35	Age	60-69	1 (2.9%)
			70 -79	11 (31.4%)
			>79	23 (65.7%)
PS	125	PS	1	7 (5.6%)
			2	49 (39.2%)
			3	58 (46.4%)
			4	11 (8.8%)
Comorbidity	108	Comorbidity	Nil	5 (4.6%)
			Low	64 (59.3%)
			High	39 (36.1%)
Patient refusal	16			

There was a statistically significant difference in age ($p < 0.001$), PS ($p < 0.001$) and comorbidity ($p < 0.001$) between the group offered radical treatment and those offered palliative therapy with the palliative group being older, having a higher PS and more comorbidity (Table 8.5). Deprivation was again not statistically significant ($p = 0.368$)

Table 8.5 Comparison of factors between those being offered chemotherapy and supportive care in Stage IIIb/IV NSCLC + SCLC. (n =447)

	Chemotherapy offered (N=222)	Supportive care (+/- palliative RT) offered (N=225)	P value
Age group (%)			<0.001
<60	53 (23.9%)	28 (12.4%)	
60-69	83 (37.4%)	52 (23.1%)	
70-79	71 (32%)	97 (43.1%)	
>80	15 (6.8%)	48 (21.3%)	
PS (%)			<0.001
0	31 (14%)	13 (5.8%)	
1	109 (49.1%)	50 (22.2%)	
2	66 (29.7%)	84 (37.3%)	
3	16 (7.2%)	67 (29.8%)	
4	0	11 (4.9%)	
Comorbidity (%) missing = 4			<0.001
nil	35 (15.9%)	22 (9.9%)	
low	165 (75%)	147 (65.9%)	
high	20 (9.1%)	54 (24.2%)	

8.5 Discussion

Survival in lung cancer remains very poor; our study population, in which the median survival is 6.1 months, confirms this. This is despite advances in surgical techniques, new radiotherapy options such as SABR and novel chemotherapy agents. In a significant number of patients the treatment options will be reduced due to poor fitness, PS, comorbidity and advanced stage at presentation. However a number of publications (Blum et al., 2014; Forrest LF et al., 2014; Koshy et al., 2015) have suggested that treatment disparities are a complicated and multifactorial issue and that clinician selection bias may have at least some influence. There has also been a recent publication suggesting that social class / deprivation may also influence treatment choice (Forrest LF et al., 2014) but this has not been identified in our study.

We wished to determine the clinician's reason(s) for treatment offered and how that compared with the actual objective fitness, PS, comorbidity and age of the patients.

We have shown that for the majority of patients, both in the early and advanced stage at presentation, the treatment decision appears to be appropriate given the recorded fitness, PS and comorbidity. However in a small but significant number of patients there did appear to be discrepancies between the clinician's reasons for sub-optimal therapy and the recorded objective assessment of the patient in question. We identified low levels of comorbidity as a reason for not offering either radical treatment in the early stage group or chemotherapy in the advanced stage group. A previous publication (Grose et al., 2015) undertaken by ourselves demonstrates that low levels of comorbidity has little impact upon survival and that only high levels of comorbidity

influence outcome significantly and it may be that clinicians are being unduly influenced by the clinically irrelevant comorbidity.

It is not clear to what extent such potential under treatment will affect overall survival of this group of patients but as we are faced with the challenges of significant advances in therapy in an increasingly old population it is clear that more detailed objective assessment of patients is required to ensure that all are offered the most appropriate therapy. Significant work (Laird et al., 2013; McMillan. 2013) has been undertaken utilizing markers of systemic inflammation such as the modified Glasgow Prognostic Score (mGPS) along with PS to predict outcome and survival in advanced cancer including lung cancer and this has demonstrated additional prognostic benefits over more conventional assessments. Such tools together with our own extensive work in co morbidity should go some way to addressing this increasing challenge.

CHAPTER 9: CONCLUSION AND FUTURE WORK

9.1 Conclusions

The overall aim of the Thesis was to examine the impact of comorbidity in lung cancer, to attempt to quantify the extent and severity of comorbidity and to explore its relationship with treatment and survival.

This work has demonstrated that it is possible to collect very detailed audit data on a large number of patients across several centres in Scotland in real time during the MDT process and to prospectively analyse survival data.

During the course of this work, a number of other publications have explored the role of comorbidity upon outcome in Lung Cancer. A recent prospective observational study (Calvo-Espinos et al., 2015) showed lower survival rates among lung cancer patients with higher age-adjusted Charlson Comorbidity Index, although numbers were small (n=66). A far larger population based cohort study of 5,683 patients captured using the Nebraska Cancer Registry demonstrated that the presence of comorbid conditions was associated with reduced survival, however it did not attempt to grade severity of the conditions (Islam et al., 2015). A specific study of SCLC patients utilizing the Netherlands Cancer Registry also supported the view that increased comorbidity had a negative prognostic effect on survival (Aarts et al, 2015). However a retrospective study in Denmark of 20,552 non-surgically treated patients from 2005 – 2011 (Mellemgaard et al., 2015) appeared to show that comorbidity (utilizing the Charlson Comorbidity Index) had a limited effect upon survival. It is difficult to collect retrospective comorbidity data and the authors acknowledged this. This only serves to highlight the need for comorbidity assessment to be taken prospectively and at the time of diagnosis.

A further retrospective study utilizing the ACE -27 comorbidity scoring system in a variety of tumours including lung cancer, in patients undergoing radiotherapy, (Owen et al., 2014) demonstrated an association between increased comorbidity and reduced active treatment rates. Its main conclusion was that further tumour specific, validated tools would be beneficial. Two recent studies have made use of the extensive Danish Lung Cancer Registry to assess the role of the CCI. Iachina et al(2014) explored the impact of the CCI on survival in NSCLC in 3135 patients diagnosed in 2010. It showed that higher levels of comorbidity were associated with reduced survival, however there was significant missing data, which the authors acknowledged, was related to the retrospective nature of the work. The second paper (Deleuran et al., 2013) was a population based cohort study from 2000 to 2011 including 9369 patients. It demonstrated a small but significant increase in survival over this time period except in those patients with high levels of comorbidity. The conclusion for this was that those patients with high levels of comorbidity are unlikely to be offered the newer treatment options such as doublet chemotherapy or radiotherapy due to poorer fitness. The Simplified Comorbidity Score (SCS) had previously been discussed in the initial literature review in chapter 2. A recent paper by Ball et al (2013) retrospectively analysed 921 lung cancer patients to assess the impact of the SCS on survival. However when age, PS and stage was taken into account the SCS had no additional effect upon survival.

The link between comorbidity (utilizing the CCI), socio-economic status and outcome has been assessed in two recent papers. In the first 15,582 patients in the South of England with Lung Cancer (Berglund et al., 2012) were retrospectively analysed. It was demonstrated that levels of comorbidity increased with poorer socioeconomic status. 29.6% of patients had high levels of comorbidity in the most deprived quintile vs 23.8% in the least deprived quintile ($p<0.001$). It also revealed an associated trend towards survival differences in these groups. The second paper by Woolhouse (2011) also highlighted the previously discussed differences

between the UK and the remainder of Europe with regards to lower levels of treatment and poorer outcomes and identified the need for further research to identify reasons for such differences.

As can be seen from the above updated assessment of the literature there remains an unmet need for detailed research into comorbidity in lung cancer and its influence upon outcome. It has been clearly highlighted by much of the research that prospective work to validate a novel tool would be hugely beneficial.

The results of the work presented in this Thesis have demonstrated the significant prevalence and severity of comorbidity through utilization of a novel comorbidity scoring system, the Scottish Comorbidity Scoring System (Grose et al., 2014). In addition it has shown that there appears to be a relationship with both treatment offered and survival, particularly in patients who have potentially curable lung cancer (Grose et al., 2014).

During the course of this work there have been significant developments in our understanding of Lung Cancer. At the time of the work commencing NSCLC was seen as a single entity. However we now see this as several very specific sub-types with particular targeted mutations such as Epidermal Growth Factor (EGFR) and Anaplastic Lymphoma Kinase (ALK) with associated varying treatment options (Rosell et al., 2012; Solomon et al., 2014) leading to potentially different outcomes. Any future work would need to very take into account such advances.

National data has demonstrated that a significant percentage of patients initially present as an emergency admission and that such patients have a poorer outcome (Rich et al., 2011). Unfortunately the data capture in this work did not include a breakdown of mode of presentation. This is a weakness of this work as there would be significant interest to explore if there are differences in comorbidity, socio-economic status, systemic

inflammation and outcomes between those patients who present as an emergency and those who are referred via primary care.

As discussed in Chapter 6, there has been significant research recently undertaken both in cancer in general and lung cancer in particular exploring the role of systemic inflammation upon outcomes and survival (Scagliotti et al., 2008; Du Clos et al., 2004; Nozoe et al., 2000; Coussens et al., 2002; Abramovitch et al., 1999; Canna et al., 2008).

The prognostic value of the combination of CRP and albumin, the (modified) Glasgow Prognostic Score (McMillan, 2014) has been demonstrated across a large number of clinical scenarios including lung cancer. Initially this has been seen as a predictive marker of outcome. However several new studies of a novel targeted agent, Ruxolitinib which is a Janus Kinase Inhibitor, are exploring treating patients with evidence of systemic inflammation indicating a potential role for stratifying patients by mGPS (Hu et al., 2014).

It is of interest that particularly in those patients undergoing radical treatment, both mGPS and SCSS appear to impact upon survival in a multivariate model suggesting they both play an important role in determining outcome (Grose et al., 2014).

Previously the most widely used determinant of comorbidity was the Charlson Comorbidity Index (CCI) and it noteworthy that in this cohort it did not appear to have a statistically significant relationship with outcome. The reasons for this are not clear but as previously discussed the CCI is now almost 30 years old and treatment and prognosis of a number of the diseases has dramatically changed in this period. It is clear that an updated Comorbidity Scoring System taking account of these changes is required and this work has demonstrated that the SCSS is one such potential tool.

It is encouraging that within this population it appears that the majority of patients were offered appropriate treatment as per national guidelines. It is likely that the MDT provides a strong role in this and this work supports the assertion that all lung cancer patients should be discussed within a specialist MDT setting with access to both thoracic surgical and clinical oncology input to ensure that radically treatable patients are discussed with the relevant clinicians.

Despite this the outcome for patients generally remains very poor.The median overall survival of 6.1 months (95% CI 5.3 – 7.0) and the 12 months survival of 32% are stark reminders to all clinicians treating this disease of the very poor outcome for the vast majority of patients and their family and carers. As has been shown in Chapter 8 a small but significant number of patients appear to have been offered potentially sub optimal therapy based perhaps upon inaccurate clinical assessments and this reinforces the necessity for development of new clinical tools to help in the decision making process. The SCSS has been validated within this clinical setting to be easily recordable and provide clinically meaningful prognostic information. It is likely that the combination of such a comorbidity tool along with PS, stage and assessment of systemic inflammation (mGPS) will in the future provide increasingly accurate assessment of patients to aid in the increasingly complex and challenging decision making process.

9.2 Utilisation of the Scottish Comorbidity Scoring System + Proposed Future Work

The aim of the research leading to this Thesis was to examine the impact of comorbidity in lung cancer, to attempt to quantify the extent and severity of comorbidity and to explore its relationship with treatment and survival. In addition the development and validation of the novel comorbidity scoring system has the potential for usage in future research work.

Three current and future research projects are utilizing and developing upon the work in this Thesis.

The Scottish Lung Cancer Forum has carried out a prospective audit of comorbidity, inflammation and management in small cell lung cancer. It is the hypothesis that there are differences in outcome and treatment delivered that occur between regions within the UK and also internationally. The hypothesis is that this may be due to variations in comorbidity, inflammation and demographics. This study has utilized both the data collection tool developed for this Thesis and the SCSS to analyse comorbidity.

This International study involves 9 Centres from across Scotland, England and also Berlin in Germany. Recruitment lasted from June 2009 until December 2012. So far we have at least 2 year follow up on approximately 700 patients. Data analysis is currently ongoing with preliminary results being anticipated by late 2015.

From the results of the research presented in this Thesis it is clear that a very detailed assessment of comorbidity such as the SCSS would not be practical or indeed useful in all newly diagnosed patients. However it appears to have significant merit particularly in those patients who are of

borderline fitness for radical treatment such as surgery or radical radiotherapy. In such patients a very detailed assessment of comorbidity may identify patients who would be suitable for active steps to try to improve their fitness to allow such treatments. I am already beginning work with two groups specifically investigating this premise.

Professor Roma Maguire based at the University of Surrey School of Health Sciences has published extensively in Lung Cancer with her main interest being in attempting to link markers of the inflammatory response to patient outcomes and symptoms with the hypothesis that significant levels of inflammation may correspond to increasing burden of symptoms. We intend to analyse the relationship between symptoms, SCSS and mGPS. In those with high burdens of comorbidity and inflammation the intention is to develop focused supportive care interventions targeting the inflammatory response including pharmacological or non-pharmacological (e.g. exercise) along with interventions to reverse comorbidity whenever possible.

Dr Jo Bowden is a Consultant Palliative Care Physician at Edinburgh University. Her proposed MD will be to explore the relationship between comorbidity, muscle wasting in lung cancer and to assess how this impacts on physical function, treatment completion and survival. She is in the planning stage of an epidemiological study using a database of patients diagnosed with lung cancer pre-2010 in Scotland. The Edinburgh Research Team have developed software that allows the quantification of muscle mass from patients' staging/follow-up CT scans and are looking to combine this with information about patients' cancer characteristics and comorbid illnesses.

Her proposal will include body composition analysis from our patient database and to then combine this with our comorbidity, inflammation and survival data.

The hypothesis is that these findings will help to identify patients who are the best (or better at least) candidates for cachexia management - whether in anticipation of starting cancer-modifying treatment (a 'prehabilitation' approach), alongside treatment or even in the no treatment group.

As can be seen from the above collaborations there will be significant future work utilizing the work undertaken in this Thesis and it is hoped that both the improved understanding of the role of comorbidity and inflammation in lung cancer along with potential future interventions may improve the poor outcome currently seen in this disease.

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APPENDIX 1: DATA COLLECTION PROFORMA

Patient Details

M / F Age____ Postcode (1st part)_____ Weight_____

Home circumstances Live alone/Independant
Requiring support from Partner/Family

Current Performance Status 0 1 2 3 4 (circle)

Where PS>0, what is deciding reason

1 Effect of lung cancer (acute poor PS)

2 General frailness / chronic comorbidity (chronic poor PS)

3 Combination (acute on chronic poor PS)

Relative estimate of PS 6 months prior to diagnosis_____

Creatinine_____ Albumin_____ CRP_____(if measured)

FEV1_____% Predicted_____ MRC Dyspnoea score- Grade_____

Significant comorbidity (ie affecting PS or requiring treatment)

COPD	0	1	2	3
IHD	0	1	2	3
Heart failure	0	1	2	3
CVA	0	1	2	3
Dementia	0	1	2	3
Diabetes Mellitus	0	1	2	3
Renal Failure	0	1	2	3
Other malignancy	0	1	2	3
Weight loss	0	1	2	3
PVD	0	1	2	3
Alcohol	0	1	2	3
Significant other	0	1	2	3

Smoking _____ pack years

Staging CT performed Yes No

MDT

Patient not discussed at MDT	yes	no
Patient discussed at MDT	yes	no

Patient discussed at MDT then seen at specialist clinic (within 2weeks) seen not seen

Please record staff present at MDT

Respiratory Physician	yes	no
Clinical Oncologist	yes	no
Thoracic Surgeon	yes	no
Radiologist	yes	no
Palliative care Physician	yes	no
Pathologist	yes	no
Specialist nurse	yes	no

Non-small cell lung cancer Stage I

Local symptoms yes no

Proposed for surgical resection

If not, reason?

Age
Poor PS
Comorbidity
Patient refusal

Alternative treatment recommended

Radical radiotherapy

Chemotherapy + Radical radiotherapy

Chemotherapy

High dose palliative radiotherapy

Palliative radiotherapy

Specialist palliative care referral

Active supportive care

Non-small cell lung cancer Stage II

Local symptoms yes no

Proposed for surgical resection

If not, reason?

Age
Poor PS
Comorbidity
Patient refusal

Alternative treatment recommended

Radical radiotherapy

Chemotherapy + Radical radiotherapy

Chemotherapy

High dose palliative radiotherapy

Palliative radiotherapy

Specialist palliative care referral

Active supportive care

Non-small cell lung cancer Stage IIIa

Local symptoms yes no

Proposed for Radical treatment

Surgery
Radical radiotherapy
Chemotherapy + Radical radiotherapy
Induction chemotherapy

If not, reason?

Age
Poor PS
Comorbidity
Disease volume too great
Patient refusal

Alternative treatment recommended

High dose palliative radiotherapy

Palliative radiotherapy

Palliative chemotherapy

Specialist palliative care referral

Active supportive care

Non-small cell lung cancer Stage IIIb

Local symptoms yes no

Proposed for radical treatment

Radical radiotherapy

Chemotherapy + Radical radiotherapy

Induction chemotherapy

If not, reason?

Age
Poor PS
Comorbidity
Disease volume too great
Patient refusal

Alternative treatment recommended

High dose palliative radiotherapy

Palliative radiotherapy

Palliative chemotherapy

Specialist palliative care referral

Active supportive care

Non-small cell lung cancer Stage IV

Local symptoms yes no

Proposed for chemotherapy

If not, reason?

Age
Poor PS
Comorbidity
Patient refusal

Alternative treatment recommended

High dose palliative radiotherapy

Palliative radiotherapy

Biological treatment

Specialist palliative care referral

Active supportive care

Small cell lung cancer Limited stage

Local symptoms yes no

Proposed for concurrent chemoradiotherapy

Proposed for initial combination chemotherapy

If not, reason?

Age
Poor PS
Comorbidity
Patient refusal

Alternative treatment recommended

Single agent chemotherapy

Palliative radiotherapy

Specialist palliative care referral

Active supportive care

Small cell lung cancer Extensive disease

Local symptoms yes no

Proposed for combination chemotherapy

If not, reason?

Age
Poor PS
Comorbidity
Patient refusal

Alternative treatment recommended

Single agent chemotherapy

Palliative radiotherapy

Specialist palliative care referral

Active supportive care

Clinical/radiographic diagnosis (no histology)

Investigations

Biopsy procedure attempted? Yes No

If yes - procedure(s) attempted
Bronchoscopy
Percutaneous lung biopsy
Transbronchial lung biopsy
Mediastinoscopy
VATS
Neck node FNA/Biopsy

If no, reason?

Age

Poor PS

Comorbidity

Inaccessible

Patient refusal

Clinical/radiological stage

T

N

M

Stage I IIa IIb IIIa IIIb IV

Unknown

TreatmentRecommended

Radical radiotherapy

High dose palliative radiotherapy

Palliative radiotherapy

Chemotherapy

Specialist palliative care referral

Active supportive care