AN INVESTIGATION OF THE DETERMINATES OF SURVIVAL IN PATIENTS WITH INOPERABLE NON-SMALL CELL LUNG CANCER: THE ROLE OF THE SYSTEMIC INFLAMMATORY RESPONSE

By

Lynn M Forrest

BSc, RGN

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SCLC	Small Cell Lung Cancer
NSCLC	Non-Small Cell Lung Cancer
ECOG-ps	Eastern Co-operative Oncology Group Performance Status
WHO	World Health Organisation
CT	Computerised Tomography
TNM	Tumour Nodal Metastasis
PCI	Prophylactic Cranial Irradiation

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VI. DECLARATION

I declare that the work presented in this thesis has been carried out solely be myself, except where indicated below.

Measurements of serum albumin, C-reactive protein and full blood count analysis were performed in the Institute of Biochemistry and Department of Haematology Glasgow Royal Infirmary, North Glasgow University NHS Trust, and the departments of Biochemistry and Haematology Wishaw General Hospital, Lanarkshire.

V. DEDICATION

To Dad who lost his brave fight against cancer.

Who during his lifetime, taught me that through hard work and determination, even the apparent impossible tasks of life may become possible.

VI. SUMMARY

Lung cancer is the commonest cause of cancer related death in North America and Western Europe. It comprises of two subgroups, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

Non-small cell lung cancer accounts for approximately three quarters of all patients presenting with lung cancer. The majority of patients present with advanced disease, survival is extremely poor with a median survival rate of 6 to 9 months. Many patients are unfit for radical treatments such as surgery / radiotherapy, and therefore receive palliative treatment only. Traditionally, selection of these patients for active or supportive treatment has been based on clinico-pathological criteria, including age, stage, performance status, weight loss or hypoalbuminaemia. Palliation of symptoms, improvement in patient's quality of life and prolongation of survival are the main aims of treatment.

Various factors have been associated with the poor survival rates of patients with inoperable non-small cell lung cancer. These include stage of disease, performance status and loss of weight. In these patients, weight loss has been reported to be associated with either reduced energy intake or increased energy expenditure, or as a combination of both. The resultant negative energy balance leads to a loss of adipose tissue and protein mass, resulting in tissue wasting, reduced performance status and ultimately death. The reasons for the negative energy balance remain unclear. However, previous studies of advanced cancer have reported that various factors contribute to an increased resting energy expenditure including the presence

of a systemic inflammatory response, as evidenced by raised circulating concentrations of C-reactive protein. Therefore it may be that the presence of the systemic inflammatory response may be associated with poor survival.

The primary aim of this thesis was to assess the impact of the systemic inflammatory response on survival in patients with inoperable non-small cell lung cancer. In addition, an inflammation based prognostic score was constructed and evaluated.

Various studies have shown that a reduction in physical function, as assessed by performance status, was associated with loss of weight in patients with advanced cancer. A study of 50 patients with inoperable non-small cell lung cancer was undertaken to examine the relationship of ECOG performance status (ECOG-ps), anthropometric and blood parameters (including full blood count, white cell count, albumin concentration and C-reative protein). This study demonstrated that mid-upper arm circumference was strongly associated with ECOG-ps in patients with inoperable non-small cell lung cancer. This study demonstrated that albumin concentrations were strongly associated with ECOG-ps.

Previous studies have proposed that the combination of albumin and C-reactive protein may form the basis of a useful standardised and non-subjective assessment of outcome in advanced cancer patients. The following studies compared the above combination with ECOG-ps and various haematological and biochemical factors in patients with inoperable NSCLC.

A study of an unselected cohort of 161 patients with inoperable non-small cell lung cancer was performed to assess the value of combining C-reactive protein and recognised prognostic factors such as stage, performance status and hypoalbuminaemia to form new prognostic scores. The study demonstrated that both the established indicators of the presence of a systemic inflammatory response, white cell count and C-reactive protein, were predictive of survival in patients with inoperable NSCLC. This study also demonstrated that when C-reactive protein concentrations were combined with stage, ECOG-ps and albumin to form new prognostic scores, these combined scores improved the prediction of survival based on stage, ECOG-ps or albumin alone. Furthermore, the results of this study showed that a cumulative score based on C-reactive protein and albumin provides comparable prognostic information to that of stage and ECOG-ps. This cumulative score has the advantage of being simple to measure, routinely available and well standardised.

Following the construction of the cumulative prognostic score, the Glasgow Prognostic Score (GPS), the value of this score was assessed prospectively in patients receiving platinum based chemotherapy for inoperable non-small cell lung cancer. A total of 109 patients were included in the study. When the GPS was compared to ECOG-ps, the GPS was found to be superior to performance status in predicting outcome in patients receiving chemotherapy. This suggests that the GPS offers additional prognostic information and may be useful in the selection of patients with inoperable non-small cell lung cancer for chemotherapy.

Since the inflammation based prognostic score (GPS) was found to have a similar prognostic value to that of stage and performance status, and to be superior in

predicting survival in patients receiving platinum-based chemotherapy, a prospective study was undertaken to compare the reproducibility of the GPS and ECOG-ps in a second centre. Eighty seven patients with inoperable NSCLC were included. This study confirmed that the GPS was at least equivalent to that of ECOG performance status in predicting the survival of patients with inoperable NSCLC.

The previous study chapters have shown that the cumulative prognostic score based on C-reactive protein and albumin (GPS) has prognostic value, independent of performance status, in patients with NSCLC. In the final study chapter, the temporal changes in the GPS were compared with those of performance status in patients with inoperable NSCLC. The results of this study demonstrated that the components of the GPS were more sensitive indicators of disease progression than the GPS itself. This suggests that the GPS may require more refinement in order to improve the monitoring of disease progression in patents with inoperable NSCLC.

In conclusion, the work presented in this thesis suggests that the Glasgow Prognostic score may be useful in the assessment of patients with inoperable non-small cell lung cancer. Further work should be carried out to assess its value in other advanced cancers.

CHAPTER 1

1 INTRODUCTION AND AIMS

1.1 Incidence and mortality of lung cancer

World-wide, lung cancer is the commonest cause of cancer-related death, responsible for over 800,000 deaths each year (International Agency for Research on Cancer, 2001). Recently, the incidence has been falling slightly amongst men, but rising considerably amongst women, and in some countries seems set to overtake breast cancer as the commonest cause of cancer related death in women (Boyle *et al.,* 2000). It has a greater global incidence than that of colorectal, cervical and breast cancer combined. It has been reported that lung cancer causes more than 1 million deaths world-wide; this global death rate has rose at 0.5% per annum since the 1930's (Souhami and Tobias 1998; Spiro and Porter, 2002). This is in contrast to other cancers which, in the developed nations, have shown a decline in death rates over the past 20 years (Devita *et al.,* 1997).

In the European Community there are approximately 158,000 new patients with lung cancer registered each year. Forty thousand new cases of lung cancer are registered each year in the United Kingdom. Within the male population, this incidence has decreased over the past 20 years in line with a reduction in cigarette smoking in the Western World. However, a similar decline is not evident amongst females. Indeed the incidence rates in women are increasing at a rate similar to those seen 20 years ago in men (Splinter, 1997; Spiro and Porter, 2002). For example, in 1952 the male: female ratio for lung cancer was 13:1, however, more recently this has been reported to be 2:1 (Souhami and Tobias, 1998).

In Scotland, in 1997, lung cancer was the most commonly diagnosed neoplasm in men comprising 22% of all cancer registrations. Whilst, in women, lung cancer was the second most commonly occurring cancer after breast cancer, comprising 14% of registrations (Harkness *et al.,* 2002). The West of Scotland has the highest incidence rate of lung cancer in the world (De Vos Irvine *et al.,* 1993). Within this population, Glasgow has the highest incidence rate, 30% above the Scottish average (Kesson *et al.,* 1998).

Lung cancer is also responsible for a quarter of all cancer-related deaths (Thatcher and Spiro, 1994; Simmonds, 1999). In Scotland, lung cancer is the leading cause of cancer-related death, being ranked third overall behind ischaemic heart disease and cerebrovascular disease as the cause of death (Kesson *et al.,* 1998; Scottish Cancer Intelligence Unit 2000).

Recent reports predicted, that deaths from lung cancer amongst women are set to overtake breast cancer as the leading cause of cancer-related death amongst women (Cote *et al.,* 1998, Boyle *et al.,* 2000). Indeed within the United Kingdom, it has recently been reported that mortality rates from lung cancer have now overtaken that of breast cancer, with lung cancer accounting for 18% and breast cancer accounting for 17% of cancer related deaths amongst women (2002, CRC Cancerstats, www.cancerresearchuk.org).

1.2 Aetiology of lung cancer

1.2.1 Environmental factors related to lung cancer

Smoking is the major risk factor for lung cancer. Approximately 90% of all lung cancers result from smoking (Wingo *et al.,* 1999). Small cell and squamous cell lung cancer have a particularly strong association with cigarette smoking: indeed only 1% of small cell lung cancers occur in non-smokers (Devita *et al.,* 1997; Osann *et al.,* 2000). Smoking at an early age appears to increase the susceptibility to this form of lung cancer. A study by Peto and co-workers (2000) showed that the cumulative risk of lung cancer amongst men who continued to smoke was 15.9% by 75 years of age. For those who stopped smoking, the risks were 9.9%, 6%, 3% and 1.7% for those who stopped at 60, 50, 40 and 30 years of age respectively. Peto and co-workers (2000) also demonstrated a similar pattern for women, the cumulative risk amongst women who continued to smoke at 75 years of age being 9.5%, compared with 5.3% and 2.2% amongst those women who had ceased smoking at 60 and 50 years of age respectively. Passive smoking is also an important issue, as 17 to 24% of lung cancer cases amongst non-smokers can be attributed to high levels of exposure to cigarette smoke during their childhood and adolescence (Devita *et al.,* 1997; Hackshaw *et al.,* 1997).

The risk of developing lung cancer is also increased as a result of exposure to asbestos, radon, chloromethyl, polycyclic aromatic hydrocarbons, chromium, nickel, and inorganic arsenic compounds (Devita *et al.,* 1997; Souhami and Tobias, 1998).

The risk of developing lung cancer from asbestos is largely dependent on the intensity of the exposure; asbestos is thought to be responsible for 3 to 6% of all lung cancer deaths (De Vos Irvine *et al.,* 1993; Devita *et al.,* 1997). In the West of Scotland exposure to asbestos was traditionally associated with the shipbuilding industry on the River Clyde (Samet, 1993; De Vos Irvine *et al.,* 1993); it also occurred in the insulation, boiler and cement industries.

Environmental pollution, in particular industrial pollutants, may also be considered as a causative factor of lung cancer. Various studies (Lloyd *et al.,* 1985; Smith *et al.,* 1987) report that whilst foundry workers are more likely to develop lung cancer than other occupational groups, an association also exists between the industrial pollutants from the steel foundries and the lung cancer rates in the residential areas surrounding them. Gustavson and co-workers (2000) reported that occupational hazards (eg. aluminium production, arsenic, asbestos, bis-chloromethyl ether, beryllium, cadmium, hexavalent chromium, coke and coal gasification fumes, crystalline silica, nickel, radon and soot) also have a carcinogenic effect on human lung tissue. Nyberg and co-workers (2000) concluded that the incidence of lung cancer could be reduced if occupational exposure to diesel exhaust, asbestos, and combustion products were reduced to a "safe" level.

Therefore, if sufficient means were taken to reduce these multiple factors, then it may appear that lung cancer is largely a preventable disease (Splinter, 1997).

1.2.2 Genetic factors relating to lung cancer

Genetic predisposition has been reported to be a factor in the development of lung cancer. There is increasing evidence to suggest that the metabolites of carcinogens cause malignancy, and the metabolisms of these metabolites are genetically determined. In non-small cell lung cancer, mutation of the p53 gene (the tumour suppressor gene) may be correlated with exposure to tobacco smoke carcinogens. The role of the p53 gene is to maintain genomic integrity which may occur from DNA damage. It serves as a transcription factor to activate the expression of genes that control cell cycle checkpoints, apoptosis, DNA repair and angiogenesis. The p53 gene is the most frequently mutated tumour suppressor gene in human malignancies, affecting approximately 90% of small cell and 50% of non-small cell lung cancers. These mutations frequently occur in several types of non-small cell lung cancer, affecting approximately 51% of squamous cell and 54% of large cell carcinomas, but are less commonly observed in adenocarcinomas (Devita *et al.,* 2001; Mitsudomi *et al.,* 2001; Ushijima *et al.,* 2001).

The ras-family gene, composed of H-ras-I; K-ras and N-ras, can be activated to play a role in the development of cancer by point mutation. In non-small cell lung cancer, changes have been shown to exist in the single transduction of the K-ras gene. Mutation of this gene occurs in approximately 20% of non-small cell lung cancers. This mutation is commonly associated with adenocarcinoma (30%), and is less frequently seen (12%) in patients with squamous and large cell carcinoma (Johnson, 1995).

Such genetic mutations may be useful as markers in future stratification for treatment and in the context of clinical trials (Johnston, 1995; Devita *et al.,* 2001; Mitsudomi *et al.,* 2001).

1.3 Pathology of lung cancer

In 1981,The World Health Organisation (WHO) developed a classification for lung cancer, and this is used world-wide to define tumour type (Turner-Warwick *et al.*, 1991; Devita *et al.*, 1997)

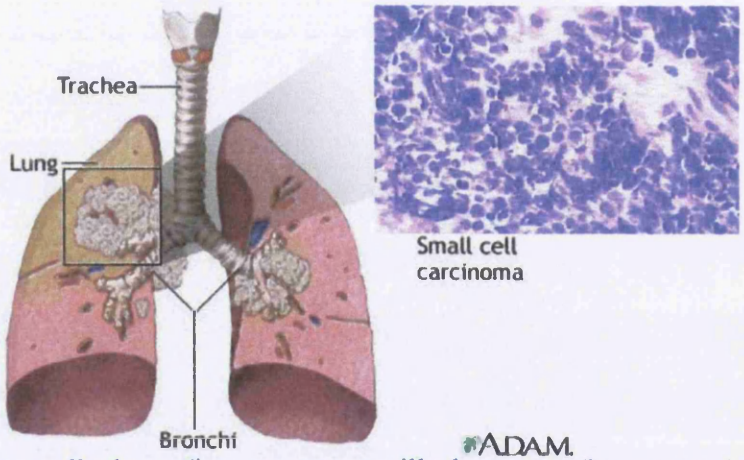
I	Benign
II	Dysplasia and carcinoma in situ
III	Malignant
A	Squamous cell carcinoma (epidermoid and spindle cells)
B	Small Cell Carcinoma 1. Oat Cell 2. Intermediate cell 3. Combined oat cell
C	Adenocarcinoma 1. Acinar 2. Papillary 3. Bronchoalveolar 4. Mucus Secreting
D	Large Cell Carcinoma 1. Giant Cell 2. Clear Cell

Figure 1.1 World Health Organisation Histological Classification of Epithelial Bronchogenic Carcinoma

Lung cancer can be divided into two broad categories; Small cell lung cancer (SCLC) and Non-small cell lung cancer (NSCLC). SCLC accounts for approximately 25% of all cases, whilst NSCLC accounts for 75% (Simmonds, 1999).

1.3.1 Small cell lung cancer

SCLC was first recognised by Barnard in 1926. Prior to this it was regarded as an oat cell sarcoma of the mediastinum (Devita *et al.*, 1997). This tumour is so termed because the nuclei are thought to resemble oat grains (see Figure 1.2).



(www.mesotheliomamedical.com/images; www.willroberts.com/lungcancer)

Small cell carcinoma consists of small cells with dense nuclei, their cytoplasm being very sparse with moulding of adjacent nuclei where the cells are in close contact with each other. They are derived from the Kulchitsky cells of the bronchial wall (Brewis, 1991), develop in cell clusters not following any pattern (Turner-Warwick *et al.*, 1991, Chiti *et al,* 1999), and are characterised by a high mitotic rate, inconspicuous nuclei, finely granular ("salt and pepper") nuclei, as well as the

overall size of the cell. These cells are in general less than the diameter of three resting lymphocytes (Franklin, 2000).

In 1981, The World Health Organisation classified small cell lung cancer into three subtypes; oat cell or small cell undifferentiated, intermediate-cell type, and combined small cell carcinoma (Turner-Warwick *et al.,* 1991; Devita *et al.,* 1997). However, this classification has since been revised (Franklin, 2000), and these groups are now combined into one single category of small cell carcinoma.

Approximately 70% of all patients with small cell lung cancer present with extensive disease, and have evidence of metastatic spread at time of diagnosis, especially liver, adrenal, bone, bone marrow and brain (Hoffman *et al.,* 2000). It has long been recognised that the number of metastatic sites is proportional to the extent of disease, resulting in a poorer prognosis. Moreover, liver and cerebral mestatases confer a significantly shorter survival compared with bone, soft tissue or bone marrow involvement. (Vincent *et al.,* 1987; Elias, 1998; Chiti *et al.,* 1999; Yip and Harper, 2000).

1.3.2 Non-small cell lung cancer

NSCLC accounts for approximately three quarters of all histological types of lung cancer related deaths world-wide (Ihde and Minna, 1991; Hespanhol *et al.,* 1995; Juretic *et al.,* 1999; Ferrigno and Buccheri, 2000). It comprises several types, namely squamous cell carcinoma, adenocarcinoma and large cell, which account for 50%; 30% and 20% respectively (Souhami and Tobias, 1998).

Squamous cell carcinoma

This is the commonest type of lung cancer, it is mostly found in men, and has been reported to have a strong association with cigarette smoking (Barbone *et al.,* 1997; Kreuzer *et al.,* 1999; Payne 2001). The tumour tends to arise most frequently in the proximal segmental bronchi, almost always growing from the hilum, and is associated with squamous metaplasia (see Figure 1.3).

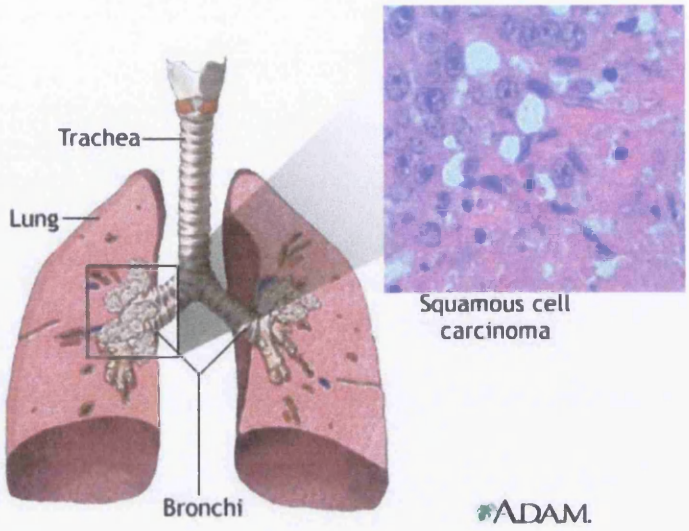


Figure 1.3 Squamous cell carcinoma of the lung

(www.nlm.nih.gov/medlineplus/ency/imagepages/18017.htm;

www.willroberts.com/lungcancer)

These tumour cells are composed of epithelial cells, which may be either poorly or well differentiated and have a keratinised appearance (Devita *et al.*, 1997).

In the early stages stratified squamous epithelium is replaced by malignant squamous cells without invasion through the basement membranes (Turner-Warwick *et al.*,1991; Devita *et al.*, 1997, Chiti et al 1999). Squamous cell lung cancers may be detected at an early stage either by cytological or histopathological examination. Bronchoscopy remains the most frequent method of obtaining tissue for diagnosis. However, in certain situations bronchial biopsy is not possible as a result of an inaccessible site or if the patient is at risk of haemorrhage. In such instances

cytopathology maybe used to obtain a tissue diagnosis via the sputum, washings or brushings obtained at the time of bronchoscopy (Piaton *et al.,* 1995).

In the later stages squamous cell carcinomas of the lung may be found to invade the basement membranes, extend into the bronchial lumen and produce an obstruction which may result in atelectasis or pneumonia. At the time of diagnosis, 50% of cases have disease limited to the thorax, although mediastinal involvement is common (Turner-Warwick *et al.,*1991; Devita *et al.,* 1997, Chiti *et al.,* 1999).

Adenocarcinoma

This form of lung cancer is the second most common cause of NSCLC, and appears to be slightly more common in women than in men (Devita *et al.,* 1997). However, in recent years the histological patterns of lung cancer have changed, with a world-wide increase in adenocarcinoma, and a decrease in the proportion of squamous cell lung cancer (Payne, 2001). Indeed, in the United States, adenocarcinoma has become the most frequent subtype of NSCLC (Kreuzer *et al.,* 1999). In Europe however, adenocarcinoma still remains the second most common cause of NSCLC despite substantial increase in incidence over the past twenty years (Harkness *et al.,* 2002). This increased incidence of adenocarcinomas is thought, in part, to be related to the decrease in the number of men smoking. Interestingly, it has also been suggested that the introduction of the low tar cigarettes towards the end of the 20th century may also be responsible for the increase in the number of adenocarcinomas being diagnosed (Levi *et al.,* 1997; Payne, 2001). This is thought to be the case as the smoker, in order to satisfy the craving for nicotine, tends to compensate by

increasing the number and depths of puffs. The bronchioloaveolar regions and the smaller bronchi, which lack protective epithelium, and where adenocarcinomas generally occur, are therefore exposed to higher concentrations of carcinogens (Levi *et al.,* 1997).

These tumours are usually peripheral in origin and are found in the terminal bronchioles. They arise from glandular cells, such as mucous goblet cells, clara cells and type II pneumocytes, and are composed of cuboidal or columnar cells forming papillary structures. It has been suggested that they develop from either epithelium, bronchial mucosal glands or areas of scar tissue from old infarcts. However, it is also possible that this scar tissue is a product of the tumour itself. (Devita *et al.,* 1997)

Under microscopic examination these tumours may be subdivided into several types:- acinar; papillary and mucus secreting. As the disease progresses, the tumour spreads along the alveolar walls and frequently invades the pleura (see Figure 1.4).

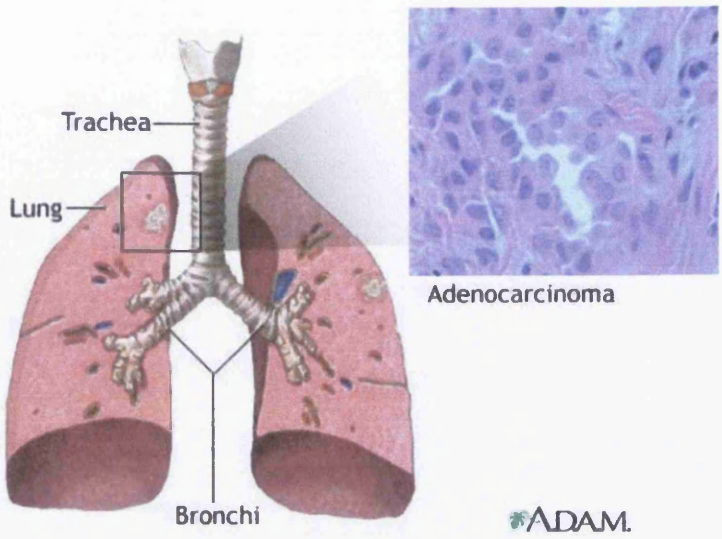


Figure 1.4 Adenocarcinoma of the lung

(www.nlm.nih.gov/medlineplus/ency/imagepages/18014.htm; www.willroberts.com/lungcancer)

These tumours are known to progress rapidly and spread from lobe to lobe, ultimately encompassing both lungs. Adenocarcinoma is known to have a worse prognosis than squamous cell carcinoma, and at the time of diagnosis, distant spread is frequent (Devita *et al,* 1997; Chiti *et al.,* 1999).

Bronchiolo-alveolar carcinoma is a subtype of adenocarcinoma of the lung, (Higashiyama *et al.,* 1999). It is a relatively uncommon primary malignant pulmonary neoplasm, accounting for 2 to 14% of all pulmonary malignancies (Liu *et al.,* 2000). The World Health Organisation categorise bronchiolo-alveolar carcinoma as a subtype of adenocarcinoma, and the increasing incidence of this subtype is thought to be contributing to the higher incidence of adenocarcinoma which has been

observed in recent decades (Breathnach *et al.,* 1999; Liu *et al.,* 2000). The aetiology of this increase in the incidence of bronchiolo-alveolar carcinoma is unclear. It tends to occur most frequently in female patients who have never smoked (Breathnach *et al.,* 1999). The current definition of bronchiolo-alveolar carcinoma is, "malignant neoplasms of the lung that have no evidence of extrathoracic primary adenocarcinoma, an absence of a central bronchogenic source, a peripheral parenchyma location, no distortion of the pulmonary interstitium, and neoplastic cells growing along the alveolar septa" (Liu *et al.,* 2000).

The histological criteria for bronchiolo-alveolar carcinoma includes a peripheral tumour manifesting the growth of well-differentiated cuboidal or columnar tumour cells along intact alveolar walls with no evidence of a primary adenocarcinoma at some extrapulmonary site. The cytologic criteria for a diagnosis of bronchiolo-alveolar carcinoma includes the prominence of monolayered tumour sheets, fine chromatin pattern, abundant cytoplasm showing uniformity, a high nuclear-cytoplasmic ratio, and mild cellular pleomorphism. Nuclear folds are a common finding, and cells nearly always lack cilia (Breathnach *et al.,* 1999). Indeed, bronchiolo-alveolar carcinoma in lung adenocarcinoma, in which the tumour cells grow upon the pre-existing alveoli walls without damaging the underlying lung structure is often observed (Higashiyama *et al.,* 1999). This type of tumour has been found to have a better prognosis than other types of non-small cell lung cancer.

Large Cell Carcinoma

Large cell lung carcinoma is the least common type of non-small cell lung cancer, and represents only 10 to 20% of all non-small cell lung cancers that originate in the bronchi. Like squamous cell lung cancer, large cell lung cancer has a strong association with smoking. Although, the origin of the cells has not been established, it sometimes arises in the distal bronchus (see Figure 1.5).

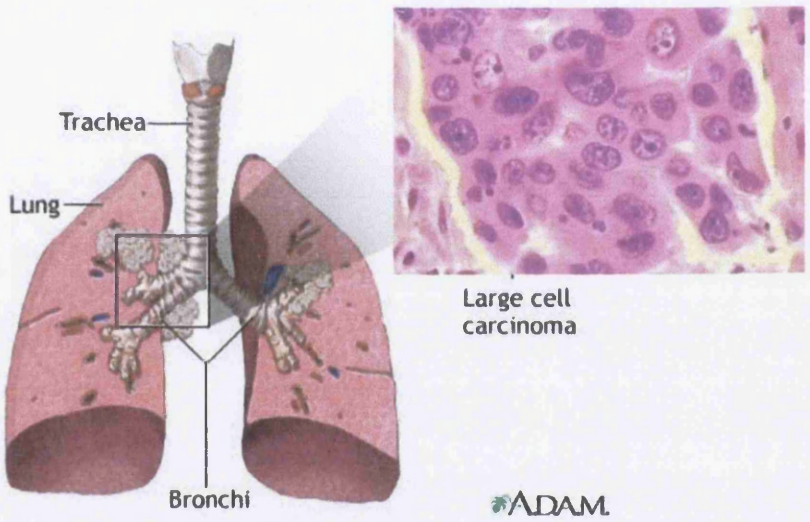


Figure 1.5 – Large cell carcinoma of the lung

(www.nlm.nih.gov/medlineplus/ency/imagepages/18015.htm;

www.willroberts.com/lungcancer)

The cells are multinucleated and lack density; they also have moderate amounts of cytoplasm that lack evidence of mucus storage or keratinization (Turner-Warwick *et al*; 1991). This form of lung cancer may also exhibit giant cell forms, and occasionally the cytoplasm is pale staining. Hence, this tumour can be subdivided

into two groups, giant cell and clear cell. Giant cell tumours represent a poorly differentiated subgroup and appear to have a poor prognosis.

At the time of diagnosis these tumours are usually large, and they are often accompanied by extensive tissue damage and distant spread (Devita *et al,* 1997). Of the three types of non-small cell lung cancer, large cell carcinoma has the worst prognosis. Similar to adenocarcinoma, the overall prognosis of those patients with advanced large cell lung cancer is poor with approximately 8% surviving five years (Devita *et al.,* 1997; Chiti *et al.,* 1999).

1.4 Clinical assessment of lung cancer

1.4.1 Signs and symptoms of lung cancer

The majority of patients (90%) are symptomatic at the time of their diagnosis (Beckles *et al.,* 2003). Cough and breathlessness are two of the most commonly occurring symptoms. For example Muers and Round (1993), in a study of 289 patients with non-small cell lung cancer, found cough and breathlessness to be the most common symptoms experienced by the patient. Three-quarters of the patients included in the study were reported to have been experiencing cough and breathlessness, and this was found to be moderate or severe in approximately half of these patients. This has also been reported by Kuo and co-workers (2000), who in their study of old and young patients with non-small cell lung cancer, also found cough to be the most commonly presenting symptom, followed by breathlessness and chest pain. However, since these symptoms commonly occur in smokers, they are often not recognised until the disease in advanced.

It is also common for patients diagnosed with lung cancer to report haemoptysis at the time of diagnosis. However, this is rarely severe and usually consists of blood streaked sputum (Beckles *et al.,* 2003). Chest pain is another common presenting symptom in patients with lung cancer, with more than 50% of patients reporting chest wall pain during the course of their disease. The pain tends to be unrelated to breathing or coughing being instead persistent and poorly localised. If however, a patient presents with chest wall pain which is particularly severe and localised, it is usually related to either direct invasion of the pleura or chest wall by the primary

tumour, a rib metastasis or associated pneumonia or pulmonary infections (Beckles *et al.,* 2003). Muers and Round (1993) reported that haemoptysis and chest pain occurred in approximately one third of the patients included in their study.

Other clinical features may include: anorexia, unexplained weight loss and / or loss of appetite, fatigue, pyrexia of unknown origin, bone pain or pathological fracture or hoarseness due to left recurrent laryngeal nerve palsy. Dysphagia may also develop if enlarged mediastinal nodes exert pressure on the oesophagus (Hancock and Bradshaw, 1981). Superior vena cava obstruction (SVCO) is also a frequent presentation of lung cancer, its clinical presentation includes oedema and vein distension of the head and neck and upper extremities and thorax, dyspnoea and in severe cases, confusion, impaired attention and coma (Urruticoechea *et al.,* 2004). Many of these symptoms may be palliated by treatments such as radiotherapy (Muers and Round 1993).

For the majority of patients, irrespective of the type of lung cancer, treatments are based on the clinical stage of disease and the symptoms experienced by the patient (Muers and Round 1993).

Despite the continual high incidence of lung cancer within the Western world, five year survival remains low at 7 to 13%. This occurs as a result of approximately 80% of patients presenting with advanced inoperable disease. It is recognised that improvements in survival are only possible through patients being diagnosed sooner with resectable disease, which could perhaps increase five year survival to 70% (Porter and Spiro, 2000).

1.4.2 Diagnosis and staging of small cell lung cancer

Over the past decade the proportion of patients with small cell lung cancer has decreased from 17.4% to 13.8%. Small cell lung cancer, like squamous cell lung cancer has a strong association with cigarette smoking; however the clinical nature of small cell lung cancer tends to be more aggressive. Without treatment, median survival is usually 2 to 4 months. (Brewis, 1991, Devita *et al.,* 1997; Johnson, 1999; Simmonds, 1999; Simon *et al.,* 2003). Accurate assessment of these patients is therefore essential to allow for the most effective treatment to be planned.

Small cell lung cancer is staged using a simple two stage system: limited or extensive stage, as described by the Veterans Administration Lung Cancer Study Group in 1965 (Naruke *et al.,* 1997; Devita *et al.,* 1997). Patients with limited disease are described as having involvement which is restricted to one hemithorax, although some definitions allow the ipsilateral supraclavicular nodes to be affected. Patients who are found to have metastatic disease in other parts of the body are defined as having extensive disease (Souhami, 1992; Simon *et al.,* 2003).

Vincent and co-workers (1987) have questioned the value of this method of staging (due to the elaborate investigations involved), and suggested that a simpler clinically based system of staging may be more appropriate. This would include the use of clinical performance status and few simple biochemistry tests, which may provide better prognostic sub-groupings than that of conventional staging by extent of disease (Souhami *et al.,* 1985; Osterlind and Anderson, 1986). Presently, the traditional methods of staging small cell lung cancer according to evidence of

disease extent remains widely used (Yip and Harper, 2000), although many clinicians also used clinical and biochemical parameters as further guides to prognosis. For example, Souhami (1992) reported that in terms of survival, biochemical abnormalities such as a raised alkaline phosphate or lactic dehydrogenase or a low serum albumin or sodium concentrations are adverse prognostic factors.

In patients who are newly diagnosed with small cell lung cancer, a full medical history and physical examination should be performed. As part of this assessment, it is important to consider the patient's performance status, since this will reflect the patient's ability to tolerate treatment (Souhami, 1992; Simon *et al.,* 2003). Histopathology specimens obtained at the time of diagnosis (by either bronchoscopy or biopsy) should be examined to determine the cell type (Simon *et al.,* 2003). A CT scan of the chest and upper abdomen should be performed to assess the extent of the tumour; the whole liver and both adrenal glands being examined at this stage to determine any metastatic involvement. If neurological history or examination prove to be abnormal, a CT scan of brain may be performed (Yip and Harper, 2000; Simon *et al.,* 2003). Baseline blood parameters of full blood count, urea and electrolyte levels, liver function tests and lactic dehydrogenase levels are also usually performed (Simon *et al.,* 2003).

Two thirds of those patients with SCLC present with extensive disease, and the remainder, 30 to 40% of patients, will be deemed as having limited disease, with no sign of the cancer beyond one side of the chest (Devita *et al.,* 1997; Simmonds 1999).

It has been argued that TNM staging (see Figure 1.6) should also be applied in small cell lung cancer, as this provides significant information on prognosis and tumour spread (Souhami, 1992; Devita *et al.,* 1997). Limited disease would correspond to stages I to IIIA, whilst extensive disease would correspond to stages IIIb to IV (Naruke *et al.,* 1997). However, as CT detection of early spread is limited, this is not widely practised.

1.4.3 Diagnosis and staging of non-small cell lung cancer

It is well recognised that in patients, with NSCLC, those who present with early stage disease (stage I and II) have the best possibility of cure, with a five year survival rate of 50 to 80% (Hespanhol *et al.,* 1995; Juretic *et al.,* 1999; Ferrigno and Buccheri, 2000). This however, represents less than 25% of this patient group (Nesbitt *et al.,*1995).

The majority of patients with NSCLC present with advanced disease, and this is associated with poor prognosis (Martins *et al.,* 1999). The median survival in patients with NSCLC varies depending on the stage of their disease. Within Europe, across all stages of NSCLC, five year survival is reported to be less than 10% (Sant *et al.,* 2001). However, in advanced stage IV disease less than 1% survive 5 years (Hespanhol *et al.,* 1995; Ferrigno and Buccheri, 2000). The aim of staging in lung cancer is therefore to identify suitable patients for surgical resection and also those who many benefit from aggressive treatment (eg. Radical radiotherapy) of their locally advanced disease (Leong *et al.,* 1999; Hoffman *et al.,* 2000).

The staging assessment for NSCLC includes three main issues: the extent of spread within the chest; the presence of distant metastasis and the general health and physical function of the patient.

The chest is generally assessed by chest X-ray, bronchoscopy, pulmonary function testing and computerised tomography (CT scan). A chest X-ray may assist in the diagnosis of primary lung cancer, for example, by allowing for the identification of a spiculated, irregular pulmonary nodule or a lung mass with cavitation. Mediastinal adenopathy, pleural space abnormalities (e.g. mass, effusion) or skeletal abnormalities may also be identified (Grondin and Liptay, 2002).

Bronchoscopy is commonly performed to assess the extent of proximal bronchial disease, to exclude any additional lesions and to take biopsies for histology (30% of central tumours are diagnosed via bronchoscopy). Bronchial brushings and lavage may also be undertaken and a transbronchial biopsy of the peripheral lung may also be performed under radiological screening to obtain a tissue diagnosis (Hoffman *et al.*, 2000; Grondin and Liptay, 2002).

A CT scan of the chest is carried out to assess any invasion by the tumour of the adjacent structures, and to look for hilar and mediastinal adenopathy. Although CT scanning has an accuracy of 88% in detecting mediastinal involvement, the presence of enlarged mediastinal lymph nodes on CT scan does not necessarily exclude the patient from surgery, as this may be a false positive result (due to post-obstructive infection of the resultant inflammatory lymphadenopathy). In such instances positron-emission tomography (PET) may be used, since this is a highly sensitive

and specific scan for mediastinal staging. If mediastinal spread is suspected, then a mediastinoscopy may be performed to assess the involvement of the ipsilateral and contralateral mediastinal lymph nodes (Hoffman *et al.,* 2000; Grondin and Liptay, 2002). Magnetic Resonance Imaging (MRI) may also be useful in evaluating any intrathoracic spread. Other newer staging techniques include isotope labelled neospect scanning, video assisted thoracoscopy and transbronchial needle biopsy of mediastinal nodes (Deslauriers and Gregoire, 2000; Hoffman *et al.,* 2000).

As previously acknowledged, metastatic involvement in patients with NSCLC is common. Grondin and Liptay (2002) reported that approximately 30% of patients have metastatic disease at the time of diagnosis. Common sites for metastatic spread include brain, bone, liver and adrenal glands (Deslauriers and Gregoire, 2000). In the assessment of metastatic spread the medical history and physical examination of the patient is useful. Full blood count, urea and electrolyte levels and liver function tests are also helpful. Elevated liver function tests are suggestive of liver metastases, while elevation in alkaline phosphate or calcium is suggestive of bone metastases (Grondin and Liptay, 2002). Metastases to the liver and adrenal glands are commonly diagnosed by means of an abdominal CT scan; in some patients these lesions are too small to accurately characterise with CT scanning, and in such instances ultrasound clarification may be of added benefit. For those patients suspected of having bony metastases isotope bone scanning may be employed to confirm these (Deslauriers and Gregoire, 2000). If brain metastases are suspected these may be diagnosed by a CT scan of the brain. However in those patients with a negative CT scan who have symptoms suspicious of brain metastases, MRI scanning may be useful.

Assessment of the health and physical function of the patient usually involves a combined judgement about the patients performance status and their ability to tolerate certain treatments (Hoffman *et al.,* 2000; Grondin and Liptay, 2002). In particular, assessment of cardio-respiratory fitness is important.

Staging of NSCLC is based on the TNM classification which was first proposed by Pierre Denoxi in 1946 as an anatomical basis for unifying staging (Naruke *et al.,* 1997; Beadsmoore and Screaton, 2003). Since its development the TNM classification has been modified several times, most recently in 1997 by Mountain. Despite these modifications, the original concept upon which staging was based remains (Beadsmoore and Screaton, 2003).

The T component of the classification provides information on the size and local extent of the primary tumour (Deslauries and Gregoire, 2000; Beadsmoore and Screaton, 2003).

The N component of the classification indicates the presence or absence of lymph node involvement (Deslauries and Gregoire, 2000; Beadsmoore and Screaton, 2003).

The M component of the classification provides information about the presence or absence of distant metastase (Deslauries and Gregoire, 2000; Beadsmoore and Screaton, 2003). See Figure 1.6

Classifications	Descriptions
Primary tumour(T) Tx =	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0 =	No evidence of primary tumour
T is =	Carcinoma in situ
T1 =	Tumours <3cm in diameter, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobular bronchus (ie. Not in the main bronchus)
T2 =	Tumour with any of the following features- • > 3cm in greatest dimension • Involves the main bronchus, ≥2cm distal to the carina • Invades the 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 (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus < 2cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
T4 =	Tumour of any size that directly invades any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina; or tumour with a malignant pleural or pericardial effusion, or with satellite tumour nodule(s) within the ipsilateral primary-tumour lobe of the lung
Regional lymph nodes(N)	
NX =	Regional lymph nodes cannot be assessed
N0 =	No regional lymph node metastasis
N1 =	Metastasis to ipsilateral peribronchial and/ or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumour
N2 =	Metastasis to ipsilateral mediastinal and/ or subcarinal lymph node(s)
N3 =	Metastasis to contralateral mediastinal, contralateral hilar or ipsilateral or contralateral scalene or supraclavicular lymph node(s)
Distal metastasis(M)	
MX =	Presence of distant metastasis cannot be assessed
M0 =	No distant metastasis
M1 =	Distant metastasis present

Figure 1.6 TNM Description

NSCLC may be allocated into four categories in accordance with TNM staging. (See Figure 1 7).

STAGE	Description	5-year survival rate (%)
IA	T1, N0, M0 – Peripheral "coin" lesion	60 – 80
IB	T2, N0, M0 – Involving the mainstem bronchus ≥ 2cm distal to carina; Involving visceral pleura Small tumour, no evidence of lymph node or other distant metastasis	
IIA	T1, N1, M0 - ≤ 3cm involving peribronchial lymph nodes (by direct extension)	25 – 50
IIB	T2, N1, M0 – Involving visceral pleura and peribronchial and hilar lymph nodes T3, N0, M0 – Involving main bronchus < 2cm distal to carina	
III A	T1 – T3, N0 – N2, M0 Various size tumours involving ipsilateral hilar and mediastinal lymph nodes	25 – 40
III B	Any T4 or anyN3, M0 Primary tumour invasion of the mediastinum and metastasis to contralateral hilar, contralateral mediastinal or scalene / supraclavicular lymph nodes	<5
IV	Any T, any N, M1 Distant metastasis	<5

Figure 1.7 - Staging using TNM classification (Deslauries and Gregoire 2000; Mountain, 1997, Devita *et al.,* 1997, Naruke *et al.,* 1997)

However, Leong and co-workers (1999) suggested that as patients with pleural effusions have a poor survival, similar to that of patients with stage IV disease (ie. spread to the brain or liver), they should be reclassified as having stage IV disease.

Accurate assessment of lung tumours is necessary to allow for appropriate treatment to be planned (Leong *et al.,* 1999).

1.55 Treatment Options

The treatment for lung cancer may differ depending on whether the cancer is classified as small cell lung cancer or non-small cell lung cancer (Simmonds, 1999).

1.55.1 Small cell lung cancer

Small cell lung cancer (SCLC) comprises approximately 20 to 25% of all lung cancers. Due to the systemic nature of small cell lung cancer, it is almost invariably disseminated or at least so locally advanced at the time of diagnosis that surgery is rarely a feasible option (Kumar, 1997; Spiro and Porter, 2002). If untreated, patients with limited SCLC have a median survival of three months, compared with only six weeks in those patients with extensive disease (Kelly, 2000; Spiro and Porter, 2002).

In the 1970's it was recognised that SCLC was extremely sensitive to cytotoxic chemotherapy; indeed, there was a time in the 1980's when SCLC was considered to be potentially curable. This resulted in numerous clinical trials to investigate the efficacy of different chemotherapy combinations, alternating chemotherapy and the durration of chemotherapy (Splinter, 1997; Spiro and Porter, 2002).

Simmonds (1999) suggested that chemotherapy should commence within two weeks of a confirmed histological diagnosis, as this can provide rapid palliation of symptoms and may improve survival time. The treatment given to patients with SCILC will largely depend on extent of disease, performance status, and biochemical results eg. alkaline phosphate, lactate dehydrogenase (Souhami, 1992). For those

patients with limited disease, accounting for approximately one third of all SCLC cases, chemoradiation therapy may be employed (Kumar, 1997; Johnson, 1999; Spiro and Porter, 2002; Simon and Wagner, 2003). Combined chemotherapy in most instances is usually administered for six courses, as fewer treatments have been associated with a reduction in the disease free interval after chemotherapy (Spiro and Poter, 2002). It is well recognised that despite the high response rates to chemotherapy in patients with SCLC, relapse and progression commonly occurs (Kumar, 1997; Johnson, 1999; Kelly, 2000).

Kumar (1997) reported that although chest irradiation has been used in the treatment of SCLC over the past four decades, its standard role in the treatment of limited stage disease has only been established over the past decade. It has also been reported that the addition of thoracic radiotherapy to chemotherapy usually results in a halving of local failure rates from more than 60% with chemotherapy alone to approximately 30% with combined chemotherapy and radiotherapy. An improvement in three year survival from 10 to 15% following chemoradiation was also reported (Kumar, 1997).

Due to the systemic nature of SCLC, the current treatment for limited disease integrates chemotherapy for the management of undetected micrometastases which are usually present at diagnosis, with thoracic radiotherapy to improve locoregional tumour control (Kumar, 1997).

It has recently been reported that of those patients treated with chemoradiation therapy for limited SCLC, approximately 20% of patients will achieve complete remission of the disease (Simon and Wagner, 2003). However, despite this, several

issues remain problematic in the administration of chemoradiation therapy in treatment of limited SCLC. These include timing and concurrent vs sequential vs alternating treatment (Kumar, 1997; Johnson, 1999). It has been suggested that the best survival results are achieved when using early concurrent thoracic radiotherapy with cisplatin based chemotherapy as opposed to sequential or alternating regimes (Kumar, 1997; Johnson, 1999). This improvement in survival may be associated with an increase in toxicity. However, for the combination of cisplatin and etoposide, a commonly used regime, long term toxicity appears to be modest, with short term toxicities consisting primarily of oesophagitis which is manageable (Johnson, 1999).

Spiro and Porter (2002) reported in their review of those patients treated with either chemotherapy alone or chemoradiation therapy, who achieved a complete response to their treatment, that the cumulative risk of developing a brain metastasis was 50%. This is often the first site of relapse, with survival after such relapses being short and morbidity high. Prophylactic cranial irradiation (PCI) has been reported to reduce the incidence of cerebral metastasis when administered to those patients who have achieved a complete response after treatment. Clear evidence exists from meta-analysis that PCI improves overall and disease-free survival rates for patients with SCLC in complete remission. (Johnson, 1999; Spiro and Porter, 2002; Pottgen *et al.*, 2004).

The prognosis for those patients diagnosed with extensive disease is extremely poor. Four to six courses of platinum based chemotherapy tends to be the first line treatment of choice for patients with extensive disease (Hanna and Einhorn, 2002;

Spiro and Porter, 2002). However, a balance must be obtained between the toxicities exerted by the chemotherapy agents, and patient quality of life and survival. Patients are unlikely to live for many months even with chemotherapy, and "aggressive" management must be reviewed in this light. In order to reduce toxicity, the number of courses or the strength of each dose of chemotherapy may be required to be reduced (Simmonds 1999; Spiro and Porter, 2002). Overall response rates from treatment range from 60 to 80% with a median survival of less than 14 months; less than 30% of patients remain disease free for two years (Devita *et al.,* 1997, Johnson, 1999).

1.5.2 Non-small cell lung cancer

It has long been recognised that the treatment of non-small cell lung cancer is one of the most frustrating areas in oncology (Mulshine *et al.,* 1986).

Since the first surgical resection for a primary lung cancer was performed in 1933 by Graham and Singer, surgical treatment for patients with stage I and II, and some patients with IIIA disease remains the 'gold standard' (Delauries and Gregoire, 2000; Orlowski and Szczensy, 2001). Unfortunately, despite surgery being the only treatment to offer the best chance of long term survival and cure, the majority of patients present with inoperable disease as the tumour is either locally advanced or has metastasised elsewhere within the body (Juretic *et al.,* 1999; Simmonds, 1999; Bunn *et al.,* 2000; Gridelli *et al.,* 2003). Indeed, fewer than 25% of patients will present with stage I or stage II disease, with the average five year survival reported at approximately 65% and 40% respectively (Nesbit *et al.,* 1995). Even with complete

resection at least half the patients will relapse with locally advanced and or metastatic disease within five years, resulting in a five year survival of between 20 to 60% (Simmonds 1999; Deslauries and Gregoire, 2000; Ferrigno and Buccheri, 2000; Griddelli *et al.,* 2003; Maas *et al.,* 2003; Westeel and Depierre, 2003).

Approximately, 30% of patients present with stage IIIa or IIIb disease, which is classed as loco-regional disease as it is confined to the chest wall without any obvious distant metastases. The potential role for surgery between these stages of disease is different, with stage IIIa being classed as potentially resectable; despite it carrying a high rate of recurrence and a post-operative 5 year survival of only 10 to 30%. In general, stage IIIb disease is considered to be unresectable (Ferrigno and Buccheri, 2000).

Full pre-operative staging work up is essential to select those patients who are most suitable for surgery. This includes, assessment of the patients performance status, physical function and cardio-respiratory function. The extent of disease should be assessed by staging procedures such as Chest X-ray; CT, MRI, PET scanning or mediastinoscopy, and reference to the TNM classification (Souhami, 1992; Bauman *et al.,* 2001; Orolowski and Szcensy, 2001).

For those patients with stage I disease whose tumour is limited to a lobe, lobectomy is the most common operative procedure. When the tumour crosses the fissure and extends into the main bronchus (stage II disease), pneumonectomy is more commonly performed. In some patients with early stage disease, pulmonary reserve is poor and this results in wedge resection with chest wall resection. Occasionally, in

patients with peripheral T3 tumours, where the malignancy invades the chest wall, lobectomy with chest wall resection may still be considered suitable surgery. However, this type of surgery carries a three fold increased risk of local recurrence. In view of this increased risk of local recurrence, post-operative radiotherapy is routinely recommended (Deslauries and Gregoire, 2000; Bauman *et al.,* 2001).

Nevertheless, a proportion of patients technically suitable for surgery, do not undergo surgery for a variety of reasons. The majority of patients with lung cancer are middle aged or elderly, and are inoperable as a result of pre-existing comorbidity, mostly cardiopulmonary, that prohibits surgery due to a predicted high peri-operative risk. A small group of patients will refuse surgery. Those patients deemed unsuitable for surgery are usually offered radical radiotherapy either alone or in combination with chemotherapy. This is considered the 'standard' treatment approach and is thought to offer the only chance of cure in localised NSCLC (Hoffman *et al.,* 2000; Baumann *et al.,* 2001; Jeremic *et al.,* 2002).

Radical radiotherapy is usually given to patients with stage IIIa and IIIb disease in an attempt to improve survival and reduce the incidence of local recurrence (Spiro and Porter, 2002). This consists of 1.8 to 2.0Gy per fraction and five fractions per week to total doses of 60Gy (Juretic *et al.,* 1999; Baumann *et al.,* 2001; Jeremic *et al.,* 2002). Hoffman and co-workers (2000) reported cure rates of 25% in patients with early stage NSCLC who are treated with radical radiotherapy. Local tumour control with this form of treatment is only 10 to 20%, with local failure being reported as the leading cause of death after radiotherapy (Baumann *et al.,* 2001). Indeed median

survival of patients treated with radiotherapy alone is 10 months or less, with a five year survival of 5 to 10% (Numico *et al.,* 2001).

The introduction of the highly accelerated radiotherapy CHART regime (continuous hyperfractionated accelerated radiotherapy), where treatment is administered three times daily as 1.5Gy for a total of 54Gy, has been reported to improve two year survival by 9% compared with standard radiotherapy (Baumann *et al.,* 2001; Spiro and Porter, 2002). Baumann and co-workers (2001) reported that, radiotherapy may be combined with chemotherapy (mainly platinum based), given either sequentially or concurrently. This is now established as a standard treatment for patients with stage III NSCLC, with a 4% survival benefit observed at two years. It is however, important to remember that with advances in treatment, the toxicity experienced by the patient may also increase. Therefore patients need to be carefully selected for treatment (i.e. those patients with good performance status) and maximum tolerated doses need to be defined for each of these treatment approaches, in order to obtain maximum benefit (Baumann *et al.,* 2001).

At the time of diagnosis, approximately 50% of patients have advanced (stage IV) disease (Nesbitt *et al .,* 1995; Chiiti *et al.,* 1999). Prognosis in this cohort of patients is extremely poor, with 80% of patients dying within one year of diagnosis (Hespanhol *et al.,* 1995; Espinosa *et al.,* 1995 Naruke *et al.,* 1997; Numico *et al.,* 2001). The advanced nature and high metastatic potential of NSCLC results in widespread organ involvement which may cause a variety of symptoms including breathlessness, cough, anorexia, and weight loss. These tumour related symptoms commonly affect the patient's quality of life. The aim of treatment is therefore

directed towards the palliation of these symptoms, in an attempt to improved quality of life (Numico *et al.,* 2001). Radiotherapy, chemotherapy, chemoradiation or supportive care is commonly offered to patients, and may have a role in the palliation of symptoms, improvement in quality of life and perhaps prolongation of survival.

On the basis of various meta-analysis, chemotherapy whenever practicable is recognised as a useful treatment for patients with stage IV disease, as it has been found to confer a small but statistically significant survival advantage (Ferrigno and Buccheri, 2000). Cisplatin has been incorporated into almost all chemotherapy regimes, since it has been shown to lengthen survival (Splinter, 1997; Bunn *et al.,* 2000). Prior to 1990, single agent chemotherapy such as Cisplatin was shown to produce response rates of 30%, with one year survival rates of 10 to 12%. Since the 1990's several new agents have been introduced. These include the taxanes (paclitaxel and docetaxel), gemcitabine and vinorelbine; when these agents are combined with cisplatin overall response rates of 30 to 40% have been reported, with median survival of 8 to 10 months and one year survival of 35% (Hespanhol *et al.,* 1995; Ferrigno and Buccheri, 2000).

Most oncologists tend to agree that due to the poor outlook for patients with inoperable NSCLC, platinum based chemotherapy should only be offered to those patients with a good performance status (i.e. ECOG-ps 0–1), as those with a poor performance status (i.e. ECOG-ps 2-4) have been shown to have a poor response to such treatment (Espinosa *et al.,* 1995; Manegold, 2001). Those patients with ECOG-ps 2, will be considered by many oncologists to be of 'good or bad' performance

status and in such instances may consider the patient for single agent chemotherapy (eg. gemcitabine) since platinum based combinations have been shown to have no survival benefit (Manegold, 2001). This method of selection may be seen to be rather inconsistent and possibly the use of various haematological and biochemical factors (e.g. haemoglobin, white cell count, lymphocyte count, albumin concentration and C-reactive protein), which are recognised prognostic factors, may be of assistance (Sorensen *et al.,* 1989; Paesmans *et al.,* 1997; Herndon *et al.,* 1999). Thus, helping to better identify those patients suitable for oncological intervention.

For those patients who are ineligible for chemotherapy (eg. ECOG PS < 2) or when local symptoms are prevalent, palliative radiotherapy may help to relieve local symptoms of lung cancer. Chest pain, cough and breathlessness, may be relieved in some cases, with haemoptysis being controlled in 90% of cases. The median duration of such palliation is however often only 7 to 14 weeks (Numico *et al.,* 2001; Spiro and Porter, 2002).

It is also well recognised that patients with lung cancer, especially when advanced, suffer from progressive weight loss and cachexia. This leads to muscle wasting, a reduction in performance status and ultimately death (Vansteenkiste *et al.,* 1996; Brown and Radke, 1998). Various studies have demonstrated that those patients suffering from cancer cachexia have a poorer response to treatment and reduced survival (Heckmayr and Gatzemeier, 1992; Tisdale, 1998). Therefore it is important to consider the mechanisms underlying the progression of cachexia (Bruera, 1998) in the lung cancer patient.

1.6 Weight loss and physical function in lung cancer

The majority of lung cancer patients with advanced disease suffer from significant weight loss, known as cancer cachexia. The term cachexia describes emaciate disease states and is based on the Greek word "*kakos*" meaning bad and "*hexis*" meaning condition (Gough *et al* .,1996; Bruera and Portenoy, 1998). Cancer cachexia is a major cause of cancer associated death.

It has been reported that between 45 to 60% of patients with lung cancer experience weight loss at the time of diagnosis, increasing to almost 100% as the disease progresses (Brown and Radke, 1998; Bruera and Portenoy, 1998).

This progressive involuntary weight loss, in lung cancer patients, is associated with a decreased physical functioning, decreased psychological well being and poor quality of life. Irrespective of tumour type, patients with significant weight loss also have a poorer response to treatment (Chlebowski *et al.,* 1996). Furthermore, survival may be decreased by 30 to 50% even in moderate weight loss (Chlebowski *et al.,* 1996). Indeed a significant proportion of these patients will die as a result of severe wasting (Leij-Halfwerk *et al.,* 2000). Attempts to reverse this wasting by the use of enteral or parenteral nutrition have failed to improve survival (Bruera and Portenoy, 1998).

The pattern of increased energy expenditure experienced by these patients in the face of anorexia and reduced calorie intake is one of the features that distinguishes the cachetic syndrome from starvation. In healthy individuals, when calorie intake is

reduced, energy expenditure is diminished and body lipids are utilised, lean muscle being preserved (Bruera and Portenoy, 1998).

In the cachetic cancer patient it is the loss of adipose tissue that constitutes the majority of the weight loss. However, it is thought that it is the depletion of skeletal muscle which occurs later in this syndrome which is more significant in terms of the survival of these patients. This loss of skeletal muscle results directly from a depletion in the host protein (McMillan *et al.,* 2001b). Therefore, any therapies directed at halting or reversing that cachexic syndrome should focus on the preservation of the host proteins, as loss of the protein stores may result in the death of these patients once the critical mass has been reduced (Bruera and Portenoy, 1998). The loss of skeletal muscle mass experienced by these patients has also been identified as a causative factor in the reduced performance status seen in these patients (McMillan *et al.,* 2001b).

Several authors have examined the effects of drug therapy on the cachexia associated with lung cancer. A number of studies have suggested a role for megestrol acetate or similar progestagens (eg. medroxyprogesterone acetate) to improve appetite and promote non-fluid weight gain in lung cancer patients (Vansteenkiste *et al.,*1996; Chlebowski *et al.,*1996; Bruera and Portenoy 1998). Corticosteroids have also been used to improve performance status and weight gain. However, this improvement is short lived and the prolonged use of corticosteroids in this situation may lead to significant muscle myopathy (Hardy *et al.,* 2001).

In lung cancer it is thought that the cachectic state occurs due to both insufficient energy intake and hypermetabolism. The resultant negative energy balance leads to a loss of adipose tissue and protein mass (Mullen 1994; Jebb *et al.,* 1994; Fredrix *et al.,*1997; Bruera and Portenoy, 1998) The resultant loss of this lean body mass, leads to reduced performance status, reduced quality of life, reduced survival and ultimately death (Vansteenkiste *et al.,* 1996).

It has long been recognised that in patients with lung cancer, physical function as assessed by performance status is an important prognostic factor independent of the extent of disease, presence or absence of weight loss, bone pain and liver metastases (Capewell and Sudlow, 1990; Yip and Harper, 2000). Physical function tests (e.g. chair tests) may also be important in assessing hospital outcome (Covinsky *et al.,* 1997). However, such functional tests have not yet been used extensively to predict outcome.

Lung cancer has also been reported to have a greater impact on the physical function and ability of the patients to undertake their activities of daily living independently, than other types of cancer. For example, those patients with advanced staged lung cancer appear to experience more problems with physical functioning than patients with advanced stage colonic cancer, and they also experience more impairments of physical functioning and global quality of life than advanced prostate cancer patients (Ganz *et al.,* 1991; Stafford and Cyr, 1997).

The occurrence of fatigue and functional decline has long been associated with chemotherapy and radiotherapy treatments (Smets *et al.,* 1993). Sarna (1994) also

considered the functional status of women with lung cancer, and observed that 50% of the studied group had a serious reduction in energy levels and fatigue.

1.7 The Inflammatory Response in Lung Cancer Patients

The inflammatory response that may occur in cancer patients has been likened to that of wound healing. Dvorak (1986), described a tumour as "a wound that does not heal". This is because unlike simple wound healing, the tumour causes continuous activation of white blood cells, secretion of a vascular permeability factor, vascular endothelial growth factor. This can lead to increased fibroblast activity, resulting in continuous generation of the extracellular matrix.

In addition, it has been reported that pro-inflammatory cytokines and chemokines (eg. tumour necrosis factor (TNF), IL-1 and IL-6), which can be produced by the tumour cells may contribute directly to malignant progression (Balkwill and Mantovani, 2001).

TNF is a major mediator of inflammation, with actions contributing to both tissue destruction and recovery. Whilst dealing with the death of diseased cells at the site of inflammation, TNF stimulates fibroblast growth. As part of the local systemic response TNF selectively destroys the tumour blood vessels. However, in states of chronic inflammation (systemic inflammatory response) this cytokine may act as an endogenous tumour promoter, contributing to the tissue remodelling and stromal development necessary for tumour growth and spread.

Balkwill and Mantovani (2001), in their review, reported that inflammatory cytokines and chemokines have the potential to prevent cell apoptosis, and some of them may also act as growth and survival factors for malignant cells. IL-6 is a

growth factor, whilst IL-1 has growth stimulating activities. In many tumours, including lung cancer, pro-inflammatory and inflammatory cytokines and chemokines are involved in the regulation of tumour growth.

This systemic reaction can also be characterised by alterations in protein metabolism resulting in the loss of lean tissue. It has been suggested that the metabolic changes underlying cancer cachexia may be due to pro-inflammatory cytokines, for example tumour necrosis factor (Tracey *et al.,* 1988), interleukin 1β (Dinarello, 1988) and interleukin 6 (Fearon *et al.,* 1991). The production of acute phase proteins, such as C-reactive protein (CRP) and lipopolysaccharide-binding protein (LBP), is also associated with the inflammatory response. Of these, the serum C-reactive protein concentration is the most commonly used inflammatory marker (Heinrich *et al.,* 1990).

Interleukin 6 (IL-6) has been identified as one of the principle regulators of the acute phase response (Heinrich *et al.,* 1990). Work has shown that an increase in the circulating concentrations of IL-6 and C-reactive protein is correlated and associated with weight loss in lung cancer patients (Scott *et al,*. 1996). Furthermore, there is some evidence that these pro-inflammatory cytokines, may also be produced by the lung tumour cells themselves (Martin *et al,*. 1999).

At the time of diagnosis most patients with non-small cell lung cancer have been shown to have evidence of an inflammatory response. This is commonly identified by increased circulating concentrations of C-reactive protein levels or interleukin 6 (Scott *et al,*. 1996). Scott and co-workers (1996) also reported that the presence of

the acute phase response may be identified by the presence of a raised white cell count and neutrophil count. Martins and co-workers (1999) reported that concentrations of cytokines (e.g. IL-1, IL-6) and acute phase proteins (e.g. C-reactive protein) were similar in patients with either small cell or non-small cell lung cancer.

As previously discussed these pro-inflammatory cytokines and acute phase proteins have been reported to be associated with the increased resting energy expenditure and an increase loss of lean tissue (see Section 1.6).

Therefore, it may be, as suggested by Scott and co-workers (1996), that the use of anti-inflammatory agents would moderate the systemic inflammatory response, thus reducing resting energy expenditure and loss of lean tissue, hopefully improving performance status and ultimately the survival of patients with non-small cell lung cancer. However, before such studies are carried out it would be important to establish the relationship between the systemic inflammatory response, performance status and survival in patients with inoperable NSCLC.

1.9 Aims of thesis

The prognosis of patients with inoperable non-small cell lung cancer remains bleak. Traditionally, various factors have been linked to the observed poor survival rate; these include stage of disease, performance status and weight loss. It has been proposed that the presence of the systemic inflammatory response is an important underlying factor contributing to the weight loss seen. Despite this, few studies have examined the value of the systemic inflammatory response as a prognostic factor in patients with inoperable non-small cell lung cancer.

The aims of this thesis are:

1. To examine the relationship between anthropometric parameters, the systemic inflammatory response and ECOG-performance status in patients with inoperable non-small cell lung cancer

2. To develop and evaluate an inflammation based prognostic score in patients with inoperable non-small cell lung cancer.

Chapter 2

2 METHODS: - ASSESSMENT OF BODY COMPOSITION

2.1 Introduction

As recognised in section 1.6, weight loss is a common presenting feature in patients with lung cancer. Approximately 60% of patients have experienced weight loss at the time of their diagnosis, with almost 100% experiencing weight loss as their disease progresses (Brown and Radke, 1998; Bruera and Portenoy, 1998). Since it is acknowledged that this weight loss is associated with decreased physical functioning, psychological well being, quality of life and ultimately decreased survival (Chlebowski *et al.,* 1996; Simons *et al.,* 1999; McMillan *et al.,* 2001b), it is essential to attempt to understand these weight changes, in relation to the tissue alterations which occur within these patients. Several studies have reported that weight loss in patients with cancer cachexia reflects wasting of both fat mass and body cell mass. This is demonstrated mainly by loss of adipose tissue and skeletal muscle (Heymsfield and McManus, 1985; McMillan *et al.,* 1994; Simons *et al.,* 1999; Leij-Halfwerk *et al.,* 2000). Indeed, in lung cancer patients, this weight loss is recognised to be secondary to a systemic effect of the tumour. Weight loss has also been shown to be related to increased morbidity and to be of prognostic significance, both in terms of decreased response to treatment and reduced survival (Brown and Radke, 1998).

The human body can be considered to be composed of various components. Several models have been used to describe these. Commonly, body mass is described as being composed of two major elements; fat free mass and fat tissue which contain

water and no water respectively. The fat free mass can further be subdivided into two compartments; body cell mass and extra-cellular mass. The body cell mass is composed of muscle mass (60%), viscera (20%), and other components including red cells, tendon, bone and cartilage (20%). The extra-cellular mass includes fluids and solids (Shizgal, 1985), (see Figure 2.1). Over five decades ago Pace and Rathburn (1945) reported that the fat-free mass consists of approximately 73% (range 70% – 76%) of water, and consequently if body weight and body water are known, this percentage can be used to estimate both fat mass and fat free mass.

In patients with advanced cancer, body composition is commonly assessed by measurements of height and weight. A patient's body weight may be recorded at the initial presentation of their illness; this may be compared to their pre-illness weight, and the percentage of weight loss calculated. Weight can be combined with height to give the standardised measurement of Body Mass Index (BMI, normal range 20 – 25).

Despite weight and BMI being simple and easy to perform, they are limited as measurements of nutritional status. A major limitation of such measurements is their inability to distinguish between body fat and lean tissue, since weight may be increased due to the presence of ascitic fluid or peripheral oedema (Talbot and Lister, 1995). Moreover, a large tumour or organomegaly can mean that a patient may have lost little weight, but has lost significant amounts of fat and skeletal muscle (Heymsfield and McManus, 1985; Heymsfield and Matthews, 1994; Burman and Chamberlain, 1996). For this reason other methods of assessing body

composition are employed to evaluate the wasting experienced by these patients (Pichard and Kyle, 1998).

2.2 Fat and fat free mass

The measurement of skinfold thickness and arm circumference is an effective and useful method of distinguishing the percentage of body fat compared with fat free mass (Talbot and Lister, 1995). It is well recognised that in healthy individuals the majority of fat is stored subcutaneously; as a result various skinfold thickness measurements have been developed to estimate the total body fat of an individual (Durnin and Womersley, 1974; Burman and Chamberlain, 1996). The skinfold calliper is the instrument used to measure subcutaneous fat. This is a portable, non-invasive and accurate method of assessing the patients skinfold thickness. Recognised areas for sampling include triceps, biceps, subscapular and suprailiac skinfolds. This method makes the assumption that subcutaneous fat is a reflection of total body fat and that the average thickness of fat is the same as at the selected skinfold sites (Jebb and Elia, 1993; Burman and Chamberlain, 1996). A series of regression equations have been developed which allow for the prediction of total body fat and fat free mass from a combination of sites (see Figure 2.2). Although these measurements are probably the most widely used technique for estimating fat mass, significant inter-observer variability is well recognised. It has been reported that there is a variation of 6 – 24% in skinfold thickness measurements (Burkinshaw *et al.,* 1973; Harries *et al.,* 1983). Despite these limitations, various studies have showed it to be a useful method of detecting differences between weight losing and non-weight losing cancer patients (Watson and Sammon, 1980; Bozzetti *et al.,* 1982; Hansell *et al.,* 1986, O'Gorman *et al.,* 1998).

Mid upper arm circumference is another well-recognised method of assessing muscle mass and lean tissue within the body (Harries *et al.,* 1983; Burman and Chamberlain, 1996). This is carried out using a non-stretchable tape measure, the measurement should be taken at the mid point between the lateral projection of the acromion process of the scapula and the inferior margin of the olecranon process of the ulna. Compared with skinfold anthropometric measurements, errors are approximately 10 fold less using this method (Harries *et al.,* 1985).

In order to calculate muscle circumference the limb circumference (C_{limb}) is corrected for subcutaneous adipose tissue, the skinfold calliper measurement (S) is assumed to be twice the subcutaneous adipose tissue thickness (Lee *et al.,* 2000).

Mid upper arm circumference may therefore be useful a method of assessing the loss of lean tissue in the weight losing cancer patient, as it reflects muscle and fat, and is related to function. Indeed, in a recent study by McMillan and co-workers (2002) it was reported that mid upper arm circumference showed good correlation with performance status.

The ease of observer use and good patient compliance with anthropometric measurements means that these methods are suitable for the assessment of body composition in lung cancer patients, however this assessment is not frequently used in clinical practice.

In studies of weight losing cancer patients, fat free mass can also be derived from the measurement of total body water. Since total body water has been identified as the

largest chemical component in mammals, in health it is closely associated with lean tissue (Wang *et al.,* 1999). Total body water can be measured using the technique of bioeletrical resistance impedance (BIA), in which the property of electric ionic conduction of soft tissue is measured to estimate intracellular and extracellular water. The basic principle of this method of assessment is that lean tissue conducts, whereas fat acts as an insulator. However, it is now widely recognised that alterations in the degree of hydration of the fat free mass, usually resulting in an increase in extracellular fluid, may confound this estimation. For example, in a recent study, McMillan and co-workers (2000) showed that compared with the reference method of total body potassium, the measurement of total body water over-estimates the amount of metabolically active tissue by approximately 20%.

In summary, it is important that any weight changes resulting from treatment can be assessed by establishing in which type of tissue the alteration has occurred (adipose or lean tissue). In the present work, body composition was estimated using minimally invasive measurements of height, weight, skinfold thickness (triceps and biceps), and mid-upper arm circumference in patients with inoperable non-small cell lung cancer.

2.3 **Body Composition Measurements**

2.3.1 Height, Weight and Body Mass Index

The height of individual patients was measured at each clinic visit. Asking patients to stand upright in stocking feet, a standiometer was used to measure their height to the nearest centimetre.

Their weight was measured using a set of Weylux scales (Made in England, Model 424), with patients wearing indoor clothing and no shoes. Weighing took place on a flat non-carpeted floor. Weight was recorded (to the nearest 0.1kg) in the patient's casesheet. The following equation was used to calculate body mass index:

$$\text{Body Mass Index } (KG/M^2) = \text{Weight (kg)} \div \text{Height}^2\ (m^2)$$

2.3.2 Skinfold and Mid- upper arm circumference

Skinfold thickness was measured using Harpenden skinfold callipers (Holtain Ltd., Crymych, United Kingdom). A stretch resistant measuring tape was used to accurately measure limb circumference. The two sites identified for measuring skinfold thickness were biceps and triceps (see Figure 2.2). Once the measurement site was identified, the skinfold was grasped firmly between the thumb and the index finger. To ensure that fat and not muscle was measured the patient was asked to contract the muscle beneath the site of measurement. This ensured a true measurement of subcutaneous fat. The patient was then asked to relax their arm, and the callipers applied 1 cm below the observer's fingers. When the two surfaces

of the callipers are parallel, the pressure of the callipers and the calliper needle stabilises, then the measurement can be taken. In order to minimise error, measurements were made in triplicate and the average score recorded as recommended by other workers in this field (Womersley and Durnin, 1973; Burkinshaw *et al.,* 1973; Jebb and Elia, 1993; Talbot and Lister, 1995; Burman and Chamberlain, 1996). To minimise inconvenience to this frail, sick group of patients subscapular and suprailiac measurements were not carried out.

The triceps skinfold thickness measurement was performed using the mid point of the triceps muscle between the acromion process of the scapula and the olecranon of the ulna of the arm. The biceps skinfold thickness was measured at the same level as the triceps, over the biceps muscle, midway between the auxiliary fold and the antecubital fossa. During both measurements the patients were standing with their arms extended and relaxed by their side (see Figure 2.3).

Mid-upper arm circumference was measured with reference to the acromion process and the olecranon, i.e., at the same point as the skinfold measurements. The tape was maintained in a horizontal position, touching the skin lightly, but not compressing the underlying skin (see Figure 2.3).

All measurements were repeated three times, and performed by the same investigator in an attempt to reduce the error margin.

Figure 2.1 Simple models of body composition

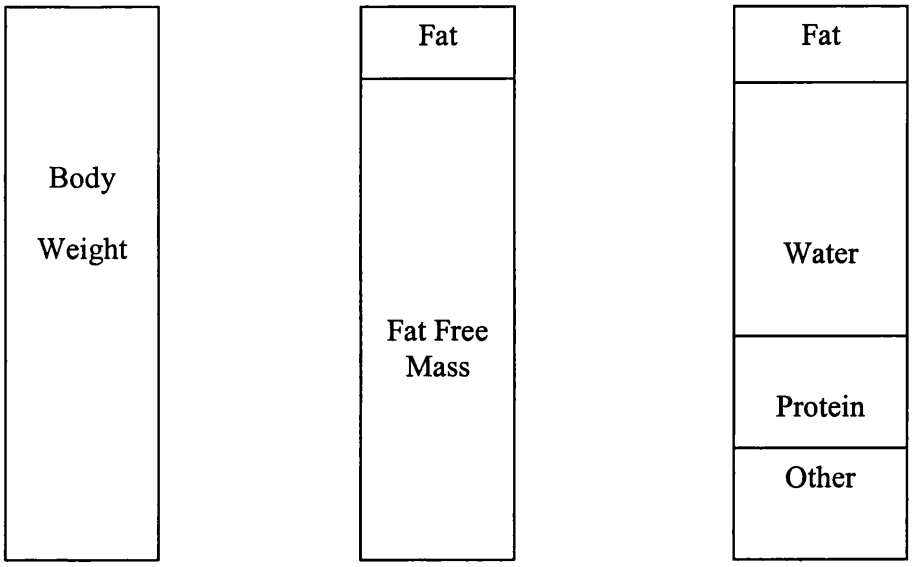


Figure 2.2 Anthropometric measurements- calculation of fat and fat-free mass

Since during the course of this study the two areas chosen to perform skinfold anthropometric measurements were triceps and biceps only these equations are listed below

1. Determine the patients height and weight (kg)
2. Add skinfold thickness for triceps and biceps (Σ)
3. Compute the logarithm Σ
4. Apply one of the following age /sex adjusted equations to calculate body density

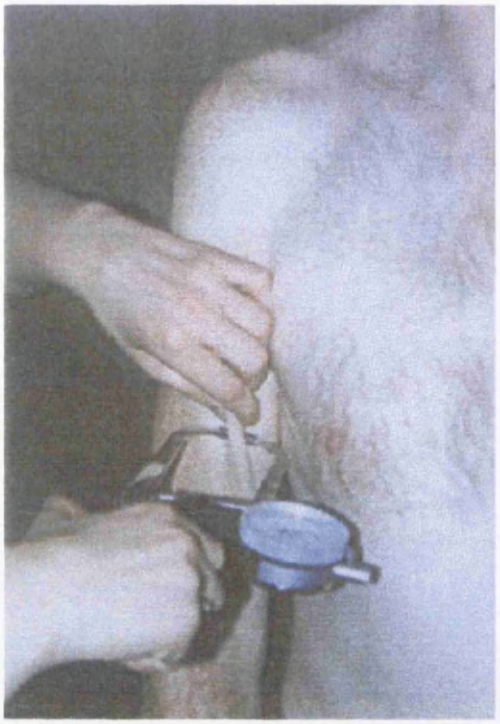
Men

Age range

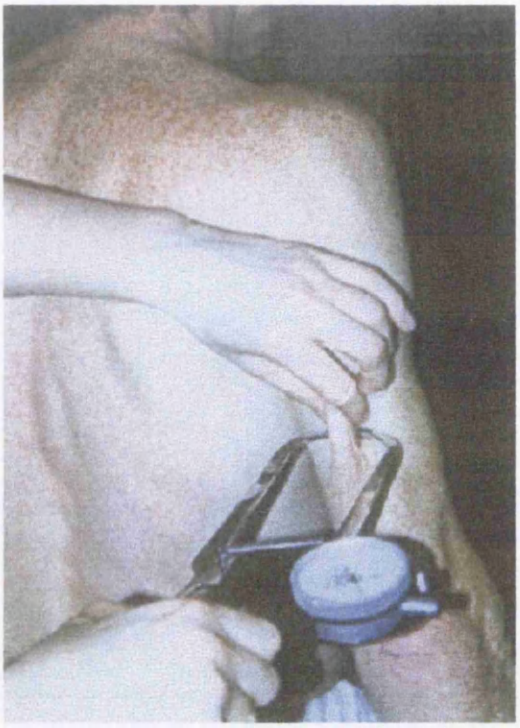
17 – 19	$D = 1.1423 - 0.0687 \times (\log\Sigma)$
20 – 29	$D = 1.1307 - 0.0603 \times (\log\Sigma)$
30 – 39	$D = 1.0995 - 0.0431 \times (\log\Sigma)$
40 – 49	$D = 1.1174 - 0.0614 \times (\log\Sigma)$
50+	$D = 1.1185 - 0.0683 \times (\log\Sigma)$

Figure 2.3 Photographs of skinfold anthropometry

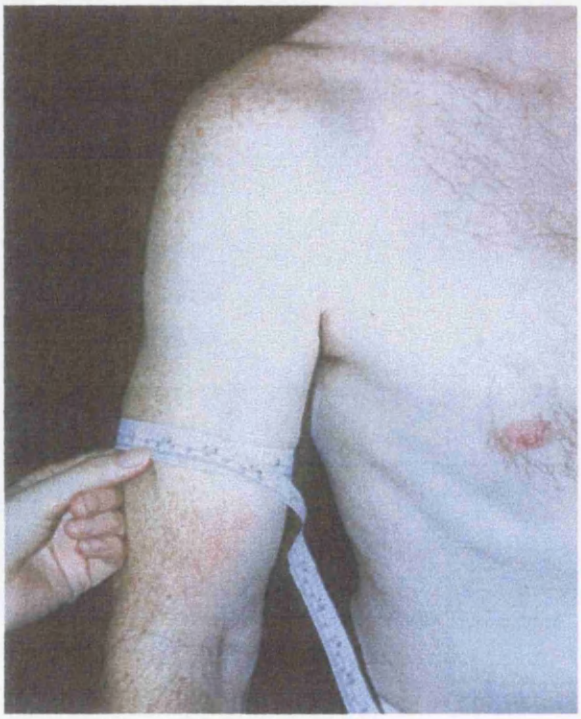
Biceps



Triceps



Mid-upper arm circumference



Chapter 3

3 METHODS:- PROGNOSTIC FACTORS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

3.1 Introduction

Over the past decade a number of clinical and laboratory parameters have been shown to have prognostic value in patients with inoperable NSCLC.

The possibility of cure for patients with inoperable non-small cell lung cancer is limited as previously discussed in section 1.4.3. Median survival is known to decrease with increasing age, stage of disease, poor performance status, low haemoglobin levels, raised white cell count and hypoalbuminaemia (Numico *et al.,* 2001). For example, in those patients with advanced inoperable disease (approximately 50%), prognosis tends to be poor, and survival seldom exceeds 6-9 months (Hespanhol *et al.,* 1995; Espinosa *et al.,* 1995 Naruke *et al.,* 1997). Traditionally patients have been selected for active or supportive treatment depending on clinicopathological criteria including age, stage of disease, performance status, weight loss or hypoalbuminaemia (Numico *et al.,* 2001). Other prognostic factors which have been associated with a reduction in survival in patients with advanced lung cancer include: gender, tumour type, haemoglobin and white cell count levels (Espinosa *et al.,* 1995; Hespanhol *et al.,* 1995; van Zanwijk *et al.,* 1995; Palomares *et al.,* 1996; Fu *et al.,* 1999; Martins and Pereira, 1999; Buccheri and Ferrigno, 2001; Choi *et al.,* 2001; Numico *et al.,* 2001; Brundage *et al.,* 2002). Recent reports also suggest that the systemic inflammatory response, as evidenced

by an elevated C-reactive protein concentration, may be a significant factor in the survival of patients with advanced non-small cell lung cancer (Scott *et al.,* 2002).

Oncologists have long been aware of the importance of good functional status in cancer patients; they routinely use a performance status score, for example the Karnofsky Performance Status index (KPS) or the Eastern Co-operative Oncology Group performance status (ECOG-ps) to measure the impact of the illness and the effect of any treatment that has been administered.

The Karnofsky Performance Status index (KPS) is a widely used method of quantifying the functional ability of the cancer patient, and has been demonstrated to be one of the most important prognostic factors in nearly all cancers (Karnofsky and Burchenal, 1949; Batel-Copel *et al.,* 1997). It was originally designed to provide a measurement of the nursing workload in relation to the lung cancer patient's palliative treatment. The scale is composed of an eleven point rating scale, which ranges from normal functioning (100) to dead (0) (Mor *et al.,* 1984) and focuses on the physical performance and dependency of the patients (see Figure 3.1). Whilst it is recognised that brain metastases produce the greatest debilitating effect on functioning, these are however only moderately associated with a lower Karnofsky Performance Status. This perhaps highlights the subjective nature of the assessment of performance status, and suggests the difficulty in the interpretation of performance status in relation to the appropriate selection of patients for treatment. Indeed, a down-side of the Karnofsky Performance Status is that it has been shown to have an unreliable inter-rater applicability, and is dependent on the experience of the assessor (Ando *et al.,* 2001). Moreover, despite the fact that it has long been

recognised that low activity and poor physical function are important prognostic factors in patients with lung cancer, unless the patient is entered into a clinical trial this assessment tends to be neglected (Capewell and Sudlow, 1990).

The Eastern co-operative oncology group has also developed a five-point observation scale to assess the performance status of these patients (see Figure 3.2). Taylor and co-workers (1999) suggested that ECOG-ps is a simpler format for clinicians to utilise, as it contains a five-point scale rather than the eleven-point scale used in the Karnofsky Performance Status. Both these scores have been shown to be interchangeable; however, Buccheri and co-workers (1994) suggested that ECOG-ps may have better predictive validity than that of Karnofsky Performance Status. These performance scales attempt to quantify the patients' actual level of function, ability for self-care and level of ambulation (Taylor *et al.,* 1999). Indeed, a high performance status has been reported to be correlated with survival and the patient's ability to tolerate treatment (Taylor *et al*, 1999). ECOG-ps may be considered to be the most simple and most reproducible scale to use to predict outcome in patients with non-small cell lung cancer (Espinosa *et al.,* 1995; Taylor *et al.,* 1999).

The physician's assessment of a patient's physical abilities and limitations may vary from the patient's own assessment of themselves (Blagden *et al.,* 2003). Self reported performance status measurement using the activities of daily living could therefore be used to assess functional status in cancer patients (Reuben, 1997; Stafford and Cyr, 1997). However, Stafford and Cyr (1997) recognised that self-reported health status differs in patients with and without cancer and amongst various cancers. Lung cancer patients had the poorest self-reported health status,

54% rating their overall health status as fair / poor. Indeed this study indicated that independent of other factors, patients with cancer reported small but significant increases in self reported poor health and functional limitations compared to elderly individuals without cancer. Objective physical functional tests (e.g. chair stands, etc) may therefore prove to be more sensitive to such changes (Sarna, 1994).

As previously recognised in section 1.6, progressive weight loss is a common phenomenon in patients with advanced cancer. For example, O'Gorman and co-workers (1998) in their study of 119 patients with advanced gastrointestinal cancer considered the impact of weight loss on the quality of life of these patients. They demonstrated that weight loss was associated with lower anthropometric measurements, albumin concentrations and poorer performance status. Interestingly, they also found that 71% of the weight losing patients had an elevated C-reactive protein concentration, compared with 27% of weight stable patients, thus suggesting that an elevated C-reactive protein concentration influences the weight loss in patients with advanced cancer.

As previously acknowledged, the extent of disease, weight loss and performance status of the patient have been shown to be important prognostic factors in patients with advanced non-small cell lung cancer (Jeremic and Shibamoto, 1995; Brundage *et al.,* 2002). However, it has also been suggested that additional factors such as haematological and biochemical factors may provide additional prognostic information, which may be useful in the selection of patients for the appropriate treatments (Brundage *et al.,* 2002).

Borges and co-workers (1996) considered various prognostic factors in the assessment of response to treatment in 1052 patients receiving platinum based chemotherapy for unresectable non-small cell lung cancer. Of the haematological factors considered, they reported that those patients with a haemoglobin level >12g/l and a white cell count <10 $x10^9$/l were found to have higher response rates to the chemotherapy. Herndon and co-workers (1999), as part of their study of patients with advanced non-small cell lung cancer, examined the prognostic importance of various clinical factors. They reported that those patients who had a haemoglobin level <12g/l had a poorer prognosis. They also found that those patients with an albumin concentration of <35g/l had a poorer prognosis. Indeed, it has also been reported by McMillan and co-workers (2001b) that this reduction in albumin concentration, which is frequently observed in patients with advanced cancer, (eg. lung and gastrointestinal cancer) is recognised to be part of the inflammatory response. As the albumin concentrations fall, other acute phase proteins such a C-reactive protein rise (Margarson and Soni, 1998). This fall in albumin concentration has also been associated with a reduction in weight and reduced performance status in patients with advanced cancer (O'Gorman *et al.,* 1998).

In summary, following consideration of the various prognostic factors associated with patients who have advanced non-small cell lung cancer, a proforma (Figure 3.3) was developed to identify the prognostic factors discussed during the following studies. This included: age, gender, stage of disease, tumour type, ECOG-performance status (ECOG-PS), haemoglobin, white cell count, albumin, C-reactive protein and treatment received.

Figure 3.1 Karnofsky Performance Status

Condition	Percentage	Comments
A. Able to carry on normal activity and to work. No special care needed	100	Normal, no complaints, no evidence of disease
	90	Able to carry on normal activity , Minor signs or symptoms of disease
	80	Normal activity with effort, some signs or symptoms of disease
B. Unable to work. Able to live at home, care for most personal needs. A varying degree of assistance is needed	70	Cares for self. Unable to carry on normal activity or do active work
	60	Requires occasional assistance, but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
C. Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled, require special care and assistance.
	30	Severely disabled, hospitalisation is indicated although death is not imminent
	20	Hospitalisation necessary, very sick, active support treatment necessary.
	10	Moribund, fatal processes progressing rapidly
	0	Dead

Figure 3.2 ECOG Scale

Grade	
0	Able to carry out all normal activity without restriction
1	Restricted in physical strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of walking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

Figure 3.3 Proforma used to collect information in patients with Non-Small Cell Lung Cancer

Hospital Number	
Patients Name	
Date of Birth	
Age (years)	
Gender - Male / Female	
Date of Diagnosis	
Date of Death	
Tumour	
Tumour Type (Squamous/ Adenocarcinoma/ Large Cell/ Other)	
Stage of Disease (I/ II/ IIIA/ IIIB/ IV)	
ECOG Performance Status (0/ 1/ 2/ 3/ 4)	
Haemoglobin (g/l)	
White cell count ($10x10^9$/l)	
Albumin (g/l)	
C-reactive protein (mg/l)	
Treatment (active / palliative)	

Chapter 4

4. PATIENT STUDY: BODY COMPOSITION PARAMETERS AND PERFORMANCE STATUS IN PATIENTS WITH INOPERABLE NON-SMALL CELL LUNG CANCER

4.1 Introduction

Physical function as assessed by performance status remains an important predictor of response to treatment in patients with non-small cell lung cancer, NSCLC (Conill, *et al.,* 1990; Firat *et al.,* 2001; Hensing *et al.,* 2003). It has been long recognised that, in patients with cancer, reduction in physical function is associated with the loss of protein mass, in particular skeletal muscle. Simple techniques such as height, weight and skinfold anthropometry may be used in this assessment (Ferrigno and Buccheri, 2000; McMillan *et al.,* 2002; Kamimura *et al.,* 2003). Recently, McMillan and co-workers (2001b) proposed that, in advanced cancer patients, albumin concentrations are primarily determined by the protein mass of the body (as estimated by total body potassium) and the systemic inflammatory response (as estimated by C-reactive protein). They also suggested that the systemic inflammatory response is a major factor in the erosion of protein mass in the body.

The aim of the present study was to examine the relationship of ECOG performance status (ECOG-ps), anthropometric and blood parameters in patients with inoperable NSCLC.

4.2 Materials and Methods

4.2.1 Subjects

Fifty patients with inoperable non-small cell lung cancer from a multidisciplinary clinic within a single institution (Royal Infirmary, Glasgow) were included in the study. Patients were either receiving supportive care only, or were prior to receiving chemotherapy or radiotherapy.

4.2.2 Experimental design

Patients were assessed on an outpatient basis. At the clinic visit ECOG-ps together with height, weight, biceps, triceps skinfold thickness and mid-upper arm circumference measurements were carried out and a blood sample was taken for analysis of albumin and C-reactive protein.

The study was approved by the Research Ethics Committee of Glasgow Royal Infirmary. All patients were informed of the purpose of the study and all gave written informed consent.

4.2.3 Analytical Methods

Height and weight: These patients' details were obtained as detailed in section 2.2.1. These measurements were then used to calculate the body mass index:

$$\text{Body Mass Index } (KG/M^2) = \text{Weight (kg)} \div \text{Height}^2\ (m^2)$$

Performance Status : This assessment was undertaken using the ECOG-ps (as described in Section 3.1) to assess the functional ability of patients. This is a five-point scale, which is scored 0 – 4 depending on the level of functional independence achieved by the patient (see Figure 3.2).

Skinfold anthropometry : this was performed as detailed in Section 2.2.2. The sites measured included biceps, triceps and mid-upper arm circumference.

Blood parameters: Venous blood samples were taken from each patient for routine laboratory measurements of C-reactive protein and albumin. Albumin was measured by a BCG dye-binding method and C-reactive protein was measured using a turbidometric assay after binding to a specific antibody on an Advia 1650 analyser (Bayer Corporation, Tarrytown, NY, USA). For C-reactive protein the limit of detection was 5 mg/l. The inter-assay coefficient of variation was less than 3% and 5% over the sample concentration range for albumin and C-reactive protein respectively.

4.2.4 Statistics

Data are presented as median and range. Where appropriate, comparison of patient groups was carried out using the Kruskal-Wallis test for analysis of variance. Analysis was performed using the SPSS software package (SPSS, Chicago,IL).

4.3 Results

Fifty patients (33 males and 17 females) with inoperable non-small cell lung cancer were studied. The clinical characteristics of the patients included in the study are detailed in Table 4.1. The majority of patients were male (66%), over the age of 60 years, had a BMI, skinfold anthropometry and albumin concentrations in the normal range. The majority of patients had an elevated C-reactive protein concentration and an ECOG performance status of 1.

Patients were grouped according to ECOG-ps (Table 4.2). With a poorer performance status there was a lower BMI ($p<0.05$), biceps skinfold thickness ($p<0.05$), triceps skinfold thickness ($p<0.05$), mid-upper arm circumference ($p<0.01$) and albumin concentrations ($p<0.01$).

4.4 Discussion

Conventionally, the selection of inoperable cancer patients for active or supportive treatment has been based on clinicopathological criteria, including age, stage, performance status, weight-loss or hypoalbuminaemia (Numico *et al.,* 2001). However, the limitations of weight loss are well recognised (see section 2.1). In contrast, performance status is a useful global assessment of function and has been used to aid the selection of patients for treatment, stratification into clinical trials, measurement of the efficacy of new therapies and to assess the prognosis of patients with advanced cancer. However, the assessment of performance status may be subjective. For example, significant differences in the assessment of performance status have been reported between oncologists, nurses and patients, oncologists being the most optimistic in their assessment and patients the least (Ando *et al.,* 2001).

In the present study mid-upper arm circumference was shown to be strongly associated with ECOG-ps in patients with advanced non-small cell lung cancer. These results are consistent with the previous strong correlation between mid-upper arm circumference and Karnofsky performance status in patients with advanced gastrointestinal cancer (McMillan *et al.,* 2002) and would support the concept that mid upper arm circumference primarily reflects lean tissue and that it is the loss of such tissue that determines performance status in advanced cancer.

In the present study it was of interest that albumin concentrations were also strongly associated with ECOG-ps. However, in the present study there was less variation in the measurement of albumin concentrations compared with that of mid upper arm

circumference. Therefore, it may be that the measurement of albumin offers a better standardised method of measuring the loss of lean tissue and physical function in the patient with advanced non-small cell lung cancer.

It has recently been proposed that the combination of albumin and C-reactive protein may form the basis of a useful standardised and non-subjective assessment of outcome in patients with advanced cancer (McMillan *et al.,* 2001a). On the basis of the results of the present study a comparison of such an assessment with ECOG-ps is worthy of further study in patients with inoperable non-small cell cancer.

Table 4.1. Characteristics of patients with inoperable non-small cell lung cancer

	Patients (n= 50)
Age (yr)	66 (43–78)
Gender (male/ female)	33 / 17
BMI (kg/m^2)	23.8 (14.2–33.6)
Triceps skinfold thickness (mm)	12 (2.2–23)
Biceps skinfold thickness (mm)	8.8 (2.2–21.2)
Mid-upper arm circumference (cm)	26.6 (17–32)
Albumin (g/l)	40 (31–45)
C-reactive Protein (mg/l)	38 (<6–258)
Stage (III/ IV)	23 / 27
ECOG PS (0/ 1/ 2)	13 / 27 / 10

Table 4.2. The relationship between ECOG-ps, anthropometric and blood parameters in patients with inoperable non-small cell lung cancer.

	ECOG-ps 0 (n=13)	ECOG-ps 1 (n=27)	ECOG-ps 2 (n=10)	p-Value
Age, yrs	65 (45 – 74)	66 (43 – 78)	73 (61 – 78)	0.070
Gender (male/ female)	9 / 4	19 / 8	5 / 5	0.496
BMI (kg/m^2)	27.7 (21 – 30.8)	23.7 (14.2 – 33.6)	21 (14.2 – 32.5)	0.029
Triceps skinfold thickness (mm)	15.8 (6.4 – 23)	12 (3.6 – 21.8)	8.7 (2.2 – 13.2)	0.022
Biceps skinfold thickness (mm)	10.2 (5.6 – 18)	8.8 (3.4 – 21.2)	5.4 (2.2 – 15.2)	0.013
Mid-upper arm circumference (cm)	28 (24 – 30)	26.6 (17 – 32)	24.3 (19 – 30)	0.009
Albumin (g/l)	42 (38 – 44)	40 (32 – 45)	37 (31 – 41)	0.002
Albumin ≥35 g/l	13	26	7	
<35 g/l	0	1	3	0.015
C-reactive Protein (mg/l)	16 (<6 – 163)	42 (<6 – 258)	67 (<6 – 116)	0.258
C-reactive protein				
≤10 mg/l	5	3	3	
>10mg/l	8	24	7	0.117
Stage (III/ IV)	8 / 5	11 / 16	4 / 6	0.433

Chapter 5

5 PATIENT STUDY: EVALUATION OF A CUMULATIVE PROGNOSTIC SCORE BASED ON THE SYSTEMIC INFLAMMATORY RESPONSE IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

5.1 Introduction

Since the 1930's lung cancer has increased in incidence to become the most frequently diagnosed neoplasm in the western world, accounting for 80% of all pulmonary tumours. Lung cancer kills more people than any other cancer and its incidence is on the rise (Souhami and Tobias, 1998). Non-small cell lung cancer constitutes approximately three quarters of all histological types of lung cancer deaths world-wide (Ihde and Minna, 1991; Hespanhol *et al.,* 1995; Juretic *et al.,* 1999; Ferrigno and Buccheri, 2000). Mateva and co-workers (1999) demonstrated that early diagnosis of lung cancer is of crucial importance for surgical management and prognosis of lung cancer patients. However, due to the aggressive nature of this tumour type most patients present with advanced inoperable disease (approximately 50%) and consequently the survival of these patients is extremely poor (Splinter, 1991; Hespanhol *et al.,* 1995; Juretic *et al.,* 1999; Ferrigno and Buccheri, 2000).

Conventionally, the selection of these patients for active or supportive treatment has been based on certain clinico-pathological criteria, including age, stage, performance status, weight loss or hypoalbuminaemia (Gomm *et al.,* 1990; Espinosa *et al.,* 1995; Katsumata *et al.,* 1996, Palomares *et al.,* 1996; Charloux *et al.,* 1997; Wigren *et al.,*

1997, Fu *et al.,* 1999; van Dijck *et al.,* 2001, Plataniotis and Theofanopoulou, 2001, Numico *et al.,* 2001).

In order to assess the value of pre-treatment characteristics in patients with inoperable non-small cell lung cancer who were treated with platinum based combination chemotherapy, Paesmans and co-workers (1997) prospectively collected data on 23 pre-treatment variables and objective response following three cycles of chemotherapy in 1052 patients who were registered into a clinical trial of the European Lung Cancer Working Party between December 1980 and August 1991.

Pre-treatment variables included – sex, age, loss of body weight, histology, prior therapy, Karnofsky performance status, extent of disease, type of lesion, white blood cell count, neutrophil count, platelet count, haemoglobin, alkaline phosphate, bilirubin, creatinin, lactate dehydrogenase, calcium, evidence of metastases. The results of this study highlighted that an overall response to treatment is the strongest marker of prolonged survival, and they also suggested further prognostic information could be improved by using pre-treatment therapeutic markers of full blood count, Karnofsky Perfomance Status and extent of disease.

Similarly, Hesphanhol and co-workers (1995) undertook a prospective study of 411 patients between 1984 and 1990. They reported that, on both univariate and multivariate analysis poor performance status, weight loss ($\geq$10%) and hypoalbuminemia ($\leq$35g/l) were poor prognostic factors. These results highlight the

predictive value of performance status, weight loss and serum albumin, when combined with TNM staging classification.

Recent studies have shown that the presence of a systemic inflammatory response, as evidenced by increased circulating concentrations of C-reactive protein, is a prognostic factor independent of age, stage, the presence or absence of weight-loss and performance status in patients with advanced cancer including NSCLC (Martins, *et al.,* 1999; O'Gorman *et al.,* 2000; Mahmoud and Rivera, 2002; Scott *et al.,* 2002).

Scott and co-workers (2002) examined 106 patients with inoperable NSCLC (between January 1995 and November 1998), observing the extent to which weight loss, albumin and C- reactive protein concentrations, performance status and quality of life impacted on the survival of these patients. Patients were grouped according to the extent of the systemic inflammatory response, $\leq$10, 11 - 100 and >100mg/l. An increase in the systemic inflammatory response was associated with increased weight loss, reduction in haemoglobin and albumin concentrations, and a reduced performance status. They also found that survival was affected by the magnitude of the systemic inflammatory response: in those patients with C-reactive protein concentrations $\leq$10mg/l, survival time was 11 months, whilst in those patients with C-reactive protein concentrations >100mg/l survival time was poor at only three months. The results of this study highlighted that the greater the magnitude of the systemic inflammatory response, the greater the weight loss, the poorer the performance status, and the poorer the survival.

The aim of the present study was to assess the value of combining C-reactive protein and recognised prognostic factors as stage, performance status and hypoalbuminaemia to form new prognostic scores for patients with inoperable non-small cell lung cancer.

5.2 Materials and Methods

5.2.1 Study Design

Patients with inoperable non-small cell lung cancer (stage III and IV) who presented at the multidisciplinary oncology clinic in Glasgow Royal between January 1997 and October 2002 were included in the study. Data for 1997 – 1999 were collected retrospectively and that for 2000 – 2002 prospectively. All patients had to have cytologically or histologically confirmed disease and were staged according to the American Thoracic Society TNM classification on the basis of clinical findings, chest X-ray, and where appropriate, bronchoscopy, liver ultrasound, isotope bone scan and computerised tomography of the thorax (Mountain, 1991).

Clinical stage, tumour type and ECOG performance status were recorded at time of diagnosis. A blood sample was also obtained for measurement of haemoglobin, white cell count, and C-reactive protein concentrations. Patients were considered to have undergone active treatment if they received chemotherapy (mainly cisplatin based) and / or radical radiotherapy. Patients receiving palliative radiotherapy and / or palliative care (symptom control) were considered to have had supportive treatment.

The study was approved by the Research Ethics Committee of Glasgow Royal Infirmary.

5.2.2 Methods

Blood parameters: Routine laboratory measurements of haemoglobin, white cell count, and C-reactive protein concentration were carried out as previously described in Section 4.2.3. The coefficient of variation for these methods, over the range of measurement, was less than 10% as established by routine quality control procedures.

5.2.3 Statistics

Data are presented as median and range. Grouping of the continuous variables, age, haemoglobin and white cell count was carried out as previously described (Vincent *et al.,* 1987; Paesmans *et al.,* 1995; Herndon *et al.,* 1999). C-reactive protein concentrations were also grouped (≤10/>10mg/l) as previously described (O'Gorman *et al.,* 2000; McMillan *et al.,* 2001a).

Prognostic scores were constructed by assigning one point for each of the following criteria: stage IV, ECOG-ps 2-4, albumin <35g/l and C-reactive protein >10mg/l. Cumulative scores were obtained by combining C-reactive protein with each of the other variables. For example, patients with hypoalbuminaemia (<35g/l = 1) and an elevated C-reactive protein (>10mg/l = 1) were assigned a score of two.

Univariate survival analysis was performed using the Kaplan-Meier method. Multivariate survival analysis and calculation of hazard ratios (HR) were performed using Cox regression analysis with prognostic scores as covariates. Deaths up to

31st March 2003 were included in the analysis. Analysis was performed using SPSS software (SPSS Inc., Chicago, Illinois, U.S.A.).

5.3 Results

261 patients were initially identified as being suitable for inclusion in the study (119 patients from 1997 – 1999, 142 patients from 2000 – 2002), as they had been diagnosed with advanced inoperable non-small cell lung cancer. Common to all studies which include both retrospective and prospective data, missing data meant that some patients had to be excluded from the final analysis. The majority of patients (50 patients between 1997 – 1999 and 45 patients between 2000 – 2002) were excluded because performance status was not documented in the medical records. Two patients were excluded as no date of diagnosis was available, a further two patients were excluded as no C-reactive protein or albumin level was available, and one patient was lost to follow up. One hundred and sixty one patients were therefore included in the final analysis.

The characteristics of patients with inoperable NSCLC (n= 161) are shown in Table 5.1. The majority were male, over the age of 60 years, had stage IV disease and had good performance status. Approximately, 20% had hypoalbuminaemia and 80% had an elevated C-reactive protein concentration. One third of patients received active treatment (64% received cisplatin based chemotherapy); the remaining patients received supportive treatment.

One hundred and eighteen (73%) of patients died during the follow-up period. On univariate survival analysis, stage ($p<0.05$), tumour type ($p<0.01$), ECOG-ps ($p<0.001$), white cell count ($p<0.01$), albumin ($p<0.001$) and C-reactive protein ($p<0.01$) were significant predictors of survival. On multivariate survival analysis, all

these variables, with the exception of white cell count, remained significant independent predictors of survival.

The relationship between the prognostic scores based on the combinations of C-reactive protein with stage, ECOG-ps and albumin respectively and the median survival is shown in Table 5.2. All these prognostic scores had hazard ratios in the range 1.7-2.0 which was comparable with that for the score based on the combination of stage and ECOG-ps.

When the three scores based on the combinations of the systemic inflammatory response and stage, ECOG-ps and albumin were compared with the combination of stage and ECOG-ps, only the score based on the combination of the systemic inflammatory response and albumin (HR 1.70, 95%CI 1.23-2.35, p=0.001) and the score based on stage and ECOG-ps (HR 1.48, 95%CI 1.12-1.95, p=0.006) retained independent significance.

5.4 Discussion

Despite well documented evidence that performance status is an important prognostic factor for survival in patients with non small cell lung cancer (Paesmans *et al.,* 1995; Ando *et al.,* 2001), many patients within this study had to be excluded as no performance status was recorded in their medical records. It is likely that the study cohort excludes more patients who received supportive care only, since those patients who received active treatment were most likely to have had their performance status recorded during their treatment.

In the present study, both the established indicators of the presence of a systemic inflammatory response, white cell count and C-reactive protein, were predictive of survival in patients with inoperable NSCLC. This is consistent with previous studies, which have shown that a raised white cell count (Paesmans *et al.,* 1997) and C-reactive protein concentrations (Scott *et al.,* 2002), have prognostic value, independent of stage, in patients with inoperable NSCLC.

When C-reactive protein concentrations were combined with stage, ECOG-ps and albumin to form new prognostic scores, these combined scores improved the prediction of survival based on stage, ECOG-ps or albumin alone. Indeed, in each of the cumulative scores, the presence of an elevated C-reactive protein was associated with a halving of survival. Furthermore, when these three combinations were compared to the conventional combination of stage and ECOG-ps, the combination of the systemic inflammatory response and albumin and the conventional clinical combination stage and ECOG-ps were found to have comparable prognostic value.

These results are consistent with the evidence that chronic activation of the systemic inflammatory response is detrimental to the outcome of patients with NSCLC, being associated with an increase in weight loss (Staal-van den Brekel *et al.,* 1995; Scott *et al.,* 1996) and fatigue (Scott *et al,* 2003), loss of lean tissue (McMillan *et al.,* 1998; Simons *et al.,* 1999), decreased performance status and survival (Martins *et al.,* 1999; Scott *et al.,* 2002).

The mechanism by which a systemic inflammatory response is evoked in patients with NSCLC is not clear. One possibility is that since many patients have co-existing pulmonary infection, the resultant increase in white blood cells would lead to increased pro-inflammatory cytokine release and a subsequent increase in circulating C-reactive protein concentrations. However, in this study, although the white cell count was significantly correlated with C-reactive protein concentrations the magnitude of the relationship was small (r^2 less than 15%). This would suggest that infection was not the main stimulus to the increased C-reactive protein concentrations.

An alternative explanation would be that pro-inflammatory cytokines are produced by the tumour. Indeed, there is evidence that pro-inflammatory cytokines are produced locally by tumours in patients with NSCLC (Arias-Diaz *et al.,* 1994). In particular, interleukin-6 is recognised as a primary mediator of increased C-reactive protein concentrations in these patients (Yanagawa *et al.,* 1995; Scott *et al.,* 1996). However, whether interleukin-6 is produced directly by lung cancer cells remains unclear.

In conclusion, the results of the present study showed that a cumulative score based on C-reactive protein and albumin provides comparable prognostic information to that of conventional prognostic criteria. However, the cumulative score based on C-reactive protein and albumin (Glasgow Prognostic Score) has the advantage that of being simple to measure, routinely available and well standardised.

Table 5.1 Clinical characteristics and survival in patients with inoperable NSCLC: Univariate survival analysis

		Patients	Survival (months)	P value
		161 (100%)	Median (95% CI)	
Age	<60 yrs	37 (23)	10.3 (8.2-12.4)	
	≥60 yrs	124 (77)	8.2 (6.1-10.3)	0.593
Sex:	Male	105 (65)	9.1 (6.6-11.6)	
	Female	56 (35)	8.9 (5.9-11.8)	0.810
Stage	III	57 (35)	12.0 (8.1-15.9)	
	IV	104 (65)	6.9 (4.0-9.9)	0.015
Type	Squamous	64 (40)	9.7 (5.9-13.5)	
	Adenocarcinoma	53 (33)	9.0 (2.6-15.3)	
	Other	44 (27)	3.9 (0.2-7.9)	0.003
ECOG-ps	0-1	91 (57)	12.0 (8.7-15.4)	
	2-4	70 (43)	4.2 (1.6-6.7)	<0.001
Haemoglobin	≥12 g/l	101 (63)	9.1 (6.3-11.9)	
	<12 g/l	60 (37)	8.9 (6.4-11.3)	0.187
White Cell Count	$\leq 10x10^9/l$	82 (51)	12.4 (7.9-16.9)	
	$>10x10^9/l$	79 (49)	6.5 (2.9-10.0)	0.003
Albumin	≥35 g/l	126 (78)	10.1 (7.4-12.8)	
	<35 g/l	35 (22)	3.7 (2.3-5.1)	<0.001
C-reactive protein	≤10 mg/l	29 (18)	16.4 (11.0-21.7)	
	>10 mg/l	132 (82)	7.1 (4.9-9.3)	0.003

Table 5.2 Cumulative prognostic scores and survival in patients with inoperable NSCLC (n=161)

CRP/ stage	(n)	CRP	Stage	Cumulative scores	Survival (months)	Hazard ratio (95%CI)
	14	≤10mg/l	III	0	18.2 (14.5-21.9)	
	15		IV	1	10.4 (7.9-12.8)	
	43	>10mg/l	III	1	8.9 (5.5-12.3)	1.73 (1.23-2.33)
	89		IV	2	6.1 (3.4-8.7)	p<0.001
CRP/ ECOG-ps		CRP	ECOG-ps			
	23	≤10mg/l	0-1	0	17.9 (15.5-20.3)	
	6		2-4	1		
	68	>10mg/l	0-1	1	9.0 (4.3-13.6)	1.79 (1.37-2.35)
	64		2-4	2	4.2 (2.2-6.2)	p<0.001
CRP/ albumin		CRP	Albumin			
	27	≤10mg/l	≥35g/l	0	17.0 (11.4-22.6)	
	2		<35g/l	1		
	99	>10mg/l	≥35g/l	1	8.9 (6.3-11.4)	2.00 (1.47-2.70)
	33		<35g/l	2	3.9 (0.8-7.1)	p<0.001
Stage/ ECOG-ps		Stage	ECOG-ps			
	40	III	0-1	0	16.1 (9.5-22.6)	
	17		2-4	1	9.7 (3.5-15.8)	
	51	IV	0-1	1	10.4 (5.8-14.9)	1.73 (1.33-2.24)
	53		2-4	2	3.6 (1.7-5.6)	p<0.001

CRP C-reactive protein, median survival (95% CI)

Chapter 6

6 PATIENT STUDY: COMPARISON OF AN INFLAMMATION BASED PROGNOSTIC SCORE WITH PERFORMANCE STATUS IN PATIENTS UNDERGOING CHEMOTHERAPY FOR INOPERABLE NON-SMALL CELL LUNG CANCER

6.1 Introduction

As noted previously, non-small cell lung cancer is the most common cause of cancer death in North America and Western Europe. Most patients present with advanced inoperable disease, with only one fifth of patients being suitable for radical treatment. Consequently the prognosis of these patients is extremely poor, with over two-thirds of patients dying within the first year of diagnosis (Espinosa *et al.,* 1995;Hespanhol *et al.,* 1995; Numico *et al.,* 2001; Kosmidis, 2002).

In the majority of patients treatment is aimed at palliation of symptoms, improvement of quality of life and prolongation of survival. The incidence of these symptoms may vary at the time of diagnosis, with 80% of patients experiencing symptoms in the terminal phase of their illness (Numico *et al.,* 2001). These symptoms include, breathlessness, anorexia, asthenia and cough.

The survival benefit gained by conventional treatments such as chemotherapy and / or radiotherapy, is modest and translates into limited survival prolongation (Numico *et al.,*2001). Survival rates in these inoperable patients remain extremely poor; indeed in those patients with advanced disease who receive best supportive care, only 10% will survive one year, more than 70% of patients experience local

progression and the majority die with distant disease (Kosmidis, 2002). A meta-analysis of chemotherapy in NSCLC patients (which included Cisplatin-based chemotherapy) suggested that chemotherapy regimes have an absolute advantage in terms of one year survival of 10% (NSCLC collaborative group, 1995), with a gain in the median survival estimated at two months, when compared to best supportive care (Klastersky and Paesmans, 2001; Belani and Langer, 2002).

However, for some patients active treatment with chemotherapy is inappropriate. In such cases patients are treated with best supportive care in an attempt to improve their symptoms. Best supportive care has been defined by Thatcher and co-workers (1997) as "any palliative therapeutic modality that may be offered to a patient with non-small cell lung cancer excluding chemotherapy but including radiotherapy and non-cytotoxic medications." It has been reported by Numico and co-workers (2001) that in patients receiving palliative radiotherapy for the palliation of local symptoms such as thoracic pain and haemoptysis, this is achieved in 60 – 80 % of cases. They also reported that general symptoms (for example, malaise, anorexia, weight loss and asthenia) are only partially improved. The median duration of such palliations is 7 – 14 weeks.

Conventionally, the selection of patients for chemotherapy has been based on clinico-pathological criteria, including age, stage and performance status (Numico *et al.*, 2001). However, the assessment of performance status may be subjective (Ando *et al.*, 2001).

In Chapter 5, in an unselected cohort of patients with inoperable NSCLC, an inflammation-based prognostic score, the Glasgow Prognostic Score (GPS), was shown to have similar prognostic value to that of stage and ECOG performance status. The question of whether the GPS would be useful in the selection of appropriate treatment for patients with inoperable NSCLC remains to be determined.

The aim of this study was to assess the prognostic value of the GPS in patients receiving chemotherapy for inoperable NSCLC.

6.2 MATERIALS AND METHODS

6.2.1 Study Design

Patients presenting with inoperable NSCLC (stage III and IV) to a single multi-disciplinary oncology clinic in Glasgow Royal Infirmary between March 2000 and June 2003 were studied prospectively. All patients had cytologically or histologically confirmed disease and were staged on the basis of clinical findings, chest X-ray, and where appropriate, bronchoscopy, liver ultrasound, isotope bone scan and computerised tomography of the thorax, according to the American Thoracic Society TNM classification (Mountain, 1991).

Clinical stage, tumour type and ECOG-ps were recorded at time of diagnosis. A blood sample was also obtained for measurement of white cell count, albumin and C-reactive protein concentrations. Patients received between one and six cycles of platinum-based chemotherapy.

The study was approved by the Research Ethics Committee of Glasgow Royal Infirmary.

6.2.2 Methods

Blood parameters: Routine laboratory measurements of white blood cell count, albumin and C-reactive protein concentration were carried out. The coefficient of

variation for these methods, over the range of measurement, was less than 10% as established by routine quality control procedures.

The GPS was constructed as previously described in Chapter 5. Briefly, hypoalbuminaemia (<35g/l = 1) and an elevated C-reactive protein (>10mg/l = 1) were combined to form a cumulative prognostic score (0, 1, 2).

6.2.3 Statistics

Data are presented as median and range. Grouping of the variables age, tumour type, ECOG-ps and white cell count was carried out using standard thresholds (Paesmans *et al.,* 1997; Herndon *et al.,* 1999).

Univariate survival analysis was performed using the Kaplan-Meier method. Multivariate survival analysis and calculation of hazard ratios (HR) were performed using Cox regression analysis with prognostic scores as covariates. Deaths up to 31st October 2003 were included in the analysis. Analysis was performed using SPSS software (SPSS Inc., Chicago, Illinois, U.S.A.).

6.3 Results

The characteristics of patients with inoperable NSCLC receiving platinum-based chemotherapy (n= 109) are shown in Table 6.1. The majority were male and over the age of 60 years. Approximately, 50% had stage III disease, 90% had an ECOG-ps of 0-1, 75% had an elevated C-reactive protein and 10% had hypoalbuminaemia. Of the 69 patients with a GPS of 1 only 13 patients had hypoalbuminaemia. The majority (68%) received cisplatin-based chemotherapy and the remainder carboplatin-based chemotherapy.

Seventy one (65%) of patients died during the follow-up period. On univariate survival analysis, both white cell count (HR 1.67, 95% CI 1.05 – 2.67, $p<0.05$) and GPS (HR 1.88, 95% CI 1.25 – 2.84, $p<0.01$) were significant predictors of survival. On multivariate analysis only GPS (HR 1.77, 95% CI 1.16 – 2.69, $p=0.008$) was a significant independent predictor of survival.

6.4 Discussion

The results of the present study show that an inflammation-based prognostic score, the GPS, is superior to ECOG-ps in predicting outcome following platinum-based chemotherapy for inoperable non-small cell lung cancer. The median survival of patients with a GPS of 0, 1 and 2 were approximately 17 months, 12 months and 7 months respectively. This suggests that the GPS may be useful in the selection of these patients for chemotherapy.

The reasons for the superiority of the GPS over ECOG-ps in predicting outcome in these patients are not altogether clear. It may be because the assessment of performance status is subjective and reflects functional status at a specific point in time. In contrast, the GPS, based as it is on the presence of an ongoing systemic inflammatory response and hypoalbuminaemia, predicts the progressive nutritional decline of the patient (McMillan *et al.,* 2001a; Scott *et al.,* 2002). Indeed, it has long been recognised that weight loss is associated with poor tolerance to chemotherapy (Chlebowski *et al.,* 1996; Paesmans *et al.,* 1997).

More recently, it has been reported that Cytochrome P450 3A activity, the principal drug metabolising enzyme in a variety of chemotherapeutic agents including cisplatin and carboplatin, is compromised in advanced lung cancer patients with an elevated C-reactive protein concentration (Rivory *et al.,* 2002; Slaviero *et al.,* 2003). One might therefore postulate that the presence of a systemic inflammatory response would be associated with increased toxicity in patients receiving platinum-based chemotherapy. It was therefore of interest that 40% of patients with a GPS of 0

received six cycles platinum based chemotherapy compared with 9% of those with a GPS of 1 ($p<0.05$). This suggests that the presence of a systemic inflammatory response may be an important factor in determining the ability of patients to tolerate platinum-based chemotherapy.

Moreover, in view of the importance of the systemic inflammatory response in determining outcome in patients with inoperable NSCLC, it may be that the addition of anti-inflammatory agents would provide additional therapeutic benefit.

Conventionally, in patients with inoperable NSCLC, the decision of whether or not to offer chemotherapy is primarily based on performance status. However, the toxicity, inconvenience and cost of chemotherapy has led many physicians to question whether chemotherapy is better than best supportive care or other palliative treatment in patients with inoperable NSCLC (Adelstein *et al.,* 1995; Klatersky and Paesmans, 2001). The results of the present prospective study indicate that the GPS adds value as a guide to the selection of appropriate patients with inoperable non-small cell lung cancer for platinum-based chemotherapy.

Table 6.1 Clinical characteristics and survival in patients with inoperable NSCLC receiving platinum-based chemotherapy: Univariate survival analysis

		Patients	Survival (months)	P value
		109 (100%)	Median (95% CI)	
Age	<60 yrs	41 (38)	10.6 (3.8 – 17.3)	
	≥60 yrs	68 (62)	13.5 (11.2 – 15.9)	0.681
Sex:	Male	63 (58)	15.1 (11.0 – 19.2)	
	Female	46 (42)	10.6 (10.1 – 11.1)	0.434
Stage	III	52 (47)	13.5 (9.1 – 18.0)	
	IV	57 (52)	12.2 (7.8 – 16.6)	0.338
Type	Squamous	40 (37)	15.1 (7.9 – 22.4)	
	Adenocarcinoma	46 (42)	14.0 (9.5 – 18.6)	
	Other	23 (21)	11.7 (9.7 – 13.6)	0.098
ECOG-ps	0	29 (27)	16.0 (9.2 – 22.7)	
	1	71 (65)	12.2 (9.9 – 14.5)	
	2	9 (8)	7.1 (1.7 – 12.4)	0.181
White Cell Count	$< 10 \times 10^9/l$	62 (56)	16.6 (13.1 – 20.1)	
	$\geq 10 \times 10^9/l$	47 (44)	11.7 (9.4 – 14.0)	0.031
GPS	0	27 (25)	17.0 (14.0 – 19.9)	
	1	69 (63)	12.1 (10.0 – 14.1)	
	2	13 (12)	7.1 (4.9 – 9.2)	0.002

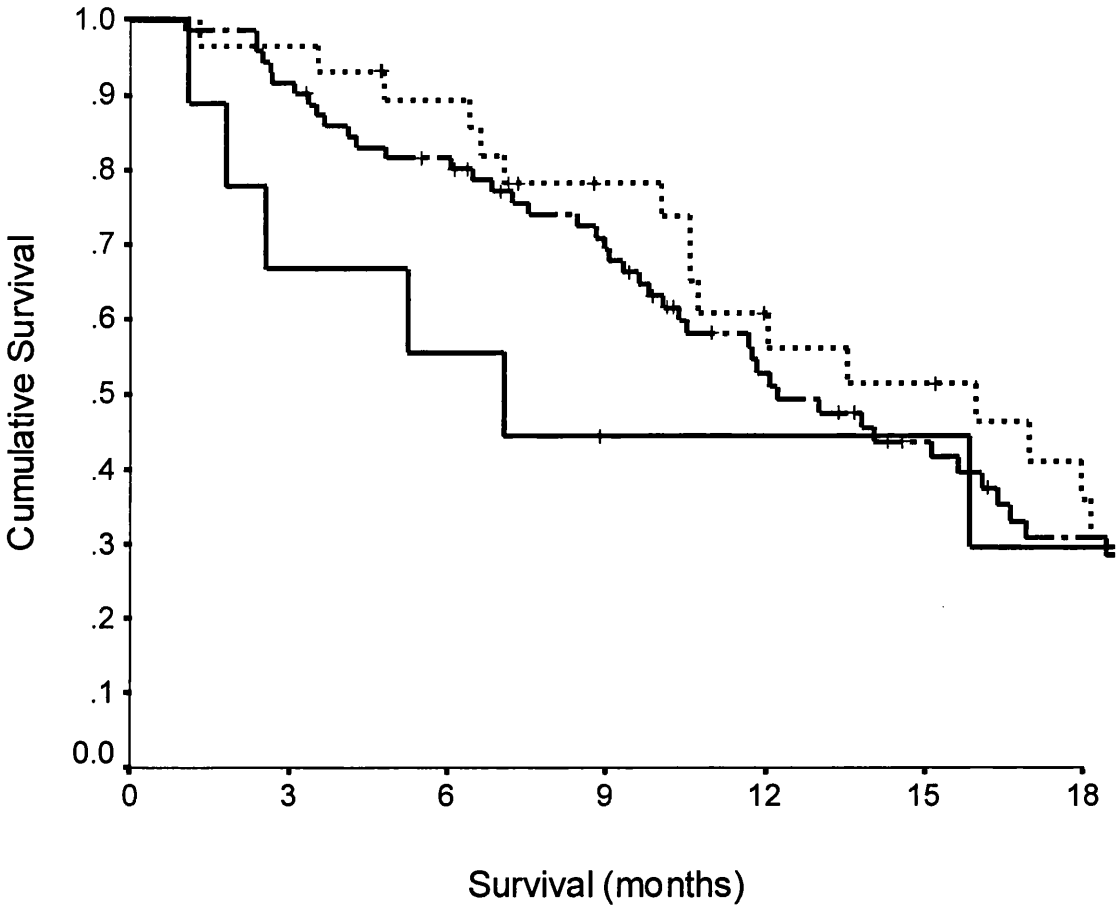


Figure 6.1a The relationship between ECOG performance status (0 ……., 1 ..-..--.-- , 2 ____) in patients with inoperable non-small cell lung cancer receiving platinum-based chemotherapy

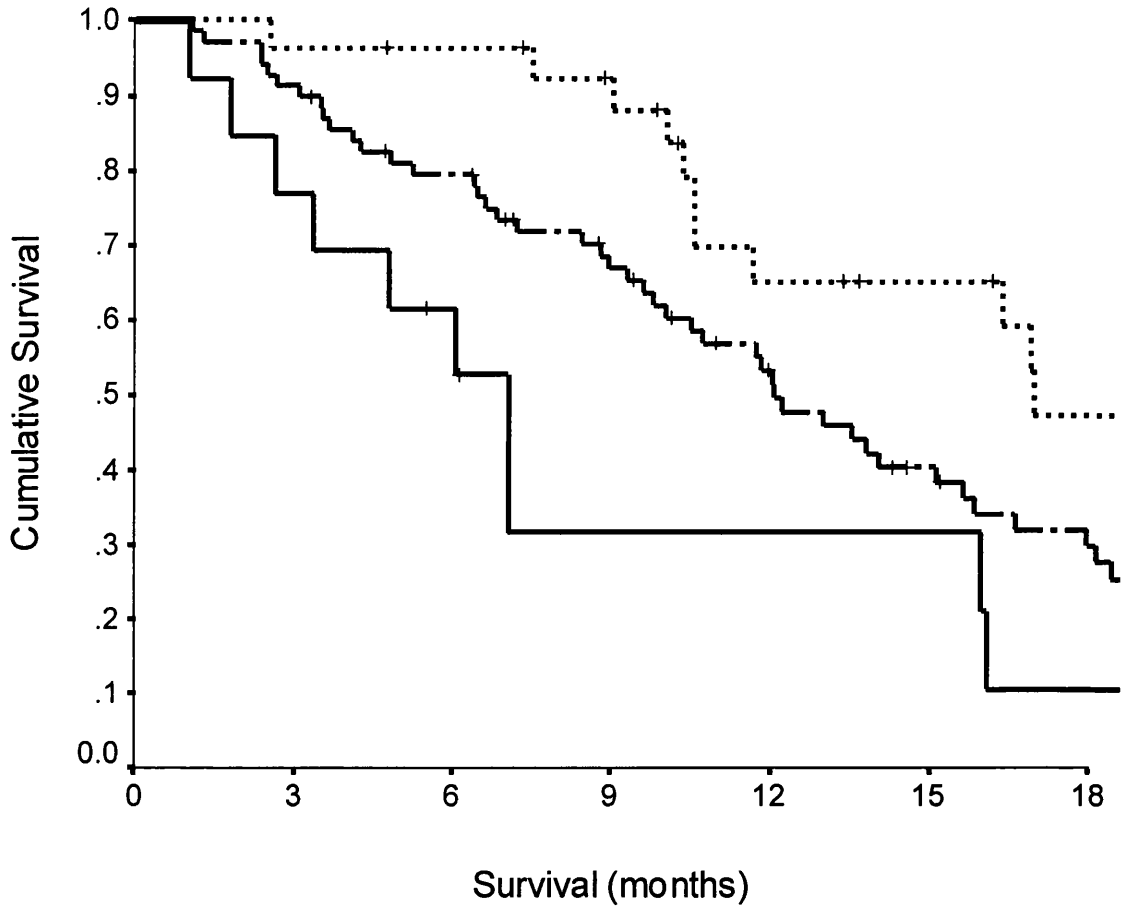


Figure 6.1b The relationship between the GPS (0 ……., 1 ..-..--.-- , 2 ____) in patients with inoperable non-small cell lung cancer receiving platinum-based chemotherapy

Chapter 7

7. PATIENT STUDY: A PROSPECTIVE EVALUATION OF AN INFLAMMATORY BASED PROGNOSTIC SCORE (GPS) IN PATIENTS WITH INOPERABLE NON-SMALL CELL LUNG CANCER

7.1 Introduction

As noted previously, non-small cell lung cancer (NSCLC) accounts for approximately three quarters of all lung cancers, and is recognised to be the most common cause of cancer related death in North America and Western Europe (Hespanhol *et al.,* 1995; Kosmidis, 2002). Most patients present with inoperable disease, and die within 12 months of diagnosis. For the majority, treatment tends to focus on palliating symptoms, improvement of quality of life and prolongation of survival (Numico *et al.,* 2001).

Radical radiotherapy and platinum-based chemotherapy have been shown to benefit some patients (Klastersky and Paesmans, 2001). Conventionally, such patients are selected for active treatment on the basis of stage and performance status (Numico *et al.,* 2001). Performance status is widely utilised in oncology practise as it has been found to correlate well both with response to treatment and survival (Blagden *et al.,* 2003). Assessment of performance status is however recognised to be subjective, physicians, nurses and patients differing in their assessment (Ando *et al.,* 2001).

Ando and co-workers (2001), in their study of 206 patients with stage III and IV disease asked patients to score their own performance status and compared this to scores performed by nurses and oncologists. The oncologist were found to be most optimistic,

while the patients were found to be most pessimistic. Performance status scored by the oncologist was found to correlate most closely with survival. The authors concluded that oncologists were better at evaluating performance status than the patients themselves. This nonetheless highlights the subjective nature of this method of assessment. Possibly a more objective measurement might be of more benefit in the selection of patients for appropriate treatment.

It has been shown in Chapter 5, using an unselected cohort of patients with inoperable NSCLC, that an inflammation-based prognostic score, the Glasgow Prognostic Score (GPS), had similar prognostic value to that of stage and ECOG performance status (ECOG-ps). Furthermore, this new prognostic score, is an objective assessment, based as it is on the measurement of C-reactive protein and albumin, appeared to be superior in predicting survival in patients receiving platinum-based chemotherapy (Chapter 6).

The aim of this study was to prospectively assess the value and reliability of the GPS and ECOG-ps in predicting survival in patients with inoperable NSCLC who were treated in another centre.

7.2 Materials and methods

7.2.1 Study Design

Patients presenting with inoperable NSCLC (stage III and IV) at Wishaw General Hospital, Lanarkshire between October 2002 and September 2003 were studied prospectively. All patients had cytologically or histologically confirmed disease and were staged on the basis of clinical findings, chest X-ray and, where appropriate, bronchoscopy, liver ultrasound, isotope bone scan and computerised tomography of the thorax, according to the American Thoracic Society TNM classification (Mountain, 1991).

Clinical stage, and ECOG-ps were recorded at time of diagnosis. ECOG-ps were assessed by the respiratory physicians. A blood sample was also obtained for measurement of white cell count, haemoglobin, albumin and C-reactive protein concentrations. Patients were considered to have undergone active treatment if they received chemotherapy (mainly cisplatin based) and / or radical radiotherapy. Patients receiving palliative radiotherapy and / or palliative care (symptom control) were considered to have had supportive treatment.

The study was approved by the Research Ethics Committee of Wishaw General Hospital.

7.2.2 Methods

Blood parameters: Routine laboratory measurements of haemoglobin, white cell count, albumin and C-reactive protein concentration were carried out. The coefficient of variation for these methods, over the range of measurement, was less than 10% as established by routine quality control procedures.

The GPS was constructed as previously described in Chapter 5. Briefly, patients with both an elevated C-reactive protein (>10mg/l) and hypoalbuminaemia (<35g/l) were allocated a score of 2. Patients in whom only one of these biochemical abnormalities was present were allocated a score of 1. Patients in whom neither of these abnormalities was present were allocated a score of 0.

7.2.3 Statistics

Univariate survival analysis was performed using the Kaplan-Meier method with the logrank test. Multivariate survival analysis and calculation of hazard ratios (HR) were performed using Cox regression analysis with stratification by centre. Deaths up to 31st March 2004 were included in the analysis. Analysis was performed using SPSS software (SPSS Inc., Chicago, Illinois, U.S.A.).

7.3 Results

The characteristics of patients with inoperable NSCLC are shown in Table 7.1. The majority of patients were male and were over the age of 60 years. Approximately 50% had stage IV disease and had good performance status. Approximately, 25% had low haemoglobin, 40% had an elevated white cell count and 70% had an abnormal GPS. Of the 45 patients with a GPS of 1, three patients had hypoalbuminaemia. Approximately a quarter of patients received active treatment and the remaining patients received supportive treatment.

In all, 68 (72%) patients died during the follow-up period. On univariate analysis, only the GPS (p=0.017) was a significant predictor of survival.

7.4 Discussion

It has been previously shown in Chapters 5 and 6, that an inflammation-based prognostic score, the Glasgow Prognostic Score (GPS), was useful in predicting survival in patients with inoperable NSCLC. Given that the GPS is simple to measure, routinely available and well standardised we wished to prospectively examine its value compared with ECOG-ps in patients with inoperable NSCLC presenting in another centre. In the present study, the GPS was superior to ECOG-ps in predicting survival.

The superior value of the GPS may be in part due to the subjective nature of performance status and the fact that ECOG-ps reflects the functional status of the patients at a specific point in time, whereas the GPS, based as it is on the presence of an ongoing systemic inflammatory response and hypoalbuminaemia, predicts the progressive nutritional decline of the patient (McMillan *et al.,* 2001b; Scott *et al.,* 2002).

In summary, the results of the present study confirm that the GPS is at least equivalent to ECOG-ps in predicting the survival of patients with inoperable NSCLC. It is an objective measurement which is simple to measure, routinely available and well standardised.

Table 7.1 Clinical characteristics of patients with inoperable NSCLC:

Univariate survival analysis

		Patients	Survival (months)	P value
		87 (100%)	Median (95% CI)	
Age	<60 yrs	13 (15)	12.2 (2.1 – 22.3)	
	≥60 yrs	74 (85)	6.9 (4.4 – 9.5)	0.497
Sex:	Male	50 (58)	6.3 (1.8 – 10.8)	
	Female	37 (42)	8.5 (5.7 –11.4)	0.254
Stage	III	43 (49)	8.9 (7.6 – 10.1)	
	IV	44 (51)	5.3 (2.8 – 7.8)	0.169
Haemoglobin	$\geq 12 gl^{-1}$	65 (75)	8.8 (6.6 – 11.0)	
	$< 12 gl^{-1}$	22 (25)	3.1 (0.0 – 6.6)	0.084
White Cell Count	$< 10 \times 10^9/l$	52 (60)	8.9 (7.8 – 10.0)	
	$\geq 10 \times 10^9/l$	35 (40)	4.6 (2.5 – 6.6)	0.054
ECOG-ps	0	9 (10)	10.3 (0.0 – 23.7)	
	1	33 (38)	6.1 (1.9 – 10.3)	
	2	28 (32)	8.7 (6.9 – 10.3)	
	3	17 (20)	5.2 (0.0 – 10.8)	0.358
GPS	0	26 (30)	9.6 (7.5 – 11.7)	
	1	45 (52)	8.5 (5.6 – 11.5)	
	2	16 (18)	2.2 (0.3 – 4.2)	0.017
Treatment	Active	20 (23)	10.3 (7.4 – 13.1)	
	Palliative	67 (77)	6.5 (3.9 –9.0)	0.150

Chapter 8

8. PATIENT STUDY: A PROSPECTIVE LONGITUDINAL STUDY OF THE SYSTEMIC INFLAMMATORY RESPONSE IN PATIENTS WITH INOPERABLE NON-SMALL CELL LUNG CANCER

8.1 Introduction

Non-small cell lung cancer (NSCLC) is the most common cause of cancer death in North America and Western Europe. Most patients present with advanced inoperable disease and the majority die within 12 months.

There is increasing evidence that the progressive nutritional decline of patients with advanced cancer is, at least in part, secondary to the presence of a systemic inflammatory response. This is consistent with recent work showing that the presence of a systemic inflammatory response, as evidenced by an elevated circulating concentration of C-reactive protein and reduced concentrations of albumin, is associated with poor survival independent of stage and performance status in a variety of common solid tumours (O'Gorman *et al.,* 2000; Scott *et al.,* 2002). Furthermore, we have shown that the Glasgow Prognostic score (GPS) has prognostic value, independent of performance status, in patients with inoperable NSCLC (Chapter 5; Chapter 6; Chapter 7).

Since it appears that an underlying systemic inflammatory response is responsible for the progressive nutritional decline of the advanced cancer patient, it might be expected that the GPS or its components (i.e. C-reactive protein or albumin) would also be useful in the temporal assessment of patients with inoperable NSCLC.

The aim of the present study was to examine the temporal changes in the GPS compared with that of performance status in patients with inoperable NSCLC.

8.2 Material and Methods

8.2.1 Study Design

Patients presenting with inoperable NSCLC (stage III and IV) to a multi-disciplinary clinic at Wishaw General Hospital, Lanarkshire between January 2002 and November 2003 were studied prospectively. All patients had cytologically or histologically confirmed disease and were staged on the basis of clinical findings, chest X-ray and, where appropriate, bronchoscopy, liver ultrasound, isotope bone scan and computerised tomography of the thorax, according to the American Thoracic Society TNM classification (Mountain, 1991).

Weight, clinical stage, and performance status (Eastern Cooperative Oncology Group, ECOG-ps) were recorded at time of diagnosis. Performance status was assessed by a respiratory physician. A blood sample was also obtained for measurement of white cell count, haemoglobin, albumin and C-reactive protein concentrations.

These measurements were also repeated 2- 6 months after diagnosis.

Patients were considered to have undergone active treatment if they received chemotherapy (mainly cisplatin based) and / or radical radiotherapy. Patients receiving palliative radiotherapy and / or palliative care (symptom control) were considered to have had supportive treatment.

The study was approved by the Research Ethics Committee at Wishaw General Hospital, Lanarkshire.

8.2.2 Methods

Blood parameters, routine laboratory measurements of haemoglobin, white cell count, albumin and C-reactive protein concentration were carried out. The coefficient of variation for these methods, over the range of measurement, was less than 10% as established by routine quality control procedures. The Body Mass Index was also calculated by dividing the patient's weight by the patient's height in meters squared.

The GPS was constructed as previously described (Chapter 5). Briefly, patients with both an elevated C-reactive protein (>10mg/l) and hypoalbuminaemia (<35g/l) were allocated a score of 2. Patients in whom only one of these biochemical abnormalities was present were allocated a score of 1. Patients in whom neither of these abnormalities was present were allocated a score of 0.

8.2.3 Statistics

Data are presented as median and range. Where appropriate, comparisons of data from different time periods were carried out using the Wilcoxon signed rank test and where appropriate the Sign test was applied. Analysis was performed using SPSS software (SPSS Inc., Chicago, Illinois, U.S.A.).

8.3 Results

Ninety one patients with inoperable NSCLC were included in the study. During the follow up period 38 patients died without being reassessed and 15 patients were unfit to attend the clinic, therefore only 38 patients were available for analysis.

The clinical characteristics of the 38 patients with inoperable NSCLC who had a follow-up assessment between 2 – 6 months (median 3.4 months) are shown in Table 8.1. The majority were male (67%), over the age of 60 years (79%), were stage III disease (65%), had good performance status (66%), and white cell count (55%), haemoglobin (50%) and albumin (95%) concentration within the normal range. Nineteen (50%) of the patients received active treatment. Twenty seven (71%) of patients had an elevated GPS. All but 11 of these patients had an elevated C-reactive protein concentration. Of the 25 patients with a GPS of 1 no patients had evidence of hypoalbuminaemia.

At 2 – 6 months follow-up, no significant differences observed in BMI, haemoglobin or white cell count (Table 8.1). In contrast, there was a more significant change in ECOG-ps between the two visits. In 16 patients (42%) ECOG-ps deteriorated, while it was found to improve in only five patients (13%) ($p=0.01$).

There was a significant fall in albumin from a median of 39g/l at diagnosis to 37g/l at the subsequent clinic visit ($p<0.01$). Only two patients (5%) were hypoalbuminaemic (<35g/l) at the time of the first assessment. However, by the time of the second clinic visit, eight patients (21%), including the original two, had

developed hypoalbuminaemia (p=0.03). There was also a significant increase in C-reactive protein concentrations from a median of 19mg/l at diagnosis to 26mg/l at the subsequent clinic visit. Overall, a deterioration in GPS was also found (p=0.20). In eight patients (21%), the GPS increased between the first and second visit, while in four patients (11%) the GPS decreased.

Over the follow-up period there was a significant inverse correlation between the change in albumin and the change in C-reactive protein concentrations (r_s= -403, p=0.009).

8.4 Discussion

The present study examined the longitudinal changes in a new inflammation based prognostic score (Glasgow Prognostic Score, GPS), and its components and performance status (ECOG-ps) in patients with inoperable NSCLC. However, of the initial 91 patients studied only 38 patients were available for analysis at 2 to 6 months. This high attrition rate is consistent with previous longitudinal studies of advanced cancer patients (McMillan *et al.,* 1999).

The results showed that, despite there being no alteration in body weight over the follow up period, there was a significant fall in albumin concentrations and an increase in C-reactive protein concentrations. These results are consistent with the hypothesis that the presence of a chronic inflammatory response results in an increased demand for specific amino acids and promotes degradation of the body's protein stores including albumin and body cell mass (Preston *et al.,* 1995; McMillan *et al.,* 2001b). Despite these changes there was only a trend towards a higher GPS. This was due to four patients going from an elevated C-reactive protein (>10mg/l) to a normal level (<10mg/l). The reasons for this are unclear. However, it was of interest that two patients had just started on steroid therapy prior to their second clinic visit.

In contrast ECOG-ps increased over this period. Compared with ECOG-ps, the GPS appears to be less sensitive to changes in disease status over time. However, both components of the GPS C-reactive protein and albumin did alter over the time period. It might be expected that ECOG-ps with four categories would be more

sensitive to changes in disease status than the GPS with its three categories. Further studies are required to examine and refine the GPS, such that in addition to being a prognostic tool it may also be used to monitor disease status in patients with inoperable NSCLC.

Table 8.1. Parameters of patients with inoperable NSCLC at diagnosis and 2-6 months later.

	At diagnosis (n= 38)	Subsequent clinic visit 2–6 months (n= 38)	Change 2–6 months (n= 38)	p-value
Age (years)	69 (45 to 85)			
Sex (m / f)	26 / 12			
Treatment				
Active / Palliative	19 / 19			
BMI	24.3 (16.7 to 45)	23.8 (14.4 to 44)	-0.3 (-3.9 to 2.6)	0.158
Haemoglobin (g/l)	12.2 (8.7 to 17.9)	12.4 (8.5 to 16.1)	-1.0 (-4.8 to 3.7)	0.455
White Cell Count (10^9/l)	9.2 (5.0 to 38.4)	9.0 (6.2 to 19.7)	-1.0 (-27.3 to 6.4)	0.940
ECOG (0 / 1 / 2 / 3)	10 / 15 / 10 / 3	6 / 13 / 11 / 8	5 / 17 / 16*	0.009
Albumin (g/l)	39 (27 to 45)	37 (25 to 44)	-2.0 (-8 to 4)	0.003
C-reactive protein (mg/l)	19 (6 to 168)	26 (6 to 314)	7 (-156 to 276)	0.036
GPS (0 / 1 / 2)	11 / 25 / 2	11 / 20 / 7	4 / 26 / 8*	0.197

*Decreases/ Remains the same/ Increases

Chapter 9

9. Conclusions

9.1 Introduction

In Chapter 1 the aims of this thesis were defined as follows:

1. To examine the relationship between anthropometric parameters, the systemic inflammatory response and ECOG-performance status in patients with inoperable non-small cell lung cancer

2. To develop and evaluate an inflammation based prognostic score in patients with inoperable non-small cell lung cancer.

9.2 General Conclusions

It has long been established that weight loss results in a reduced performance status and ultimately leads to death in patients with advanced cancer. Chapter 4 examined the reduction in lean body mass in patients with inoperable non-small cell lung cancer and found that the observed reduction was associated with a reduced performance status and reduced albumin concentrations.

Previous studies have suggested that the reduction in albumin concentrations may be linked to the systemic inflammatory response in advanced cancer patients. It has also been suggested that combining the inflammatory marker, C-reactive protein, and

albumin either may be useful prognostic indicator or may allow for the development of a useful prognostic tool.

In Chapter 5, this model was tested and it was found that a combined score of C-reactive protein and albumin concentration was comparable to ECOG performance status in predicting survival in an unselected cohort of inoperable non-small cell lung cancer patients.

In Chapter 6, this inflammatory based prognostic score, the Glasgow Prognostic Score (GPS), was found to be superior to ECOG-ps in the prediction of survival in inoperable NSCLC patients receiving platinum-based chemotherapy.

In Chapter 7, the reproducibility of the GPS was assessed within another centre and once more was found to be equivalent to ECOG-ps in the prediction of survival in patients with inoperable non-small cell lung cancer.

In Chapter 8, the temporal changes of the GPS and its components were compared to that of ECOG-ps in patients with inoperable NSCLC. In this study, when compared to ECOG-ps, the GPS appeared to be less sensitive to changes in disease status over time. However, the number of patients with follow-up assessments was small and further work is required to define the role of the GPS in monitoring patients with inoperable NSCLC. Furthermore, it might be expected that ECOG-ps with four categories would be more sensitive to changes in disease than GPS with only three categories.

Nevertheless, the GPS appears to be a useful prognostic tool. Part of this is clearly related to the detrimental role of nutritional decline in the survival of the advanced cancer patient. Indeed, Vigano and co-workers (2000) concluded that the association between malnutrition and reduced survival is possibly initially best measured serum albumin.

In conclusion, the work presented in this thesis suggests that the Glasgow Prognostic Score may be useful in the assessment of patients with inoperable non-small cell lung cancer. Further work should be carried out to assess its value in other advanced cancers.

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Publications arising from this thesis

Forrest, L.M. McMillan, D.C. McArdle, C.S. Angerson, W.J. Dunlop, D.J. (2003) Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. *Br J Cancer.*, **89**, 1028-1030.

Forrest, L.M. McMillan, D.C. McArdle, C.S. Angerson, W.J. Dunlop, D.J. (2004) Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small cell lung cancer. *Br J Cancer.*, (In press).

Forrest, L.M. Dunlop, D.J. McArdle, C.S. Angerson, W.J. Dagg, K. Scott, H.R. McMillan, D.C. (2004) Further evaluation of an inflammation-based prognostic score (GPS) in patients with inoperable non-small cell lung cancer. (submitted).