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A Study of Prognostic Markers in Advanced Cancer

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Declaration

I declare that the thesis has been composed by myself and that the work has not been submitted for any other degree or professional qualification. All work is my own unless specifically stated.

Claribel P.L. Simmons 2018

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Abstract

Background: Prognostication is a core skill fundamental to the clinical management of patients with advanced cancer. This skill is exercised to guide appropriate clinical decisions, plan supportive services and allocate resource utilisation. Prognostication by clinicians is often erroneous, optimistic, informal and subjective. Clinicians base survival predictions upon clinical experience, clinical intuition and knowledge of cancer trajectories. Prognostic factors have been identified and validated in patients with cancer. These can be clinical markers or biomarkers. Clinical markers including weight loss and Performance Status (PS), and biomarkers such as C-reactive protein (CRP), lactate dehydrogenase (LDH), White cell count (WCC) and albumin, all representative of systemic inflammation, have been shown to be predictive of survival. Several prognostic factors have been combined to develop prognostic tools to improve prognostication accuracy. The aims were to examine all these prognostic markers and the tools, to clarify which prognostic markers are most predictive of survival in advanced cancer.

Methods: To meet these aims a systematic review, an analysis of a prospectively collected biobank of patients with lung cancer and finally a large de novo multi-centre (UK) observational cohort study (Inflammatory biomarkers in Prognosis in Advanced Cancer [IPAC] study), were undertaken. The latter examined prognostic factors and was informed by the systematic review and biobank analysis. The prognostic factors evaluated throughout included demographic factors, disease characteristics, clinical factors and biomarkers. Literature appraisal and synthesis, survival analysis and logistic regression methods were employed as appropriate.

Results: The systematic review concluded that numerous prognostic tools predict survival in patients with advanced cancer; however comparison was difficult due to the heterogeneity of the tools and the methods used to determine their accuracy. Some tools incorporate prognostic factors that have been independently validated to be of prognostic significance in advanced cancer whilst other tools may include some factors which are not validated. The prognostic tools demonstrating greatest accuracy in determining survival are the Palliative Performance Scale (PPS), the Palliative

Prognostic Score (PaP), the Palliative Prognostic Index (PPI), and the Glasgow Prognostic Score (GPS) including the modified variant (mGPS). These tools have all been externally validated in more than 2000 patients with advanced cancer and were independently associated with survival ($p<0.001$).

The biobank analysis identified the markers (clinical and biomarkers) which are most predictive of survival in advanced lung cancer. The prognostic markers included in many of the prognostic tools with greatest survival prediction accuracy are PS and mGPS ($p<0.001$).

A prospectively acquired biobank identified the markers (clinical and biomarkers) which are most predictive of survival in advanced incurable lung cancer. The prognostic markers which are included in many of the prognostic tools with greatest survival prediction accuracy are PS and mGPS.

The prospective observational study demonstrated that CPS (Clinician Predicted Survival), mGPS, ECOG-PS (Eastern Cooperative Oncology Group - Performance Status), dyspnoea, Global Health, cognitive impairment, anorexia, weight loss, LDH, WCC and neutrophil count (NC) predicted survival at 30 days (univariate analysis). CPS, ECOG-PS, mGPS, dyspnoea, Global Health, cognitive impairment, anorexia, weight loss, LDH, WCC and NC, predicted survival at 3 months. On multivariate analysis, ECOG-PS, mGPS and neutrophil count predicted survival at 30 days while ECOG-PS, mGPS, weight loss, LDH and WCC predicted survival at 3 months.

Conclusion: In patients with advanced cancer, the most accurate prognostic factors include clinical markers (Performance Status, weight loss) and biomarkers of the systemic inflammatory response (CRP and albumin [combined in the mGPS], NC, WCC). The next step in this work is assessing how these can be utilised in clinical practice.

Lay Summary

Assessing how long a patient with cancer has to live is very important to guide their medical care and aids future planning, both in terms of the patient's preferences and medical management. It is difficult for clinicians to give an estimate of how long a patient has left to live and frequently their estimate is incorrect, often over-estimating their expected survival time. Clinicians estimate a patient's survival time based upon their knowledge of the patient's condition and their experience in looking after other patients with similar conditions. This varies from clinician to clinician. Factors that help survival estimation are known and include patient factors and blood tests. The blood tests are often related to inflammation or systemic upset. Several of these tests have been used together and combined into a tool to improve survival estimation.

Three studies were performed as part of this thesis to evaluate survival factors, in an attempt to clarify the survival factors of greatest significance in advanced cancer. These studies were a review of previous studies, a study looking at survival factors in patients with lung cancer, and a large prospective study designed to test all the survival factors in patients with advanced cancer. The survival factors included demographic details of the patients and details of their cancer including symptoms, fitness level, weight loss and blood tests. The survival results were analysed using the appropriate statistical packages to ensure accurate analysis.

The first study was a review of previous studies looking at the numerous tools estimating survival for patients with incurable cancer. Studies selected for review had a study population of at least 100 patients and patients were diagnosed with incurable cancer. Fifty one studies were included. The review concluded that there are numerous tools estimating survival in patients with advanced cancer however direct comparison is difficult due to the variety of tools and variations in their study design and presentation of results. Some tools incorporate survival factors which have been studied extensively and have been proven to estimate survival in their own right. Some

tools incorporate survival factors which have not been tested as rigorously. The tools which have been rigorously tested in patients with cancer and have been shown to accurately estimate survival are the Palliative Performance Scale (PPS), the Palliative Prognostic Score (PaP), the Palliative Prognostic Index (PPI), and the Glasgow Prognostic Score (GPS).

The second study looked at survival factors in patients with incurable lung cancer which are namely Performance Status (fitness), the modified Glasgow Prognostic Score (mGPS: a survival factor using blood factors of inflammation) and weight loss. These are known survival factors in advanced lung cancer however have never been directly compared. This study was an analysis of an existing set of data from Greece. The data of 390 patients were analysed and using appropriate statistical packages, comparison of these survival factors was performed. Fitness and the mGPS best predicted survival and when combined, survival accuracy improved more.

The third study, our IPAC study, then evaluated all the established survival factors in real time to compare them fully with each other to ascertain their survival estimate accuracy. The design was modelled on the second study and was conducted in several hospitals and hospices throughout the UK. Data collected about each patient included markers of their fitness, blood tests looking at inflammation, details of their cancer and cancer treatment, symptoms, and clinical signs. The data of 478 patients were analysed using appropriate statistical modelling packages. The IPAC study identified the factors at best predicting survival were the clinician's knowledge of the patient, the patient's fitness, the patient's Global Health questionnaire result, blood tests looking at inflammation, breathlessness, confusion, loss of appetite and weight loss. When all the factors were compared, the factors best predicting survival were the blood tests looking at inflammation, the patient's fitness and weight loss.

This thesis has identified and tested the prognostic accuracy of many survival factors in patients with advanced cancer. The blood tests looking at inflammation have all

been shown to be predictive of survival. When specific blood tests looking at inflammation are combined (mGPS) their prognostic accuracy increases. Using objective markers of systemic inflammation in cancer can aid survival prediction and thus improve clinical management in patients with advanced cancer.

Abbreviations

AD	Anno Domino
Alb	Albumin
ANOVA	analysis of variance
AUC	area under the receiver operating curve
BC	before Christ
BCI	B12/CRP index
BL	Barry Laird (Clinician)
BMI	body mass index
c	circa
CI	confidence interval
C-index	concordance statistic
CPS	clinician predicted survival
CRF	case report form
CRP	C-reactive protein
CS	Claribel Simmons (Clinician)
CT	computerised tomography
d	day
DNA	deoxyribonucleic acid
D-PaP	The Delirium- Palliative Prognostic Score

e.g.	exempli gratia
EAPC	European Association for Palliative Care
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group - Performance Status
EGF	epidermal growth factor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of life Questionnaire Core 30
ESAS	Edmonton Symptom Assessment System
g/L	grams per litre
GCS	Glasgow Coma Scale
GPS	Glasgow Prognostic Score
HMGB1	high mobility group box 1, homo sapiens
HR	hazard ratio
ICH GCP	International Conference on Harmonisation - Good Clinical Practice
IL	interleukin
IL-1	interleukin 1
IL-1α	interleukin 1 alpha
IL-1β	interleukin 1 beta
IL-6	interleukin 6
IL-8	interleukin 8
IPAC	Inflammatory biomarkers in prognosis in advanced cancer
IQR	interquartile range

KM	Kerry McWilliams (Clinician)
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
mg/l	milligrams per litre
mGPS	Modified Glasgow Prognostic Score
n	sample size
NADH	nicotinamide adenine dinucleotide
NC	neutrophil count
NFkB	nuclear factor kappa-light chain enhancer of activated B cells
NPV	negative predictive value
NSCLC	non small cell lung cancer
OR	odds ratio
PaP	Palliative Prognostic Score
PiPS	Prognosis in Palliative Care Study
pmol/l	picomoles per litre
PPI	Palliative Prognostic Index
PPS	Palliative Performance Scale
PPV	positive predictive value
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROMS	patient reported outcome measures
PS	Performance Status

REMARK	Reporting recommendations for tumour marker prognostic studies
RNA	ribonucleic acid
SCLC	small cell lung cancer
SD	standard deviation
sens	sensitivity
spec	specificity
SPSS	Statistical Package for Social Sciences
ST	Sharon Tuck (Statistician)
TGF-β	transforming growth factor β
TNF	tumour necrosis factor
TNFα	tumour necrosis factor α
TNM	Tumour Node Metastases
U/L	units per litre
UK	United Kingdom
VEGF	vascular endothelial growth factor
vit B12	vitamin B12
WCC	white cell count
wk	week
α	alpha
β	beta

Chapter 1 Introduction

1.1 Cancer terminology and its origins in ancient history

Cancer is a malignant tumour resulting from an uncontrolled division of cells. Inflammation has been linked to cancer for more than a thousand years and in order to understand the significance of inflammation with regard to cancer, the history of cancer and its terminology must be reviewed.

1.1.1 Classical Greek history of cancer and its link to macroscopic inflammation

Carcinos refers to both the Greek word for crab and the ancient mythological creature Karkinos (or Carcinos), a giant crab who was crushed by Heracles in battle. Karkinos was then placed among the stars, as a reward by the goddess Hera, an enemy of Heracles. The astronomical constellation of the crab is referred to as the constellation Cancer. The ancient Egyptians worshipped the stars and metaphorical symbolism was important to daily life. In Ancient Egyptian astronomy, the Cancer constellation was illustrated by the figure for a crab. The Egyptians viewed Cancer, both the constellation and its metaphorical crab as a sacred emblem of immortality and it implied indestructibility, however it was also viewed as being closely connected to death. The features of being ineradicable and its link to death are from where the origins of the word cancer come.

Hippocrates (460-370 BC), a Greek physician who is widely considered to be the 'Father of Medicine' used the term 'carcinos' to described tumours, both benign and malignant; what we refer to as cancers. He examined patients with large masses, some of which were ulcerating in nature. His examination findings concluded that these lesions were 'hard as a rock, exquisitely painful with a superficial surface of ulceration which bled or had sores that oozed and refused to heal'. He named this condition Karkinos, from the Greek word for crab. His choice of name and reasoning behind it referred to the hard shell of a crab, the ferocious pinch of a crab claw and the tenacity with which a crab bites and refuses to let go. This resembled how stubbornly a malignant tumour adhered to the body, no matter how it was manipulated. Hippocrates had already witnessed that while some masses were benign, others were malignant and tended to spread quickly through the body, similar to a crab's claws extending out, and resulted in death[1]. After the death of Hippocrates, other Greek physicians continued to research cancer, including one notable physician called Claudius Galenus.

Claudius Galenus, a Greek surgeon to gladiators (AD129 – c200) used Hippocrates' term "cancer" to describe certain inflammatory tumours of the breast in which the superficial veins appeared swollen and radiated like the claws of a crab. Later the name was extended to include all malignant and infiltrating growths. These signs noted on clinical inspection by Hippocrates and Galenus were of macroscopic inflammation and therefore were the first links to cancer and inflammation. Cancer and inflammation were investigated further, by a Roman called Aulus Cornelius Celsus who was a medical encyclopaedist. It is thought that he may have been a practising surgeon, but he is notable for advancing Hippocrates' theories regarding macroscopic inflammation in cancer. In the 1st century AD Celsus described the four cardinal signs of inflammation namely rubor (redness), calor (heat), tumor (swelling) and dolor (pain)[2].

1.2 Cancer and its link to microscopic inflammation

It was not until the 19th century that the link between inflammation and cancer was noted microscopically by Rudolf Virchow, a German doctor and the 'father of modern pathology'.

The microscopic examination of leukocytes within tumours by Virchow provided the first indication of a possible link between inflammation and cancer[3]. There is now good evidence that inflammation impacts upon every step of tumorigenesis from initiation through tumour productions and onto metastatic progression[4]. The tumour microenvironment has been investigated and it is known that various components interact to play a critical role in establishing fertile ground for tumour growth and progression[5]. The host reaction to a cancer also promotes an inflammatory microenvironment which can promote cancer development[6].

1.2.1 Cancer biology and its relationship to inflammation

It is important to gain an appreciation of cancer biology and its relationship to inflammation, tumour production and metastatic disease, however a detailed analysis is beyond the remit of this thesis. As a brief summary, general hallmarks of cancer-related inflammation include the presence of inflammatory cells and inflammatory mediators (e.g. chemokines, cytokines and prostaglandins) in tumour tissues, tissue remodelling and angiogenesis similar to that seen in chronic inflammatory processes and tissue repair. Inflammatory cells and mediators are present in the microenvironment of most, if not all,

tumours, irrespective of the trigger for development. The cytokines interleukin-6 (IL-6), tumour necrosis factor alpha (TNFα) and interleukin-1- alpha (IL-1α) and beta (IL-1β) are critical mediators of the systemic inflammatory response. As a result, these cytokines are main stimulators for the synthesis of an acute phase response[7]. A variety of other modulators may affect acute phase responses which include glucocorticoids, insulin and growth factors such as epidermal growth factor, hepatocyte growth factor and transforming growth factor β[7]. To this effect, the presence of a systemic inflammatory response detected through the measurement of acute phase reactants is considered a poor prognostic factor for various cancers. The interaction between cancer and inflammation is summarised in Figure 1-1.

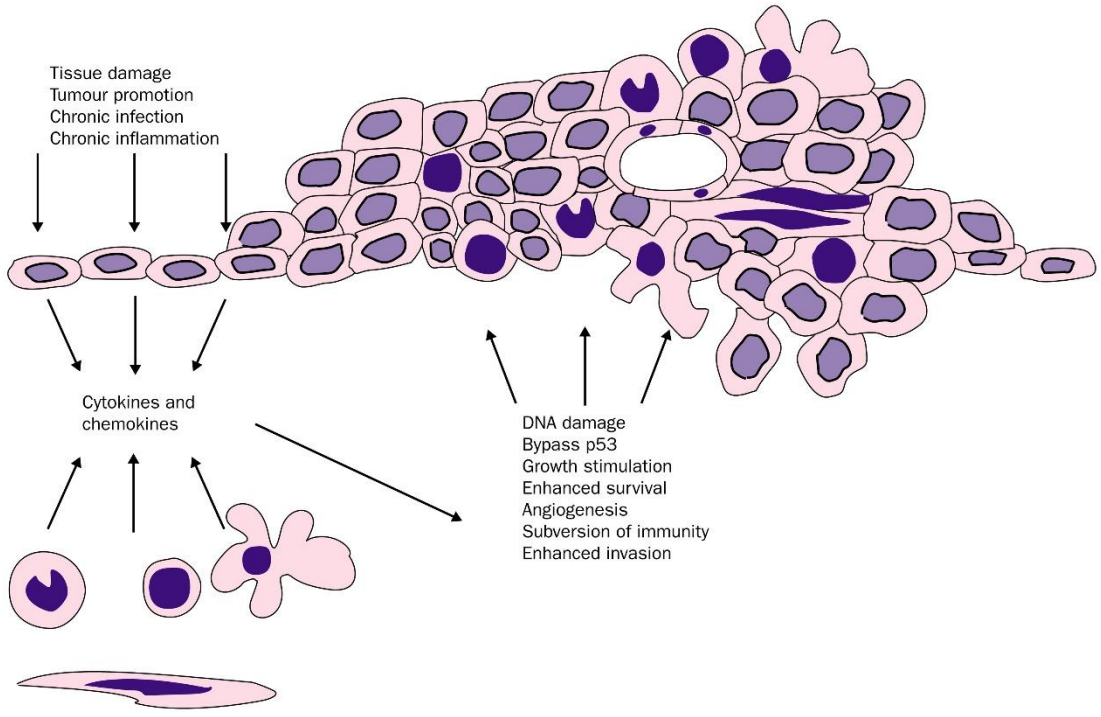

Figure 1-1: An Illustration of the interaction between cancer and inflammation

The figure demonstrates the interplay between inflammation due to cancer, the cancer microenvironment and both contributing to further inflammation.

1.2.2 Important features of tumour production, tumour propagation and metastatic disease

All solid tumours at some point outpace their blood supply and become oxygen and nutrient deprived. This results in necrotic cell death at the tumour's core and the release of proinflammatory mediators such as IL-1 and HMGB1 (high mobility group box 1, homo sapiens)[8]. The ensuing inflammatory response promotes neoangiogenesis and provides surviving cancer cells with additional growth factor, produced by newly recruited inflammatory and immune cells[4,9]. This intrinsic inflammatory response which follows tumour development, in turn promotes the tumour microenvironment.

Based on the continuous cell renewal and proliferation induced by tumour associated inflammation, tumours have been referred to as 'wounds that do not heal'[10]. In some animal models, dominant oncogenes are unable to induce cancer unless accompanied by injury and subsequent tissue regeneration[11,12].

Tumours secrete a vascular permeability factor called vascular endothelial growth factor (VEGF) that can lead to persistent extravasation of fibrin and fibronectin and continuous generation of extracellular matrix. Platelets in wounds are a critical source of cytokines, especially transforming growth factor-β (TGF β) and VEGF. Release of such factors from platelets may also be important in tumourangiogenesis[13].

There is now evidence that inflammatory cytokines and chemokines, which can be produced by the tumour cells, tumour-associated leucocytes and platelets, may contribute directly to malignant progression. Many cytokines and chemokines are inducible by hypoxia, which is a major physiological

difference between tumour and normal tissue[14]. Examples are TNF, IL-1α and β, IL-6 and chemokines. These are examples of pro-inflammatory chemokines. IL-6 is a pro-inflammatory cytokine and is highly correlated with C-reactive protein. The latter can be more easily measured in patients.

TNF stimulates fibroblast growth and can also induce death of diseased cells at the site of inflammation. The chronic production of Nuclear factor kappa light chain enhancer of activated B cells (NF-kB) in malignant disease acts as an endogenous tumour promotor contributing to the tissue remodelling and stromal development necessary for tumour growth and spread. Animal models have demonstrated that antagonism of IL-1α reduces tumour development. Chemokines recruit leucocytes to sites of inflammation, which triggers an uncontrolled accumulation of leukocytes, even after the initial antigenic stimulus has disappeared.

NF-κB is important in cancer progression since this nuclear transcription factor is known to influence the tumour microenvironment directly. NF-κB has been shown to promote cancer progression directly in several cancers. NF-κB amplifies epidermal growth factor (EGF) signalling in glioblastoma, promotes the tumour microenvironment in Hodgkin's disease through Hodgkin and Reed-Sternberg cells, induces growth factor secretion by inflammatory cells in hepatocellular carcinoma, induces inflammatory cell trophic and angiogenic cells in colorectal cancer, induces B cells directly to cause hormone-free survival of cancer cells in prostate cancer, promotes tumour cell survival in multiple myeloma and induces trophic factor in multiple myeloma[15]. NF-κB is viewed as a growth factor in cancer cells and therefore has an important role in tumour metastasis, thereby directly linking inflammation and the pro-inflammatory cytokines to tumour progression, which is metastasis in clinical terms.

These inflammatory chemokines are thought to be critically important in cancer cell motility, homing and proliferations at specific metastatic sites[16]. Cancer metastasis is complicated in that it arises from the cancer cell invasion, angiogenesis, the movement of cancer cells within the blood stream, extravasations, organ specific targeting and growth. Clinically, metastasis is the most critical aspect of tumorigenesis because over 90% of cancer mortality is caused by metastasis.

1.2.3 Clinical symptomatology and its relationship to inflammation

Symptoms in cancer are the physical and psychological manifestations of the underlying disease process and there is evidence demonstrating that the majority of cancer symptoms are associated with inflammation[17]. Symptoms such as pain, fatigue and anorexia are highly prevalent in patients with advanced cancer[18]. The symptoms of pain, anorexia, cognitive dysfunction and breathlessness have all been shown to be associated with systemic inflammation in patients with advanced cancer[17]. Studies have linked increased concentrations of pro-inflammatory cytokines including IL-1 receptor antagonist, TNF-α, IL-6, IL-8 and epidermal growth factor to severe levels of fatigue, cognitive impairment, and reduced quality of life[19].

The symptom of pain in patients with advanced cancer has been shown to correlate positively with CRP, raising the possibility of a relationship between pain and systemic inflammation in cancer[20]. Animal models have suggested the ability of pro-inflammatory cytokines, including TNFα, to induce exaggerated pain responses[21].

Other symptoms present in patients with advanced cancer include weakness, malaise, fever and depressed activity. These non-specific symptoms have collectively been named ‘sickness behaviour’ and have been documented in all animal species studied with systemic inflammation secondary to infection[22]. There is evidence to support a role for pro-inflammatory cytokines in inducing sickness behaviours[23,24]. Sickness behaviours include the symptoms of lethargy, depression, anorexia and reduced social functioning, and it has been hypothesised that the pro-inflammatory cytokines released in cancer are also related to these symptoms[24].

It can therefore be seen that high levels of tumour burden are associated with high levels of systemic inflammation and symptomatology. This raises the possibility that biomarkers of systemic inflammation together with symptomatology may be of potential use in a clinical setting, that they can be used as markers of disease severity in advanced cancer, and in turn be associated with prognosis.

1.3 Clinical markers of inflammation and prognosis

In the clinical environment, certain inflammatory biomarkers and clinical markers are thought to be useful in prognostication and surrogate markers of disease severity and systemic inflammation. These markers are surrogate markers of the pro-inflammatory tumour microenvironment and systemic cytokine response.

Systemic inflammation resulting from tumour presence results in changes in protein metabolism and the establishment of the acute phase response. A key component of this is the hepatic production of acute phase proteins such as C-reactive protein (CRP). As the half-life of CRP is 19 hours, levels only remain elevated when there is on-going stimulus. CRP is regulated by interleukin-6 (IL-6). CRP can therefore be viewed as a surrogate marker of IL-6[25,26]. Elevated levels of CRP, as a marker of the systemic inflammatory response, have been shown to be an important prognostic factor independent of tumour stage[27]. The magnitude of the elevation in CRP has also been shown to correlate with reduced survival in patients with cancer, particularly advanced cancer, independent of tumour stage. Studies have found that serum CRP concentration is a useful prognostic indicator in patients with unresectable pancreatic cancer[28], gastro-oesophageal cancer[28], urinary bladder cancer[29], renal cancer[30], and non-small cell lung cancers[31]. The presence of an acute phase protein response has also been identified as an index of tumour recurrence[32].

The relationship between CRP and albumin is similar in patients with cancer regardless of tumour type. Albumin concentration is a reflection of both systemic inflammation and the amount of lean tissue. In patients with cancer, serum albumin concentration reduces as CRP increases[33,34]. An abnormal low albumin itself, however, has not been shown to be an independent prognostic indicator[35,36].

Other biomarkers, have been found to be associated directly with prognosis in advanced cancer. For example white cell count (WCC) has been identified as a statistically significant prognostic marker in patients with non-small cell lung cancer (NSCLC) on univariate analysis and the same study also demonstrated that CRP and WCC both independently correlated with prognosis[37].

Leucocytosis and lymphocytopenia have been identified as predictors of survival in advanced cancer[38,39].

The reduction of pyruvate by nicotinamide adenine dinucleotide (NADH) to form lactate is catalysed by LDH. NADH is involved in all cell damage repair and enzyme reactions in the body. It is therefore involved in the propagation of the tumour microenvironment. LDH and lactate are known to reflect the tumour burden and the invasive potential of tumour. Elevation of the serum enzyme LDH has been associated with reduced survival. This has been reported in lung cancer[40], renal cancer[41], head and neck cancer[42], pancreatic cancer[43], colorectal cancer[44], prostate cancer[45], and haematological cancers[46]. It has also been identified as an independent prognostic factor of poor survival in patients with advanced cancer both in the terminal[47] and non-terminal stages of illness[48].

Clinical markers have also been investigated as prognostic indicators of survival. These include Performance Status (PS). PS is a measurement of the level of a patient's functioning in terms of being able to care for themselves, and physical activity level. The Karnofsky Performance Scale (KPS) is the most commonly used tool for quantifying the functional status of patients with cancer[49]. It is an 11 point rating scale which ranges from normal function (score 100) to dead (score 0). A direct relationship has been confirmed between KPS and survival[50]. One study of the KPS noted that it accurately predicted early deaths, however it also noted that elevated initial KPS scores did not necessarily predict long survival[51]. PS in combination with tumour type, however, has been shown to be a useful prognostic indicator[52]. Survival data for individual cancers exist but are not tailored to an individual patient. The addition of PS in combination with tumour type in predicting prognosis is easy to apply in a clinical setting, relevant to the individual patient and quick to perform.

1.3.1 Combined Clinical Markers of Prognosis

As stated, certain symptoms in cancer are linked directly to systemic inflammation. There are specific clinical symptoms or indices which have been validated to show a direct association with cancer survival and will be discussed later in this thesis. Some clinical biomarkers are used in combination and demonstrate the burden of systemic inflammation upon prognosis in advanced cancer.

There are many other important clinical markers. Certain clinical signs in addition to symptoms which together characterise the clinical condition termed 'the common terminal pathway' have a prognostic impact. These are nutritional status, symptoms of the cancer anorexia-cachexia syndrome, dysphagia and xerostomia[53]. Dyspnoea, anorexia-cachexia, dysphagia and xerostomia were identified in The National Hospice Study as having independent predictive value in estimating survival time[54]. Early satiety[55], fatigue[56], cognitive impairment[57], and nausea[58] have also been seen to be independently associated with reduced survival. Absence of depressed mood has been identified as an independent predictor of survival[58]. Conversely, it is of interest that studies have also demonstrated a relationship between depression or depressed mood and cancer progression[59].

In pancreatic cancer it has been noted that the absolute number of symptoms increases with deteriorating PS and this combination is associated with shorter survival[60]. Similarly, in gastric cancer persistent vomiting at diagnosis has been shown to be independently inversely associated with length of survival[61]. There are other signs and symptoms which have occasionally been shown to

be significant, namely constipation, dizziness, anxiety, diarrhoea, haemorrhage and poly-morbidity[53].

In summary a prognostic factor provides information on survival and is not influenced by treatment. At this point, it is important to emphasise the difference between prognostic and predictive factors. This thesis focusses on prognostic factors in advanced cancer. A predictive factor is a condition, finding or biomarker that can be used to help predict the effect of a therapeutic intervention such as chemotherapy or radiotherapy. A predictive factor can be a target for therapy. Predictive factors may be predictive for one treatment and not another. Predictive factors may alone be proven to have prognostic value after identification and validation however the term prognostic and predictive should not be used interchangeably.

1.4 The importance of prognostication

Prognostic indicators and prognostication as a whole are crucial in cancer care management. Prognostication helps the clinician predict the likely disease trajectory, helps guide treatment plans, predict response to treatment and this allows the patient to be given a tailored treatment plan which avoids unnecessary investigations and treatments. It also aids the clinician in predicting the length of survival which also assists patients with future planning and advance care plans.

1.5 Conclusion

Systemic inflammation has always been implicated in both cancer genesis and maintenance of the cancer state; Mantovani described inflammation as the 7th hallmark of cancer[62]. In some cancers, pre-existing inflammation may predict tumour development (e.g. ulcerative colitis and colonic carcinoma). The presence of inflammation may also be necessary for the maintenance of the tumour microenvironment and promote tumour growth. Markers of inflammation in cancer have been discovered and can be linked to tumour progression and ultimately survival in advanced cancer. These are termed prognostic markers.

Numerous prognostic markers have been identified, both clinical (e.g. symptoms and signs) and laboratory based (e.g. biomarkers such as. CRP). They have been tested on univariate analysis for accuracy of survival prediction in advanced cancer. They have been combined in prognostic tools to act synergistically and improve prognostic accuracy. Which tool or marker is best, however, is as yet undetermined since despite much research, they have not been directly compared in a single study.

1.5.1 Thesis Aim

The overall aim of this thesis was to examine prognostic markers and prognostic tools in advanced cancer. Specific aims were:

- To identify the validated prognostic markers and prognostic tools in advanced cancer.

● To compare all the validated prognostic markers in advanced cancer and then determine which prognostic marker is of greatest significance in estimating survival in advanced cancer.

● To perform a systematic review and to examine prognostic tools for use in patients with advanced cancer. Since 2003, a number of additional prognostic tools have been developed and validated using several of the prognostic factors and the aim of the systematic review was to examine these tools. This is examined in Chapter 2. This systematic review has been published as a peer reviewed paper in the Journal of Pain and Symptom Management, a copy of which is in Appendix II.

● To analyse a biobank data set with the purpose of testing and potentially validating prognostic markers of greatest significance in patients with advanced lung cancer. This is examined in Chapter 3. This study has been published as a peer reviewed paper in Lung Cancer, a copy of which is in Appendix II.

● To perform a prospective observational study to examine fully all the prognostic markers already established as having independent prognostic significance in the systematic review and biobank analysis, and determine which are most predictive of survival in patients with advanced cancer. This is examined in Chapter 4. This study has been submitted for publication.

Chapter 2 Systematic review of prognostic tools in patients with advanced cancer

The chapter is based on the paper by Simmons et al[63](Appendix II).

2.1 Background

The prediction of probable prognostic outcome is a core skill fundamental to the clinical management of patients with advanced cancer. The Tumour, Node, Metastasis (TNM) staging system is an anatomical staging system based upon the tumour size, lymph nodes affected and the presence of metastases[64]. It was developed in the 1940s and is still used today to classify cancer stage, primarily to guide treatment decisions. The letter T refers to the primary tumour, its size and whether it has extended into adjacent structures. N refers to the extent of lymph node involvement and M refers to the presence or absence of metastasis. The precise TNM classification of each cancer stage varies according to the underlying primary cancer. Metastatic staging also varies in relation to the number and type of organs involved depending on the primary cancer. Although not developed as a prognostic tool per se, it may be used as a surrogate prognostic tool. However in patients with metastatic disease, the ceiling value of TNM classification is reached and as such it does not provide any discriminatory power beyond this. When a patient has an "M1" TNM classification, other measures are needed to guide clinical management. For example, if a patient has an M1 classification they may be amenable to and receive benefit from anti-cancer therapy, but conversely may not, and as such the decision as to whether to give anti-cancer therapy can be challenging. This is where a patient's PS is very important and will help guide further management. As mentioned in Chapter 1, the KPS is the most commonly used tool for quantifying the functional status of patients. Another tool used is the Eastern Cooperative Oncology Group (ECOG) Performance Status scale

which was developed by the Eastern Cooperative Oncology Group and scores patients as being fully active (ECOG 0) to dead (ECOG 5)[65]. Both KPS and ECOG are excellent tools for assessing the degree of functional impairment experienced by a patient, however they are limited due to being subjective and frequently dependent upon what a patient reports as their functional ability, rather direct observation by the clinician. Such subjectivity can lead to inaccuracy in the assessment of PS and make planning further management more difficult. It is for this reason that prognostic tools were developed to estimate survival and thus could be used to plan further clinical management. This is of clinical relevance since currently, treatments such as chemotherapy and radiotherapy are often given late in the disease and at times, given inappropriately[66,67]. The treatment focus for patients with advanced cancer should be optimum overall clinical management, rather than prescribing additional medications with potential side effects to add to the list of symptoms already suffered as a direct consequence of their cancer. The focus of life prolonging treatments has moved from discussing their risks, including mortality risks, to focussing on their overall benefits, including improved quality of life for patients with an advanced stage of cancer with limited lifetime left.

In the clinic, prognosis is based on various factors including stage of disease, PS, the treating clinician's previous clinical experience and their knowledge of cancer trajectories. Using these individual factors, which are frequently subjective, to estimate prognosis can result in prognostication by clinicians being often erroneous, optimistic, informal and subjective[68,69] with one in five prognoses being inaccurate[70]. A combination of specific prognostic factors, tested and validated for their accuracy in estimating survival, may result in better prognostication.

The prognostic tools that have been validated for use in advanced cancer comprise of several indices, the majority of which have been proven on

univariate analysis to have prognostic significance in patients with advanced cancer. Systematic review of existing tools may allow identification of the significant individual prognostic markers in advanced cancer and also review which tool has the greatest accuracy in terms of survival prediction. The tools with greatest prognostic accuracy can be inferred to be comprised of prognostic markers with greatest prognostic accuracy and also highlight the prognostic markers which should be included for further examination in a prospective study.

In 2005, the European Association for Palliative Care (EAPC) recommended key prognostic factors for use in advanced cancer and these recommendations were published in the Journal of Clinical Oncology, with the aim of improving prognostic accuracy in patients with advanced cancer[53]. The recommendations were informed by eight studies examining different prognostic tools which had been published in the preceding decade (1993-2003). The tools were notable for their ease and rapidity of use in determining life expectancy and included the Terminal Cancer Prognostic Score (incorporating dysphagia, cognitive failure and weight loss), the Palliative Performance Scale, the Palliative Prognostic Index, the Palliative Prognostic Score and the Delirium- Palliative Prognostic Score. The tools were assessed for bias based upon a quality and study type classification system (Level I to IV) which was adaptation of a classification system on the Centre for Evidence based Medicine Website. The EAPC concluded that the level of evidence for these tools was either Level II (heterogeneous met-analyses or confirmatory studies) or Level III (exploratory studies) both with a low risk of bias.

Since 2003, a number of additional prognostic tools have been developed and validated using several of these key prognostic factors. As part of this thesis, a systematic review was performed to examine these. The aim of the systematic review was to examine prognostic tools for use in patients with

advanced cancer in the period since the previous recommendations were published in 2003 and update the recommendations made previously.

2.2 Methods

The following databases were searched; Medline (2003–2015), Embase Classic + and Embase (2003-2015) using the search terms stated in Appendix I. The searches focussed on studies of prognostic tools in patients with advanced cancer regardless of the original primary tumour site. The date of the last literature search was 30th April 2015. Given that this was a systematic review, ethical approval was not required.

2.2.1 Eligibility Criteria

Eligible studies met the following criteria: population with advanced cancer (defined as an incurable cancer); original studies; study population (n) greater $\geq$100; study population aged $\geq$ 18 years; quantitative clinical and/or biomarkers were examined; a multivariate statistical model was described; the tool had been examined and validated in two or more independent data sets; published in English; published after 2003 (end date of original literature search) [71]. The primary outcome measurement examined was survival prediction based on the use of the prognostic tool in the specific patient population. Studies were excluded if: a univariate survival analysis only was described; the tool was designed for use in one specific population with one specific cancer type (e.g. only patients with specific stage of lung cancer) or qualitative indices were exclusively used to predict survival.

2.2.2 Data extraction and analysis

The initial database search was undertaken and duplicates removed. Two researchers (CS and KM) independently screened each study for eligibility based on the title, then abstract and finally each full text article. Any discrepancies between the two researchers were settled after discussion with a third party (BL). From this the necessary data for descriptive and quantitative analyses, were extracted onto a paper proforma initially, then transcribed into an electronic table once agreement had been reached as to the papers to include in the systematic review. This process was based on the mandate of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Symposium (PRISMA)[72]. The data extracted included the descriptors of the patient population, length of survival and information regarding survival prediction. The analysis of each study was performed using standard quality assessment criteria which were then summarised for statistical analysis and comparison where possible[73]. Studies were presented according to the prognostic tool described.

2.3 Results

2.3.1 General Considerations

The literature search process is shown in Figure 2-1. Following title and abstract review, 179 articles were reviewed in full which resulted in 51 studies fulfilling the eligibility criteria. Where studies examined populations with both

cancer and non-cancer diagnoses, only those populations with cancer were included.

In total 1038 studies did not fulfil the inclusion criteria. The reasons for exclusion included if a univariate statistical model was described, the model was specific to a population with one cancer type e.g. patients with lung cancer, the model focussed on non-malignant life limiting conditions e.g. cardiac failure, qualitative indices were exclusively used to predict survival, the model focussed upon subjective patient indices e.g. patient generated subjective global assessment, the model was based upon exclusive or direct relationship to the histological staging of the cancer, the model was based upon or tested after therapeutic intervention e.g. post surgery, post radiotherapy, and if the model was based upon or tested in patients receiving life prolonging intervention e.g. chemotherapy.

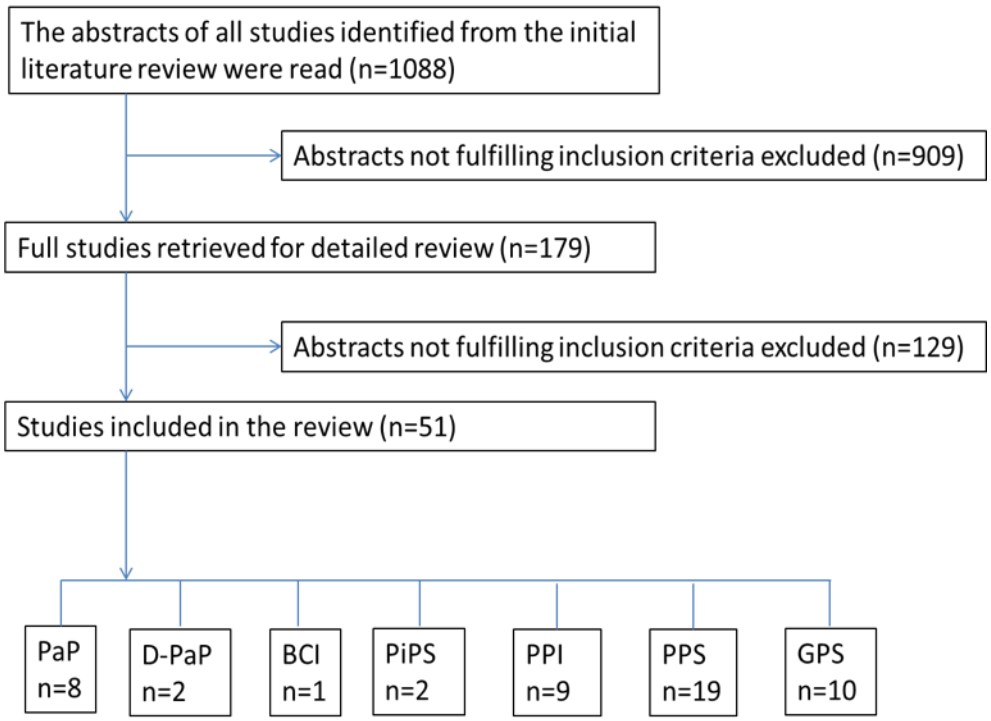

Figure 2-1 Flowchart detailing the search process

From the 51 eligible studies, seven different prognostic tools were identified which were evaluated across different places of care, different primary cancer types and assessed survival prediction ranging from 3 weeks to overall survival. A summary of these is detailed in Table 2-1.

Table 2-1 Summary of individual prognostic tools

Tool	Number of variables		Cancer types (mixed/single)	Number of studies*
	Clinical	Biomarkers		
PaP	4	2	Mixed and single	8
D-PaP	5	2	Mixed only	2
BCI	0	2	Mixed only	1
PiPS A PiPS B	13 9	0 8	Mixed	2
PPI	5	0	Mixed only	9
PPS	6	0	Mixed only	19
GPS/ mGPS	0	2	Mixed and single	10

The term “Clinical” refers to signs elicited by clinical examination or symptoms described by the study subjects. The term “Biomarkers” refers to serum biomarkers of prognostic significance. *Studies which were eligible for inclusion. PaP refers to The Palliative Prognostic Score, D-PaP refers to The Delirium- Palliative Prognostic Score, BCI refers to B12/CRP index, PiPS refers to Prognosis in Palliative Care Study (Parts A and B), PPI refers to Palliative Prognostic Index, PPS refers to Palliative Performance Scale, GPS refers to The Glasgow Prognostic Score and mGPS refers to the Modified Glasgow Prognostic Score.

The tools identified were the Palliative Prognostic Score (PaP) [8 studies], Delirium-PaP (D-PaP) [2 studies], B12/CRP Index (BCI) [1 study], Prognosis in Palliative Care Study (PiPS) [2 studies], Palliative Prognostic Index (PPI) [9 studies], Palliative Performance Scale (PPS) [19 studies] and the Glasgow Prognostic Score (GPS) [10 studies]. All seven tools could predict survival in advanced cancer with statistical significance ($p<0.05$).

Table 2-2 details each of the prognostic tools and reports survival prediction. These prognostic tools used a combination of clinical and/or serum biomarker parameters. The most common clinical parameters used were PS which was included in six tools and anorexia and dyspnoea, both of which were included in four tools each. The most common biomarkers were C-reactive protein (CRP), WCC, Lymphocyte count and Albumin. CRP was included in four tools and WCC, Lymphocyte count and Albumin were each included in three tools. The number of parameters used in each tool ranged from two (GPS, BCI) to 17 (PiPS B), and the median number reported was seven. All seven tools were independent in their ability to predict survival in advanced cancer, $p<0.05$. The individual clinical and serum biomarkers are summarised in Table 2-3.

Table 2-2 Prognostic Tools and survival predictions

Tool	No. of studies	Author	Country	Year	Cancer type	Total (n)	Survival Outcome (continuous/categorical)	Median Survival (weeks)	HR	Statistical Test used if not HR	p value	Summary of predictive accuracy
PaP	8	Glare et al[74]	Australia	2004	Various	100	Categorical (4wk)	12	-	Log rank	<0.0001	log rank trend test (χ^2_1) 25.65 p<0.0001
		Tassinari et al[75]	Italy	2008	Various	173	Continuous	26	-	Unclear	0.022	p=0.022
		Naylor et al[76]	Brazil	2010	Various	250	Categorical (30d)	1 – 20		Log rank	<0.0001	log rank test =125.5 p<0.0001
		Hyodo et al[77]	Japan	2010	Various	208	Continuous	2- 12	0.536-3.72	-	Range	HR 0.536-3.72 p 0.002 - <0.001
		Tarumi et al[78]	Canada	2011	Various	777	Continuous	5	0.279-0.476	-	<0.001	HR 0.279-0.476 p<0.001
		Maltoni et al[79]	Italy	2012	Various	549	Categorical (21d and 30d)	3	-	AUC/ log	<0.0001	AUC 0.72, log rank 322.65
		Kim et al[80]	Canada	2014	Various	415	Categorical (4wk)	-	-	-	-	Optimal scores for predicting 4wk survival over 10
		Hui et al[81]	USA	2014	Various	222	Continuous	15	1.08	-	0.008	95% CI 1.02-1.13
						(n=2694)						
D-PaP	2	Maltoni et al[79]	Italy	2012	Various	549	Categorical (21d and 30d)	3	-	AUC	<0.0001	AUC 0.73 (95%CI 0.71-0.74) , p<0.0001
		Scarpi at al[82]	Italy	2011	Various	361	Categorical (30d)	4	1.6	-	<0.001	HR 1.6 (95%CI 1.22-1.99) p<0.0001
						(n=910)						
BCI	1	Kelly et al[83]	UK	2007	Various	329	Categorical (90d)	4 - 10	-	Log rank	<0.001	Log rank test for Trend χ^2 = 18.38 p<0.001
						(n=329)						
PiPS	2	Kim et al[84]	Korea	2013	Various	202	Categorical (2wk, 7wk, >8wk)	-	-	Sens./Spec.	-	Sensitivity 37.1% -64%, Specificity 61.6% -87.7%

		Gwilliam et al[85]	UK	2011	Various	1018	Continuous	< 1 - 14	-	AUC	-	AUC= 0.79-0.86
						(n=1220)						
PPI	9	Stone et al[86]	Japan	2008	Various	194	Continuous	<1 - 10	-	PPV, NPV	-	PPV 86%, NPV 76%
		Hakim et al[87]	Egypt	2011	Various	100	Continuous	11-15	-	Surv	-	Median survival range 77 – 107d
		Maltoni et al[79]	Italy	2012	Various	549	Categorical (21d and 30d)	3	-	AUC/ log	<0.0001	AUC 0.62, log rank 80.54
		Cheng et al[88]	Taiwan	2012	Various	623	Categorical (21d)	1-10	0.2-0.5	-	≤0.001	HR 0.2 for PPI 0-4, HR 0.5 for PPI 4.5-6
		Kim et al[80]	Canada	2014	Various	415	Categorical (4wk)	-	-	scores	-	Optimal scores for predicting 4wk survival over 4.5
		Arai et al[89]	Japan	2014	Various	374	Categorical (3wk)	-	6.6	-	<0.01	Initial PPI associated with death within 3 weeks HR 1.3 (95% CI 1.2-1.4) p<0.01 A change in PPI associated with death within 3 weeks HR 6.6 (95% CI 4.9-9.0) p<0.01
		Kao et al [90]	Taiwan	2014	Various	2392	Continuous	5	0.63	AUC	<0.001	Combination of initial PPI and change in PPI is useful AUC 0.71(95%CI 0.694-0.731), 72.5% accuracy, sensitivity 66.9%, specificity 77%, PPV 70.6%, NPV 73.8%
		Hui et al[81]	USA	2014	Various	222	Continuous	15	-	-	0.003	Correlation with survival on univariate analysis only
		Miura et al[91]	Japan	2015	Various	1160	Categorical (3wk, 6wk)	Up to 8	1.56	other	<0.001	PPI ≥6, HR 1.56 (95% CI 1.27-1.92), p<0.001

												(For 3 week prognosis: Sensitivity 0.684, Specificity0.705, PPV 0.620, NPV 0.760) (For 6 week prognosis: Sensitivity 0.583, Specificity 0.765, PPV 0.811, NPV 0.514)
						(n= 6029)						
PPS	19	Head et al[92]	USA	2005	Various	261	Continuous	4	-	Risk ratio	<0.05	PPS score associated with survival p<0.05
		Harrold et al[93]	USA	2005	Various	214	Categorical (7d, 30d, 90d, 180d)	-	0.96	-	<0.001	Better accuracy in predicting early deaths in cancer patients
		Sanchez et al[94]	Spain	2006	Various	250	Continuous	5	4.33, 2.5	-	≤0.003	HR 4.33 for PPS <40 p= 0.000, HR 2.5 for PPS =50 p=0.003
		Lau et al[95]	Canada	2006	Various	647	Continuous	1	1.204-18.022	-	≤0.493	HR 1.204-18.022 p 0.493 - <0.001
		Olajide et al[96]	USA	2007	Various	157	Continuous	1	1.65	-	<0.0001	HR 1.65 p<0.0001
		Lau et al[97]	Canada	2008	Various	126	Continuous	2	0.291-0.937	-	≤0.811	HR 0.291-0.937 p 0.001-0.811
		Lau et al[98]	Canada	2009	Various	347	Continuous	3	0.039-0.402	Log rank	<0.001	HR and Log rank p<0.001

		Weng et al[99]	USA	2009	Various	492	Continuous	3	-	Cox	<0.001	B -0.04, SE 0.01, Exp 0.96
		Younis et al[100]	USA	2009	Various	180	Continuous	-	1.73	-	<0.001	HR1.73 p<0.001
		Lau et al[101]	Canada	2009	Various	5097	Continuous	1	0.056-0.542	-	<0.001	HR 0.056-0.542 p<0.001
		Selby et al[102]	Canada	2011	Various	1622	Continuous	13	-	OR	≤0.1982	OR 0.460-1.705, p<0.0001 and p=0.1982 (range)
		Mhaskar et al[103]	USA	2011	Various	590	Continuous	-	-	Brier score	-	Hosmer-Lemshow goodness of fit p-value >0.1 for PPS, Brier score <0.25, AUROC >0.5
		Tarumi et al[78]	Canada	2011	Various	777	Continuous	5	0.214-0.722	-	≤0.054	HR 0.214-0.722 p 0.054 - <0.001
		Casarett et al[104]	USA	2012	Various	7391	Categorical (7d)	-	-	AUC	<0.0001	AUC 0.74
		Maltoni et al[79]	Italy	2012	Various	549	Categorical (21d and 30d)	3	-	Other	<0.001	Log rank 97.8 p<0.001, C index 0.63
		Mei et al[105]	Singapore	2013	Various	296	Categorical (90d)	5	0.31-0.52	Log ,OR	≤0.03	HR reported, Log rank p<0.05, OR 0.98 (0.96-1.00) p=0.03
		Kim et al[80]	Canada	2014	Various	415	Categorical (4wk)	-	-	-	-	Optimal scores for predicting survival ≤ 30
		Lee et al[106]	South Korea	2014	Various	606	Continuous	1	2.66	-	-	Change in score >30% significantly associated with survival, 95% CI 2.19-3.22

		Jang et al[107]	Canada	2014	Various	1655	Continuous	19	-	Log rank, AUC	<0.001	AUC 0.63 Log rank test for trend p<0.001
						(n= 21672)						
GPS	10	Sharma et al[108]	UK	2008	Ovary	154	Continuous	160	1.68	-	0.007	HR 1.68 p=0.007
		Crumley et al[109]	UK	2006	Gastro-oesophageal	258	Continuous	8 - 82	1.51	-	<0.001	HR1.51 (95% CI 1.22-1.86)p< 0.001
		Glen et al[110]	UK	2006	Pancreas	187	Categorical (12mth)	8 - 32	1.72	-	<0.001	HR 1.72 (95%CI 1.40-2.11) p<0.001
		Ramsey et al[111]	UK	2007	Renal	119	Continuous	32	2.35	-	<0.001	HR 2.35 (95% CI 1.51-3.67) p<0.001
		Forrest et al[112]	UK	2005	Lung (NSCLC)	101	Continuous	6 - 62	2.32	-	<0.001	HR 2.32 (95%CI = 1.52-3.54) p<0.001
		Partridge et al[113]	UK	2012	Various	296	Categorical (2wk, 4wk)	-	1-2.712	-	0.014	HR 1-2.712 p=0.011-0.484, p=0.014overall
		Leung et al[114]	UK	2012	Lung (NSCLC)	261	Continuous	32	1.67	-	<0.0001	HR 1.67 (95% CI 1.28-2.19) p<0.0001
		Pinato et al[115]	UK	2012	Lung (Mesothelioma)	171	Continuous	39	2.6	-	<0.001	HR 2.6 (95%CI 1.6-4.2) p<0.001
		Laird et al[116]	Biobank	2013	Various	2456	Categorical (3mth)	13-28	1.51-2.27	-	<0.01	HR 1.51-2.27
		Miura et al[91]	Japan	2015	Various	1160	Categorical (3wk, 6wk)	3 – 8	1.36	Other	0.046	GPS = 2, HR 1.36 (95% CI 1.01-1.87), p=0.046 (For 3 week prognosis: Sensitivity 0.879, Specificity0.410, PPV 0.512, NPV 0.828)

												(For 6 week prognosis: Sensitivity 0.822, Specificity 0.484, PPV 0.733, NPV 0.611)
						(n= 5163)						

The table summarises the clinical studies examining each of the prognostic tools and includes the country of origin, cancer type examined, the sample size for each study, survival outcome measurement, median survival, hazard ratio (HR) and description of statistical analysis with summary of statistical conclusion. PaP refers to The Palliative Prognostic Score, D-PaP refers to The Delirium- Palliative Prognostic Score, BCI refers to B12/CRP index, PiPS refers to Prognosis in Palliative Care Study (Parts A and B), PPI refers to Palliative Prognostic Index, PPS refers to Palliative Performance Scale and GPS refers to The Glasgow Prognostic Score. Some studies compared several of these tools in one paper which explains the disparity in the total number of studies versus papers. All seven tools were independent in their ability to predict survival in advanced cancer, $p<0.05$.

Table 2-3 Details of individual prognostic markers within each tool

Tool	Clinical Marker																						Biomarker					
	PS	CPS	Anorexia	Dyspnoea	Delirium	ambulation	activity	Evidence of disease	GCS	oedema	Global health	Breast cancer	Male genital organs	Distant metastasis	Bone meta - stasis	Liver meta - stasis	Mental test score	Heart rate	Anorexia	Dysphagia	Weight loss in last month	Fatigue	Other	WCC	Lymph	CRP	Alb	Vit B-12
PaP	x	x	x	x																				x	x			
D-PaP	x	x	x	x	x																			x	x			
BCI																										x		x
PiPS A	x			x							x	x	x	x	x	x	x	x	x	x	x							
PiPS B	x										x		x	x	x		x	x	x			x	Ur, neut, alt, alp,	x	x	x	x	
PPI	x		x	x	x	x	x	x	x	x																		
PPS	x		x			x	x	x	x																			
mGPS																										x	x	
GPS																										x	x	

This table details the individual clinical and biomarkers used in individual prognostic tools. The number of markers ranges from two (GPS) to 17 (PiPS-B). PaP refers to The Palliative Prognostic Score, D-PaP refers to The Delirium- Palliative Prognostic Score, BCI refers to B12/CRP index, PiPS refers to Prognosis in Palliative Care Study (Parts A and B), PPI refers to Palliative Prognostic Index, PPS refers to Palliative Performance Scale, mGPS refers to The modified Glasgow Prognostic Score and GPS refers to The Glasgow Prognostic Score

2.3.2 Summary of individual tools

PaP (Palliative Prognostic Score) and D-PaP (Delirium PaP)

The PaP tool (Table 2-4) was constructed by the Italian Multicentre and Study Group in Palliative Care and validated in patients with advanced incurable cancer using thirty day survival probability. The D-PaP Tool (Table 2-5) is a modified version of the PaP, incorporating a delirium assessment which slightly improved the predictive accuracy of the PaP. The PaP and D-PaP are the only prognostic tools included in this review which use clinician predicted survival (CPS) as one of their indices. The PaP has six parameters; four subjective (clinical) parameters and two objective biomarkers. The PaP and D-PaP both rely heavily on CPS, a subjective parameter which can add an extra 8.5 points to the total score (PaP maximum 17.5; D-PaP maximum 19.5). The other parameters (biomarkers and symptoms) contribute a maximum of 2.5 points making this tool heavily reliant on the clinician's expertise in prognostication.

There have been eight studies (n=2694) examining the PaP in patients with advanced cancer. Patient cohorts were unselected cancer diagnoses and included patients with a variety of cancer diagnoses (colorectal, lung, melanoma, breast, adenocarcinoma of unknown primary, genitourinary, prostate, gastrointestinal, non-small cell lung, gynaecological [cervix, ovary, uterus, vagina], head and neck, stomach, oesophageal, urological, hepatobiliary and central nervous system, endocrine and haematological). The studies were from groups in Australia (1 study), Italy (2 studies), Brazil (1 study), Japan (1 study), Canada (2 studies) and USA (1 study) thereby providing external validation of the tool. One study compared the performance of the PaP to other prognostic tools including the D-PaP, PPS, and PPI and concluded that the PaP showed greatest accuracy and reproducibility[79]. The PaP was also directly compared with the PPS and PPI tools in separate

studies[78,80]. One study comparing it with the PPS showed similar hazard ratios for the PPS (0.214 – 0.722) and the PaP (0.279 and 0.476) [78].

Another study comparing the PaP with the PPI and PPS concluded that the PaP performed better[80]. Here the accuracy of these tools and their individual subgroups were compared with the accuracy of other tool subgroups and therefore resulted in a more detailed examination of the tools compared to other methods of evaluation. Statistical methods for data analysis varied among the eight studies looking at the PaP score and the heterogeneity of the survival accuracy results means direct comparison is difficult. However all studies reported accurate survival prediction based on hazard ratios.

A key component of the PaP is CPS. From the eligible studies it was noted that oncologists' (i.e. non palliative care specialists) CPS was shown to be well calibrated but individual predictions imprecise. Studies using the CPS from non-specialists still enabled the PaP to predict the short term survival (30 days) of patients with advanced cancer 'reasonably well', however this is based on the oncologists correctly predicting less than one month survival in 70% of the patients. There was no statistical comparison of this survival accuracy to the PaP.

Two studies, comprising data on 910 patients reported the prognostic value of the D-PaP in patients with advanced incurable cancer[79,82]. Population cohorts included patients with gastrointestinal cancer, lung cancer, genitourinary cancer, hepatobiliary cancer, breast cancer and head and neck cancer. One study compared the performance of the D-PaP to other prognostic tools including the PaP, PPS, and PPI and concluded that the D-PaP was highly accurate and identified homogeneous subgroups in terms of survival, however,

D-PaP had not been validated as extensively as the other tools in advanced incurable cancer[79].

In conclusion, there is evidence that the PaP and D-PaP both predict survival in patients with advanced cancer. The D-PaP tool has not been as extensively validated compared with the PaP and both perform similarly when compared to each other. One study suggested that the D-PaP performed slightly better than the PaP (D-PaP score 0.860; PaP score 0.853), however only by a slight discriminating factor and therefore implying that modification of the PaP, a tool with a high discriminating ability score and more extensive validation, was not necessary[82] .

Table 2-4 The PaP Tool

Criterion for PaP		Score
Dyspnoea	Yes No	1 0
Anorexia	Yes No	1.5 0
KPS	≥30 10-20	0 2.5
CPS (weeks)	>12 11-12 7-10 5-6 3-4 1-2	0 2 2.5 4.5 6 8.5
Total WBC (x 109/L)	Normal ≤8.5 High 8.6-11 Very High >11	0 0.5 1.5
Lymphocyte Percentage	Normal 20-40% Low 12-19.9% Very low <12%	0 1 2.5
Risk Group	30 day survival	Total Score PaP
A B C	>70% 30-70% <30%	0-5.5 5.6-11 11.1-17.2

The PaP tool gives a score based on clinical criteria being present, which is used to estimate 30 day survival.

Table 2-5 The D-PAP Tool

Criterion for D-PaP		Score
Dyspnoea	Yes No	1 0
Anorexia	Yes No	1.5 0
KPS	≥30 10-20	0 2.5
CPS (weeks)	>12 11-12 7-10 5-6 3-4 1-2	0 2 2.5 4.5 6 8.5
Total WBC (x 109/L)	Normal ≤8.5 High 8.6-11 Very High >11	0 0.5 1.5
Lymphocyte Percentage	Normal 20-40% Low 12-19.9% Very low <12%	0 1 2.5
Delirium	Yes No	2 0
Risk Group	30 day survival	Total Score D-PaP
A B C	>70% 30-70% <30%	0-7 7.1-12.5 12.6-19.5

The D-PaP tool gives a score based on clinical criteria being present, namely delirium in addition to the PaP criteria, which is used to estimate 30 day survival.

Vitamin B12/CRP Index (BCI)

The BCI (Table 2-6) was developed by a group at the University of London, UK, following the EAPC's recommendations in 2005. It was initially validated in patients with advanced incurable cancer admitted to an elderly care facility and has been validated to estimate up to 90 day mortality. Of interest is that the BCI incorporates vitamin B12 levels as a marker of prognosis; the authors' rationale for this is that levels are elevated in myeloproliferative disorders, hepatocellular carcinoma and metastatic liver cancer. The BCI consists of two objective (biomarker) parameters, CRP and B12. However vitamin B12 is not

always analysed routinely in patients and this may reflect the lack of further research into this tool. One study comprising 329 patients reported the prognostic accuracy of the BCI in patients with advanced cancer[83]. The patient population included those with a diagnosis of neurological, head and neck, lung, urological, haematological, gastrointestinal, gynaecological and breast cancers. It reported statistical accuracy (log rank $p<0.001$) however, mortality rates differed from the sentinel study in that their mortality estimates did not fall into the 95% confidence intervals for the sentinel study. It can be concluded that the BCI can predict survival independent of the conventional factors, but requires more external validation.

Table 2-6 The BCI Tool

Total BCI score = multiply serum vitamin B12 level (pmol/l) by serum CRP level (mg/l)	
Risk Group	BCI Score
1	≤ 10000
2	10001-40000
3	>40000

The BCI score categorises patients into a risk group depending on score value.

Palliative Prognostic Index (PPI)

The PPI tool (Table 2-7) was developed in Japan in 1999, in patients with advanced incurable cancer. Depending on a patient's PPI score, survival is divided into one of three groups and estimates survival up to 6 weeks. Risk group A (PPI score ≤4) has an estimated survival of more than six weeks. Risk group B (PPI score 5) has an estimated survival of less than six weeks but greater than three weeks. Risk group C (PPI score >6) has an estimated survival of less than three weeks. The PPI tool consists of nine subjective parameters (the Palliative Performance Scale [PPS], oral intake, oedema,

dyspnoea at rest and delirium) and reports the presence or absence of signs and symptoms, with similar weighting given to the different parameters. One of the parameters used is the PPS which is a prognostic tool in its own right.

Nine studies comprising data on 6029 patients with advanced cancer looked at the prognostic value of the PPI.[79,80,86-89,117-120] The patient groups included those with a diagnosis of lung, colorectal, breast, haematological, genitourinary, urological, hepatobiliary, gynaecological, haematological, gastrointestinal, and head and neck cancer.

The studies were based in Japan (3 studies), Egypt (1 study), Italy (1 study), Taiwan (2 studies), USA (1 study) and Canada (1 study) thereby providing external validation of the tool. One study compared the performance of the PPI to other prognostic tools including the PaP, D-PaP and PPS, and other tools were found to be more accurate, in spite of the PPI showing statistically significant predictive capacity ($p<0.01$) [79]. The survival of patients varies between different studies and differentiation of the three prognostic groups was noted to be difficult at times. Statistical methods for data analysis varied between all the studies and the heterogeneity of the results means direct comparison is difficult. The studies demonstrated the PPI aided survival prediction, however the accuracy was not uniform across the different PPI groups (HR range from 0.2 - 8.0). Indeed there is no consensus for the cut off points differentiating the three prognostic groups. Following on from this, more recent research has focussed on survival in relation to a change in the PPI score[89]. A worsening PPI score has consistently been found to demonstrate a 3 week survival, a much shorter survival estimate compared with the other tools and more clinically relevant to the specialty of palliative medicine.

In conclusion, the PPI has been studied in 6029 patients and demonstrates accuracy in predicting survival; however consistency in the accuracy initially varied considerably in spite of fairly extensive validation when looking at PPI scores in isolation. A more recent approach is to review a change in PPI scores and this approach to researching the PPI appears more consistent, accurate and clinically useful.

Table 2-7 The PPI Tool

Criterion		Score
Palliative Performance Scale	10-20 30-50 ≥60	4 2.5 0
Oral Intake	Severely reduced Moderately reduced normal	2.5 1 0
Oedema	Present absent	1 0
Dyspnoea at rest	Present absent	3.5 0
Delirium	Present absent	4 0
Risk Group	Survival	PPI score
A B C	Longer than 6 weeks Shorter than 6 weeks Shorter than 3 weeks	≤4 >4 >6

The PPI tool gives a score based on clinical criteria being present which is used to estimate 3 to 6 week survival.

PPS (Palliative Performance Scale)

The PPS (Table 2-8) was validated in a palliative care population in Canada. It was originally developed as a tool to measure functional status in palliative medicine and its indices reflect different aspects of a functional activity. It provides a percentage score based upon subjective indices giving a survival estimate up to 3 months. Survival accuracy of intermediate scores has been

noted to be variable. It consists of six subjective parameters. Many of these parameters are focussed on aspects of PS including ambulation, activity levels and PS itself. PS is the gold standard in assessing a patient's fitness, therefore this tool is biased towards PS in that synonyms of PS are included as parameters (e.g. levels of ambulation, activity and self-care). One of the other parameters is conscious level, which could have been objectified by incorporating the GCS[121].

Nineteen studies comprising data on 21,672 patients with advanced cancer look at the prognostic value of the PPS. Patients included those with diagnoses of skin, central nervous system, haematological, colorectal, prostate, gastrointestinal, lung, gynaecological, genitourinary, head and neck, breast, urological and hepatopancreaticobiliary cancers. The studies were based in USA (7 studies), Spain (1 study), Canada (8 studies), Italy (1 study), Singapore (1 study) and South Korea (1 study) thereby providing external validation of the tool. In spite of variation in the reporting of the statistical methods, the PPS performed well in survival accuracy, however some of the results vary in significance. Hazard ratios vary from 0.39 up to 18.022. Due to the numerous subgroups within the tool, earlier studies in 2005 stated it was not highly discriminating in the intermediate scores. Studies taking place after 2005 tackled this issue and focussed on the significance of a 10% decrement in PPS score or poorer PPS scores and demonstrated a strong ordering effect across the different PPS categories, with highly accurate scores for a PPS of 40% or less. Patients with PPS categories greater than 50% had lower hazard ratios than patients with lower PPS scores. The PPS was compared with the PPI and PaP and again its survival accuracy was noted to be best with a PPS of 30% or less. When the PPS was compared with the PaP, D-PaP and PPI, its accuracy was not greater than 50% in spite of subgroup analysis. Direct comparison with the PaP in another study showed similar hazard ratios for the PPS (0.214 – 0.722) and the PaP (0.279 and 0.476)[78].

The PPS has been extensively studied in a large patient population with advanced cancer, including multiple cancer types. It has performed well in the majority of the studies looking at the tool individually, the only criticism being its better accuracy with lower PPS scores. It has also been compared several times with other prognostic tools with varying results and again demonstrates comparable accuracy to other tools with lower PPS scores.

Table 2-8 The PPS Tool

PPS	Range	Level of Function/condition
	100% → 0%	Normal → Death

The PPS tool gives a percentage score based on level of functioning.

The Glasgow Prognostic Score (GPS) and the modified Glasgow Prognostic Score (mGPS)

The GPS was originally developed in patients with non-small cell lung cancer and subsequently refined to the modified GPS (mGPS) (Table 2-9). The GPS combines CRP and albumin to give a score of 0, 1 or 2, with increasing score suggesting decreased survival: CRP<10=0; CRP≥10=1 (albumin ≥35); and CRP>10 + albumin<35 =2. It has been validated in individual cancer types in addition to large populations of patients with advanced incurable cancer [116]. The GPS/mGPS is entirely objective as the information needed to calculate the score is based on biomarker results. The GPS/mGPS has been developed since the EAPC's recommendations in 2005 and meets the requirements set that any prognostic tool is quick and easy to use, and its scoring system is very simple.

Ten studies examining the GPS/mGPS (n=5163) have been performed in patients with advanced cancer, across a wide range of primary cancer types.

Eight studies were from groups based in the UK, one study was from Japan and one study examined data from an international bio-bank of patients. There has, therefore, been extensive external validation of this tool. All the studies reported the accuracy of the GPS/mGPS using hazard ratios which ranged from 1.0 to 2.71. The GPS/mGPS has also been tested in individual cancer types, namely ovarian, gastro-oesophageal, pancreatic, renal and lung with similar survival accuracy, however these studies are out with the scope of this review. In terms of comparing the GPS/mGPS to other prognostic tools, comparison has been made with the PPI[91] and PS[116] (used in the PiPS, PPS, PaP, D-PaP and PPI tools) and it performed similarly to PS in terms of prognostic accuracy.

In conclusion, the GPS/mGPS has been studied extensively in a large cohort of patients with advanced cancer. It has been shown to predict survival independent of PS and has been externally validated. Its accuracy has been directly compared to the PPI, and has also been compared to PS, a key component of other prognostic tools. The GPS/mGPS is also able to predict survival accurately several months prior to death. It fulfils the EAPC's recommendations of being quick and easy to use, along with robust evidence of its accuracy.

Table 2-9 The GPS and mGPS Tools

	CRP	Alb	Score
GPS	CRP ≤10 mg/L	Albumin ≥ 35 g/L	0
	CRP > 10 mg/L	Albumin ≥ 35 g/L	1
	Normal CRP	Albumin < 35 g/L	1
	CRP > 10 mg/L	Albumin < 35 g/L	2
mGPS	CRP ≤ 10 mg/L	albumin ≥ 35 g/L	0
	CRP > 10 mg/L	albumin ≥ 35 g/L	1
	CRP > 10 mg/L	Albumin < 35 g/L	2

The GPS/mGPS tools gives a score based on level of inflammation determined by C-reactive protein (CRP) and Albumin (Alb) levels.

Prognosis in Palliative Care Study (PiPS)

The PiPS tool (Table 2-10) was developed in a UK population with locally advanced or metastatic cancer. There are two versions of the tool (PiPS A and PiPS B) and they differ in that PiPS B incorporates serum biomarkers when assessing survival. Data demonstrate that it predicts survival up to and greater than 55 days. The PiPS A has 13 subjective parameters whereas the PiPS B has nine subjective and eight objective (biomarker) parameters. Obviously the greater the number of parameters within a tool, the greater the information gained on the patient, which can assist in prognostication. Again the PiPS, similar to other tools, relies on subjective parameters, however in this case, they are orientated towards specific symptoms, signs and disease burden, and many are suggested by the EAPC as individual prognostic factors. The relative weighting of each of the prognostic factors is not available in the public domain, instead the tool is accessed electronically and a score issued. The strength of using a prognostic tool relies on utilising tools in which the evidence is clear and transparent.

Two studies comprising 1220 (UK n= 1018, Korea n= 202) patients have been performed examining the PiPS. The patients included those with diagnoses of gastrointestinal, lung, unknown primary, breast, urological, gynaecological, central nervous system, haematological, and head and neck cancers. There has been external validation of this tool. One study measured survival accuracy using sensitivity (up to 64%) and specificity (up to 87.7%) predictions[84]. The area under the curve varied between 0.79 and 0.86. Direct comparison is difficult between the two studies. The smaller of the two studies concluded that the PiPS was superior to CPS. The larger study concluded that the PiPS was equal to if not better than the CPS. Overall, these data suggest

PiPS predicts survival in patients with advanced cancer, however further studies examining this and comparing it to other tools would be of interest.

Table 2-10 The PiPS Tool

PiPS A	PiPS B	Score
Breast cancer Male Genital Organs Distant metastases Liver metastases Bone metastases Mental test score (0-10) Pulse (bpm) Anorexia Dyspnoea Dysphagia Loss of weight in previous month ECOG (0-4) Global Health (1-7)	Male Genital Organs Distant metastases Bone metastases Mental test score (0-10) Pulse (bpm) Anorexia Fatigue ECOG (0-4) Global Health (1-7) WBC Neutrophils Lymphocytes Platelets Urea ALT Alk Phos Albumin CRP	The presence/absence of the indices is entered into electronic tool which calculates survival

The PiPS tool gives an electronic score based on clinical criteria being present which is used to estimate survival

2.4 Discussion

Since the EAPC recommendations for prognostic tools were published in 2005, there has been a multitude of prognostic tools developed and/or validated. Based on the findings of this systematic review, the prognostic tool which has been studied in the largest number of patients (n=21,672) is the PPS. Other prognostic tools which are notable in terms of their validation include the PaP, the PPI, and the GPS/mGPS, which have been studied in

more than 2000 patients with advanced cancer and predict survival, p<0.001. Based on the variety of tools available, the clinician is faced with the challenge of deciding which tool, if any, they should use. However, it would appear that these tools have not been incorporated into routine daily practice. Indeed, the KPS which was initially published in 1947, and refined through the Eastern Cooperative Oncology Group Performance Score, remains the most used and highly regarded in clinical practice[122,123]. The question, therefore, remains as to why such prognostic tools, reported here, are not widely used?

One possible reason is that the majority of prognostic tools require multiple parameters, and many of these (e.g. CPS) are by definition, subjective. Furthermore, the multitude of tools now available, each using overlapping parameters, is confusing and makes comparison challenging.

This systematic review addresses the question, by comparing all established prognostic tools for the first time. It is, therefore, a step towards recognising the importance of rationalising these subjective assessments into a simpler scheme with judicious selection and refinement of existing tools[124].

This review also demonstrates that the leading prognostic clinical and biomarkers recommended by the European Association for Palliative Care in 2005, have been honed through validation to the PPI, the PPS, PaP and D-PaP. New tools, namely the GPS/mGPS, have been developed which perform equally well and have been more extensively validated than some older tools which is contrary to PRISMA's recommendation. Of note, however, is that the GPS/mGPS adheres most closely to the EAPC's recommendation that a tool should be quick and easy to use.

However, nothing is faster and more easy to use than asking the clinician their survival prediction in a clinical setting. The CPS is one subjective parameter under much debate and is included in the PaP score. It has been argued that CPS is dependent on physicians having sufficient knowledge and experience to make this assessment adequately. The inclusion of CPS, therefore, does not detract from the PaP score being a unique combination of physician's judgement, corrected and integrated with a series of other objective parameters, optimising the score. In spite of this, this tool is not used routinely. This may be due to its heavy reliance on CPS and perhaps clinicians do not need to use a tool which weights their existing opinion heavily, and therefore, they could argue, will not alter their survival estimate. The other components of the PaP have been individually validated for their accuracy in estimating prognosis, however the individual weighting of each parameter is not known, given no study has compared every clinical and biomarker important in prognosis in advanced cancer. Anecdotally, it is often said that the auxiliary healthcare assistants who perform daily personal care for patients are better at providing a survival estimate, compared to the clinician who sees the patient once they are presented to them after full personal care. However it has been shown that the multidisciplinary team as a whole are better at predicting survival than one individual clinician, be that a doctor, nurse or other healthcare professional. [125]. Again the heterogeneity of the studies examining survival accuracy of various members of the multidisciplinary team hampers further sub analysis. Healthcare assistants have been shown to be better able to predict imminent death compared to other members of the multidisciplinary team[126]. This proves the value of the clinicians, in ascertaining survival in a world where the use of technology is ever increasing. In palliative care it is the unique combination of empathy and care tailored to the individual which aids survival both quantitatively and qualitatively.

It can be said that subjectivity and the inclusion of more subjective parameters is the short fall of incorporating the PPS into the PPI. A tool with many more

parameters may increase the prognostic accuracy, however it may increase bias and complexity, which may be counter-productive. The components of this tool are heavily biased towards PS and disease burden, emphasising the importance of these objective clinical markers in prognosis.

The PPS is not useful to the treating clinician in other respects due to having too many subgroups. A tool with many subgroups is only of use if the patient is being reviewed by the clinician with sufficient frequency to fall into all these groups where their deterioration and survival trajectory are able to be followed carefully. Realistically, patients are seen more frequently in palliative medicine and oncology compared to other specialties, however in a world where the population is increasing and ageing, the current practice may be difficult to sustain, and therefore the PPS may not be suitable to use in modern healthcare.

A tool relying on objective parameters is attractive to a clinician, however the BCI is of no use clinically when vitamin B12 is not routinely tested in clinical practice unless there is a clinical indication. It could be argued that two simple blood tests help predict survival, however this tool is outperformed by the other tools both in terms of survival accuracy and validation.

The GPS/mGPS is a tool which appears to match many of the desirable attributes of the tools in terms of survival accuracy, ease of use and objectivity and also incorporates two simple blood tests performed on a routine basis in patients regardless of the healthcare setting. These blood tests are cheaper to perform since they can be analysed in batches and are freely available in all UK laboratories irrespective of geography. In the clinical setting the GPS/mGPS is quick to calculate and may be preferred by more junior clinicians who can use this to estimate survival accurately, in spite of their own relative

inexperience in prognostication. Applicability of a tool in terms of ease of obtaining the relevant information and calculation speed are important issues to consider in a time pressured healthcare system.

Many of the tools incorporate several parameters which, although may make it more laborious for the clinician to collate the information, have the advantage of accuracy of survival prediction. The PaP and D-PaP have the correct balance of objective and subjective parameters and have been validated in many populations. The treating clinician is more likely to trust these tools which incorporate objective clinical indices and are complementary to and value the addition of the clinician's opinion and expertise in prognostication.

Ultimately prognostication is used to guide patient care and the value of estimating survival of less than one month is important in the UK palliative care system, where there is a limited supply of inpatient palliative care beds. This is the advantage of the PPI which gives accurate survival estimates for a subgroup expected to survive less than three weeks.

Identifying the optimal prognostic tool for use in patients with advanced cancer is challenging. In some ways the findings of this systematic review have made it less so by rigorously assessing the supporting evidence for each tool. However, the heterogeneity of the populations studied across the tools limits the strength of recommendation that can be made. For example, various settings (patients in a cancer centre versus those patients in a specialist palliative care unit), various tumour types (given, prognosis varies significantly in a patient with metastatic lung cancer versus one with metastatic breast cancer) and various survival methodology analyses (Hazard Ratio's, PPV etc) means that a direct comparison of these tools is not possible.

Based on simplicity, its objective nature and similarity with PS in terms of survival prediction, the GPS/mGPS is placed in a favourable light. However the evidence within this review is insufficient to advocate its use over other existing prognostic tools[116 116,127].

The strengths of this review are that two researchers performed the data extraction of all the studies which looked at a broad array of patients with different cancers being looked after in different healthcare settings. This in-depth review has resulted in a clear definition of the research priorities in this field.

There are several limitations worthy of mention. Data looking at how well the tools performed in non-malignant terminal illnesses were excluded from the review. However, it could be argued that a tool which predicts death regardless of the underlying condition is more accurate and of greater use for all patients at the end of life. Studies were excluded if they were descriptive, that is qualitative research studies, and did not address survival accuracy related to individual tool scores. Other limitations were that the review selected only studies reported in the English language, excluded haematological malignancies and focussed on the adult populations. Direct comparison of the tools was limited due to heterogeneity of the results.

Future research must therefore rigorously test and validate all the prognostic tools in all populations with all cancer types and compare them using the same statistical methods. The tools incorporating objective clinical indices, namely biomarkers, still require rigorous testing and validation in all populations and cancer types, using comparable statistical methods. Using the same

population to train and test a tool offers internal validation but more external validation is required to compare the different tools with each other. External validation is complex and time consuming, especially as it should be performed prospectively. The heterogeneity of the reporting measures in this review precluded direct comparison of all the prognostic tools, which is essential to compare their efficacy and accuracy, robustly. Only some of the tools have been compared to each other. There is now a pressing need to rationalise such information and a prospective study is required to test all the tools in non-training populations.

2.5 Conclusion

The EAPC recommended there is an urgent need to rationalise core tools in patients with advanced cancer, that new tools are not required but that 'judicious selection and refinement of existing tools with appropriate properties should be advocated'[128]. Since the report in 2005, it is clear that the decade-old recommendations for developing and validating prognostic tools have been followed. There is a greater awareness of the importance of accurate survival estimates demonstrated by ongoing validation of prognostic tools, with more of the tools being validated incorporating biomarkers, all adhering to the recommendations of the EAPC.

Evidence based medicine is now at the forefront of all clinical practice and the choice of prognostic tools used in patients with advanced cancer should not be an exception to this rule. This review demonstrates that although validation of prognostic tools has been performed, these tools are not yet ready for routine use in the clinic. Further validation was required in 2005 and some has occurred, however not enough for clinicians to incorporate the tools into their clinical practice. Prognosis remains a central tenet of care in cancer, and

validated tools, applied correctly, may serve to improve patient care. Future research should focus on the parameters of greatest prognostic significance from the best performing existing tools. They should then be tested and refined to create one accurate and simple tool with fewer parameters, which should then be validated in a prospective study rather than using retrospective data analysis of existing populations.

Chapter 3 Exploratory Analysis of Potential Prognostic Markers in Advanced Lung Cancer – a biobank analysis study

The chapter is based on the paper by Simmons et al[127](Appendix II).

3.1 Background

By examining and comparing the available prognostic tools, it is clear there are numerous prognostic markers which, in combination, have been validated to be accurate in estimating survival. The literature review detailed in Chapter Two highlighted that the tools comprised of objective biomarkers perform equally as well as those comprised of more subjective clinical markers, and confirmed that inflammatory biomarkers have been demonstrated to help predict prognosis in advanced cancer, with the GPS/mGPS performing similarly to PS in terms of survival predictions[63].

This chapter reports a biobank analysis which was performed to focus on the prognostic markers of greatest significance in patients with advanced lung cancer. The purpose of this study was to perform retrospective analysis of an existing dataset of subjects with lung cancer, with the purpose of testing and potentially validating prognostic markers in advanced lung cancer. The process could then be extrapolated to evaluate fully all prognostic markers in advanced cancer in a further prospective study which is outlined in Chapter 4.

The majority of the tools utilise PS as a prognostic marker, yet it is a subjective index based upon information obtained by the clinician. However in spite of this, there is

clear reliance and bias towards PS and also weight loss, which are prognostic markers entrenched in current clinical practice.

PS is an independent prognostic factor which is established in cancer and is often used to guide treatment [129]. A PS is one of several criteria to be considered when treating patients with lung cancer[130]. The use of PS as a prognostic factor in lung cancer is particularly relevant as up to 40% of patients with lung cancer presenting at oncology clinics have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 2 (defined as being 'ambulatory and capable of self-care but unable to carry out any work activities; up and about for more than 50% of waking hours) [65,123]. A PS of ECOG 2 is the minimum level of fitness required by a patient prior to being considered for treatment. Furthermore, patients with lung cancer are more likely to have a poor PS compared to those with other cancers[131]. Indeed poor PS may also preclude patients from participating in clinical trials, thereby potentially excluding them from the opportunity to receive maximal treatment[131].

Although PS remains the gold standard prognostic marker and is used to guide treatment stratification, limitations such as its subjective nature have been the impetus for the development of objective measures of prognosis.

There are numerous objective indices to stage and quantify the disease burden in a patient with cancer and many are themselves, predictive of survival. One clinical objective index which is measured routinely in oncology clinics including lung cancer clinics, is weight and the presence of weight loss. Weight loss is a very common symptom in lung cancer with 60% of patients having significant weight loss (10% loss of body weight) in the preceding six months[132].

Studies have linked weight loss in patients with lung cancer to reduced survival regardless of treatment received. In a study of patients receiving chemotherapy, those

with weight loss were less likely to complete their full cycle of chemotherapy treatment and more likely to experience toxicity from therapy, thereby reducing their opportunity to receive maximal anti-cancer treatment[133]. It is also recognised that patients with severe weight loss are often excluded from receiving concurrent chemo-radiotherapy, thereby precluding these patients from being administered possibly effective therapies[134]. Limitations of the treatments available and also the poor prognosis for all patients with lung cancer, will inevitably contribute to the increased psychological distress which patients with lung cancer are known to experience[135]. In lung cancer, patients with weight loss have greater levels of psychological distress, lower quality of life and increased levels of fatigue[136]. Weight loss itself has been investigated and has been found to be an independent prognostic factor in patients with small cell lung cancer, non-small cell lung cancer and mesothelioma. Furthermore, stabilisation of weight during treatment for lung cancer can be associated with less disease progression in non-small cell lung cancer[133], clearly demonstrating the importance of weight loss in this patient population. Therefore, in lung cancer weight loss has both symptomatic and prognostic relevance.

Measures of the systemic inflammatory response have now been established as having independent prognostic value in cancer. Both CRP and albumin, two biomarkers of systemic inflammation, independently and combined as part of the GPS score, have been found to be of prognostic value in patients with advanced cancer[116,137]. The GPS has also been shown to be an independent predictor of survival in patients with inoperable lung cancer[138]. In addition, the GPS score has also been shown to correlate with weight loss in patients with advanced cancer[137]. The mGPS score has also been shown to correlate with weight loss in patients with advanced cancer, and is associated with increased treatment toxicity, reduced treatment response and poor nutritional status[139-141]. The GPS must, however, be tested in a prospective study and its accuracy compared to other important clinicopathological factors.

Although weight loss, PS and the mGPS/GPS have each been shown to be of independent prognostic value in lung cancer, they have not been compared directly with each other.

The primary aim of this study was to test and potentially validate these prognostic factors in patients with advanced lung cancer by analysing a biobank data set. A secondary aim was to assess if independent prognostic factors could be combined to improve survival prediction in patients with lung cancer.

This study was of great importance to the thesis because methodologically it was a proof of concept study prior to the subsequent prospective study (Chapter 4). The data selection and analysis served as a platform on which to plan the subsequent prospective study.

3.2 Materials and Methods

The study was a retrospective analysis of a prospectively acquired biobank dataset which recruited consecutive patients from two University Hospitals in Greece: the first cohort was evaluated in the University Hospital of Herakleion between 6 February 2006 and 12 October 2010 (with follow-up until 27 October 2011), and the second in University Hospital of Larissa between 30 March 2010 and 13 December 2013 (with follow-up until 1 June 2013). Whilst the data were collected by colleagues in Greece, data analysis was performed by the thesis author (CS). Ethical approval was granted for this study in Greece.

Eligible patients were 18 years of age or older, had newly diagnosed advanced lung cancer (stage IV) and were due to start systemic anti-cancer therapy.

The following data were collected: sex, age, cancer type, body mass index (BMI), percentage weight loss in the preceding 3 months, PS, albumin, CRP, and survival status at follow-up.

Age, percentage weight loss in the preceding 3 months, PS, CRP and albumin were categorized using standard thresholds to aid comparison and stratification of results.

PS was measured according to the ECOG classification which ranges from grade 0 (fully active) to grade 5 (dead). ECOG grades 0 and 1 were grouped into one category owing to similar survival in these groups. Age was divided into patients under 65 years of age, between 65 and 74 years and greater than 74 years of age. Cachexia was defined as >5% weight loss, in line with the international consensus classification[20].

CRP and albumin values were used to calculate the mGPS score for each patient. The limit of detection for CRP was 5mg/L. The mGPS was calculated as follows: CRP≤10mg/L = 0, CRP > 10mg/L = 1, CRP > 10mg/L and albumin < 35g/L = 2.

Statistical analysis was performed using SPSS version 19. All statistical testing was conducted at the 5% level, and 95% confidence intervals (CI) are reported throughout. Where n≤10, these groups were not reported.

Individuals' demographic indices and categories were analysed and compared to their survival status. Survival time was calculated in days and defined as the time from study entry until death, or censored if alive at follow-up date. Survival at 90 days was used as an outcome measure since clinical practice often uses an estimated survival of 90 days to decide between palliation and active treatment.. Survival curves were

plotted using Kaplan-Meier methods and the log-rank test was applied. Survival analysis was performed using Cox proportional hazards model and hazard ratios (HR) were calculated. Multivariate survival analysis was conducted using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival. Stratification by lung cancer histology was performed for the survival analysis. Factors that were predictive of survival in the multivariate analyses were finally grouped together to assess whether they had better prognostic accuracy when grouped together.

The study has been conducted and adheres to the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines[142].

3.3 Results

There were 390 patients included and their demographics are detailed in Table 3-1. All patients had advanced lung cancer (all stage IV). The patients had non-small cell (n=288) (73.8%) or small cell lung cancer (n=102) (26.2%). The majority of patients were male (n=341, 87.4%) and the median age was 66 years (IQR 59-73). The median PS was 1 (IQR 1-2). Median survival was 7.8 months (IQR 3.5-13.6) reflecting the advanced disease staging of the population.

Table 3-1 Patient Demographics (n= 390)

Parameter	n	%	Median (IQR)
Sex (M/F)	341 / 49	87.4 / 12.6	
Primary Cancer Type Non-small cell lung Small cell lung	 288 102	 73.8 26.2	
Age (≤65/ 65-74/ ≥ 74years)	154 / 150 / 86	39.5 / 38.5 / 22.1	Median age 66.0 (59.0-73.0)
Survival (months)			7.8 (3.5-13.6)
Weight loss in past 3 months	294	75.3	5.04 (0.8-10.2)
Weight loss category in past 3 months (%) Weight loss < 5.0% Weight loss >5.1% (cancer cachexia)	 195 195	 50.0 50.0	
BMI (kg/m(2))			25.2 (22.5-28.5)
Performance Status (ECOG) (0-1/2/3/4)			1 (1-2)

(SD = standard deviation, IQR = interquartile range) ([a] defined as weight loss >5%) The table details patient demographics including sex Male (M) or female (F), cancer type including Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), number of patients in each age group, median survival, the presence of weight loss and degree of weight loss experienced, body mass index (BMI) and ECOG Performance Status summary. Interquartile range (IQR) listed.

The minimum and median follow-up for survivors was 0.6 months and 12.8 months, respectively. At the time of cessation of data collection, 107 patients were alive and 283 had died. The median weight loss in the previous three months was 5.0% (IQR 0.8-10.2). The median BMI was 25.2 (IQR 22.5-28.5). The relationship between clinico-pathological factors and survival is illustrated in Table 3-2. On univariate survival analysis, older age ($p=0.004$), male sex ($p=0.009$), histological subtype ($p=0.007$), weight loss (%) in the previous 3 months ($p=0.001$), PS ($p<0.001$) and mGPS ($p<0.001$) were significant predictors of survival. On multivariate analysis only PS ($p<0.001$) and mGPS ($p<0.001$) were predictors of survival.

Table 3-2 The relationship between clinic-pathological factors and survival in patients with metastatic lung cancer (n=390)

Parameter	n	%	Univariate		Multivariate	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Sex (M/F)	341/ 49	87.4/12.6	0.60 (0.41-0.88)	0.009		
Age (≤65/ 65-74/ ≥ 74years)	154 /150/86	39.5/38.5/22.1	1.28 (1.08–1.50)	0.004		
Histologic Subtype (NSCLC vs SCLC)	288/102	73.8/26.2	1.39 (1.10-1.77)	0.007		
Weight loss (%) Category in past 3 months (1/2)[a]	195/195	50.0/50.0	1.49 (1.18-1.88)	0.001		
Performance Status (ECOG) (0-1/2/3/4)	271/75/31/13	69.5/19.2/7.9/3.3	1.90 (1.65-2.18)	<0.001	1.74 (1.50-2.02)	<0.001
mGPS (0/ 1/ 2)	103/183/104	26.4/46.9/26.7	1.84 (1.54-2.19)	<0.001	1.67 (1.40-2.00)	<0.001

([a] Weight loss (%) category: 1 = weight loss <5%, 2= weight loss >5.1% (cancer cachexia)) The table details patient demographics including sex Male (M) or female (F), cancer type including Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), number of patients in each age group, median survival, the presence of weight loss and degree of weight loss experienced, body mass index (BMI), ECOG Performance Status summary(ECOG score of 0-4) and number of patients with mGPS scoring of 0-2. Hazard ratio (HR) and statistical significance for each variable detailed after testing on univariate and multivariate analysis.

Figure 3-1, Figure 3-2 and Figure 3-3 show Kaplan Meier survival curves for weight loss, PS and mGPS respectively. Figure 3-1 shows that weight loss is associated with reduced survival (log rank p = 0.001).

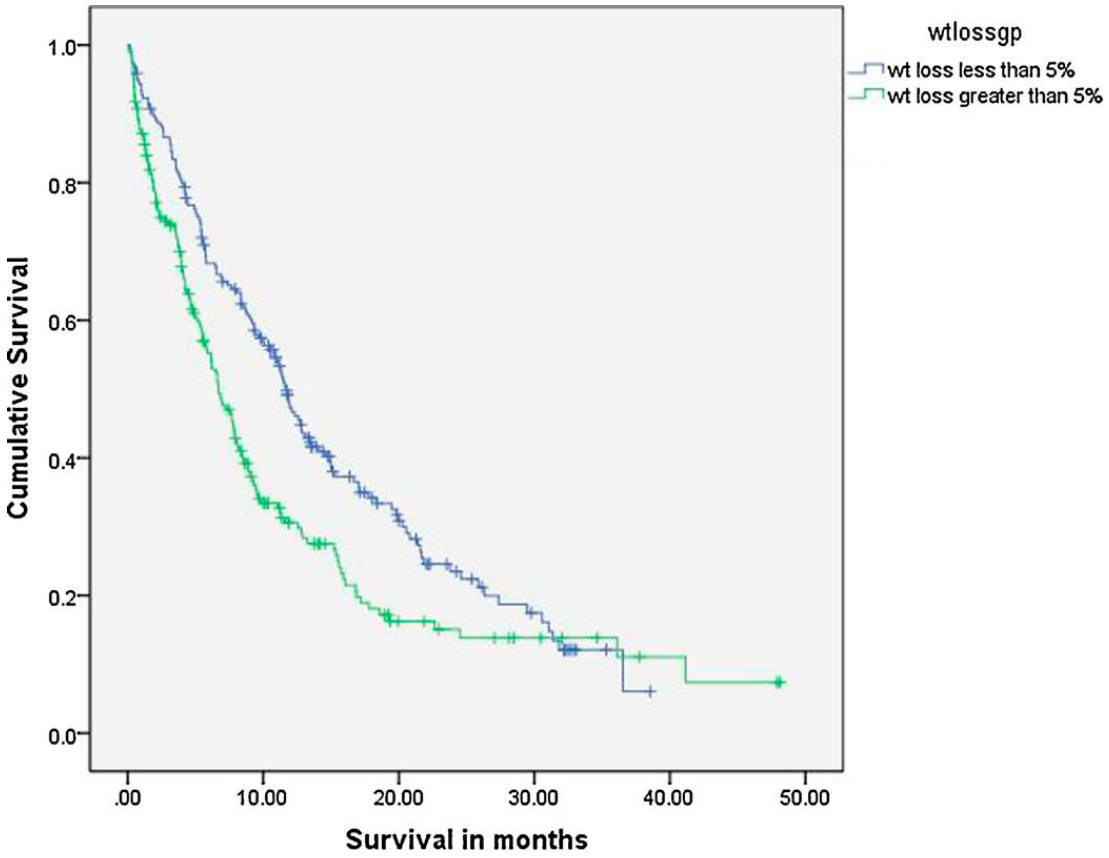

Figure 3-1 Kaplan Meier curve demonstrating the relationship between weight loss and survival.

The graph details survival in months on x-axis and cumulative survival which is the probability of surviving on the y-axis. The blue line refers to the patients with a weight loss less than 5% in the preceding 3 months. The green line refers to the patients with a weight loss greater than 5% in the preceding 3 months. A weight loss greater than 5% in the preceding 3 months is associated with worse survival. Weight loss is associated with reduced survival (log rank *p*=0.001).

Figure 3-2 shows that decreasing PS was associated with worse survival (log-rank p< 0.001).

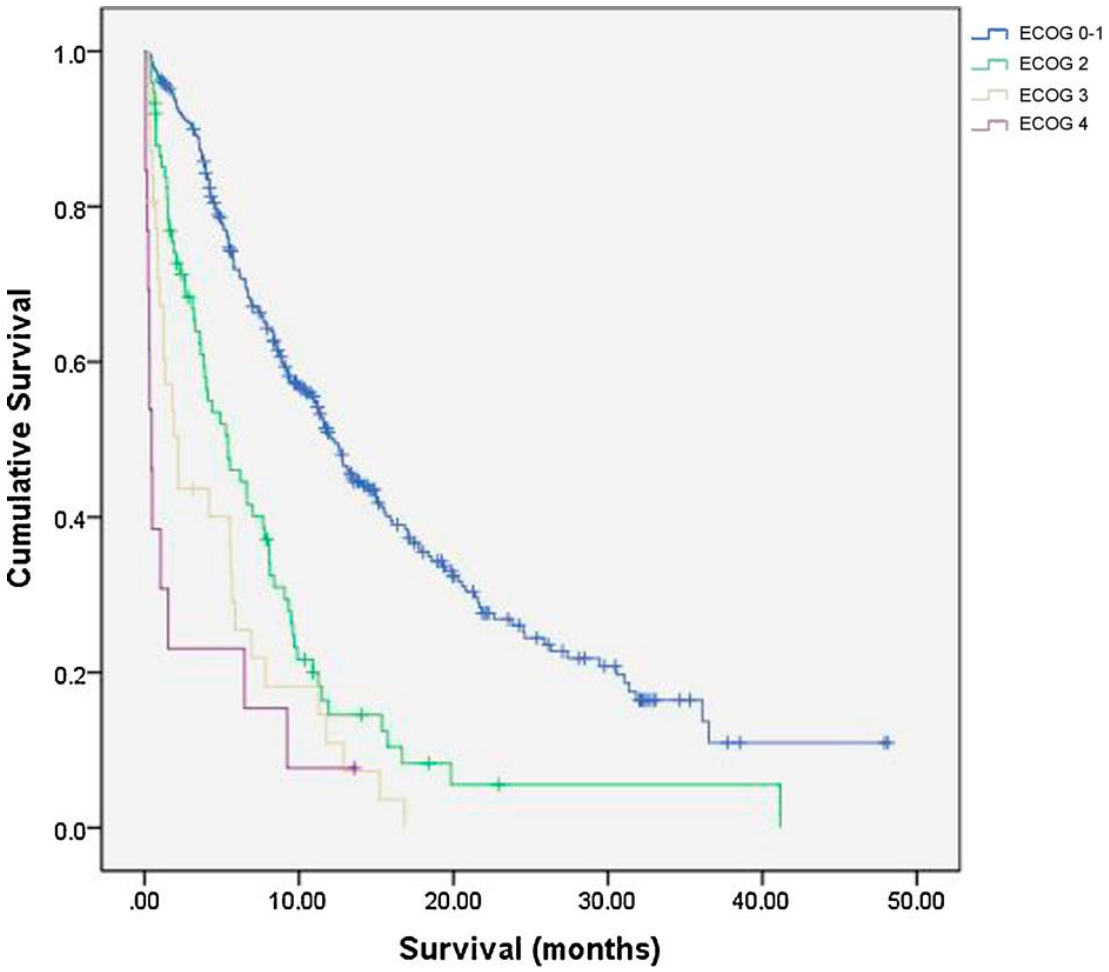

Figure 3-2 Kaplan-Meier curve demonstrating the relationship between Performance Status and survival

The graph details survival in months on x-axis and cumulative survival which is the probability of surviving on the y-axis. The blue line refers to the patients with an ECOG Performance Status of 0-1. The green line refers to patients with an ECOG Performance Status of 2. The grey line refers to patients with an ECOG Performance Status of 3. The purple line refers to patients with an ECOG Performance Status of 4. ECOG Performance Status of 4 is associated with worse survival.

Figure 3-3 shows that increasing mGPS was associated with poorer survival (log-rank p< 0.001).

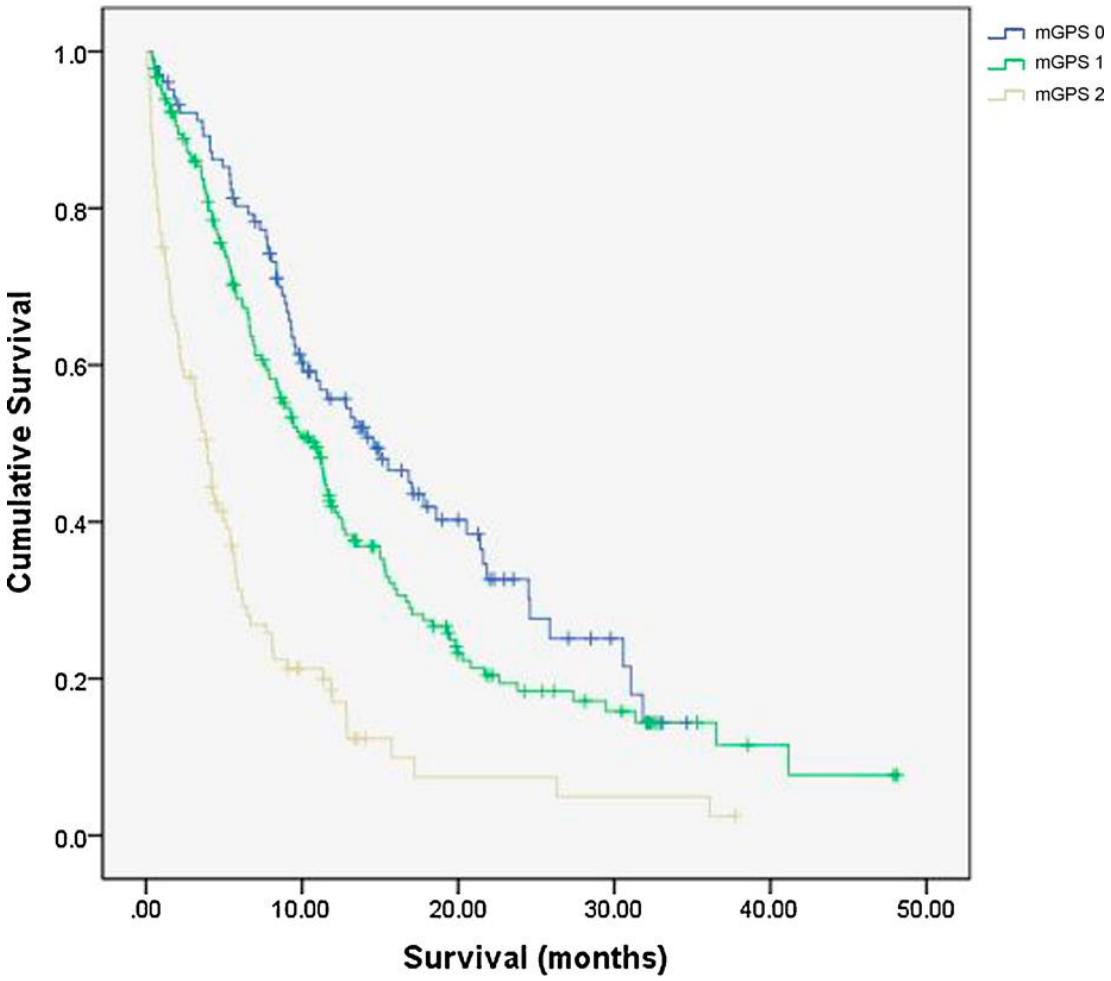

Figure 3-3 Kaplan-Meier curve demonstrating the relationship between mGPS and survival

Figure 3-3 shows that increasing mGPS was associated with poorer survival (log-rank p< 0.001). The graph details survival in months on x-axis and cumulative survival which is the probability of surviving on the y-axis. The blue line refers to the patients with an mGPS score of 0. The green line refers to patients with an mGPS score of 1. The grey line refers to patients with an mGPS of 2. An mGPS score of 2 is associated with worse survival.

Table 3-3 shows the relationship between survival at 90 days and mGPS and PS. Survival was compared across all categories for both mGPS and PS.

Table 3-3 Relationship between mGPS, PS, and survival at 90 days

Performance Status (ECOG grouping)	mGPS 0	mGPS 1	mGPS 2	mGPS 0-2
0-1	99% n=79	95% n=133	71% n= 59	91% n= 271
2	74% n=19	71% n=34	59% n=22	68% n=75
3	 n=4	55% n=12	33% n=15	44% n=31
4	 n=1	 n=4	 n=8	23% n=13
0-4	92% n=103	87% n=183	58% n=104	81% n=390

The table details the relationship between worsening ECOG Performance Status and increasing mGPS score. The lowest row demonstrates the 90 day survival relationship between any PS and worsening mGPS score. The end column demonstrates the 90 day survival relationship between any mGPS score and worsening ECOG Performance Status. Each percentage details the number of patients alive at 90 days. Where n<10, analysis was not performed.

On multivariate analysis only PS (HR 1.74 CI 1.50-2.02) and mGPS (HR 1.67, CI 1.40-2.00) predicted survival (p<0.001). For PS, survival at 90 days ranged from 99%

(ECOG 0-1) to 74% (ECOG 2). For mGPS, survival at 90 days ranged from 99% (mGPS0) to 71% (mGPS2). When used in combination, survival at 90 days ranged from 99% (mGPS 0 and ECOG 0-1) to 33 % (mGPS=2 and ECOG 3, Table 3-3).

3.4 Discussion

The results of this study show that older age, male sex, weight loss, histological cancer type, poorer PS and markers of the systemic inflammatory response (mGPS), all have prognostic value in patients with advanced lung cancer. PS and the mGPS carry the greatest prognostic value, however it is of interest that the mGPS has strong prognostic accuracy and performs almost identically to PS. In addition, the combination of PS and mGPS points to a potential new approach to prognostication in advanced lung cancer.

PS (measured either by Karnofsky or ECOG classification) still remains the gold standard prognostic measure and the results of the present study support this[143,144]. However, the key limitation of PS is that it is an entirely subjective assessment of a patient's physical activity and functioning[129,145,146]. It has been shown that marked discrepancies often exist between clinicians' and patients' assessments of PS[147]. Furthermore, clear inter-observer variability has been demonstrated[148]. Therefore it is important that the limitations of using a prognostic measure which is subjective and is variable, such PS, are considered. This aspect is of fundamental importance when the majority of treatment decisions in advanced lung cancer are deeply influenced by PS.

These findings demonstrate that the mGPS has independent prognostic value in advanced lung cancer, however a potential advantage over PS is that it is objective and is not subject to inter-observer bias[138]. It is simple to measure, inexpensive and is widely available. Used either in isolation or, perhaps in combination with PS, the

present findings demonstrate its relevance in increasing accuracy of survival prediction in metastatic lung cancer[137]. This has also been shown in other cancer types[116].

Weight loss has long been regarded a “poor” prognostic sign in lung cancer. This study specifically examined weight loss greater than 5%. Cancer cachexia is defined as weight loss greater than 5% and felt by many to be the most adverse weight-related prognostic factor in cancer. However the findings suggest that the use of weight loss as an early, prognostic factor in lung cancer is of considerably less value compared to both PS and mGPS and therefore it could be suggested that weight loss should not be assessed routinely in the clinic. For this to happen it would potentially mean a change to current practice, as weight loss is a source of concern for patients, families and clinicians. It is regularly recorded at clinic appointments and may be used as a trigger for additional investigations (suspected disease recurrence or progression) and dietetic referral, or as a starting point for end of life discussions. In addition, the confirmation of weight loss in cancer is often upsetting for patients and they should receive information regarding how to manage it.

Although weight loss has traditionally been thought of as a prognostic factor, its role may be limited. The findings demonstrate that PS and mGPS perform better than weight loss and are both independent predictors of survival in lung cancer. This study does confirm that weight loss is an important patient factor in lung cancer and also showed that the majority of patients with lung cancer experience weight loss; however other patient parameters are more strongly linked to survival. There are other studies looking at many cancer types which have demonstrated weight loss to be adversely associated with prognosis[149]. Weight loss has been identified as an independent prognostic marker for survival in patients with pancreatic cancer in one study[150] and high weight loss has been shown to correlate with poor prognosis in patients with gastrointestinal cancer[151]. Yet in other research, weight loss has not been shown to be an independent prognostic variable in pancreatic cancer[152]. There has also been conflicting evidence in hospice patients with advanced cancer stating that weight loss

is linked to survival and other research stating it was not shown to be a statistically significant predictor of prognosis[153].

Weight loss is clinically important in patients with cancer, however weight loss per se does not distinguish between a loss of lean mass (muscle) and loss of fat mass. These aspects of weight loss are very important in patients with cancer and may explain why there is conflicting evidence on the impact of a patient's overall weight and weight loss on prognosis in advanced cancer[154].

A patient with weight loss in combination with anorexia and systemic inflammation can be labelled as having cancer cachexia[152]. Cancer cachexia is a multifactorial clinical syndrome in which there is loss of skeletal muscle mass which may be accompanied by loss of fat mass. The diagnostic criteria for cachexia are weight loss greater than 5% or weight loss greater than 2% in individuals already showing depletion according to bodyweight and height (Body Mass Index<20kg/m^2) or skeletal muscle mass (sarcopenia)[155]. The relevance of this is that cachexia is associated with poor prognosis in patients with cancer[151]. Cachexia is also present in 50% of patients who have active cancer and 80% of patients at the time of death[156].

In this study, the majority of patients (75.3%) had experienced weight loss in the preceding 3 months with a mean weight loss of 6.89%, which meets the diagnostic weight loss criterion for cachexia. There was also a clear association between systemic inflammation measured using the mGPS, and survival in this group of patients. The findings also demonstrate that cachexia (as per current definition) [155] and BMI did not offer additional prognostic value in the presence of PS and mGPS. However, if these factors have limited prognostic use, their relative value should be re-evaluated. This emphasises and also adds to the argument that a large component of cancer cachexia, a syndrome of weight loss associated with anorexia and systemic inflammation, is driven by systemic inflammation. It is significant because it is already known that high levels of systemic inflammation are associated with poor prognosis in

patients with advanced cancer[113]. Anorexia, another component of cachexia, is independently associated with an adverse prognosis in patients with cancer, irrespective of its link to the anorexia-cachexia syndrome[53]. The contribution that each of the components of cachexia contributes to survival is not clear, however the study's results clearly demonstrate that systemic inflammation, which is a component of cachexia, is strongly related to survival in patients with cancer. Attempts have been made to improve cachexia either through parenteral nutrition or a multimodal approach, and monitoring the effect of both on systemic inflammation and cachexia management, in the hope that there is improvement in the patient's tolerance of cancer treatment and prognosis[33,157].

There are other markers of systemic inflammation but the mGPS has been consistently tested and proven to demonstrate a strong association with prognosis regardless of tumour type[116]. PS was also shown to be equally significant on multivariate analysis in predicting prognosis in patients with advanced cancer. The statistical handling of the data results in this study has resulted in rigorous testing of the effect of mGPS and PS in prognostication in advanced cancer. In patients with cancer cachexia, the mGPS can be used as a composite summary of systemic inflammation and therefore inform the clinician on the degree of active inflammation impacting upon their cancer cachexia and prognosis. This could help guide treatments for cancer cachexia, specifically guiding when to intervene and attempt to alter the progression of systemic inflammation, which in turn could aid and advise the opportunities and appropriateness for maximal therapeutic treatment, or optimal supportive care, when looking after patients with cancer. Early recognition of cancer cachexia through monitoring systemic inflammation associated with cancer cachexia could permit the early intervention of nutritional support, physical activity and reduce the systemic inflammatory response, the multimodal interventional approach to cachexia. Identifying and targeting each component of cancer cachexia is thought to be crucial in altering prognostic outcomes in patients with advanced cancer.

Other studies have demonstrated the prognostic importance of weight loss in patients with lung cancer and other cancers, which is not seen in this study's cohort of patients. This may be due in part to the small sample size which also focussed on lung cancer and did not include all tumour types. Other studies have included populations of patients with much greater percentages of weight loss. Specifically, the current study did not include gynaecological cancers or breast cancer. Much of the research linking weight changes to prognosis has been performed in patients with endometrial, cervical, breast and ovarian cancers and therefore the tumour types studied limit how the results can be extrapolated to apply to patients with different cancer types.

There is an urgency for improved survival prediction in metastatic lung cancer. Recent work has demonstrated that approximately 10% of metastatic lung cancer patients receive anti-cancer therapy in the last 30 days of life, and patients with the shortest survival time after diagnosis received more anti-cancer therapy near the end of life[67]. A key consideration in deciding appropriate treatment in an advanced lung cancer patient is prognosis. In these patients, the benefits of anti-cancer therapy must be weighed against potential disadvantages, such as multiple hospital visits, adverse side effects and potentially life-threatening toxicity. Accurate assessment of prognosis is needed to inform such complex decisions between patients and clinicians.

The results of the present study show that the combination of mGPS and PS are more accurate in survival prediction than either in isolation. It has been shown in other cancer types and has now been demonstrated in advanced lung cancer[116]. Using the combination of mGPS and PS may have considerable application in considering treatment options in advanced lung cancer; for example when to use chemotherapy in patients near the end of life. This approach has been supported in recent work which has shown the value of using the mGPS as a stratification factor in very advanced disease to reduce chemotherapy use[67]. The present study takes this approach one step further by combining mGPS with PS, to increase prognostic accuracy. This novel approach could then be used to guide the choice of oncology treatment in advanced lung cancer patients.

The present study has several limitations. There was a high proportion of men and SCLC in the cohort studied in keeping with the epidemiology of lung cancer in Greece. Furthermore, not all previously studied prognostic factors in advanced NSCLC have been examined. However as PS remains the gold standard prognostic marker in use clinically, its inclusion here is important. Details on cancer treatment are not available which would be of interest to assess the effect of response of chemotherapy in patients in poor prognostic groups. Although weight loss was examined, loss of lean mass as a component of this, was out with the remit of this thesis. The prognostic value of lean mass remains of interest.

3.5 Conclusion

To conclude, weight loss is obviously a key parameter of the cachexia syndrome, however it does not distinguish between loss of lean mass and fat mass. As such while it may have prognostic value, in the setting of lung cancer, it is less useful than other factors such as PS or the mGPS which are superior prognostic factors in metastatic lung cancer and, in combination, increase survival prediction in advanced lung cancer.

With regard to the mGPS, the ability to calculate and determine objectively the severity of systemic inflammation, a key component of cancer cachexia, serves as a far more useful parameter and prognosticating tool, throughout all stages of a patient's illness with cancer.

This study demonstrates that markers of systemic inflammation predict survival in advanced lung cancer. The next step is to compare directly the markers of systemic inflammation in cancer to other clinical and biomarkers of proven prognostic significance in all types of cancer.

Chapter 4 IPAC study: Inflammatory biomarkers in the Prognostication of Advanced Cancer

4.1 Introduction

It is clear that prognostication in cancer is possible, however accuracy of survival prediction depends on the accuracy of the tools or individual prognostic indices. The evidence from the systematic review and retrospective biobank analysis has highlighted a wide variety of prognostic factors, as determined by univariate and multivariate survival analyses, which predict survival in advanced cancer. Many individual prognostic markers can be viewed as surrogate markers of inflammation.

Some prognostic markers are of greater significance than others. This has been demonstrated by the biobank analysis where on univariate analysis weight loss demonstrated prognostic accuracy, however it was outperformed by the mGPS and PS. There are numerous prognostic markers identified thus far in this thesis. Which tool or marker is best is as yet undetermined and in spite of much research they have not yet been directly compared in a single study. In order to refine prediction of prognosis in patients with advanced incurable cancer, a multicentre prospective observational study was performed; Inflammatory biomarkers in Prognosis in Advanced Cancer, the IPAC study.

4.2 Aims

The aim of the IPAC study was to examine fully all the prognostic clinical indices and biomarkers already established as having independent prognostic value in the systematic review and biobank analysis, and determine which are most predictive of

survival in patients with advanced cancer. The study would assess all the validated prognostic factors in a prospective observational study. Thereafter this study aimed to determine which prognostic marker is of greatest significance in estimating survival in advanced cancer.

4.3 Methods

4.3.1 Study Setting

The study was designed as a national multicentre study conducted in 16 oncology and palliative care units throughout the UK (including Scotland, England and Wales), all of which were coordinated from a single centre (Edinburgh). The centres were specialist palliative care in-patient units, specialist palliative care outpatient clinics, oncology in-patient units, oncology outpatient clinics, and hospice day centres.

4.3.2 Ethics

Ethical approval was granted by the National Ethics Committee (UK – 12/SS/0181) and was conducted in accordance with the Declaration of Helsinki and ICH GCP. All patients provided written informed consent. Data were collected between January 2013 and September 2016. Patients were followed up for a minimum of three months after recruitment.

4.3.3 Inclusion and Exclusion Criteria

Inclusion criteria were:

- Patients 18 years old or greater
- Advanced incurable cancer. (Defined as having metastatic disease [histological, cytological or radiological evidence] or those receiving anti-cancer therapy with palliative intent.)
- Able to provide written informed consent
- Able to provide a blood sample
- ECOG (Eastern Cooperative Oncology Group) Performance Status 1-4[65].

Exclusion criteria were:

- ECOG Performance Status 0 (since they would be expected to outlive the length of the study)
- Breast or prostate carcinomas with only bone metastases (owing to potentially long survival times, often measured in years, patients would potentially be expected to survive beyond the duration of study follow up) This was due to the fact that in many patients with breast or prostate cancer, metastatic bone disease is a chronic condition with an increasing range of treatments available to slow the progression of the underlying disease. The survival from the time of diagnosis varies among different tumour types. The median survival time from diagnosis of bone metastases from prostate cancer or breast cancer is measurable in years. The median survival for these patients was expected to extend beyond the duration of the study.

- Lack of capacity to consent (including patient with confusion, patients being treated under the Adults with Incapacity (Scotland) Act 2000 or patients being treated under the Mental Capacity Act (England and Wales) 2005).This was due to approval not being granted for the inclusion of patients with delirium by the National Ethics Committee.

The study was officially opened in January 2013 and was open to recruitment for 30 months (2 years and 6 months) until June 2016. Patients recruited into the study at the end of the recruitment period in June 2016 were reviewed for three months and survival status at three months was recorded (i.e. 2 year and 9 months) in September 2016.

4.3.4 Study Assessments

Evaluation of patients

Eligible patients who consented to take part in the study were registered on a secure web-based portal specifically designed for the IPAC study by the University of Edinburgh's Wellcome Trust Clinical Research Facility, and baseline information entered. Patients were assigned a patient identifier number for the study by the website. After registration and enrolment, an electronic Case Report Form (CRF) was generated for each patient detailing the assessments to be performed.

At baseline the assessment included a complete history and examination, demographic patient data, disease details, KPS[158], ECOG Performance Status[65], a timed up and go test, Clinician predicted survival, the European Organisation for the

Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ-C30) for global health, cognitive impairment and anorexia, ESAS (the Edmonton Symptom Assessment System) for dysphagia and xerostomia[159], physical examination of peripheral oedema and ascites, height, weight, weight loss in the previous three months and a venous serum blood sample were performed. The baseline blood analyses included CRP, Albumin, WCC (including neutrophil and lymphocyte counts) and LDH. Blood was also taken and stored for future genotyping, DNA and RNA extraction and genomic analysis.

Demographic patient data and disease details

Demographic details of the patient including age, sex, current place of care (e.g. home, hospice, hospital) and disease details were recorded. The primary site of the cancer, histological type, tumour stage and sites of metastases if known were collected. Previous treatments with number of cycles of chemotherapy and total radiation therapy dosage administered (measured in Gray) were listed. Drug history including any hormonal anti-cancer treatment was collected. Co-morbidities were listed.

Clinical indices

The work performed prior to the study opening informed which prognostic variables were most accurate and these variables formed the basis of the assessment.

KPS was recorded. The KPS is a subjective assessment of a patient's ability to perform activities of daily living. Objective assessments of PS were also performed. These included a timed 'up and go' test which measured the time taken for a patient to rise from a chair, walk 3 metres, turn around, walk 3 metres back to the chair and return to the original sitting position. A two minute walk test was undertaken and the distance walked measured. If patients were not able to complete or attempt these activity assessments, this was recorded.

Patients' symptom severity scores were recorded for the symptoms of dysphagia and xerostomia. The severity of each was rated according to the Edmonton Symptom Assessment Scale which varies from 0 (none present) to 10 (worst possible severity present)[159].

Physical examination signs detected on clinical examination, namely the presence or absence of dependent pitting oedema (sacral or peripheral leg/ankle) and ascites, were recorded. Evidence of the presence or absence of ascites was also obtained from radiological CT reports, if available. Patients were asked about whether they had experienced any weight loss in the preceding three months and if so, then asked to quantify the amount lost. Weight and height measurements were taken at the time of the baseline assessment.

The quality of the patient's life was formally assessed using the EORTC-QLQ-C30 questionnaire[160], which is specifically designed to assess the quality of life of cancer patients[161]. Formal permission was granted to use this questionnaire as part of the study assessment.

Clinician predicted survival

The treating clinician was asked to estimate survival by selecting a category. The categories were days (less than 2 weeks), weeks (2 to 8 weeks) and months (greater than 8 weeks). The estimate was recorded along with the clinician's sex, specialty, age, seniority, number of years of experience in palliative medicine or oncology, and the information which was available to them when making the survival estimate.

Laboratory biomarkers

Patients were given the option of giving a sample of venous blood for biomarker analysis. Biomarkers analysed included CRP, albumin, LDH and WCC including lymphocyte and neutrophil counts.

Follow up information

Patients were followed up for the remainder of the study or for a minimum of 3 months. Survival status was recorded at the end of the follow up period and if the patient was deceased, death details noted if known.

Statistical methods

Analysis modelling included Cox proportional hazard models and logistic regression models. Univariate log regression was used to examine individual clinical and biomarkers. Multivariate log regression was used to examine the significant variables on univariate analysis. Kaplan Meier plots and log rank statistics were used to examine survival times. Multivariate Cox proportional hazard models were used to examine variables when building a multivariate log regression model.

A database was constructed based upon the information collected in the online case report form managed by the Edinburgh's Wellcome Trust Clinical Research Facility. Data were checked for accuracy in the event of outlying values and also checked for any missing values by a statistician at the Edinburgh Clinical Research Facility. The database was only accessible by the statistician and queries were passed onto the study team for clarification. The primary objective was to compare the prognostic value of the aforementioned clinical and laboratory factors. The secondary objectives were to assess if such factors had independent prognostic value and could be combined to improve prediction of survival at 30 days and 3 months from study entry. These time points were chosen as clinically relevant for the management of patients with advanced cancer.

The following were grouped according to specific thresholds. The mGPS was grouped as: CRP ≤10 mg/L = 0, CRP >10 mg/L = 1, CRP >10 mg/L and albumin < 35 g/L = 2. Weight loss was grouped as follows: <2.5%, 2.5-5.9%, 6-10.9%, 11-14.9, >15% according to thresholds described by Martin et al[162]. White cell count (WCC), Neutrophil count (NC) and Lymphocyte count (LC) were categorised as above or below/equal to normal limits. LDH was classified as abnormal if >250 U/L. EORTC QLQ-C30 scores were calculated using scoring procedures as described by Aaronson et al[161]. EORTC QLQ-C30 scales were analysed as discrete categories representing underlying continuous constructs and Patient Reported Outcome Measures (PROMs) (symptoms and quality of life variables) were defined as being present if the score was greater than 50. CPS was categorised into days [≤14days], weeks [15-56 days] or months [≥57 days]). For categorical variables with >2 categories (e.g. mGPS, ECOG-PS, weight loss, CPS) these were treated as continuous variables in terms of Hazard Ratios in line with their proven prognostic value. The survival time was defined as the number of months from study entry until death, or censored if patients were alive at follow-up date.

Univariate logistic regression was used to examine whether the clinical and/or biomarkers were predictive of death at 30 days and three months post consent. Multivariate survival analysis was done using a stepwise forward conditional procedure to derive a final model of markers that had a significant independent relationship with survival at 30 days and 3 months. Only variables with a $p<0.1$ were included in the model. To examine how biomarkers were related to either mGPS or ECOG-PS, Chi-Square tests (and Chi-Square tests for trend when appropriate) or Analysis of Variance (ANOVA) were used. All statistical testing was done at the 5% significance level with 95% confidence intervals reported. Statistical significance was taken as $p<0.05$ and all analyses were performed using IBM SPSS Version 23.0 (SPSS, Chicago, IL). Where appropriate mean and standard deviations (SD) or median and inter-quartile range (IQR) are reported.

4.3.5 Sample Size Calculation

The study was designed with the intended sample size of 500 patients which was determined to provide adequate statistical power by a statistician (ST) based at the Edinburgh's Wellcome Trust Clinical Research Facility. Binary logistic regression is one of the most frequently applied statistical approaches for developing clinical prediction models. It relies on an Events Per Variable criterion (EPV), notably EPV ≥ 10 to determine the minimal sample size required and the maximum number of candidate predictors that can be examined. As with logistic regression, Cox regression is a large sample method and the sample size needs to be large enough for the analysis to be valid. Simulations have been performed which indicated that, for Cox regression as for logistic regression, the total number of events is the key factor rather than the total sample size. Hence the number of deaths or survivors, whichever is smaller, needs to be large enough. It has been recommended that a sample should contain at least 10 events per variable used in a Cox regression equation[163]. In this study it was estimated that there will be 25 events per parameter to plan the intended sample size, when using logistic regression to predict survival beyond the median survival time, , which compares favourably with the conventional guideline that one should have 10 to 20 events per parameter[164].

4.4 Results

Five hundred and thirty nine (539) patents were enrolled into the IPAC study between January 2013 and September 2014. Seven patients were missing assessment information and therefore were excluded from analysis. A total of 532 patients were analysed. Full data on ECOG-PS, mGPS and CPS were available on 478 patients.

The clinicopathological characteristics of the patients with advanced cancer is shown in Table 4-1. The mean (SD) age was 67.04 (12.08) years and 256 (54%) patients

were female. The minimum and median (IQR) follow up for survivors was 0 days and 198 (137-273) days respectively. When study data collection stopped 194 (41%) patients were alive. The median (IQR) survival was 4.3 (1.86-7.03) months. The most common cancer type was lung, present in 163 (36%) patients, and metastases were present in 377 (85%) patients.

Table 4-1 Clinicopathological characteristics of patients with advanced cancer (n=478)

Parameter	n (%)
Age (≤65, 65-74, ≥74)	191(40), 140(29), 147(31)
Female	256 (54)
Place of care	
Home	341(71)
Hospital	30 (6)
Specialist Palliative Care Unit	93 (19)
Other	14 (3)
Primary Cancer	
Neurological	9 (2)
Lung	163 (36)
Gastrointestinal	99 (21)
Urological	23 (5)
Gynaecological	23 (5)
Melanoma	28 (6)
Haematological	10 (3)
Breast	50 (11)
Unknown Primary	8 (3)
Other	18 (4)
Clinician Predicted Survival*	
Days	8/463 (2)
Weeks	87/463 (19)
Months	368/463 (79)
Performance Status (ECOG)	
1, 2, 3, 4	189(39), 201(42), 72(15), 16(3)
mGPS	
0, 1, 2	178 (37), 99(21), 201(42)
Patient Reported Outcome Measures [EORTC score, median (IQR)]	
Dyspnoea present	139/461 (30); [33 (0-67)]
Global Health impaired	217/459 (47); [83 (50-100)]
Cognitive impairment	331/461 (72); [83 (50-100)]
Anorexia	159/461 (34); [33 (0-67)]
Distant Metastases present	377/446 (85)
Weight loss last 3 months (%)	
<2.5, 2.5-5.9, 6-10.9,11-14.9, >15	272(57), 31(7), 60(13) ,42(9), 57(12)
Biomarkers [median (IQR)]	
Elevated LDH (>250 U/L)	335/446 (75%); [394 (251-557)]
Elevated White Cell Count (>11 $x10^9$/L)	124/470 (26%); [7.7 (5.6-11.4)]
Elevated Neutrophil Count >7.5 x 10^9/L	148/469 (32%); [5.2 (3.5-8.8)]
Elevated Lymphocyte Count >3.0 $x10^9$/L	20/469 (4%); [1.2 (0.8-1.70)]

The table details patient demographics including age, sex, place of care, primary cancer site, Clinician Predicted Survival, ECOG Performance Status, mGPS scoring, Patient reported Outcome Measures obtained from the European Organisation for Research and Treatment of Cancer Quality of life

Questionnaire Core 30 score, the presence of metastases, the percentage of weight loss in the preceding 3 months, median and Interquartile Range (IQR) for biomarkers. Table was composed jointly with BL.

The relationship between clinicopathological factors and survival at 30 days and 3 months is shown in the Table 4-2.

Table 4-2 The relationship between clinicopathological factors and survival (30 day and 3 month) in patients with advanced cancer

	Death at 30 days			Death at 3 months		
		Univariate			Univariate	
	%	HR (95% CI)	P	%	HR (95% CI)	P
Age (≤65/65-74/≥74)	13/13/18	1.23 (0.92-1.63)	0.16	28/39/37	1.19 (1.00-1.43)	0.056
Sex (male/ female)	16/13	0.78 (0.49-1.26)	0.31	39/31	0.76 (0.56-1.04)	0.084
Clinician Predicted Survival*						
Days/Weeks/Months	100/37/8	0.15 (0.10-0.22)	<0.001	100/72/25	0.20 (0.15-0.26)	<0.001
Performance Status (ECOG)						
1/2/3/4	2/13/38/75	3.71 (2.84 -4.85)	<0.001	13/37/71/94	2.90 (2.42-3.47)	<0.001
mGPS						
0/1/2	2/14/26	3.15 (2.13-4.65)	<0.001	9/38/55	2.57 (2.08-3.19)	<0.001
Patient Reported Outcome Measures						
Dyspnoea (N/Y)	10/22	2.32 (1.41-3.82)	0.001	26/49	2.26 (1.64-3.11)	<0.001
Global Health (N/Y)	19/8	0.40 (0.27-0.69)	0.001	43/24	0.46(0.33-0.64)	<0.001
Cognitive Impairment (N/Y)	21/10	0.45 (0.27-0.75)	0.002	42/29	0.61 (0.44-0.85)	0.003
Anorexia (N/Y)	10/20	2.21 (1.34-3.63)	0.002	26/46	2.09 (1.52-2.88)	<0.001
Distant Metastases (N/Y)	10/15	1.57 (0.72-3.45)	0.56	33/36	1.14 (0.73-1.77)	0.56
Weight loss last 3 months (%)						
<2.5/2.5-5.9/6-10.9/11-14.9/>15	13/3/10/7/32	1.21(1.04-1.41)	0.017	28/23/37/45/56	1.26 (1.14-1.39)	<0.001
Biomarkers						
LDH <=250/>250 U/L	5/18	3.50 (1.51-8.11)	0.003	15/40	3.09 (1.86-5.11)	<0.001
White Cell Count <=11/>11 x10^9/L	7/33	5.53 (3.24-8.76)	<0.001	24/60	3.54 (2.59-4.84)	<0.001
Neutrophil Count <=7.5/ >7.5 x 10^9/L	7/29	5.23 (3.12-8.56)	<0.001	23/57	3.45 (2.52-4.72)	<0.001
Lymphocyte Count <=3.0/>3.0 x10^9/L	14/10	0.71 (0.18-2.88)	0.63	35/15	0.39 (0.13-1.29)	0.11

The table details patient demographics including age group, sex, clinician predicted survival, ECOG Performance Status, mGPS score, Patient Reported Outcome Measures, percentage weight loss in the preceding 3 months and biomarker results. Hazard ratio (HR) and statistical significance for each variable detailed after testing on univariate analysis for both 30 day and 3 month survival. Table was composed jointly with BL.

On univariate analysis, the following factors predicted death at 30 days: CPS (p<0.001), ECOG-PS (p<0.001), mGPS (<0.001), dyspnoea (p=0.001), global health (p=0.001), cognitive impairment (p=0.002), anorexia (p=0.002), weight loss (p=0.017), LDH (p=0.003), WCC (p<0.001) and NC (p<0.001). The following factors predicted death at 3 months: CPS (p<0.001), ECOG-PS (p<0.001), mGPS (p<0.001), dyspnoea (p<0.001), global health (p<0.001), cognitive impairment (p=0.003), anorexia (p<0.001), weight loss (p<0.001), LDH (p<0.001), WCC (p<0.001) and NC (p<0.001) (Table 4-3).

The multivariate analysis of survival at 30 days and 3 months is shown in Table 4-3. The following factors independently predicted death at 30 days: ECOG-PS (HR 2.15, 95%CI 1.40-3.30, p<0.001), mGPS (HR 2.03, 95%CI 1.23-3.35, p=0.006), and NC (HR 3.18, 95%CI 1.67-6.01), p<0.001). The following factors independently predicted death at 3 months: ECOG-PS (HR 1.91, 95%CI 1.47-2.49, p<0.001), mGPS (HR 1.77, 95%CI 1.36-2.31, p<0.001), weight loss (HR, 1.15, 95%CI 1.03-1.29, p=0.013), LDH (HR 2.00, 95%CI 1.15-3.47, p=0.013) and WCC (HR 2.50, 95%CI 1.71-3.66, p<0.001).

Table 4-3 The relationship between clinicopathological factors and survival (30 day and 3 month) in patients with advanced cancer: univariate and multivariate analysis

	Death at 30 days				Death at 3 months			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (≤65/65-74/≥74)	1.23 (0.92-1.63)	0.158			**1.19 (1.00-1.43)**	**0.056**		
Sex (male/ female)	0.78 (0.49-1.26)	0.309			**0.76 (0.56-1.04)**	**0.084**	0.59 (0.41-0.86)	0.006
Clinician Predicted Survival								
Days/Weeks/Months	**0.15 (0.10-0.22)**	**<0.001**			**0.20 (0.15-0.26)**	**<0.001**	0.65 (0.42-0.99)	0.047
Performance Status (ECOG)								
1/2/3/4	**3.71 (2.84 -4.85)**	**<0.001**	2.15 (1.40-3.30)	<0.001	**2.90 (2.42-3.47)**	**<0.001**	1.96 (1.50 -257)	<0.001
mGPS								
0/1/2	**3.15 (2.13-4.65)**	**<0.001**	2.03 (1.23-3.35)	0.006	**2.57 (2.08-3.19)**	**<0.001**	1.79 (1.37-2.33)	<0.001
Patient Reported Outcome Measures								
Dyspnoea (N/Y)	**2.32 (1.41-3.82)**	**0.001**			**2.26 (1.64-3.11)**	**<0.001**		
Global Health (N/Y)	**0.40 (0.27-0.69)**	**0.001**			**0.46(0.33-0.64)**	**<0.001**		
Cognitive Impairment (N/Y)	**0.45 (0.27-0.75)**	**0.002**			**0.61 (0.44-0.85)**	**0.003**		
Anorexia (N/Y)	**2.21 (1.34-3.63)**	**0.002**			**2.09 (1.52-2.88)**	**<0.001**		
Distant Metastases (N/Y)	1.57 (0.72-3.45)	0.379			1.14 (0.73-1.77)	0.564		
Weight loss last 3 months (%)								
<2.5/2.5-5.9/6-10.9/11-14.9/>15	**1.21(1.04-1.41)**	**0.017**			**1.26 (1.14-1.39)**	**<0.001**	1.16 (1.03-1.30)	0.012
Biomarkers								
LDH <=250/>250 U/L	**3.50 (1.51-8.11)**	**0.003**			**3.09 (1.86-5.11)**	**<0.001**	2.30 (1.32-4.01)	0.003
White Cell Count <=11/>11 x10^9/L	**5.53 (3.24-8.76)**	**<0.001**			**3.54 (2.59-4.84)**	**<0.001**		
Neutrophil Count <=7.5/ >7.5 x 10^9/L	**5.23 (3.12-8.56)**	**<0.001**	3.18 (1.67-6.01)	<0.001	**3.45 (2.52-4.72)**	**<0.001**	2.67 (1.83-3.93)	<0.001
Lymphocyte Count <=3.0/>3.0 x10^9/L	0.71 (0.18-2.88)	0.627			0.39 (0.13-1.29)	0.111		

The table details patient demographics including age group, sex, clinician predicted survival, ECOG Performance Status, mGPS score, Patient Reported Outcome Measures, percentage weight loss in the preceding 3 months and biomarker results. Hazard ratio (HR) and statistical significance for each statistically significant variable after testing on univariate and multivariate analysis for both 30 day and 3 month survival. The table has removed the results for non-statistically significant prognostic markers on multivariate analysis. Table was composed jointly with BL.

The relationship between ECOG-PS and mGPS and survival at 30 days and 3 months, is shown in Table 4-4. Survival at 30 days, according to ECOG-PS, varied from 98% (ECOG-PS 1) to 25% (ECOG-PS 4). Survival at 30 days, according to the mGPS, varied from 98% (mGPS 0) to 74% (mGPS 2). When used in combination survival at 30 days ranged from 100% (ECOG-PS1, mGPS 0) to 31% (ECOG-PS 4, mGPS 2).

Survival at 3 months, according to ECOG-PS, varied from 87% (ECOG-PS 1) to 6% (ECOG-PS 4). Survival at 3 months, according to the mGPS, varied from 91% (mGPS 0) to 46% (mGPS 2). When used in combination survival at 3 months ranged from 97% (ECOG-PS1) to 8% (ECOG-PS 4, mGPS 2).

Table 4-4 The relationship between Performance Status, mGPS and the survival rate (%) at 30 days and 3 months, in patients with advanced cancer (n=478)

	mGPS 0 n=178		mGPS 1 n=99		mGPS2 n=201		mGPS 0-2 n=478	
ECOG-PS	30 days	3 months	30 days	3 months	30 days	3 months	30 days	3 months
1 n=189	100 (0) n=99	97 (2) n=99	97 (3) n=35	77 (7) n=35	95 (3) n=55	76 (6) n=55	98 (1)	87 (2)
2 n=201	97(2) n=72	87 (4) n=72	88 (5) n=48	60 (7) n=48	79 (5) n=81	45 (6) n=81	88 (2)	64 (3)
3 n=72	n=7	n=7	77 (12) n=13	46 (14) n=13	56 (7) n=52	25 (6) n=52	63 (6)	30 (5)
4 n=16	n=0	n=0	n=3	n=3	31 (13) n=13	8 (7) n=13	25 (11)	6 (6)
1-4 n=478	98 (1) n=178	91 (2) n=178	87 (3) n=99	62 (5) n=99	74 (3) n=201	46 (4) n=201	86 (2)	66 (2)

Survival rate, not reported where n<10.

The table details the relationship between worsening ECOG Performance Status and increasing mGPS score. The lowest row demonstrate the 30 days and 3 month survival relationship between any Performance Status and worsening mGPS score. The end two columns demonstrate the 30 days and 3 month survival relationship between any mGPS score and worsening ECOG Performance Status. Each percentage details the number of patients alive at 30 days and 3 months. Standard error is described in parentheses. Table was composed jointly with BL.

The relationship between circulating neutrophil counts (NC), ECOG-PS and mGPS in patients with advanced cancer in shown in Table 4-5. In those patients with ECOG-PS 0-1, the absolute NC ($p<0.001$ $_{ANOVA}$) and the proportion with elevated NC ($\chi 2_{TREND}$ $p<0.001$) was greater with higher mGPS. In those patients with mGPS 0, the absolute NC ($p=0.011$) and the proportion with elevated NC ($\chi 2_{TREND}$ $p=0.008$) was greater with higher ECOG-PS.

The relationship between ECOG-PS and NC and survival at 30 days and 3 months, is shown in Table 4-6. Survival at 30 days, according to ECOG-PS, varied from 98% (ECOG-PS 1) to 25% (ECOG-PS 4). Survival at 30 days, according to the NC, varied from 94% (normal NC) to 70% (abnormal NC). When used in combination survival at 30 days ranged from 99% (ECOG-PS1, normal NC) to 47% (ECOG-PS 3, abnormal NC). Survival at 3 months, according to ECOG-PS, varied from 87% (ECOG-PS 1) to 6% (ECOG-PS 4). Survival at 3 months, according to the NC, varied from 93% (normal NC) to 70% (abnormal NC). When used in combination survival at 3 months ranged from 91% (ECOG-PS1, normal NC) to 22% (ECOG-PS 3, abnormal NC).

Table 4-5 The relationship between circulating neutrophil counts, ECOG-PS and mGPS in patients with advanced cancer (n=469).

ECOG-PS		mGPS 0 (n=177)	mGPS 1 (n= 99)	mGPS 2 (n=193)	mGPS 0-2 (n= 469)
1	Neutrophil count (10^9)*	3.7 (2.77-4.90)	5.35 (4.25-7.86)	5.69 (4.00-9.00)	4.60 (3.20-6.89)
	Neutrophil count** ($\leq$7.5/ >7.5x10^9/L)	87/11	25/ 10	35/ 20	147/ 41
2	Neutrophil count (10^9)*	4.30 (2.99-6.10)	6.20 (3.48 -9.18)	7.39 (5.13-11.46)	5.60 (3.60-9.09)
	Neutrophil count** ($\leq$7.5/ >7.5x10^9/L)	59/ 13	32/ 16	40/ 36	131/ 65
3	Neutrophil count (10^9)*		5.56 (4.34-8.87)	7.20 (4.90-12.29)	7.10 (4.70-10.76)
	Neutrophil count** ($\leq$7.5/ >7.5x10^9/L)	3/ 4	9/ 4	25/ 24	37/ 32
4	Neutrophil count (10^9)*			9.72-4.25-11.86)	9.66 (3.97-11.68)
	Neutrophil count** ($\leq$7.5/ >7.5x10^9/L)	0/ 0	1/ 2	5/ 8	6/ 10
1-4 (n= 469)	Neutrophil count (10^9)*	3.82 (2.80-5.36)	5.60 (4.17-8.69)	7.13 (4.70 -10.81)	5.20 (3.51 -8.80)
	Neutrophil count** ($\leq$7.5/ >7.5x10^9/L)	149/ 28	67/ 32	105/ 88	321/ 148

*Median (interquartile range) **patients (n) with NC

The table details the relationship between worsening ECOG Performance Status, neutrophil count and increasing mGPS score. The lowest two rows demonstrate relationship between any Performance Status, neutrophil count and worsening mGPS score. Table was composed jointly with BL.

Table 4-6 The relationship between the neutrophil count and Performance Status and the survival rate at 30 days and 3 months, in patients with advanced cancer (n=469)

	Neutrophil count <=7.5 x 10^9/L n=321		Neutrophil count >7.5 x 10^9/L n=148		All n=469	
ECOG-PS	30 days	3 months	30 days	3 months	30 days	3 months
1 n=188	99 (1) n=147	91 (2) n=147	93 (4) n=41	73 (7) n=41	98 (1)	87 (2)
2 n=196	93(2) n=131	76 (4) n=131	78 (5) n=65	42 (6) n=65	88 (2)	64 (3)
3 n=69	78 (7) n=37	40 (8) n=37	47 (9) n=32	22 (7) n=32	63 (6)	30 (5)
4 n=16	n=6	17 (15) n=10	n=3	n=3	25 (11)	6 (6)
1-4 n=469	94 (1) n=321	93 (1) n=321	70 (4) n=148	70 (4) n=148	86 (2)	66 (2)

Survival rate (SE), not reported where n<10.

The table details the relationship between worsening ECOG Performance Status and an elevated or lowered neutrophil count. Each percentage details the number of patients alive at 30 days and 3 months. Table was composed jointly with BL.

The relationship between circulating Lactate Dehydrogenase, ECOG-PS and mGPS in patients with advanced cancer in shown in Table 4-7.

Table 4-7 The relationship between Lactate Dehydrogenase, ECOG-PS and mGPS in patients with advanced cancer (n=446).

ECOG-PS		mGPS 0 (n=167)	mGPS 1 (n=90)	mGPS 2 (n=195)	mGPS 0-2 (n=446)
1 n=179	Lactate Dehydrogenase*	324.00 (214.50-468.00)	322.00 (231.00-542.00)	273.00 (203.00-513.00)	310.00 (213.500-495.50)
	Lactate Dehydrogenase ** (≤ 250/>250 U/L)	34/59	12/21	23/32	69/112
2 n=184	Lactate Dehydrogenase*	398.00 (261.00-510.00)	482.00 (367.00-623.00)	395.00 (280.00-549.00)	416.00 (297.00-558.25)
	Lactate Dehydrogenase ** (≤ 250/>250 U/L)	15/53	2/41	15/59	31/153
3 n=65	Lactate Dehydrogenase*		572.00 (394.00-920.00)	512.00 (334.00-817.00)	572.00 (334.50-816.00)
	Lactate Dehydrogenase ** (≤ 250/>250 U/L)	2/5	0/11	7/40	9/56
4 n=16	Lactate Dehydrogenase*			537.00 (366.50-721.50)	504.50 (361.25-664.75)
	Lactate Dehydrogenase ** (≤ 250/>250 U/L)	0/0	0/3	2/11	2/14
1-4 (n= 446)	Lactate Dehydrogenase*	369.00 (234.00-495.00)	441.50 (311.00-602.75)	398.00 (251.00-626.00)	394.00 (250.75-557.25)
	Lactate Dehydrogenase ** (≤ 250/>250 U/L)	50/117	14/76	47/142	111/335

The table details the relationship between worsening ECOG Performance Status, lactate dehydrogenase level and increasing mGPS score. The lowest two rows demonstrate relationship between any Performance Status, lactate dehydrogenase level and worsening mGPS score. Table was composed jointly with BL.

In those patients with ECOG-PS 0-1, there was no relationship with higher mGPS for either LDH (p=0.914 $_{ANOVA}$) or the proportion of patients with elevated LDH (χ2p=0.795). In those patients with mGPS=2, LDH (p=0.002 $_{ANOVA}$) and the proportion with elevated LDH ($\chi 2_{TREND}$ p=0.002) was greater with higher ECOG-PS. The relationship between CPS and ECOG-PS is shown in Figure 4-1

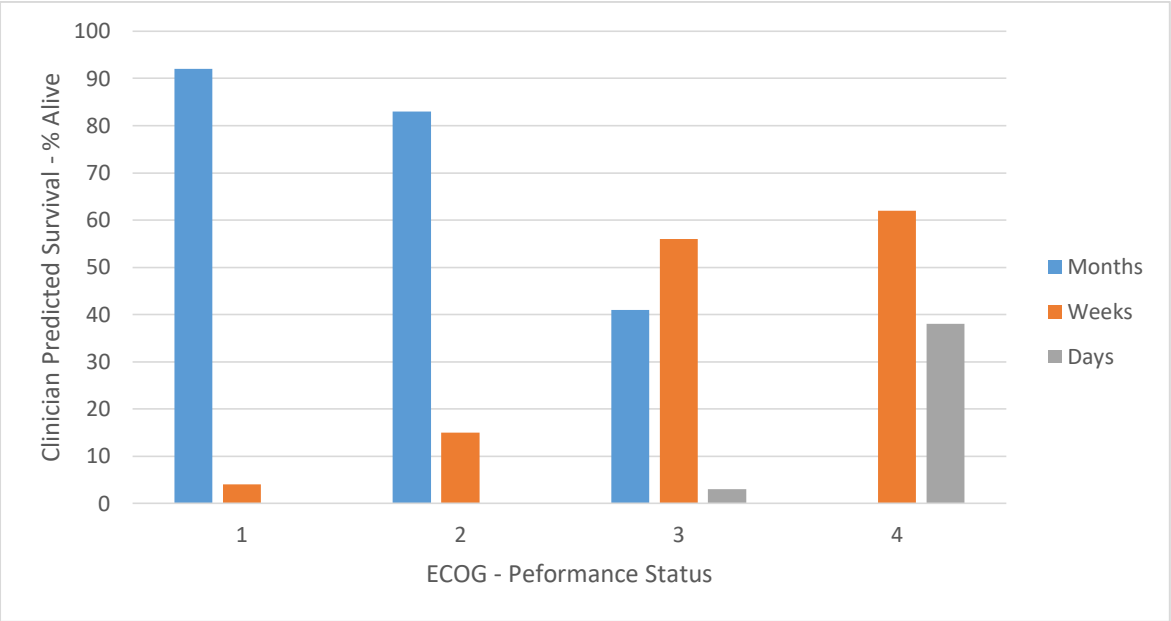

Figure 4-1 Bar chart demonstrating the relationship between clinician predicted survival and Performance Status

The bar chart details ECOG Performance Status (1-4) on the x-axis and Clinician Predicted Survival on the y-axis. The Clinician Predicted Survival refers to months (blue bar), weeks (orange bar) and days (grey bar). With an ECOG Performance Status of 1, an increased percentage of patients surviving months are alive at 3 months, and correctly identified by clinicians. With an ECOG Performance Status of 4, an increased percentage of patients identified as surviving weeks are alive at 3 months. With an ECOG Performance Status of 4, 38% of patients who were estimated to survive days are alive at 3 months. This figure was jointly composed with BL.

4.5 Discussion

The multicentre prospective observational study evaluated key biomarkers and clinical markers which were already established as having independent prognostic significance. The study identified CPS, mGPS, ECOG-PS, dyspnoea, Global Health, cognitive impairment, anorexia, weight loss, LDH, WCC and NC as having prognostic significance at 30 days on univariate analysis. The factors with prognostic significance at 3 months on univariate analysis were CPS, ECOG-PS, mGPS, dyspnoea, global health, cognitive impairment, anorexia, weight loss, LDH, WCC and NC. Multivariate analysis identified ECOG-PS, mGPS and neutrophil count as having prognostic significance at 30 days. ECOG-PS, mGPS, weight loss, LDH and WCC were identified as having prognostic significance at 3 months on multivariate analysis.

The indices with greatest prognostic significance at predicting survival were mGPS, ECOG-PS, neutrophil count and LDH.

As previously noted in the earlier chapters, mGPS, neutrophil count and LDH are objective markers of inflammation with no inter-observer bias. It should be noted that male sex and the presence of weight loss in the preceding 3 months were predictive of survival at 3 months on multivariate analysis, however these were less predictive compared to the aforementioned indices. The study confirmed that male sex is a negative predictor of survival, as it is globally, with women's life expectancy exceeding that of men's worldwide, regardless of a diagnosis of cancer especially in industrialised countries[165]. The incidence of cancer in men is declining due to recent rapid declines in prostate cancer diagnoses. This current study excluded patients with prostate cancer and bone metastases only and overall this study had few patients with a prostate cancer diagnosis, thus making the prognostic significance at 3 months of male gender due to other confounding factors, or that the men had a crucial selective combination of other prognostic factors, which this study has not extrapolated further. By identifying male sex as a negative predictor of survival, this result is comparable with other research into survival which states that 'women may be intrinsically more robust than men in coping with cancer'[166].

Socioeconomic status and social support networks, including access to palliative care, are of great importance in survival. In this study, the majority of patients were residing at home and many were enrolled at clinic settings where patients were attending for routine review and follow up appointments. The majority of the study centres were within NHS centres where a multidisciplinary team approach, including access to palliative care, is used when looking after patients with cancer, which inevitably impacts upon patient wellbeing and thus survival. Whether male patients choose to partake in or opt out of full multidisciplinary care was not reviewed in this study.

The combination of individualised ECOG-PS and mGPS scores was able to demonstrate survival at 30 days and 3 months with a range from 100% survival to 8% survival. A relationship was seen between circulating NCs, ECOG-PS and mGPS. Patients with a higher mGPS score, which reflects higher markers of systemic inflammation, had an elevated NC. Patients with an mGPS score of 0 however with a worse ECOG-PS, had elevated NCs. The combination of individualised ECOG-PS and NCs was able to demonstrate survival at 30 days and 3 months with a range from 99% survival to 22% survival. The total WCC was of prognostic significance at 3 months on multivariate analysis. This supports previous reviews and research which have identified WCC as an independent prognostic factor[167-169]. The NC is an objective marker in prognosis, however this study demonstrates that the selective combination of mGPS and ECOG-PS is a better overall predictor of survival with a wider prediction of survival and the addition of NC does not improve accuracy of survival prediction in combination with ECOG-PS. It has already been shown that the selective combination of objective markers of systemic inflammation are of prognostic significance in the form of the mGPS. When it is combined with ECOG-PS, it has again been shown to be of heightened prognostic value and additive in its survival prediction.

The relationship between LDH and its relationship to survival was of interest. LDH has been studied extensively in patients with cancer and its relationship to survival and outcome in patients undergoing either systemic chemotherapy or surgical treatment

for cancer. It should be noted that much of the research into LDH is looking at LDH on univariate analysis. It has been thought that it is a marker of inflammation and is often measured in oncology clinics as a surrogate marker of disease activity. This study did not demonstrate any direct relationship with elevated inflammation and mGPS score or poor ECOG-PS and LDH. This could be due to the fact that the patients enrolled into the study already had advanced incurable cancer, the majority of which had metastases to other main organs which is reflected in an elevated LDH level for nearly 50% of the patients enrolled. What is of more interest is that approximately 50% of the patients had normal levels of LDH in spite of having advanced incurable cancer and the majority of patients whose survival was analysed at 3 months had a normal LDH level ($p<0.001$). The study demonstrates that LDH is one biomarker which is of less use in predicting survival when compared to other objective biomarkers. The study did demonstrate a relationship between CPS and ECOG-PS demonstrating that CPS was inaccurate in patients with a good ECOG-PS and improved survival prediction accuracy with poor ECOG-PS. The most accurate survival prediction was 'months', however the accuracy of this to patients compared to the selective combination of objective markers of survival prediction was less.

Lastly, although LDH was consistently associated with survival at 30 days and 3 months on univariate analysis it was only associated with survival at 3 months on multivariate analysis. Moreover, the hazard ratio of LDH, compared with univariate analysis, was lower on multivariate analysis (HR 2.00 vs HR 3.09). This may reflect the relationship between LDH and ECOG-PS where ECOG-PS was directly associated with elevated LDH activity.

Weight loss was also shown to be of prognostic significance. Weight loss is a surrogate marker of cancer cachexia and therefore a marker of systemic inflammation. It follows that the more accurate and objective marker of systemic inflammation, namely the mGPS, is a more accurate index to use when ascertaining survival.

A number of limitations should be acknowledged. This study provided an extensive and rigorous investigation into the majority of the prognostic markers identified as being linked to survival in advanced incurable cancer. Not every marker was studied, but the main and most important prognostic indices were included. The markers selected were those identified on a rigorous systematic review and only those which were assessed in populations of greater than 100 and examined and validated in two or more independent datasets were included. The clinical syndrome of "confusion" has been noted to be an independent prognostic marker in advanced incurable cancer and was included by way of the EORTC-QLQ-C30 questionnaire in the form of cognitive impairment. Confusion per se and hypercalcaemia which is often associated with confusion were not included in this study after discussions at the National Ethics Committee. The National Ethics Committee did not grant approval for the inclusion of patients with delirium and therefore the importance and prognostic significance of this clinical factor in advanced cancer cannot be further elucidated by this study. Weight loss was not subtyped as lean muscle mass loss or fat loss and therefore more detailed examination of weight loss could have taken place and been linked to survival using muscle mass analysis from CT scans. More socioeconomic status data, including patients' access to multidisciplinary care and palliative care, could have been collected in light of the results linking poorer survival to male sex.

Overall this study combined and then compared all the prognostic markers in advanced cancer. It adds to the research already conducted and confirms that the selective combination of objective biomarkers, combined with an assessment of the patient's fitness (itself a marker of lean muscle mass and therefore usable as a marker of systemic inflammation), are the most accurate markers of survival and 30 day and 3 month prognosis in patients with advanced incurable cancer.

Through a process of thorough and rigorous statistical analysis with direct comparison of all the biomarkers, the most predictive markers of survival were identified and were mGPS, ECOG-PS, NC, weight loss, LDH and WCC. Weight loss, LDH and WCC had prognostic significance at 3 months; NC had prognostic significance at 30 days; only

mGPS and ECOG-PS both had prognostic significance and predicted survival at 30 days and 3 months.

Chapter 5 Discussion

5.1 Background to the Thesis

Cancer is one of the main causes of death in the UK. It is of great public interest to clinicians and to patients as individuals, both in terms of public health and health economics. Most cancers are incurable and diagnosed at an advanced stage or progress rapidly to an advanced stage where the focus of treatment switches to good end of life care.

The origins of cancer lie in inflammation. The local cancer microenvironment is one of inflammation and it also gives rise to systemic inflammation. Inflammation allows cancer to propagate and metastasise. The literature review outlined in this thesis suggests that there is a link between cancer inflammation and the sequelae of cancer. Cancer inflammation is directly linked to symptoms because they are caused by cancer inflammation and the inflammatory mediators released as a direct consequence of cancer or in response to the presence of cancer. This inflammatory cascade directly correlates with symptoms, disease burden and prognosis.

Traditionally PS is used to estimate prognosis since PS worsens with an increase in cancer inflammation and progression. Specific symptoms and inflammatory markers in patients with advanced incurable cancer are linked to cancer inflammation and therefore prognosis. Prognostic factors, individually or in combination, have been examined in the medical literature and scientific fields. Specific clinical markers, either related to the patient or disease history, along with biomarkers, have been identified as being independently significant prognostic indicators. Identifying these prognostic markers and ascertaining prognosis is important to enable good end of life care in incurable cancer where the only good treatment is palliative care to prevent distress.

The aim of this thesis was to determine the strongest prognostic markers in advanced incurable cancer, and to determine which, if any, of these were related to systemic inflammation. In this thesis the numerous prognostic markers have been identified, tested, compared and validated. The aims of this thesis have been met. There has been a thorough examination of all the prognostic markers and the prognostic tools in advanced cancer to clarify which prognostic markers are most predictive of survival in advanced cancer, through performing a systematic review, an analysis of a biobank dataset and a prospective observational study.

5.2 Main Findings

The literature was reviewed in Chapter 1 and Chapter 2. By looking at all existing prognostic tools, all individual prognostic markers which have been previously validated in patients with advanced incurable cancer have been reviewed. The most extensively tested and validated prognostic markers are PS, clinician predicted survival, anorexia, dyspnoea, delirium, disease status, mGPS, the presence of oedema, global health, the presence of metastases, heart rate, dysphagia, weight loss, fatigue, WCC, lymphocyte count, CPS, albumin, and vitamin B12. When these markers have been combined in selective combinations in tools, their ability to accurately predict survival increases. Some markers were notable for having been robustly validated through extensive testing on univariate and multivariate analysis.

As is evident, these prognostic markers are both clinical markers and biomarkers. A number of tools (combinations of markers) were identified. These included the PaP, PPI and GPS/mGPS and these were found to predict survival. All of these tools had links to systemic inflammation. Some of the tools are simpler to use than others and more objective, which is of greater potential clinical utility and relevance. These tools cover a variety of different populations and therefore direct comparison of studies is difficult, highlighting the fact that a larger study incorporating all the important

prognostic indices identified in the systemic review was needed to enable direct comparison.

In line with the hypothesis that inflammation is related to cancer prognosis a common theme which became evident is that inflammatory biomarkers namely CRP, WCC, Alb are linked to prognosis. There is biological rationale that the clinical symptoms which are also related to prognosis, are also related to inflammation. This applies to weight loss and reduced mobility (a surrogate for PS). Weight loss has been identified as a prognostic marker. However, the definition of weight loss per se must be interrogated and clarified prior to linking weight to prognosis in cancer. Loss of lean mass, a key component of cachexia, has been demonstrated to be linked directly to systemic inflammation and therefore is an external surrogate markers of the internal inflammation ongoing in patients with cancer.

Other symptoms such as dysphagia and xerostomia have been shown to be of prognostic significance. The action of oesophageal motility and therefore its impairment relies on muscle activity. Sarcopenia, which is loss of lean muscle mass, inevitably leads to reduced muscle activity and therefore dysphagia.

It can follow that a reduction in PS is due to or a consequence of reduced lean muscle mass and therefore the prognostic symptom of dysphagia is a consequence of sarcopenia. Impairment of oesophageal motility, reduced swallowing and sarcopenic dysphagia are therefore due to reduced PS overall and result from underlying inflammation from cancer cachexia. Similarly, for the symptom of xerostomia it can be linked to either medications prescribed for advanced incurable cancer or to sarcopenia, cachexia and reduced PS. The bite force and jaw closing muscles are associated with good muscle tone which is lower in patients with cancer, sarcopenia and cachexia. The symptom of xerostomia arises when a patient has muscle atrophy and therefore forced bite closure is not performed 100% or to the maximal effect, due

to overall weakness of muscles. Other symptoms identified as being related to systemic inflammation are anorexia, oedema, ascites and fatigue.

In the next step of this thesis, a retrospective biobank analysis of an existing prospectively collected dataset was performed. In addition to mGPS (incorporating CRP and albumin) and PS, the parameters of weight loss and BMI were specifically examined, given the literature review suggested that these parameters are also linked to systemic inflammation. It was important to compare these parameters to PS, because this is the method used in current clinic practice, to assess prognosis and cancer progression. This study clarified that although weight loss is important, CRP and albumin (combined in mGPS) performed better than weight loss and BMI, and equally as well as PS in the prediction of prognosis and cancer progression. An important finding was that inclusion of the objectively measured mGPS tool was required in the next prospective study, outlined in Chapter 4.

The ultimate aim of the thesis was to compare all the prognostic markers to identify those of greatest prognostic significance and survival accuracy. Objective markers appear to be more useful in clinical practice, but have not been directly tested against the subjective prognostic markers. Chapter 4 detailed a multi-centre prospective observational cohort study into the prognostication of advanced cancer, IPAC. This study was designed on the background of work performed and conclusion reached earlier in this thesis. The study was designed and performed to incorporate all the clinical markers of prognosis and biomarkers of prognosis and compare them all against each other, not just in one cancer population but in numerous cancer types. The study population was large and by performing the study in a number of centres throughout the UK, it is directly relevant to current clinical practice in the UK, as distinct from other previous studies which have been performed in the non-UK population. The inclusion criteria were deliberately broad to minimise bias.

An important finding from the preliminary studies, and supported by the findings in Chapter 4 is that the main clinical prognostic factor was PS and therefore symptoms related to a reduction in PS can therefore be expected to be of prognostic significance. When all the prognostic markers were compared in the IPAC study, certain prognostic themes recur after univariate and multivariate testing. These are listed below:

- The statistically significant prognostic markers for 30 day survival on univariate analysis were CPS, mGPS, ECOG-PS, dyspnoea, Global health, cognitive impairment, anorexia, weight loss, LDH, WCC and NC.

- The statistically significant prognostic markers for three month survival on univariate analysis were CPS, ECOG-PS, mGPS, dyspnoea, global health, cognitive impairment, anorexia, weight loss, LDH, WCC and NC.

- The statistically significant prognostic markers for 30 day survival on multivariate analysis were ECOG-PS, mGPS and NC.

- The statistically significant prognostic markers for three month survival on multivariate analysis were ECOG-PS, mGPS, weight loss, LDH and WCC.

- The indices with greatest prognostic significance were ECOG-PS, mGPS, LDH and WCC.

5.3 Potential Implications of Thesis Findings

It has been demonstrated that PS, the gold standard in terms of prognostication is very accurate when used to predict survival. It is a subjective clinical parameter.

This thesis has shown that mGPS, WCC and LDH are equally as accurate in predicting prognosis in patients with advanced cancer. The thesis has compared all the many validated prognostic indices, clinical and biomarkers in a robust prospective study and these four parameters have the greatest prognostic significance. These parameters are directly linked to systemic inflammation, the inflammatory burden of cancer, and therefore cancer inflammation. To the author's knowledge, it is the first time that all the validated prognostic markers have been compared in a prospective study. It is also the first time that all the prognostic markers have been examined in advanced cancer, and not just one specific cancer type. The prognostic parameters detailed above can be interpreted by clinicians across a variety of cancer specialities and used by them to estimate prognosis. These parameters are tested regularly in clinical practice and are not obscure. These parameters are readily available in all clinical settings in the UK. The prognostic indices were also examined for the first time in determining survival at three months and 30 days. Up until this work, most studies have focussed on examining prognostic markers in relation to three month survival. Determining 30 day survival is of greater benefit to patients being looked after in oncology and palliative medicine, both to guide treatment decisions and develop tailored management plans for patients.

A further important conclusion from this thesis is that prognosis in advanced cancer is directly related to the degree of inflammation. Each of the prognostic markers identified can be attributed to systemic inflammation, the cornerstone of cancer progression.

5.4 Future directions

The main foundation work for prognostication in advanced cancer has been established here through comparing all the validated prognostic markers in a prospective study. This thesis paves the way for future research now to focus on those prognostic markers which have been found to be of prognostic significance. The thesis has examined all the validated markers. Re-studying prognostic markers which are not of prognostic significance is of no benefit to advancing knowledge in prognostication in advanced cancer. The future should focus on creating a new prognostic tool to aid clinical decision making and benefit patient care.

A desirable tool is one which is likely to be used in clinical practice. At present only single parameters such as PS, are used to ascertain prognosis in clinical practice. A new tool must therefore be a combination of the indices with greatest prognostic significance and be kept to the minimum number of indices to aid better uptake and use in clinical practice.

A new prognostic tool incorporating the markers found to be of greatest prognostic significance namely ECOG-PS, mGPS, LDH, WCC, weight loss and NC could be created, tested and then validated for use in patients with advanced cancer. Alternatively tools could be created for estimating 30 day and three month survival. A prognostic tool for 30 day mortality using ECOG-PS, mGPS and NC and a prognostic tool for three month mortality using ECOG-PS, mGPS, weight loss, LDH and WCC could be created, tested and validated for patients with advanced cancer. Once validated these tools could be used to estimate a minimum of 30 day prognosis which could be of immense clinical use in guiding patient treatment and referrals to palliative care. Tools incorporating these prognostic markers would be objective, easy to use, and using parameters which are readily available in clinical practice. Prior to introducing such a tool into the clinical environment, the tool would have to be

evaluated in a testing population, then validated in a training population in a cohort of patients with all types of cancer and prognostic accuracy assessed.

The IPAC study tested ECOG in combination with albumin and CRP, the clinical markers of greatest prognostic significance, and accuracy of survival prediction was confirmed. The advantage of such a tool combining only ECOG-PS and mGPS is that it relies on a subjective clinical parameter already used extensively in clinical practice and one which clinicians are comfortable using, with the addition of objective markers using clinical markers tested routinely. It would, therefore, not incur additional cost in the UK. It is not burdensome, in that the parameters are easy to recall, easy to locate in a patient's notes, easy to test if not already performed, and cost is minimal.

The main advantage of such a tool would be the benefit to the patients in that survival accuracy in the IPAC study was proven and this would enable advance care planning and better care for patients with cancer. This type of tool, with indices which are markers of inflammation, is the natural choice in the oncology world where inflammation is the treatment target. The inflammation burden due to cancer is linked to prognosis in cancer and therefore prognostic markers should be markers of inflammation.

5.5 Strengths and Limitations

The IPAC study contained within the thesis and the thesis itself has not included haematological malignancies and patients with breast or prostate cancers with bone metastasis only. Haematological malignancies were not examined formally because they directly affect the full blood count parameters due to direct disease effect and therefore determination of the effect of inflammation due to cancer and the effect of direct disease activity would have been difficult and would have skewed the results.

The patients with breast or prostate cancer with bone metastases only were not included due to their being expected to outlive the study given survival is estimated to be several years. Cognitive impairment was included as part of the global health questionnaire, however delirium per se was not permitted by the Ethics committee as a parameter to investigate. The cohort did not include equal numbers of all different cancer types, however the results did not demonstrate any prognostic significance to patients having a diagnosis of a specific cancer, so this limitation is less clinically important. The cancer populations were those being cared for in the specific oncology or hospice centres and are subject to local variation in terms of disease incidence and prevalence.

This thesis has performed a thorough review of all the prognostic tools in advanced cancer, focussed on the inflammatory markers linked to cancer survival and performed a national multicentre study in centres across Scotland, England and Wales. It took place in oncology, hospice and palliative care centres in both inpatient and outpatient settings, enabling more patients to have access to the study. It did not interfere with any treatment patients received. The minimum follow up was for three months, which was the maximal survival time period being studied.

One limitation was that patients could only take part on one clinical study and a simultaneous study which, as a clinical CTIMP, took priority, prevented recruitment of patients to this study. Patients with cancer are frequently used in clinical trials for new medications and it was this conflict with other trials which often prevented recruitment. In some circumstances, the conflicting trial would grant permission for their patients to be recruited into the IPAC study.

In the IPAC study, the follow up times varied. Patients recruited at the start of the IPAC study were followed up for longer ,compared to those recruited at the end of the study who were only followed up for the minimum three months. Ideally the follow up time for all studies looking at prognosis would be until every patient in the study dies,

however this is not practical when results are awaited to improve and change current clinical practice and ideally benefit patients now, in addition to future patients.

The topic of patients dying and estimating survival is an emotionally charged one., However clinicians need to be targeted to utilise the results of this study to prevent patients receiving unnecessary treatment in the last three months of life, which may cause increased symptoms and distress with no survival benefit, compared to fast-tracking these patients to the palliative care teams where symptoms can be controlled. One concern is that these data could be used against patients and be used to ration treatments which are of benefit, including access to palliative care, if the patient's survival is estimated to be more than 30 days.

5.6 Final Words

This thesis has undertaken a comprehensive review and investigation into the background of systemic inflammation and its significance to prognostication. The findings of the original researchers namely Hippocrates, Galenus and Celsus have been investigated and confirmed by researchers such as Virchow, Karin and Manotovani. Their work into the importance of the systemic inflammatory response has provided the foundation on which all work on prognosis is based. This current work has demonstrated the valid importance of systemic inflammation in the tumour microenvironment, in the biomarkers used to guide clinical management and in the aetiology of clinical symptoms and signs when estimating prognosis in advanced cancer. A new prognostic tool for use in patients with advanced cancer has been proposed, namely a combination of prognostic markers, all strongly associated with systemic inflammation and, therefore, giving prognostic accuracy from a clinical, scientific and biochemical perspective.

Hippocrates was correct when he said one of the main tasks in medicine was to ‘declare the past, diagnose the present and foretell the future’. What is clear is that the origins of inflammation and its links to disease and prognosis, identified by physicians even pre-dating the original researchers, such as Hippocrates, still holds true. The basic themes and tools in medicine are unchanged. What we have gained in this thesis is greater accuracy, certainty and validity in their use and application.

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Appendix I: Systematic review search

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update, Embase Classic+Embase <1947 to 2015 Week 14>

Search Strategy:

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1 neoplasm.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (1024167)

2 cancer.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (3421033)

3 malignancy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (251965)

4 tumo?r$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (3908264)

5 carcinoma.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (1530087)

6 1 or 2 or 3 or 4 or 5 (6273610)

7 model.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (3945411)

8 tool.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (657880)

9 7 or 8 (4498731)

10 prognosis.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (1151044)

11 prediction.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (498913)

12 progno$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (1332771)

13 10 or 11 or 12 (1765582)

14 terminal care.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (48093)

15 palliat$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (173421)

16 hospice.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (26506)

17 14 or 15 or 16 (217896)

18 6 and 9 and 13 and 17 (1735)

19 limit 18 to "all adult (19 plus years)" [Limit not valid in Embase; records were retained] (1626)

20 limit 19 to english language (1499)

21 limit 20 to humans (1370)

22 remove duplicates from 21 (1088)

Appendix II: Published Papers/ Information Sheets

Review Article

Prognostic Tools in Patients With Advanced Cancer: A Systematic Review

Claribel P.L. Simmons, MBChB, MRCP, Donald C. McMillan, PhD, Kerry McWilliams, MBChB, MRCP, Tonje A. Sande, MD, PhD, Kenneth C. Fearon, MD[†], Sharon Tuck, BSc, Marie T. Fallon, MD, and Barry J. Laird, MD
University of Edinburgh (C.P.L.S., K.M., T.A.S., K.C.F., S.T, M.T.F, B.J.L.), Edinburgh; Department of Surgical Sciences (D.C.M.), University of Glasgow, Glasgow, UK; and European Palliative Care Research Centre (B.J.L.), Norwegian University of Science and Technology, Trondheim, Norway

Abstract

Purpose. In 2005, the European Association for Palliative Care made recommendations for prognostic markers in advanced cancer. Since then, prognostic tools have been developed, evolved, and validated. The aim of this systematic review was to examine the progress in the development and validation of prognostic tools.

Methods. Medline, Embase Classic and Embase were searched. Eligible studies met the following criteria: patients with incurable cancer, >18 years, original studies, population $n \geq 100$, and published after 2003. Descriptive and quantitative statistical analyses were performed.

Results. Forty-nine studies were eligible, assessing seven prognostic tools across different care settings, primary cancer types, and statistically assessed survival prediction. The Palliative Performance Scale was the most studied ($n = 21{,}082$), comprising six parameters (six subjective), was externally validated, and predicted survival. The Palliative Prognostic Score composed of six parameters (four subjective and two objective), the Palliative Prognostic Index composed of nine parameters (nine subjective), and the Glasgow Prognostic Score composed of two parameters (two objective) and were all externally validated in more than 2000 patients with advanced cancer and predicted survival.

Conclusion. Various prognostic tools have been validated but vary in their complexity, subjectivity, and therefore clinical utility. The Glasgow Prognostic Score would seem the most favorable as it uses only two parameters (both objective) and has prognostic value complementary to the gold standard measure, which is performance status. Further studies comparing all proved prognostic markers in a single cohort of patients with advanced cancer are needed to determine the optimal prognostic tool. J Pain Symptom Manage 2017;53:962–970.

Key Words
Prognostic tools, cancer, review

Introduction

Estimating prognosis is a fundamental component in the management of patients with advanced cancer for several reasons. First, accurate estimation of prognosis can help inform whether anticancer treatment is likely to be beneficial.[1,2] Second, it may relieve patient and carer anxiety associated with prognostic uncertainty.[3] Third, it can help with end-of-life care planning, including place of care.

However, in patients with advanced cancer, the ceiling limit of the TNM classification system is often reached (i.e., M_1) and as such is of limited value. As such, in the clinic, prognosis is based on various factors including stage of disease, performance status,

Drs. Simmons and McMillan are joint first authors and Drs. Fallon and Laird are joint senior authors.

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previous clinical experience, and knowledge of cancer trajectories. However, the subjective nature of these may result in estimates of prognosis that are inaccurate, potentially misleading, and may result in anticancer therapies being given inappropriately.[2,4–6]

In an attempt to improve prognostic accuracy, in 2005, the European Association of Palliative Care (EAPC) published recommendations on the use of prognostic markers in patients with advanced cancer.[7] These recommendations were informed by eight studies examining different prognostic tools, which had been published in the preceding decade (1993–2003), and recommended a number of prognostic tools and their utilization. These tools were the Terminal Cancer Prognostic Score, the Palliative Performance Scale, the Palliative Prognostic Index, and the Palliative Prognostic Score.

Because these recommendations were made, a plethora of prognostic tools devised for use in patients with advanced cancer have been developed; however, to date they have not been presented together and comparison made. To this end, the aim of this systematic review was to examine and compare prognostic tools in patients with advanced cancer and make recommendations for their use.

Methods

The following databases were searched: Medline (2003–2015) and Embase Classic and Embase (2003–2015). The search focused on studies of prognostic tools in patients with advanced cancer regardless of the original primary tumor. The search terms are listed in Appendix I. A hand search of key journals and relevant citations was carried out. The date of the last literature search was April 30, 2015.

Eligibility Criteria

Eligible studies met the following inclusion criteria: population with advanced cancer (defined as an incurable cancer), original studies, study population $n \geq 100$ and age ≥ 18 years, quantitative clinical and/or biomarkers were examined, a multivariate statistical model was described, the tool had been examined and validated in two or more independent data sets, published in English, published after 2003 (end date of original literature search), and full article was available.[7] The primary outcome measurement examined was survival prediction (likelihood of death) based on the use of the prognostic tool in the specific patient population. Studies were excluded if a univariate survival analysis was described only, the tool was designed for use in one specific population with one specific cancer type (e.g., only patients with specific stage of lung cancer), or qualitative indices were used exclusively to predict survival.

Data Extraction and Analysis

The initial database search was undertaken and duplicates removed. Two authors (C. S. and K. M.) independently screened each study for eligibility based on the abstract and finally each full text article. From this, the necessary data for descriptive and quantitative analyses were extracted by C. S. and T. S., independently. These included the descriptors of the patient population, length of survival, and information regarding survival predictions. The analysis of each study was performed using standard quality assessment criteria which were then summarized for statistical analysis and comparison where possible.[8] Studies are presented according to the prognostic tool described. Where studies examined both populations with cancer and noncancer, only those populations with cancer were included in the analysis.

Results

The literature search process is shown in Figure 1. After abstract review, 179 articles were reviewed in full and this resulted in 49 studies fulfilling the eligibility criteria.

From the 49 eligible studies, seven different prognostic tools were identified. A summary of these is detailed in Table 1. The tools identified were the Palliative Prognostic Score (PaP, eight studies), Delirium-PaP (D-PaP, two studies), B12/C-Reactive Protein Index (BCI, one study), Prognosis in Palliative Care Study (PiPS, one study), Palliative Prognostic Index (PPI, eight studies), Palliative Performance Scale (PPS, 18 studies), and the Glasgow Prognostic Score (GPS, 10 studies).

A detailed description of these seven prognostic tools is given in Appendices II and III. These tools used a combination of clinical and/or biomarker parameters. The most common clinical parameters used were performance status, anorexia, and dyspnea. The most common biomarkers were C-reactive protein, white cell count, lymphocyte count, and albumin. The number of parameters used ranged from two (GPS, BCI) to 17 (PiPS B), and the mean number was seven. The largest single population studied for each of the prognostic tools is summarized in Table 2. Details of all studies included in this review are summarized in Supplementary Table 1.

To date, there have been eight studies (combined total $n = 2694$) examining the PaP in patients with advanced cancer. Patient cohorts were unselected but included patients with a variety of cancer diagnoses including cancer of the head and neck, lung, skin, breast, gastrointestinal tract, genitourinary tract, prostate, gynecologic, neuroendocrine, and hematologic tissue. The studies were from groups in Australia

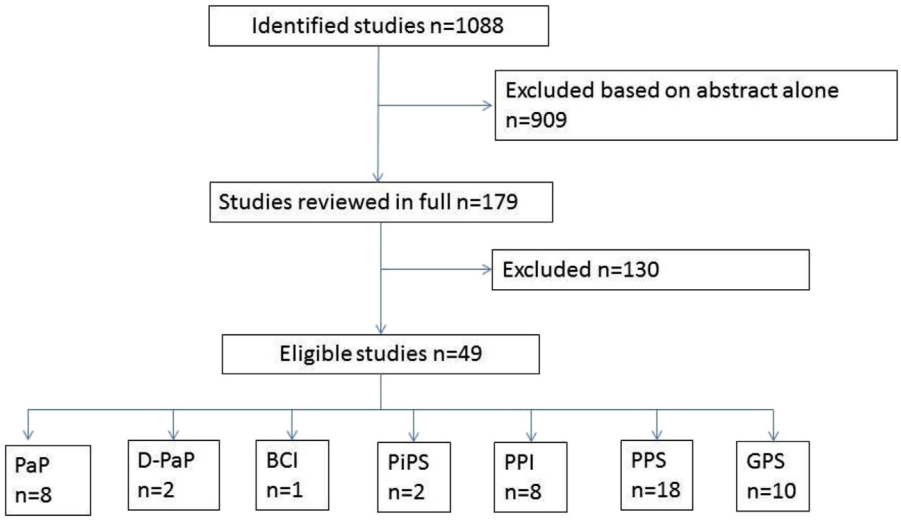

Fig. 1. Flow chart of the review process.

(one study), Italy (two studies), Brazil (one study), Japan (one study), Canada (two studies), and the U.S. (one study), thereby providing external validation of the tool. Two studies (n = 910) examined the D-Pap in patients with advanced cancer.[10,16] This included patients with cancers of the head and neck, lung, breast, gastrointestinal tract, and genitourinary tract. Both the PaP and D-PaP predict survival in patients with advanced cancer. The D-PaP tool has not been as extensively validated compared with the PaP; however, both perform similarly compared with each other.[10]

To date, one study comprising 329 patients examined the BCI in patients with advanced cancer.[11] The patient population included those with a diagnosis of cancer of the head and neck, lung, breast, gastrointestinal tract, genitourinary tract, prostate, gynecologic, neuroendocrine, and hematologic tissue. This study confirmed that an elevated BCI predicts poor survival.

One study (n = 1018) has examined the PiPS.[12] The patients included those with diagnoses of gastrointestinal, lung, unknown primary, breast, urologic, gynecologic, central nervous system, hematologic, and head and neck cancers. This study reported that the area under the curve varied between 0.79 (PiPS A) and 0.86 (PiPS B) and suggested that PiPS is at least equal to and may be better than the clinician's predicted survival.

Eight studies (n = 5929) have examined the prognostic value of the PPI.[10,17–24] The patients included those with cancer of the head and neck, lung, breast, gastrointestinal tract, genitourinary tract, prostate, gynecologic, and hematologic tissue. The studies were based in Japan (three studies), Italy (one study), Taiwan (two studies), U.S. (one study), and Canada (one study). Recently, studies have examined a change in PPI scores, and this approach to researching the PPI appears more consistent, accurate, and clinically useful.

Table 1
Summary of Prognostic Tools

Tool	Number of Variables		Cancer Types (Mixed/Single)	Number of Studies[c]
	Clinical[a] (Subjective)	Biomarkers[b] (Objective)		
PaP	4	2	Mixed and single	8
D-PaP	5	2	Mixed only	2
BCI	0	2	Mixed only	1
PiPS A	13	0	Mixed	1
PiPS B	9	9		
PPI	5	0	Mixed only	8
PPS	7	0	Mixed only	18
GPS	0	2	Mixed and single	10

PaP = Palliative Prognostic Score; D-PaP = Delirium-PaP; BCI = B12/C-Reactive Protein Index; PiPS = Prognosis in Palliative Care Study; PPI = Palliative Prognostic Index; PPS = Palliative Performance Scale; GPS = Glasgow Prognostic Score.
[a]Clinical refers to signs or symptoms which are of prognostic significance.
[b]Biomarkers refers to serum biomarkers of prognostic significance.
[c]Studies eligible for inclusion.

Table 2
Summary of Prognostic Tools—Largest Population Studied Per Tool

Tool	Authors	Cancer	*N*	Survival Outcome	Survival[a]	HR[a]	Summary	*P* value[a]
PaP	Tarumi et al.[9]	Various	777	Continuous	35 Days	—	**Multivariate Cox regression model on overall survival:** Including age, gender, diagnosis, initial PPS, initial PaP, MMSE score, and presence/absence of delirium on initial consultation. **Log-rank test:** PaP Group A vs. Group B vs. Group C	<0.001
D-PaP	Maltoni et al.[10]	Various	549	Categorical (21 and 30 days)	22 Days	—	AUC 0.73 (95% CI 0.71–0.74)	<0.0001
BCI	Kelly et al.[11]	Various	329	Categorical (90 days)	42 Days	—	**Log-rank test:** BCI Group 1 vs. Group 2 vs. Group 3	<0.001 (Group 1 vs. Group 2 $P = 0.091$)
PiPS	Gwilliam et al.[12]	Various	1018	Continuous	<1–14 Weeks	—	AUC = 0.79–0.86	—
PPI	Kao et al.[13]	Various	2392	Continuous	5 Weeks	0.63	**Multivariate Cox Regression:** Adjusting for age, gender, primary cancer origin, referring medical department, and the interval between the hospital admission and referral dates	<0.001
PPS	Casarett et al.[14]	Various	7391	Categorical (7 days)	—	—	**Multiple logistic regression:** Probability of dying between PPS groups.	<0.001
GPS	Laird et al.[15]	Various	2456	Categorical (3 months)	3.2 Months	1.51–2.27	**Multivariate Cox proportional hazards model on overall survival:** *Test sample:* Including age, cognitive function, dyspnea, appetite loss, quality of life, physical function, role function, fatigue, BMI, performance status, and mGPS. HR 1.62–2.05 *Validation sample:* Including quality of life, physical function, emotional function, pain, BMI, performance status, and mGPS. HR 1.51–2.27 **Log-rank test:** Comparing levels of mGPS	<0.001 <0.01 <0.001

PaP = Palliative Prognostic Score; D-PaP = Delirium-PaP; BCI = B12/C-Reactive Protein Index; PiPS = Prognosis in Palliative Care Study; PPI = Palliative Prognostic Index; PPS = Palliative Performance Scale; GPS = Glasgow Prognostic Score; BMI = body mass index; HR = hazard ratio.
[a]Where reported.

Eighteen studies (n = 21,082) have examined the PPS. The patients included those with diagnoses of cancer of the head and neck, lung, breast, gastrointestinal tract, genitourinary tract, prostate, gynecologic, neuroendocrine, and hematologic tissue. The studies were based in the U.S. (six studies), Spain (one study), Canada (eight studies), Italy (one study), Singapore (one study), and South Korea (one study), thereby providing external validation of the tool. Because of the numerous subgroups within the tool, earlier reports had stated it was not highly discriminating in the intermediate scores.[7] Studies taking place after 2005 tackled this issue and focused on the significance of a 10% decrement in PPS score or poorer PPS scores. A strong ordering effect across the different PPS categories was demonstrated, with highly accurate scores for a PPS of 40% or less. Patients with PPS categories greater than 50% had lower hazard ratios than patients with lower PPS scores.

Ten studies (n = 5163) have examined the GPS. The patients included those with diagnoses of cancer of the head and neck, lung, skin, breast, gastrointestinal tract, genitourinary tract, prostate, gynecologic, neuroendocrine, and hematologic tissue. Eight studies were from groups based in the U.K., one study was from Japan, and one study examined data from an international biobank of patients, providing external validation of this tool.

A descriptive comparison of the individual clinical and biomarkers parameters included in the each of the prognostic tools is listed in Table 3. The number of markers ranges from two (GPS) to 17 (PiPS B). The PPS is composed of six parameters (six subjective), the PaP composed of six parameters (four subjective, two objective), the PPI composed of nine parameters (nine subjective), and the GPS composed of two parameters (two objective).

To date, there have been limited studies on the direct comparison of the prognostic value of the above tools. One study compared the performance of the PaP to the D-PaP, PPS, and PPI and concluded that the PaP showed superior accuracy and reproducibility.[10] The PaP was also directly compared with the PPS and PPI tools in separate studies.[9,24] Tarumi et al.[9] concluded that the PPS and the PaP performed similarly in survival prediction, whereas Kim et al.[24] concluded that the PaP performed better.

Table 3
Clinical and Biomarkers Per Prognostic Tool

	Prognostic Tool								
Parameter	PaP	D-Pap	BCI	PiPS-A	PiPS-B	PPI	PPS	mGPS	GPS
Clinical marker									
PS	x	x		x	x	x	x		
CPS	x	x					x		
Anorexia/decreased oral intake	x	x		x	x	x	x		
Dyspnoea	x	x		x		x			
Ambulation							x		
Delirium		x				x	x		
Activity							x		
Evidence of disease							x		
Edema						x			
Global health				x	x				
Breast cancer				x					
Male genital organs				x	x				
Distant metastases				x	x				
Bone metastases				x	x				
Liver metastases				x					
Mental test score				x	x				
Heart rate				x	x				
Dysphagia				x					
Weight loss—last month				x					
Fatigue					x				
Biomarkers									
Lymphocyte count	x	x			x				
White cell count	x	x			x				
Neutrophil count					x				
C-reactive protein			x		x			x	x
Albumin					x			x	x
Vitamin B12			x						
Platelets					x				
Urea					x				
Alanine transaminase					x				
Alkaline phosphatase					x				

PaP = Palliative Prognostic Score; D-PaP = Delirium-PaP; BCI = B12/C-Reactive Protein Index; PiPS = Prognosis in Palliative Care Study; PPI = Palliative Prognostic Index; PPS = Palliative Performance Scale; GPS = Glasgow Prognostic Score; PS = performance status; CPS = clinician-predicted survival.

Finally, direct comparison has been carried out between the GPS and Eastern Cooperative Oncology Group (ECOG) performance status[15] and between the GPS and the PPI[25] and reported that the GPS had prognostic value independent of ECOG-PS[15] and PPI.[15,25]

Discussion

Since the European Association for Palliative Care recommendations for prognostic tools were published in 2005, there have been a number of prognostic tools developed, evolved, and validated.[7] The PPS has been studied in the greatest number of patients, externally validated, and consistently predicts survival in patients with advanced cancer. Other prognostic tools of note that have been validated and consistently predict survival are the PaP, the PPI, and the GPS. In addition, the latter (based on the combination of C-reactive protein and albumin) has been extensively validated since the original review.

Most of the prognostic tools (PPS, PaP, and the PPI) depend largely on the assessment of functional status as a core component. Therefore, their use in routine practice has been sparse compared with Karnofsky Performance Score or the simplified Eastern Cooperative Oncology Group Performance Score.[26,27] In addition, the relatively complex scoring systems of these prognostic tools may have prejudiced their routine use, whereas the similarities but clear differences in these are confusing and make comparison challenging. Therefore, it would be important to rationalize these subjective assessments into a simpler scheme with as advocated by Harding et al.[28]

From the present review, it is also clear that many of the tools, such as PaP, PPI, PPS, and even performance status, are predominantly subjective and it could be argued that where possible, these should be made more objective. For example, one such way would be to examine if skeletal muscle mass is related to functional status and whether it can be a surrogate marker of physical function. This would seem plausible as skeletal muscle indices are increasingly recognized to have prognostic value.[29]

Although various prognostic tools have been validated, they vary in their complexity, subjectivity, and therefore their clinical utility. The GPS would seem the most favorable as it uses only two parameters (both objective) and has prognostic value complementary to ECOG performance status, most commonly used assessment of patient physical function, in the oncology of advanced disease. Further studies, comparing all externally validated prognostic tools in a single cohort of patients with advanced cancer, are needed to determine the optimal prognostic tools.

The search strategy in the present review was comprehensive and included the main medical databases and a detailed search strategy (Appendix I). However, there were three notable studies not included in the review. Feliu et al.[30] reported the development and validation of a prognostic nomogram for terminally ill patients with cancer in almost 900 patients. However, it is of interest that the nomogram included the components ECOG-ps, lactate dehydrogenase, lymphocyte count, and albumin concentrations that have been used in other externally validated prognostic scores, such as PaP, that have been examined in the present review. The second study by Kim et al.[31] reported the external validation of PiPS A and PiPS B in 202 terminally ill patients with cancer. Finally, our search was limited to April 30, 2015. This excluded a large external validation study ($n = 2426$) of the modified PiPS A and PiPS B prognostic tools reported by Baba et al.[32] in May 2015. Nevertheless, the present review is therefore a step toward the viewpoint of Harding et al. that "it would be important to rationalize these subjective assessments into a simpler scheme with judicious selection and refinement of existing tools" (The PRISMA Symposium 1: outcome tool use. Disharmony in European outcomes research for palliative and advanced disease care: too many tools in practice).[28]

Limitations

It is clear that with the exception of the GPS and contrary to the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines, hazard ratio and 95% CI have been reported inconsistently in the prognostic tools developed for use in patients with advanced cancer. This precluded meaningful meta-analysis in the present systematic review. Therefore, future research should directly compare these validated prognostic tools within all advanced cancer types using similar statistical approaches, in keeping with the REMARK guidelines.[33]

The present systematic review updated a previous review published a decade ago. The majority of the prognostic tools examined had less than five independent reports of their prognostic value, and therefore, a meta-analysis of the validated prognostic tools was not meaningful and a formal estimate of bias was not carried out. However, the data from each article were presented in detail (Supplementary Table 1) enabling the reader to draw conclusions as to their quality and the likelihood of bias using standard criteria. As a result, the present systematic review is largely descriptive giving an update in the progress of prognostic tools in the field.

Several key aspects of prognostic tools remain elusive, and the present article was unable to address these due to paucity of primary data. To illustrate, it

is not clear if certain tools have greater utility in specific tumor types and/or at certain points in the cancer journey. Furthermore, the potential role of these clinical tools in clinical practice is unclear as their usefulness in treatment stratification or place of care planning is unknown; both these are unlikely to be addressed unless such tools are incorporated into routine clinical practice.

It is also clear that another challenge is to implement the right tool at the right point in the patient's cancer journey. This is important as this can affect different aspects of care, for example, whether to treat with anticancer therapy, preferred place of death, etc. To date, the application of the right tool, at the right time, remains elusive and is likely to require a combination of mixed methodologies to achieve this.

Conclusion

Prognosis remains a central tenet of care in cancer and validated tools applied correctly may serve to improve patient care. Since the previous systematic review and recommendations, many prognostic tools that have been examined are not integrated into routine clinical care. It could be argued that the multitude of tools available may have actually confused clinicians as to the optimal tool for use. Furthermore, as performance status remains at the forefront of clinical decision making regarding prognosis, tools which build on this would seem preferable, for example, the GPS and ECOG-PS. To provide some clarity as to the optimal prognostic tool, studies are needed which compare all independent prognostic markers, in a single population. Such studies are eagerly awaited.

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Supplementary Table 1
Prognostic Tools

Tool	Authors	Cancer	*N*	Survival Outcome	Survival[a]	Summary	HR[b]	*P*-value[a]
PaP	Glare et al.[34]	Various	100	Categorical (4 w)	12 w	**Log rank (test for trend):** Probability of surviving 1 month: Group A vs. Group B vs. Group C	—	<0.0001
	Tassinari et al.[35]	Various	173	Continuous	26 w	**Multivariate Cox regression model on overall survival:** Including age, tumor type, number of metastatic sites, performance status, ESAS, PaP score.	—	0.022
	Naylor et al.[36]	Various	250	Categorical (30 d)	95 d	**Log-rank test:** PaP Group A vs. Group B vs. Group C	—	<0.0001
	Hyodo et al.[37]	Various	208	Continuous	27 d	**Cox proportional hazards:** PaP Group B vs. Group A PaP Group B vs. Group C	 0.536 (0.36–0.779) 3.72 (2.59–5.35)	 0.002 <0.001
	Tarumi et al.[9]	Various	777	Continuous	35 d	**Multivariate Cox regression model on overall survival:** Including age, gender, diagnosis, initial PPS, initial PaP, MMSE score, and presence/absence of delirium on initial consultation. **Log-rank test:** PaP Group A vs. Group B vs. Group C	—	 <0.001
	Maltoni et al.[10]	Various	549	Categorical (21 and 30 d)	22 d	**Log-rank test** PaP Group A vs. Group B vs. Group C	—	<0.001
	Kim et al.[24]	Various	415	Categorical (4 w)	—	A score of >10 was the optimal cutoff for predicting survival at four weeks	—	—
	Hui et al.[38]	Various	222	Continuous	106 d	**Cox proportional hazards regression analysis with backward selection:** Incorporating age, sex, PaP, PPI, serum albumin, fat-free mass, unadjusted phase angle, handgrip strength, maximal inspiratory pressure, and standardized phase angle. **Log-rank test:** PPI Group A vs. Group B vs. Group C	1.07 (1.02–1.13)	0.008 <0.001
D-PaP	Maltoni et al.[10]	Various	549	Categorical (21 and 30 d)	22 d	D-PaP Group A vs. Group B vs. Group C	—	<0.001
	Scarpi at al[16]	Various	361	Categorical (30 d)	4 w	**"Validation by calibration" and K statistic**	1.6 (1.22–1.99)	<0.001
BCI	Kelly et al.[11]	Various	329	Categorical (90 d)	42 d	**Log-rank test:** BCI Group 1 vs. Group 2 vs. Group 3	—	<0.001
PiPS	Gwilliam et al.[12]	Various	1018	Continuous	<1–14 w	**Logistic regression** AUC = 0.79–0.86	—	—
PPI	Stone et al.[19]	Various	194	Continuous	Group 1: 68 d Group 2: 21 d Group 3: 5 d	**Cox proportional hazards:** The hazard ratio associated with a one-unit increase in PPI score	1.36 (1.29–1.43)	<0.001

(*Continued*)

Supplementary Table 1
Continued

Tool	Authors	Cancer	*N*	Survival Outcome	Survival[a]	Summary	HR[b]	*P*-value[a]
						Survival of less than three weeks was predicted with a PPV of 86% and negative predictive value NPV of 76%.		
	Maltoni et al.[10]	Various	549	Categorical (21 and 30 d)	22 d	PPI Group A vs. Group B vs Group C	—	<0.001
	Cheng et al.[22]	Various	623	Categorical (21 d)	—	**Cox proportional hazards:**		
						Group C vs. Group A:	0.19 (0.10−0.24)	<0.001
						Group C vs. Group B:	0.54 (0.43−0.69)	<0.001
	Kim et al.[24]	Various	415	Categorical (4 w)	—	Optimal scores for predicting four-week survival over 4.5	—	—
	Arai et al.[23]	Various	374	Categorical (3 w)	—	**Multivariate Cox proportional hazards model on predicting death within three weeks:** Including gender, age, BMI, BT, systolic and diastolic blood pressures, PR, initial PPI, and ΔPPI.	9.0 (4.1−20.0) to 14.4 (5.7−36.2)	<0.01
	Kao et al.[13]	Various	2392	Continuous	5 w	**Multivariate Cox regression:** Adjusting for age, gender, primary cancer origin, referring medical department, and the interval between the hospital admission and referral dates	0.63	<0.001
	Hui et al.[38]	Various	222	Continuous	15 w	**Log-rank test:** PPI Group A vs. Group B vs. Group C	— —	0.03 —
						Cox proportional hazards regression analysis with backward selection: Incorporating age, sex, PaP, PPI, serum albumin, fat-free mass, unadjusted phase angle, handgrip strength, maximal inspiratory pressure, and standardized phase angle.		
	Miura et al.[39]	Various	1160	Categorical (3 w, 6 w)	<8 w	**Cox regression analysis:**	1.11 (0.89−1.38)	0.376
						Adjusted for primary cancer site, age, and gender.		
						PPI = 4−6	1.56 (1.27−1.92)	<0.001
						PPI ≥ 6		
PPS	Head et al.[40]	Various	261	Continuous	29 d	**Cox proportional hazards model on overall survival:** Independent variables included PPS score category, comorbidity status, diagnosis, age, gender, race, and marital status.	0.18 (0.092−0.34) to 0.43 (0.28−0.66)	<0.05
	Harrold et al.[41]	Various	214	Categorical (7 d, 30 d, 90 d, 180 d)	—	**Univariate Cox proportional hazards modeling:**	0.96	<0.001
						The area under the receiver operating characteristic curve: To measure predictive accuracy in cancer patients and noncancer patients.		
	Sanchez et al.[42]	Various	250	Continuous	32 d	**Cox regression analysis on overall survival: PPS ≤ 50** Adjusted for anorexia; compromised oral intake; agitation; delirium; apathetic	2.21 (1.30−3.76) to 8.33 (4.51−15.38)	<0.05

					mental state; confused or in coma; coherent language; orientation in time, place, and person; hallucinations and/or illusions; heart rate; respiratory rate; PPS.		
Lau et al.[43]	Various	647	Continuous	10 d	**Log-rank test on overall survival:** PPS groups	—	<0.001
Olajide et al.[44]	Various	157	Continuous	9 d	**Proportional hazards regression model on overall survival:** Including PPS, dyspnea, pain, fatigue, and agitated delirium. 10% Decrease in PPS results in HR of 1.65	1.65 (1.42–1.92)	<0.001
Lau et al.[45]	Various	126	Continuous		Cox regression	0.29 to −0.93	<0.001
Lau et al.[46]	Various	347	Continuous	37 d	**Log-rank test on overall survival:**	—	<0.001
					Initial PPS groups	0.039 (0.023–0.067)	<0.001
					Increasing HR with increasing PPS group	to 0.40 (0.25–0.64)	<0.001
					Multivariable Cox proportional hazards model on overall survival: Including gender, diagnosis, site, and PPS. Increasing HR with increasing PPS group (PPS 20% [0.40] to PPS 70% [0.039])		
Weng et al.[47]	Various	492	Continuous	18 d	**Log-rank test on overall survival**	—	<0.05
					PPS Group A vs. Group B vs. Group C	0.96 (0.95–0.07)	<0.001
					Cox proportional hazards model on overall survival: Including age, gender, race/ethnicity, and PPS.		
Younis et al.[48]	Various	180	Continuous	35 d	**Multivariate analysis with Cox proportional hazards model on overall survival:** Including executed advanced directives, Medicare/Medicaid insurance, PPS, and gender.	1.73 (PPS <50)	<0.05
Lau et al.[49]	Various	5097	Continuous	39 d	**Log-rank test on overall survival**	—	<0.001
					PPS groups compared	0.056	<0.001
					Cox proportional hazards model on survival: Including age, gender, location, diagnosis category, and initial PPS. Increasing HR with PPS group (PPS 70 [0.056] − PPS 20 [0.54]).	(0.046–0.069) to 0.54 (0.49–0.61)	<0.001
Selby et al.[50]	Various	1622	Continuous	26.5 d	**Multivariate logistic regression analysis on overall survival:** Including gender and PPS.		Groups A and C: $P < 0.0001$ Group B: $P = 0.19$
Tarumi et al.[9]	Various	777	Continuous	43 d	**Cox proportional hazards model on overall survival:** Including age, gender, diagnosis, initial PPS, and survival curve time in days, initial PaP, MMSE score, and	0.021 (0.099–0.46) to 0.45 (0.31–0.66)	<0.001 <0.001

(*Continued*)

Supplementary Table 1
Continued

Tool	Authors	Cancer	*N*	Survival Outcome	Survival[a]	Summary	HR[b]	*P*-value[a]
						presence/absence of delirium on initial consultation (PPS 90% [0.21] PPS 40% [0.45])		
	Casarett et al.[14]	Various	7391	Categorical (7 d)	—	**Multiple logistic regression:** Probability of dying between PPS groups.	—	<0.001
	Maltoni et al.[10]	Various	549	Categorical (21 and 30 d)	22 d	**Log-rank test:** PPS Group A vs. Group B vs. Group C	—	<0.0001
	Mei et al.[51]	Various	296	Categorical (90 d)	—	**Multivariate Cox proportional hazards model on overall survival:** Including albumin, gender, and baseline PPS scores (PPS 60–90% [0.31] PPS 20–30% [0.52])	0.31 (0.16–0.58) to 0.52 (0.36–0.76)	<0.001 <0.001
	Kim et al.[24]	Various	415	Categorical (4 w)	—	Optimal scores for predicting survival ≤30	—	—
	Lee et al.[52]	Various	606	Continuous	—	Change in score >30% significantly associated with survival	2.66 (2.19–3.22)	—
	Jang et al.[53]	Various	1655	Continuous	133 d	**Log-rank test for trend:** Median survival between groups.	—	<0.001
GPS	Sharma et al.[54]	Ovary	154	Continuous	39.9 m	**Multivariate Cox proportional hazard model on cancer-specific survival:** Including GPS, histologic subtype, ascites, performance status, ALP, CRP, and primary debulking surgery.	1.68 (1.16–2.45)	<0.001
	Crumley et al.[55]	Gastro-oesophageal	258	Continuous	—	**Multivariate Cox regression model on cancer-specific survival:** Including tumor site, stage, alkaline phosphatase, the GPS, and treatment.	1.51 (1.22–1.86)	<0.001
	Glen et al.[56]	Pancreas	187	Categorical (12 m)	4.6 m	**Multivariate Cox regression analysis on overall survival:** Prognostic scores as covariates.	1.72 (1.40–2.11)	<0.001
	Ramsey et al.[57]	Renal	119	Continuous	8 m	**Multivariate Cox proportional hazards model on cancer-specific survival:** Including lactate dehydrogenase, hemoglobin, calcium, white cell count, neutrophil count, albumin, and C-reactive protein.	2.35 (1.51–3.67)	<0.001
	Forrest et al.[58]	Lung	101	Continuous	Active treatment: 15.5 m Palliative treatment: 5.8 m	**Multivariate Cox regression analysis on overall survival:** Stratified for treatment	2.32 (1.52–3.54)	<0.001
	Partridge et al.[59]	Various	296	Categorical (2 w, 4 w)	—	**Multivariable Cox regression model on overall survival:** Including sex, primary cancer site, age, hemoglobin, and white cell count (mGPS 2 = 2.71)	2.71 (1.25–5.88)	0.011

Leung et al.[60]	Lung	261	Continuous	8 m	Multivariate analysis on cancer−specific survival:	1.67 (1.28−2.19)	0.0001
Pinato et al.[61]	Lung	171	Continuous	9.7 m	**Multivariate Cox proportional hazard model on overall survival:** Including gender, histologic subtype, PS, the European Organization for the Research and Treatment of Cancer Prognostic Score, WBC count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, CRP, albumin, and mGPS.	2.6 (1.6−4.2)	<0.001
Laird et al.[15]	Various	2456	Categorical (3 m)	3.2 m	**Multivariate Cox proportional hazards model on overall survival:** *Test sample:* Including age, cognitive function, dyspnea, appetite loss, quality of life, physical function, role function, fatigue, BMI, performance status, and mGPS (mGPS 1 [HR 1.62] mGPS 2 [2.05]) *Validation sample:* Including quality of life, physical function, emotional function, pain, BMI, performance status, and mGPS. (mGPS 1 [1.58] mGPS [2.06]) **Log-rank test:** Comparing levels of mGPS	1.62 (1.35−1.93) to 2.05 (1.72−2.44) 1.58 (1.25−2.01) to 2.06 (1.62−2.63)	<0.001 <0.001 <0.001 <0.001 <0.001
Miura et al.[39]	Various	1160	Categorical (3 w, 6 w)	—	**Multivariate Cox regression analysis on overall survival:** Adjusted for primary cancer site, age, and gender. GPS = 1 GPS = 2	 1.07 (0.78−1.49) 1.36 (1.01−1.87)	 0.673 0.046

D-PaP = Delirium-PaP; BCI = B12/C-Reactive Protein Index; PiPS = Prognosis in Palliative Care Study; PPI = Palliative Prognostic Index; PPS = Palliative Performance Scale; GPS = Glasgow Prognostic Score; MMSE = Mini-Mental State Examination; AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value; BT = body temperature; PR = pulse rate; BMI = body mass index; CRP = C-reactive protein; PS = performance status; WBC = white blood cell; d = days, w = weeks, m = months.
Some studies compared several of these tools in one article which explains the disparity in the total number of studies versus papers.
[a]Median.
[b]Hazard ratio (confidence interval). Where cells are blank, data were unavailable.

Appendix I

Database: Ovid MEDLINE(R) 1946 to Present With Daily Update, Embase Classic+Embase <1947 to 2015 Week 14>	
Search Strategy	
1	neoplasm.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (1024167)
2	cancer.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (3421033)
3	malignancy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (251965)
4	tumo?r$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (3908264)
5	carcinoma.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (1530087)
6	1 or 2 or 3 or 4 or 5 (6273610)
7	model.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (3945411)
8	tool.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (657880)
9	7 or 8 (4498731)
10	prognosis.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (1151044)
11	prediction.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (498913)
12	progno$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (1332771)
13	10 or 11 or 12 (1765582)
14	terminal care.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (48093)
15	palliat$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (173421)
16	hospice.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (26506)
17	14 or 15 or 16 (217896)
18	6 and 9 and 13 and 17 (1735)
19	limit 18 to "all adult (19 plus years)" [Limit not valid in Embase; records were retained] (1626)
20	limit 19 to english language (1499)
21	limit 20 to humans (1370)
22	remove duplicates from 21 (1088)

Appendix II

Table A1
The PaP

Criterion for PaP	Score
Dyspnea	
Yes	1
No	0
Anorexia	
Yes	1.5
No	0
KPS	
≥30	0
10–20	2.5
CPS (weeks)	
>12	0
11–12	2
7–10	2.5
5–6	4.5
3–4	6
1–2	8.5
Total WBC ($\times 10^9$/L)	
Normal ≤8.5	0
High 8.6–11	0.5
Very high >11	1.5
Lymphocyte percentage	
Normal 20–40%	0
Low 12–19.9%	1
Very low <12%	2.5
Risk Group	Total Score PaP
30-Day survival	
A	
>70%	0–5.5
B	
30–70%	5.6–11
C	
30%	11.1–17.2

CPS = clinician-predicted survival; WBC = white blood cell.

Table A2
The D-PaP

Criterion for D-PaP	Score
Dyspnea	
Yes	1
No	0
Anorexia	
Yes	1.5
No	0
KPS	
≥30	0
10–20	2.5
CPS (weeks)	
>12	0
11–12	2
7–10	2.5
5–6	4.5
3–4	6
1–2	8.5
Total WBC ($\times 10^9$/L)	
Normal ≤8.5	0
High 8.6–11	0.5
Very high >11	1.5
Lymphocyte percentage	
Normal 20–40%	0
Low 12–19.9%	1
Very low <12%	2.5
Delirium	
Yes	2
No	0
Risk Group	Total Score D-PaP
30-Day survival	
A	
>70%	0–7
B	
30–70%	7.1–12.5
C	
<30%	12.6–19.5

D-Pap = Delirium-PaP; CPS = clinician-predicted survival; WBC = white blood cell.

Table A3
The BCI

Total BCI Score = Multiply Serum Vitamin B12 Level (pmol/L) by Serum CRP Level (mg/L)	
Risk Group	BCI Score
1	≤10,000
2	10,001–40,000
3	>40,000

BCI = B12/C-Reactive Protein Index; CRP = C-reactive protein.

Table A4
The PiPS (A and B)

PiPS A	PiPS B	Score
Breast cancer	Male genital organs	The presence/absence of the indices is entered into electronic tool which calculates survival
Male genital organs	Distant metastases	
Distant metastases	Bone metastases	
Liver metastases	Mental test score (0−10)	
Bone metastases	Pulse (bpm)	
Mental test score (0−10)	Anorexia	
Pulse (bpm)	Fatigue	
Anorexia	ECOG (0−4)	
Dyspnea	Global health (1−7)	
Dysphagia	WBC	
Loss of weight in previous month	Neutrophils	
ECOG (0−4)	Lymphocytes	
Global health (1−7)	Platelets	
	Urea	
	Alanine transaminase	
	Alkaline phosphatase	
	Albumin	
	CRP	

PiPS = Prognosis in Palliative Care Study; ECOG = Eastern Cooperative Oncology Group; WBC = white blood cells; CRP = C-reactive protein.

Table A6
The PPS

PPS	Range	Level of Function/Condition
	100% → 0%	Normal → death

PPS = Palliative Performance Scale.

Table A5
The PPI

Criterion	Score
Palliative Performance Scale	
10−20	4
30−50	2.5
≥60	0
Oral intake	
Severely reduced	2.5
Moderately reduced	1
normal	0
Edema	
Present	1
absent	0
Dyspnea at rest	
Present	3.5
absent	0
Delirium	
Present	4
absent	0
Risk Group	PPI Score
Survival	
A	
Longer than six weeks	≤4
B	
Shorter than six weeks	>6
C	
Shorter than three weeks	>6

Table A7
The GPS/mGPS

CRP	Albumin	Score
GPS		
CRP ≥ 10 mg/L	Albumin ≥35 g/L	0
CRP > 10 mg/L	Normal albumin	1
Normal CRP	Albumin <35 g/L	1
CRP > 10 mg/L	Albumin <35 g/L	2
mGPS		
CRP ≤ 10 mg/L	albumin ≥35 g/L	0
CRP > 10 mg/L	Normal albumin	1
CRP > 10 mg/L	Albumin <35 g/L	2

GPS = Glasgow Prognostic Score; CRP = C-reactive protein.

Appendix III

Palliative Prognostic Score and Delirium PaP

The PaP score was constructed by the Italian Multicentre and Study Group in Palliative Care and validated in patients with advanced incurable cancer using 30 day survival probability. The D-PaP (Delirium-PaP) is a modified version of the PaP, incorporating a delirium assessment that slightly improved the predictive accuracy of the PaP. The PaP and D-PaP are the only prognostic tools included in this review that use clinician-predicted survival (CPS) as one of their indices. The PaP has six parameters: four subjective (clinical) and two objective (biomarkers). The PaP and D-PaP both rely heavily on CPS, a subjective parameter that can add an extra 8.5 points to the total score (PaP maximum 17.5; D-PaP maximum 19.5). The other parameters (biomarkers and symptoms) contribute a maximum of 2.5 points making this tool heavily reliant on the clinician's expertise in prognostication (Tables A1 and A2).

A key component of the PaP is clinician-predicted survival. It has been argued that CPS is dependent on physicians having sufficient knowledge and experience to make assess this adequately. From the eligible studies, it was noted that oncologists' (i.e., nonpalliative care specialists) CPS was shown to be well calibrated but individual predictions imprecise. Using the CPS from nonspecialists still enabled, the PaP to predict the short-term survival (30 days) of patients with advanced cancer "reasonably well." The inclusion of CPS, therefore, does not detract from the PaP score being a unique combination of physician's judgment, corrected and integrated with a series of other objective parameters, optimising the score. In spite of this, this tool is not used routinely. This may be because of its heavy reliance on CPS, and therefore, clinicians do not need to use a tool that weights their existing opinion heavily, and therefore, they could argue will not alter their survival estimate. The other components of the tool have been individually validated for their accuracy in estimating prognosis; however, the individual weighting of each parameter is not known because no study has compared every clinical and biomarker important in prognosis in advanced cancer.

B12/CRP Index

The BCI was developed by a group at the University of London, U.K., following the EAPC's recommendations in 2005. It was initially validated in patients with advanced incurable cancer admitted to an elderly care facility. It can estimate up to 90 day mortality. Of interest is that the BCI incorporates vitamin B12 levels as a marker of prognosis; the rationale for this is that increased levels are present in myeloproliferative disorders, hepatocellular carcinoma, and metastatic liver disease. It consists of two objective (biomarker) parameters, CRP and B12. However, vitamin B12 is not always analyzed routinely in patients and may explain the lack of further research into this tool (Table A3).

Prognosis in Palliative Care Study

The PiPS was developed in a UK population with locally advanced or metastatic cancer. There are two versions of the tool (PiPS A and PiPS B) and differ, in that PiPS B incorporates biomarkers when assessing survival. It predicts survival up to and greater than 55 days. The PiPS A has 13 subjective parameters, whereas the PiPS B has nine subjective and eight objective (biomarker) parameters. The PiPS, similar to other tools, relies on subjective parameters; however, in this case, they are orientated toward specific symptoms, signs, and disease burden, and many are suggested by the EAPC as individual prognostic factors. The relative weighting of each of the prognostic factors is not available in the public domain, instead the tool is accessed electronically and a score issued (Table A4).

Palliative Prognostic Index

The PPI was developed in Japan in 1999, in patients with advanced incurable cancer. It divides survival into three groups and estimates survival up to six weeks. Risk Group A (PPI score ≤ 4) has an estimated survival of more than six weeks. Risk Group B (PPI score 5) has an estimated survival of less than six weeks but greater than three weeks. Risk Group C (PPI score >6) has an estimated survival of less than three weeks. It consists of nine subjective parameters (the PPS, oral intake, edema, dyspnea at rest and delirium) and reports the presence or absence of signs and symptoms with similar weighting given to the different parameters. One of the parameters used is the PPS that is a prognostic tool in its own right. By incorporating the PPS into the PPI, more subjective parameters are incorporated, and while this may increase the prognostic accuracy, it may increases bias and the complexity and reduce clinical utility (Table A5).

Palliative Performance Scale

The PPS was validated in a palliative care population in Canada. It provides a percentage score based on subjective indices giving a survival estimate up to three months. Survival accuracy of intermediate scores has been noted to be variable. It consists of six subjective parameters. Many of these parameters are focused on aspects of performance status including ambulation, activity levels, and performance status itself. Performance status is the gold standard in assessing a patient's fitness; therefore, this tool is bias toward performance status in that synonyms of performance status are included as parameters (e.g., levels of ambulation, activity, and self-care). One of the other parameters is conscious level, which could have been objectified by incorporating the Glasgow Coma Scale (Table A6).

In conclusion, the PPS has been extensively studied in a large patient population with advanced cancer, including multiple cancer types. It has performed well in the majority of the studies looking at the tool individually, the only criticism being its better accuracy with lower PPS scores. It has also been compared several times with other prognostic tools with varying results and again demonstrates comparable accuracy to other tools with lower PPS scores. The components of this tool are heavily bias toward performance status and disease burden emphasizing the importance of these clinical markers in prognosis.

The Glasgow Prognostic Score

The GPS was originally developed in patients with non–small cell lung cancer and subsequently refined to the mGPS. The GPS combines CRP and albumin to give a score of 0, 1, or 2, with increasing score suggesting decreased survival: CRP $<10 = 0$; CRP $\geq 10 = 1$ (albumin ≥ 35); and CRP >10 + albumin $<35 = 2$. It has been validated in individual cancer types in addition to large populations of patients with advanced incurable cancer.[25] The GPS is entirely objective as the information needed to calculate the score is based on biomarker results. The GPS has been developed since the EAPC's recommendations in 2005 and meets the requirements set that any prognostic tool is quick and easy to use, and its scoring system is very simple. The GPS is also able to predict survival accurately several months before death. It fulfills the EAPC's recommendations of being quick and easy to use, along with robust evidence of its accuracy (Table A7).

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Prognosis in advanced lung cancer – A prospective study examining key clinicopathological factors

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ABSTRACT

Objectives: In patients with advanced incurable lung cancer deciding as to the most appropriate treatment (e.g. chemotherapy or supportive care only) is challenging. In such patients the TNM classification system has reached its ceiling therefore other factors are used to assess prognosis and as such, guide treatment. Performance status (PS), weight loss and inflammatory biomarkers (Glasgow Prognostic Score (mGPS)) predict survival in advanced lung cancer however these have not been compared. This study compares key prognostic factors in advanced lung cancer.

Materials and methods: Patients with newly diagnosed advanced lung cancer were recruited and demographics, weight loss, other prognostic factors (mGPS, PS) were collected. Kaplan–Meier and Cox regression methods were used to compare these prognostic factors.

Results: 390 patients with advanced incurable lung cancer were recruited; 341 were male, median age was 66 years (IQR 59–73) and patients had stage IV non-small cell ($n = 288$) (73.8%) or extensive stage small cell lung cancer ($n = 102$) (26.2%). The median survival was 7.8 months. On multivariate analysis only performance status (HR 1.74 CI 1.50–2.02) and mGPS (HR 1.67, CI 1.40–2.00) predicted survival ($p < 0.001$). Survival at 3 months ranged from 99% (ECOG 0–1) to 74% (ECOG 2) and using mGPS, from 99% (mGPS0) to 71% (mGPS2). In combination, survival ranged from 99% (mGPS 0, ECOG 0–1) to 33% (mGPS2, ECOG 3).

Conclusion: Performance status and the mGPS are superior prognostic factors in advanced lung cancer. In combination, these improved survival prediction compared with either alone.

1. Introduction

In most patients that present with advanced lung cancer (stage III–IV), there are the options of oncology treatment (including chemotherapy, radiotherapy, targeted therapy) or best supportive care (palliative care) alone [1]. The benefits of any treatment must be balanced with the side-effects, which in cancer treatment often are considerable.

A fundamental factor influencing treatment decisions in advanced lung cancer is the expected prognosis, however clinicians are often inaccurate in survival predictions, and can have a tendency to overestimate the prognosis [2]. There are currently no good predictors of the benefit of chemotherapy; however prognosis is currently being used to select those who receive chemotherapy. The most established factor for assessing prognosis is performance status and this is advised in guidelines for lung cancer treatment [3]. Furthermore, studies have shown that many patients receive inappropriate anti-cancer treatment near the end of life [4]. Better prognostic tools are needed to avoid unnecessary, potentially harmful therapy during end of life.

In addition to performance status, various other factors have been shown to independently predict survival in advanced lung

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cancer, such as weight loss and systemic inflammation. Weight loss is common in patients presenting with lung cancer and typically worsens as disease progresses, with around 60% of patients reporting significant weight loss in their last few months of life [5]. Studies have also linked weight loss in lung cancer to reduced survival, independent of treatment received. Furthermore, patients with weight loss are less likely to complete their intended course of chemotherapy and are more likely to experience chemotoxicity than patients without weight loss, independent of tumor status [5]. Weight loss in patients with lung cancer is therefore of symptomatic, predictive and prognostic relevance.

Measures of the systemic inflammatory response are of independent prognostic value in cancer. A combination of the inflammatory markers CRP (C-reactive protein) and albumin (Alb) termed the modified Glasgow Prognostic Score (mGPS), has been the most extensively studied and validated prognostic scoring tool. The mGPS score has also been shown to correlate with weight loss in patients with advanced cancer, and is associated with increased treatment toxicity, reduced treatment response and poor nutritional status [6–8].

Although weight loss, performance status and the mGPS have been shown to be of independent prognostic value in lung cancer, they have not been compared with each other. Therefore the primary aim of the present study was to compare these prognostic factors in patients with advanced lung cancer, to assess which has the greatest prognostic value in order to guide treatment. A secondary aim was to assess if independent prognostic factors could be combined to improve survival prediction.

2. Materials and methods

A prospective observational study was conducted. Consecutive patients were recruited from two University Hospitals in Greece: the first cohort was evaluated in the University Hospital of Herakleion between 6 February 2006 and 12 October 2010 (with follow-up until 27 October 2011) and the second in University Hospital of Larissa between 30 March 2010 and 13 December 2013 (with follow-up until 1 June 2013).

Eligible patients were 18 years of age or older, had advanced lung cancer (stage IV NSCLC or extensive stage SCLC) and were due to start systemic anti-cancer therapy.

The following data were collected: sex, age, cancer type, body mass index (BMI), percentage weight loss in the preceding 3 months, performance status, albumin, CRP, and survival status at follow-up.

Age, percentage weight loss in the preceding 3 months, performance status, CRP and albumin were categorized using standard thresholds to aid comparison and stratification of results.

Performance status was measured according to the Eastern Cooperative Oncology Group (ECOG) classification which ranges from grade 0 (fully active) to grade 5 (dead). ECOG grades 0 and 1 were grouped into one category as this has been standard practice in the majority of prospective phase III trials in lung cancer and survival changes dramatically in patients with PS2 versus PS0-1 [9,10]. Age was divided into patients less than 65 years of age, between 65 and 74 years and greater than 74 years of age. Cachexia was defined as >5% weight loss, in line with the international consensus classification [11].

CRP and albumin values were used to calculate the mGPS score for each patient. The limit of detection for CRP was 5 mg/L and all samples were processed according to standardized laboratory procedures. The mGPS was calculated as follows: CRP $\leq$ 10 mg/L = 0, CRP > 10 mg/L = 1, CRP > 10 mg/L and albumin < 35 g/L = 2.

Individuals' demographic indices and categories were analyzed and compared to their survival status. Survival time was calculated in months and defined as the time from study entry until death, or censored if alive at follow-up date. Survival curves were plotted using Kaplan–Meier methods and the log-rank test was applied. Survival analysis was performed using Cox proportional hazards model and hazard ratios (HRs) were calculated. Multivariate survival analysis was conducted using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival. Stratification by primary cancer site was performed for the survival analysis. Factors that were predictive of survival in the multivariate analyses were finally grouped together to assess whether they had better prognostic accuracy when grouped together.

Statistical analysis was performed using SPSS version 19. All statistical testing was conducted at the 5% level, and 95% confidence intervals (CI) are reported throughout. Where $n \leq 10$, these groups were not reported.

The study has been conducted and adheres to the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines [12].

3. Results

There were 390 patients included and their demographics are detailed in Table 1. All patients had advanced incurable lung cancer (stage IV NSCLC or extensive stage SCLC). The majority of patients was male (n = 341, 87.4%) and the median age was 66 years (IQR 59–73). The median performance status was 1 (IQR 1–2). Median survival was 7.8 months (IQR 3.5–13.6) reflecting the advanced disease staging of the population. The minimum and median follow-up for survivors was 0.6 months and 12.8 months, respectively. At the time of cessation of data collection, 107 patients were alive and 283 had died. Patients had either non-small cell lung cancer (n = 288) (73.8%) or small cell lung cancer (n = 102) (26.2%).

The median weight loss in the previous three months was 5.0% (IQR 0.8–10.2). The median BMI was 25.2 (IQR 22.5–28.5).

Clinico-pathological factors and survival were compared for this cohort of patients and are detailed in Table 2. On univariate survival analysis, age (p = 0.004), sex (p = 0.009), tumor type (p = 0.007), weight loss (%) in the previous 3 months (p = 0.001), performance status (p < 0.001) and mGPS (p < 0.001) were significant predictors of survival. On multivariate analysis only performance status (p < 0.001) and mGPS (p < 0.001) were predictors of survival.

Figs. 1–3 show Kaplan–Meier survival curves for weight loss, performance status and mGPS respectively.

Table 1
Patient demographics (n = 390).

Parameter	n	%	Median (IQR)
Sex (M/F)	341/49	87.4/12.6	
Tumor type	288	73.8	
Non-small cell lung	102	26.2	
Small cell lung			
Age (≤65/65–74/≥74 years)	154/150/86	39.5/38.5/22.1	66.0 (59.0–73.0)
Survival (months)			7.8 (3.5–13.6)
Weight loss in past 3 months	294	75.3	5.04 (0.8–10.2)
Weight loss category in past 3 months (%)	195	50.0	
Weight loss < 5.0%	195	50.0	
Weight loss > 5.1% (cancer cachexia[a])			
BMI (kg/m^2)			25.2 (22.5–28.5)
Performance status (ECOG) (0–1/2/3/4)			1 (1–2)

SD, standard deviation; IQR, interquartile range.
[a] Defined as weight loss >5%.

Table 2
The relationship between clinic-pathological factors and survival in patients with metastatic lung cancer ($n = 390$).

Parameter	n	%	Univariate		Multivariate	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Sex (M/F)	341/49	87.4/12.6	0.60 (0.41–0.88)	0.009		
Age (≤65/65–74/≥74 years)	154/150/86	39.5/38.5/22.1	1.28 (1.08–1.50)	0.004		
Tumor type (NSCLC versus SCLC)	288/102	73.8/26.2	1.39 (1.10–1.77)	0.007		
Weight loss (%) category in past 3 months (1/2)[a]	195/195	50.0/50.0	1.49 (1.18–1.88)	0.001		
Performance status (ECOG) (0–1/2/3/4)	271/75/31/13	69.5/19.2/7.9/3.3	1.90 (1.65–2.18)	<0.001	1.74 (1.50–2.02)	<0.001
mGPS (0/1/2)	103/183/104	26.4/46.9/26.7	1.84 (1.54–2.19)	<0.001	1.67 (1.40–2.00)	<0.001

[a] Weight loss (%) category: 1 = weight loss <5%, 2 = weight loss >5.1% (cancer cachexia).

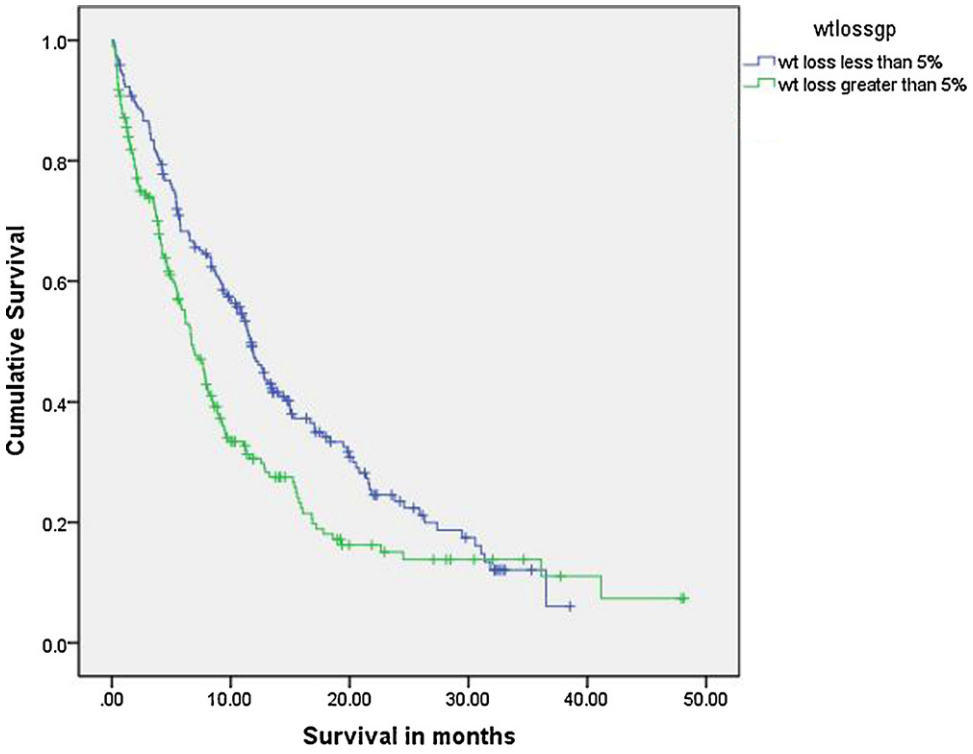

Fig. 1. Weight loss is associated with reduced survival (log rank $p = 0.001$). The area under the receiver operator curve (ROC) was 0.49 (95% CI = 0.43–0.55), $p = 0.661$.

Table 3 shows the relationship between survival at 3 months and mGPS and performance status. Survival was compared across all categories for both mGPS and performance status. For performance status, survival at 3 months ranged from 99% (ECOG 0–1) to 74% (ECOG 2). For mGPS, survival at 3 months ranged from 99% (mGPS0) to 71% (mGPS2). When used in combination, survival at 3 months ranged from 99% (mGPS 0 and ECOG 0–1) to 33% (mGPS = 2 and ECOG 3). Performance status does correlate with mGPS (Pearson coefficient is 0.0206, $p < 0.001$) however this must be taken in the context of the large sample size so limited inference can be drawn from this.

Table 3
The relationship between mGPS and performance status and the survival rate (%) at 3 months in patients with metastatic lung cancer ($n = 390$).

Performance status (ECOG grouping)	mGPS 0	mGPS 1	mGPS 2	mGPS 0–2
0–1	99% $n = 79$	95% $n = 133$	71% $n = 59$	91% $n = 271$
2	74% $n = 19$	71% $n = 34$	59% $n = 22$	68% $n = 75$
3	$n = 4$	55% $n = 12$	33% $n = 15$	44% $n = 31$
4	$n = 1$	$n = 4$	$n = 8$	23% $n = 13$
0–4	92% $n = 103$	87% $n = 183$	58% $n = 104$	81% $n = 390$

Where $n < 10$, analysis not performed.

4. Discussion

The results of this study show that age, sex, weight loss, tumor type, performance status and markers of the systemic inflammatory response (mGPS), all have prognostic value in patients with advanced lung cancer. Performance status and the mGPS carry the greatest prognostic value, however it is of interest that the mGPS has strong prognostic accuracy and performs almost identically to performance status. In addition, the combination of performance status and mGPS points to a new method of prognosis in advanced lung cancer.

Performance status (measured either by Karnofsky or ECOG classification) still remains the gold standard prognostic measure

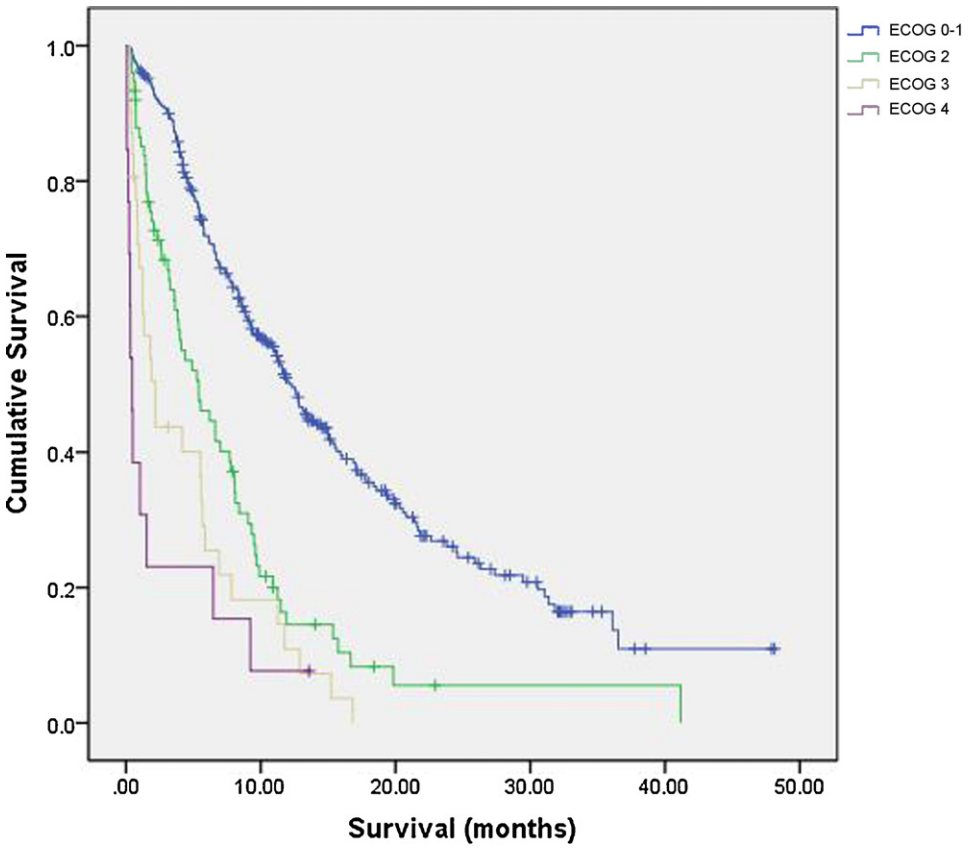

Fig. 2. Decreasing performance status was associated with reduced survival (log-rank $p < 0.001$). The area under the ROC was 0.62 (95% CI = 0.56–0.68), $p < 0.001$.

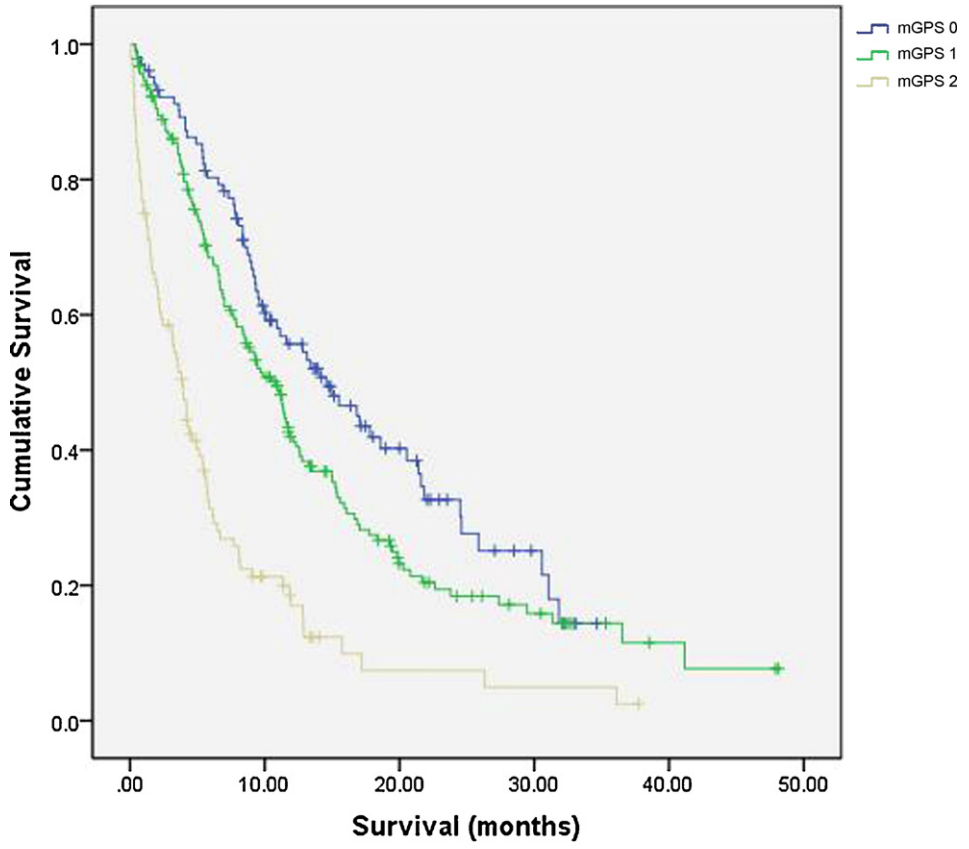

Fig. 3. Increasing mGPS was associated with reduced survival (log-rank $p < 0.001$). The area under the ROC was 0.61 (95% CI = 0.55–0.67), $p = 0.001$.

and the results of the present study support this [13,14]. However, the key limitation of performance status is that it is an entirely subjective assessment of a patient's physical activity and functioning [15–17]. It has been shown that marked discrepancies often exist between clinicians' and patients' assessments of performance status [18]. Furthermore, clear inter-observer variability has been demonstrated [19]. Therefore it is important that the limitations of using a prognostic measure which is subjective and is variable, such as performance status, are considered. This aspect is of fundamental importance when the majority of treatment decisions in advanced lung cancer are deeply influenced by performance status.

In contrast, the mGPS has clear advantages. These findings support that the mGPS has independent prognostic value in advanced lung cancer, however a clear advantage over performance status is that it is objective and has 100% inter-observer congruence. It is simple to measure, inexpensive and is widely available. Used either in isolation or, perhaps even more, in combination with performance status, the present findings demonstrate its relevance in increasing accuracy of survival prediction in metastatic lung cancer [20]. This has been shown in other cancer types [21].

The findings also suggest that the role of weight loss in advanced lung cancer should be viewed with caution. Weight loss has long been regarded a "poor" prognostic sign in lung cancer. This study specifically reviewed weight loss greater than 5%. Cancer cachexia is defined as weight loss greater than 5% and felt by many to be the most adverse weight related prognostic factor in cancer. However the findings suggest that the use of weight loss as an early, prognostic factor in lung cancer is of considerably less value than performance status and mGPS and should not be assessed routinely in the clinic. For this to happen it would mean a change of mind set, as weight loss is a source of concern for patients, families and clinicians. It is regularly recorded at clinic appointments and may be used as a trigger for more investigations (suspected disease recurrence/progression) and dietetic referral or as a starting point for end of life discussions. In addition, the confirmation of weight loss in cancer is often upsetting for patients/families and they need to receive information regarding how to manage this. The findings also demonstrate that cachexia (as per current definition) [11] and BMI did not offer additional prognostic value in the presence of performance status and mGPS. However, if these factors have limited prognostic, their relative value should be re-evaluated.

There is an urgency for improved survival prediction in metastatic lung cancer. Recent work has demonstrated that approximately 10% of metastatic lung cancer patients receive anti-cancer therapy in the last 30 days of life [22], and patients with the shortest survival time after diagnosis received more anti-cancer therapy near the end of life. A key consideration in deciding appropriate treatment in an advanced lung cancer patient is prognosis. In these patients, the benefits of anti-cancer therapy must be weighed against potential disadvantages, such as multiple hospital visits, side effects and potentially life-threatening toxicity. Accurate assessment of prognosis is needed to inform such complex decisions between patients and clinicians.

The results of the present study show that the combination of mGPS and performance status are more accurate in survival prediction than either in isolation. This has been shown in other cancer types and has now been demonstrated in advanced lung cancer [21]. Using the combination of mGPS and performance status may have considerable application in considering treatment options in advanced lung cancer; for example when to use chemotherapy in patients near the end of life. This approach has been supported in recent work which has shown the value of using the mGPS as a stratification factor in very advanced disease to reduce chemotherapy use [22]. The present study takes this approach one step further by combining mGPS with performance status, to increase prognostic accuracy. This novel approach could then be used to guide the choice of oncology treatment in advanced lung cancer patients.

The present study has several limitations. There was a high proportion of men and SCLC in the cohort studied in keeping with the epidemiology of lung cancer in Greece. Furthermore not all previously studied prognostic factors in advanced NSCLC have been examined. However as performance status remains the gold standard prognostic measure in use clinically, its inclusion here is important. Details on cancer treatment, EGFR mutations and histological subtype (for NSCLC) are not available and this would be of interest to assess the effect of response of chemotherapy in patients in poor prognostic groups. All patients in the study were due to start anti-cancer therapy and therefore the number of patients with PS 3 or 4 was small.

5. Conclusion

Performance status and mGPS are superior prognostic factors in metastatic lung cancer and in combination increase survival prediction in advanced lung cancer. In translating this to clinical care, these factors should now be examined in the setting of treatment stratification in the complex area of advanced lung cancer. Continuing studies are eagerly awaited.

Conflicts of interest

There are none to declare.

Acknowledgments

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(Form to be on hospital headed paper)

IPAC Study

Inflammatory biomarkers in Prognosis in Advanced Cancer: a multicentre prospective study

Patient Information Sheet

Invitation

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

- **Part 1** tells you the purpose of this study and what will happen to you if you take part.
- **Part 2** gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

We are approaching patients who have a diagnosis of cancer, in order to invite them to participate in a study in which we are analysing the relationship of certain symptoms, clinical markers and blood markers and their impact upon the length of survival for patients with cancer. This is to try and identify what factors help predict survival in cancer. This is with the aim of gaining information which may help clinicians predict the survival of patients with cancer in the future. This in turn should improve the care and management of future patients with cancer.

Patients with cancer have many symptoms which can impact upon their overall wellbeing and quality of life. Significant levels of certain blood markers can also impact upon the wellbeing and quality of life of patients with cancer, thereby affecting their survival.

We believe that the combination of certain clinical and blood markers can help predict survival in cancer. We believe that this may add extra information when assessing future patients with cancer and benefit their management.

The study will be funded by Medical Research Scotland and sponsored by the University of Edinburgh and NHS Lothian.

Why have I been invited?

You are being invited to take part in this study because you have been identified by your doctor or nurse as someone who has cancer.

Do I have to take part?

No. Your participation in this study is entirely voluntary. If you decide to take part, you will be given this information sheet to keep and you will be asked to sign a consent form. You may choose not to take part or you may decide to stop taking part in the study at any time, without giving a reason. This will not affect your current or future medical care.

What happens if I decide to take part?

If you are interested in taking part you will be contacted by the researcher to arrange a convenient time to meet. Before you take part in the study you will be asked to sign a consent form.

How long will the study last?

The study is open for 2 years during which time we may contact your doctor (hospital doctor or GP) to enquire on your progress.

What will being in the study involve?
If you take part in the study, the following will take place:

- One interview which will focus on the completion of questionnaires regarding symptoms
- Two brief walking tests assessing fitness and mobility (optional).
    - The first test involves timing how long it takes to stand from the sitting position in a chair, walk 3 meters and return to sitting in a chair.
    - The second test involves measuring the distance walked in 2 minutes.
- The research team recording details about your cancer and medical problems from medical records
- The research team following up on your progress at a minimum period of 3 months after entry into the study, by contacting your doctor or your GP. The study will be open for 2 years and 9 months and follow up will cease at this point.

It is part of a routine assessment by any clinical team to have a full physical examination and we will be collecting some data from recordings made at the time of this examination including height, weight and the presence of ankle or abdominal swelling. If the information is not available we would wish to perform a brief examination to examine for ankle or abdominal swelling and measure your height and weight.

In addition to the above, the research team will record details about your cancer, including relevant medical history and results of relevant scans. Most of these details will be taken from your hospital case notes. Finally we will contact either your clinical team or your GP to see how you are getting on.

Do I have to have any blood tests?
You will be asked by the study doctor if you are willing to provide a blood sample (30mls). This is entirely optional and if you do not wish to give a blood sample you are still able to enter the study. This will not affect the care you receive in any way.

It has been shown that significant levels of certain blood markers may aid in predicting survival in cancer**. If you agree to give a blood sample, part of the sample will be analysed to measure these markers or the markers can be analysed from an existing blood sample taken on the day of consent.**

It is anticipated that new blood markers will be discovered in the future to aid cancer management and help understand the course of cancer. These markers may have a genetic component to them.
If you agree, the other part of the blood sample will be completely anonymised and analysed at a future date for specific genes (DNA and/or RNA) or markers, thought to be important in predicting survival in cancer. This sample and/or data collected from this may be analysed in another country. The blood sample will not be used for any other purpose.

Will participating in the study affect my cancer treatment?
No – you will still receive your planned cancer treatment. Participating in the study will not delay or affect your treatment in any way.

Will I need to stay in hospital?
No, you will not need to stay in hospital. You may be contacted via telephone by the study doctor or nurse.

What do I have to do?

You need to answer questions on your symptoms and have a blood sample taken if you consent to this.

What are the possible disadvantages and risks of taking part?
We do not expect any risk to be involved. One blood test is required, which we understand can be painful and cause some discomfort and damage to the skin. Either a doctor or a nurse who have experience and full competencies in this routine procedure will take the blood sample.

What are the possible benefits of taking part?
We may obtain more useful information about your symptoms from the interview which could help future patients with cancer. You will not directly benefit individually from the study, and the main benefit will be to provide information that may help with treatment of future patients with cancer.

If you have any problems at any time you may wish to discuss these with your study doctor/nurse. Alternatively you can give them permission to contact your consultant, clinical nurse specialist or GP on your behalf.

What if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2.

What information will be used for the study?
We wish to record details of relevant medical conditions, information about the cancer itself, the symptoms you have as a result of cancer and your progress over your illness (minimum follow up period of 3 months) including survival. All results will be saved on computer files and transferred to the University of Edinburgh for analysis. Your personal details will be removed from results and replaced with a study number before copies are sent. The analysis will be done on NHS and University computers, and may be examined by experts from other parts of the UK or around the world. A list that links your details with the study number will be kept separate from all other information. Your involvement in the study will be recorded in your medical notes and your GP will be told that you are taking part in the study by letter. You will not be identified personally in any report arising from the study. Some of the information collected may help answer other questions about cancer management in the future. This might include sharing information with other researchers in other hospitals or countries. All information that is re-analysed or shared will be anonymous.

Your medical records may be examined by relevant authorities (for example government bodies, NHS Research and Development staff) to ensure that the study has been conducted to proper standards. You will be given a copy of the information and consent forms to keep.

If the information in Part 1 has interested you and you are considering participating, please read the additional information in Part 2 before making any decision.

Part 2

What if new information becomes available?
Sometimes we get new information during the course of a study. If this happens your research doctor or nurse will tell you and discuss whether or not you should continue in the study. If you decide not to carry on, your research doctor or nurse will make arrangements for your care to continue. If you decide to continue you may have to sign an updated consent form. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?
If you decide not to continue in the study, you are free to withdraw at any time and without having to give a reason. A decision to withdraw at any time will not affect the standard of care you receive. If you withdraw from the study we will use the information collected up to your withdrawal.

What if there is a problem?
If you have a concern about any aspect of this study, you should speak to the researchers who will do their best to answer your questions – ***Insert contact details here***.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms will be available to you.

Will my taking part in this study be kept confidential?
Yes, it is totally confidential. You will be allocated a study number to ensure you remain anonymous. Your date of birth, gender, the name of your condition and the information collected will be entered onto a secure database using NHS and University of Edinburgh computers.

You can be assured that any data collected during the course of this study and any of the results published will not identify you personally. Your medical records will only be available to the research doctors, your hospital consultant, responsible individuals from the Edinburgh Cancer Research UK Centre, trial sponsors and regulatory authority.

With your permission, we would like to inform your general practitioner of your participation in this trial. Your information will be stored securely and will be kept strictly confidential, with access provided only to authorised personnel.

Your consent to take part in this study includes your consent to allow the use of the data in your medical/clinical records for the purposes of Cancer Research. Your consent also includes allowing this data to be linked to data coming from other sources such as cancer registries and medical clinical records. All data collected on your behalf will be treated in compliance with the European and UK applicable laws to ensure your confidentiality is maintained.

Will my GP be informed?
We will inform your GP by letter if you decide to take part.

Will my oncologist (cancer doctor) be informed?
We will inform your oncologist by letter if you decide to take part.

What will happen to the results of the study?
The results of this study may help with the treatment of future cancer patients. The results will help in the development of future studies in this area. These results will also be published in a scientific journal.

Who designed the study?
A group of doctors from across the UK and Canada have designed this study. They are specialists in treating cancer symptoms and looking after patients with cancer.

Who is organising and funding the study?
It is being funded by Medical Research, Scotland and organised by the University of Edinburgh.

Who has reviewed the study?
This study has been reviewed and approved by the NHS Research Ethics Committee to confirm that this study considered the 'rights and protection of patients' health. The study has also been reviewed by Medical Research Scotland, a local charity that funds research in Scotland, which is providing funding for the study.

In addition, the study has been reviewed by the Research and Development Department of NHS GGC/Lothian and the Research and Development departments of all centres taking part. The study is sponsored by NHS Lothian/the University of Edinburgh.

Can I get further information about the study?
If you wish to discuss any other aspect of the study, you can do so with Dr. Barry Laird contactable on telephone number 0141 211 3418.

Can I get independent advice about taking part in the study?
Independent advice on taking part in medical research is available from 'INVOLVE', an NHS sponsored organisation (Website address: http://www.invo.org.uk Email address: admin@invo.org.uk Telephone number: 02380 651 088)

Contact for further information
If you have further questions about your illness or clinical studies, please discuss them with your doctor.

If you would like independent advice or further information you may also find it useful to contact Macmillan Cancer Support, an independent patient advisory group: Freephone 0808 808 00 00; website http://www.macmillan.org.uk, Head Office Address: Macmillan Cancer Support, 89 Albert Embankment, London, SE1 7UQ.

Alternatively you can contact Cancer Research UK, Freephone 0808 800 4040, website http://www.cancerresearchuk.org, and address: Angel Building, 407 St John Street, London EC1V 4AD

If during the course of the study you have any questions regarding your participation or would like further study specific information before making your decision please contact:

Doctor:
Name Dr Barry Laird Telephone Number 0141 211 3418

Thank you for taking the time to read this information.

CONSENT FORM

(Form to be on hospital headed paper)

Name of Researcher (PI): Dr Barry Laird

Patient Identification Number for this trial:

Title of Project: **IPAC Study**

Inflammatory biomarkers in Prognosis in Advanced Cancer: a multicentre prospective study

Please initial boxes

1. I confirm I have read and understand the information sheet dated **17th May (Version 4)** for the above study. I understand what is involved in taking part in this trial and I have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I agree that sections of any of my medical notes and data collected during the study may be looked at by local researchers, by responsible individuals from the Edinburgh Cancer Research UK Centre and the trial sponsors (NHS and the University of Edinburgh) where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I understand that data from the study including my gender, date of birth, details of my condition and the results of blood tests will be entered onto a secure database using NHS and University of Edinburgh computers to be shared with the Palliative Medicine Research Group researchers (University of Edinburgh). I give permission for data to be used in this way. ☐

5. I give my permission for a letter and information regarding my participation in this study to be sent to my GP and oncologist/hospital doctor. ☐

6. I agree to the information detailed in this patient information sheet to be collected as part of this study ☐

7. I agree to analysis of clinical biomarkers from a blood sample taken on the day of consent. ☐

8. I agree to a blood sample being taken stored and analysed for future genetic analysis (DNA and/or RNA). ☐

9. I agree to take part in the above study. ☐

Please sign and date below:

Name of Patient	**Date**	**Signature**

Name of Person taking consent	**Date**	**Signature**

When completed, 1 original for patient; 1 original for researcher; 1 copy to be kept with hospital notes