AN INVESTIGATION OF CT DERIVED BODY COMPOSITION, HOST NUTRITIONAL STATUS, SYSTEMIC INFLAMMATION AND CLINICAL OUTCOMES IN PATIENTS WITH COMMON SOLID TUMOURS

By

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Abstract

Colorectal and lung cancers are common solid tumours in Western populations. While colorectal cancer presents largely at an early, operable stage, lung cancer presents largely at an advanced inoperable stage. Although tumour related characteristics are important part of cancer staging, host factors are increasingly recognised to impact on oncological treatment and clinical outcomes. Recently CT-derived body composition treatment has become available to supplement other host factors such as malnutrition risk, frailty, performance status and systemic inflammation. Importantly, these host characteristics are potentially modifiable. The aim of the present thesis was to examine the relationships between CT-derived body composition, host nutritional status, systemic inflammation and clinical outcomes in patients with common solid tumours.

Chapter 1, critically reviewed the importance of CT derived body composition and the barriers to universal application of this modality for improving the staging and treatment of common solid tumours. Specifically, computed tomography (CT) based body composition analysis methods were critically reviewed and further directions to achieve body composition in routine clinical practice were highlighted. Moreover, the relationship between imaging based body composition and systemic inflammation in patients with common solid tumours was systematically reviewed. The systemic inflammatory response was directly associated with low skeletal muscle index (SMI) and low skeletal muscle density (SMD).

Chapter 2, examined the relationship between psoas and all other skeletal muscles at L3 level with regards to clinical outcomes in patients with operable CRC. Critical analysis of value of L3 skeletal muscle and psoas muscle area in 1002 patients with operable CRC was performed. Both psoas and whole skeletal muscles at L3 were moderately correlated and

both had prognostic value in terms of clinical outcomes including length of hospital stay and overall survival. However, only SMI had independent prognostic value in patients with operable CRC.

Chapter 3, examined the relationship between MUST, systemic inflammation, body composition and clinical outcomes in patients with operable colorectal cancer. In patients with mild and moderate / high nutrition risk, systemic inflammation was associated with low SMI, greater length of stay and poorer overall survival. The MUST and mGPS has complementary prognostic value and may form the basis of routine disease related malnutrition assessment in patients with primary operable CRC. It was also proposed that cachexia may be defined as disease related malnutrition with systemic inflammation. The management directions for these patients should include reducing catabolism and improving anabolic response by addressing malnutrition, SIR, muscle mass and function.

Chapter 4, examined the relationship between MUST, systemic inflammation, body composition and survival in patients with advanced lung cancer. Similar relationships were seen as in patients with CRC. The patients who were malnourished, frail, inflamed and had low SMI had poor survival as compared to patients who were not. This study suggested that combination of MUST, ECOG and mGPS provides a framework to identify the groups of patients who will benefit from aggressive oncological treatment or referral to the palliative care team. Moreover, new GLIM criteria captures components of MUST and the mGPS, highlighting the fact that host characteristics including malnutrition, systemic inflammation are important characteristics in decision making process to decide targeted treatment.

Chapter 5, examined the longitudinal relationship between MUST, SIR and body composition in patients with advanced lung cancer. Over approximately, 3 months

longitudinal study period, there was increase in malnutrition, worsened performance status, increase in SIR (mGPS and NLR), decrease in subcutaneous, visceral adiposity, SMI and SMD. Longitudinal MUST, ECOG, mGPS and NLR were associated with overall survival. No measurement of body composition was associated with overall survival. The loss of muscle was associated with SIR. The loss of body mass should be considered in the context of malnutrition risk, performance status and systemic inflammation.

Chapter 6, examined the comparative analysis of CT derived measures of body composition across two solid tumours (CRC and LC). The comparison was performed in view of significant differences in two cohorts. CRC cohort included patients with operable disease whereas LC included patients with advanced disease undergoing radiotherapy. CRC is less inflammatory cancer and patients maintain body composition over longitudinal study period, whereas LC is pro inflammatory and patients lose more fat and muscle mass. CRC involves gastrointestinal tract and LC did not. The percentage of obesity and low SMI were similar between two cohorts despite large differences in clinicopathological characteristics. It was also, highlighted in this comparison that CT derived body composition although prognostic, is a result of patient constitution rather than tumour itself. The systemic inflammatory response as evidenced by mGPS in this study can be considered as important therapeutic target and loss of muscle mass in patients with advanced cancer is related to systemic inflammatory response.

Chapter 7, examined advanced lung cancer patients who had PET-CT pre-treatment and its relationship to MUST, systemic inflammation and metabolic uptake were examined. There was direct relationship between mGPS and FDG uptake. MUST, mGPS and FDG uptake were associated with overall survival. SIR was associated with loss of muscle and frailty. The combination of clinicopathological (MUST, ECOG, frailty) and radiological

parameters (FDG uptake) provide comprehensive host assessment to guide targeted treatment. These observations are relevant in pre-treatment as well as when measured longitudinally at 3 months interval in advanced lung cancer cohort. The patients who continue to deteriorate despite radiotherapy with increased inflammation and loss of muscle mass, should be directed to the best palliative care.

Chapter 8 Conclusions

Host and tumour characteristics are important for best possible outcome in treating a patient with cancer. Staging the host as well as staging the tumour is an important concept for decision making and to provide best targeted therapy. Important host characteristics include MUST, ECOG, SIR and CT derive body composition. These characteristics when applied to the patient treatment can provide comprehensive phenotype to decide the treatment or palliation course. This thesis examined these characteristics across two solid tumour types of diverse phenotypes. Inflammation and body composition were related to each other. The longitudinal studies as well as comparative analysis between two cancers provides a significant insight to determine future directions for targeted treatment and palliation. It was observed that patients with advanced lung cancer get more malnourished, more inflamed, more muscle loss and have worse overall survival when compared to operable CRC.

Title: An investigation of CT derived body composition host nutritional status, systemic inflammation and clinical outcomes in patients with common solid tumours

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Author's Declaration

The work presented in this thesis was undertaken between 2018 and 2020 in the Academic Unit of Surgery at Glasgow Royal Infirmary. I declare that the work presented here, was undertaken by myself. In addition, the following individuals contributed:

Ross D Dolan provided help with scans validation and reviewed the final draft.

Yeung Timothy Tsz Ho assisted with scan analysis in chapter 2

Nicholas MacLeod provided initial data for lung cancer cohort

Publications

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

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- *CT derived measurement of body composition- comparative analysis of patients with operable colorectal and advanced lung cancer*

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- *Longitudinal changes in CT body composition in patients undergoing surgery for colorectal cancer and association with perioperative clinicopathological characteristics*

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- The relationship between systemic inflammation, body composition and clinical outcomes in patients with operable colorectal cancer at low and medium to high nutritional risk

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Presentations

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

Sep 2023: CCS, Edinburgh. **"Longitudinal changes in CT derived body composition and relationship with clinicopathological characteristics in patients with advanced lung cancer."** (Talking Poster)

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January 2020: ASGBI 2020, Glasgow. **"The relationship between systemic inflammation, body composition and clinical outcomes in patients with operable colorectal cancer at low and medium to high nutritional risk."** (Talking poster)

January 2020: ASGBI 2020, Glasgow. "**The relationship between computed tomography derived psoas muscle index and total skeletal muscle index and clinical outcomes in patients with primary operable colorectal cancer (CRC).**" (Oral)

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Definitions/Abbreviations

18FDG	^{18}F-2-fluoro-2-deoxy-d-glucose
AI	Artificial intelligence
ASA	America Society of Anaesthesiologist Physical Status Classification
ASPEN	American Society of Parenteral and Enteral Nutrition
BC	Body composition
BMI	Body mass index
CDSR	Cochrane Database of Systematic Reviews
CEA	Carcinoembryonic antigen
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
CRC	Colorectal cancer
CRP	C-Reactive Protein
CSS	Cancer Specific Survival
CT	Computed Tomography
CVA	cerebrovascular accident
CXR	Chest X-ray
DEXA	Dual-energy X-ray absorptiometry
DM	Diabetes mellitus
DNACPR	Do not attempt cardiopulmonary resuscitation
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
ESPEN	European Society of Parenteral and Enteral Nutrition
FELANPE	Latin American Federation of Nutritional Therapy, Clinical Nutrition and Metabolism

GIT	Gastrointestinal tract
HCC	Hepato cellular cancer
HU	Hounsfield Units
IHC	Immunohistochemistry
MeSH	Medical Subject Heading
LOS	Length of stay
MMR	Mismatch repair
MDT	Multidisciplinary team
mFI	Modified frailty index
mGPS	Modified Glasgow Prognostic Score
MTV	Metabolic Tumour Volume
NLR	Neutrophil Lymphocyte Ratio
NSAIDS	Non-Steroidal Anti Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
OR	Odds Ratio
OS	Overall Survival
PCI	percutaneous coronary intervention
PCS	prior cardiac surgery
PENSA	Parenteral and Enteral Nutrition Society of Asia
PET	Positron Emission Tomography
PFS	Progression Free Survival
PLR	Platelet Lymphocyte Ratio
PLS	Platelet Lymphocyte Score
US	Ultrasound Scan

RCT	Randomised Control Trial
ROI	Region Of Interest
SIR	Systemic Inflammatory Response
SFA	Skeletal Fat Area
SFI	Subcutaneous Fat Index
SII	Systemic immune inflammation index
SMA	Skeletal Muscle Area
SMD	Skeletal Muscle Density
SMI	Skeletal Muscle Index
SUV	Standardized Uptake Value
TFA	Total Fat Area
TFI	Total Fat Index
TIA	Transient ischaemic attack
TLG	Total Lesion Glycolysis
TNM	Tumour, Node, Metastasis
USS	Ultrasound scan
VAT	Visceral Adipose Tissue
VFA	Visceral Fat Area
VFI	Visceral Fat Index
VAT	Visceral Adipose Tissue
VO	Visceral Obesity
WCC	White Cell Count
WHO	World Health Organization
WLGS	Weight loss grading system

Dedication

To my wife Yasmin who has provided enduring support and encouragement throughout. To my sons Mohammed Ali, Ahmad, Abdullah and Abdul Hanan who have always uplifted my spirit and provided enormous motivation to complete the clinical research and to my mum Bano and Dad Allah Ditta, and my Mother in law Rashida, Father in law Mohammed Amin and sister Kauser for enormous support in everything possible.

1. Introduction

Cancer is the third leading cause of death worldwide accounting for nearly 10 million deaths in 2020 (Ferlay, Colombet et al. 2021). Colorectal cancer (CRC) is the third most common cancer whereas, lung cancer (LC) is the second most common cancer after breast cancer. Lung cancer is the most common cause of cancer death (1.79 million). While the relationship between host and tumour characteristics have been studied in CRC, there is paucity of literature in combining various cancers especially a good prognostic with poor prognostic cancer. This comparison is essential to identify the relationships between various cancers and identify the targets for treatment. Moreover, this comparison will help to understand whether, changes in body composition are constitutional or are secondary to cancer itself.

In UK, approximately 48,500 new cases of lung cancer are diagnosed every year and overall it is the third most common cancer. There were around 34,800 lung cancer deaths in the UK every year and this cancer is the most common cause of cancer death in this country (Cancer Research 2019).

1.1 Colorectal Cancer

1.1.1 Epidemiology

Colorectal cancer is the fourth most common cancer amongst men and women in the UK and is the second leading cause of cancer death after lung cancer. Colorectal cancer is one of the most commonly studied operable cancer with regards to systemic inflammation and body composition (Abbass, Dolan et al. 2019).

1.1.2 Risk factors

Colorectal cancer (CRC) is multifactorial disease i.e. genetic, environmental and inflammatory factors are all involved in development of CRC. Age is a significant risk factor for colorectal cancer. Hereditary colorectal cancer include Lynch syndrome and MMR mutations. Hereditary mutation in APC gene results in familial adenomatous polyposis (FAP). Patients with this mutation have approximately 100% risk of developing CRC by the age of 40 years. Inflammatory bowel diseases like Crohn's disease and ulcerative colitis increase the risk of developing CRC. The approach to patient with CRC is individualised and depends upon number of factors including age, family history, co-morbidities, patient ability to undergo invasive procedures i.e. colonoscopy, surgery, life expectancy, baseline risk and cost. Diets rich in red meat and low in fibre are also risk factors for CRC.

1.1.3 Aetiology

The risk factors mentioned above are considered etiological factors for CRC. A patient presenting with altered bowel habits, rectal bleeding and iron deficiency anaemia should have focussed history, clinical examination and planned investigations to identify the cause of symptoms and to exclude CRC.

1.1.4 Diagnosis

Histology evaluation and tissue diagnosis is preferable before surgery. Tattooing during endoscopic evaluation is helpful for intra operative tumour localization, gain adequate resection margins and to save time where tumour may not be easily palpable. Colonoscopic

evaluation before resection can also help in avoiding missed synchronous lesions (1-5% synchronous cancers and 10-15% synchronous adenomas). It is possible to obtain immunohistochemistry on colonoscopic biopsy. It is estimated that it is cost effective to perform immunohistochemistry as absence of PMS2 and MSH6 protein mutation excludes at least 90% of Lynch syndrome and performing this analysis on resected specimens can help in identifying tumour and stroma inflammatory infiltrate (Shia, Tang et al. 2009) .

Family history is important for evaluation of possible Lynch syndrome and prompt further genetic analysis can be performed. Preoperative evaluation includes use of colonoscopy, biopsy and staging CT chest abdomen and pelvis.

Preoperative laboratory investigations include full blood count, urea and electrolytes, liver function tests, C-reactive protein (CRP) and use of tumour markers i.e. carcinoembryonic antigen (CEA). From these biochemical parameters, markers of systemic inflammatory response (SIR) can be calculated. The two most common used markers include modified Glasgow Prognostic score (mGPS) and neutrophil lymphocyte ratio (NLR). CEA is helpful in management of patients post operatively as it is reassuring to see falling CEA to zero post operatively. CEA is also used post operative monitoring and is recommended to check 6 monthly as elevating levels could indicate recurrence / metastatic disease and should be followed by CT chest, abdomen and pelvis to look for recurrence or metastases.

1.1.5 Management

TNM staging is used for assessment of tumour stage. This is based on AJCC TNM stage 8th edition. The management decisions are complex and involve discussion in MDT.

Surgical techniques

Surgery is the cornerstone of management of colon cancer. There are some guiding principles to achieve best patient outcome. Firstly, detailed documentation of surgical exploration with examination of liver, stomach, ovaries and other sites of metastases should be provided. Secondly, tumour should be removed along with mesocolon/ mesorectum depending upon location in colon or rectum to the origin of primary feeding vessel. In case of right colon cancer, terminal ileum with its mesentery should be removed. Thirdly, tumour should be removed with its draining lymphovascular pedicle with at least ≥12 lymph nodes. Fourthly, at least 5 cm margin of tumour free colon should be resected on both sides of tumour in case of colon cancer and at least 2cm in case of rectal cancer. Fifthly, there are some special situations which should be considered in guiding surgical management of colon cancer. Synchronous colon cancers should be treated with double resection or subtotal colectomy. If there are clinically enlarged nodes at time of colon resection which are suspicious of cancer but are outside operative field, these should be either removed preferentially or at least biopsied. If the tumour is adherent to adjacent structure, it should be removed with en bloc resection as there is approximately, 40% incidence of malignant cell involvement in these cases.

There are various approaches for surgical resection and this has involved significantly over last two decades. From open to laparoscopic and now robotic surgery is the evolutionary trend and this has been shown to reduce the inflammatory insult to the patient.

Adjuvant chemotherapy

FOLFOX (folinic acid, 5 fluorouracil and oxaliplatin) is the first line chemotherapy in the adjuvant and metastatic colorectal cancer treatment. MSI-H tumours do not benefit from 5 fluorouracil.

Special circumstances

CRC metastases via hematogenous, lymphatics and local routes. Liver, lung, lymph node, peritoneal and pulmonary metastases are the most common sites of spread. Options for treatment vary depending upon number, location, extent of metastases and nodal involvement. Discussion in MDT involving relevant specialists is key to achieve the best clinical outcome. Discussion with hepatobiliary surgeon in case of liver metastases, with thoracic surgeon in case of pulmonary metastases, with peritoneal malignancy specialists in case of peritoneal metastases is very important.

In synchronous liver metastases, liver first approach or synchronous resection is performed. Asymptomatic primary cancer rarely requires resection. Ovaries are removed when grossly abnormal. Colonic stenting is a valuable tool for patients with obstructing cancer prior to elective resection.

Where lymph node or suspected liver, adrenal or other solid viscera metastases suspected, CT-PET evaluation is considered. In other special situations, where tumour is obstructed and does n't allow a complete colonoscopy, gastrograffin enema or CT colonography, PET/CT colonography should be obtained. In emergency presentations, where preoperative colonoscopy was not performed, colonoscopy post operatively or soon after completion of adjuvant chemotherapy is required. PET CT and MRI abdomen are not routine part of staging, however, are valuable options in cases of patients with contrast allergy.

1.2 Lung Cancer

1.2.1 Epidemiology

Lung cancer is the most common cause of death worldwide. It was first described in 1761 as distinct disease. There are two types of lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is further classified histologically into adenocarcinoma, squamous cell carcinoma (SCC) and large cell carcinoma.

1.2.2 Risk factors

Smoking is one of the most important factor in causation of primary lung cancer. Initially lung cancer was classified into two categories, small cell and non-small cell cancer. However, with the advancement in understanding biology of disease, lung cancer is more heterogenous disease.

1.2.3 Aetiology

The above mentioned risk factors are etiological factors for lung cancer. The approach to patient with primary lung cancer involves history taking, clinical examination, CXR and CT findings.

1.2.4 Diagnosis

The lung cancer is diagnosed from history, clinical examination and radiology. Most patients are diagnosed by finding opacity on plan CXR. CT provides more detailed dimensions of location, size, number and presence of metastatic disease. PET-CT is very valuable addition in treatment decision making in MDT. TNM staging is an important part in decision making process on choice of treatment. Patients with lung cancer mostly have insidious course and

are usually asymptomatic until the disease is advanced. Therefore, by the time of presentation, disease is advanced and prognosis is poor.

1.2.5 Management

The treatment options for lung cancer have evolved significantly over the past few decades. Treatment decisions are complex and involve discussion in MDT. These decisions are based on tumour and host characteristics. Surgery, radiotherapy, chemotherapy and immunotherapy have gone through significant changes; however, overall prognosis remains poor. Most patients with lung cancer die of advanced disease. While the performance status is important measure in treatment decision making process, this is frequently subjective. Therefore, there is continued interest in identifying other markers of prognosis in advanced cancer (Simmons, McMillan et al. 2017). Lung cancer is associated with increased systemic inflammatory response when compared to colorectal cancer. Tobacco control measures with early detection can help in reducing the mortality associated with lung cancer. Thoracoscopic and robotic surgery are increasingly used in select cases which is associated with reduced inflammatory response.

Colorectal cancer and lung cancer present two extremes with regard to patient prognosis. When taken operable colorectal cancer and advanced lung cancer cohorts, the significance of host factors including nutrition, systemic inflammation and body composition become important factors in patient prognosis.

1.3 NUTRITIONAL ASSESSMENT

Nutritional assessment is an important part of treatment of patients with cancer. 20 to 50% of hospitalised patients were malnourished depending on the criteria used for assessment of malnutrition and the patient s' characteristics (Norman, Pichard et al. 2008). There are various nutritional assessment methods used MUST, MST, Patient reported nutritional outcomes (Ottery 1996).

MUST is a five point assessment based upon BMI, weight loss and nutritional intake (see Fig 1.1). MUST is widely available assessment tool for patient admitted in NHS hospitals. This assessment tool was approved by European Society of Parenteral and Enteral Nutrition (ESPEN). This is routinely used for nutritional assessments of patients admitted to UK NHS Hospitals and was used as a nutritional assessment marker for the studies included in this thesis.

Malnutrition in patients with cancer is multifactorial. Neoplastic cells have increased metabolic rate, host is in catabolic state, release of inflammatory mediators and oxygen free radicals with limited available resources (Arends, Bachmann et al. 2017) plays an important role in nutritional decline and if not addressed lead to refractory cachexia. MUST assesses changes in BMI, nutritional intake and loss of body weight (Elia 2003).

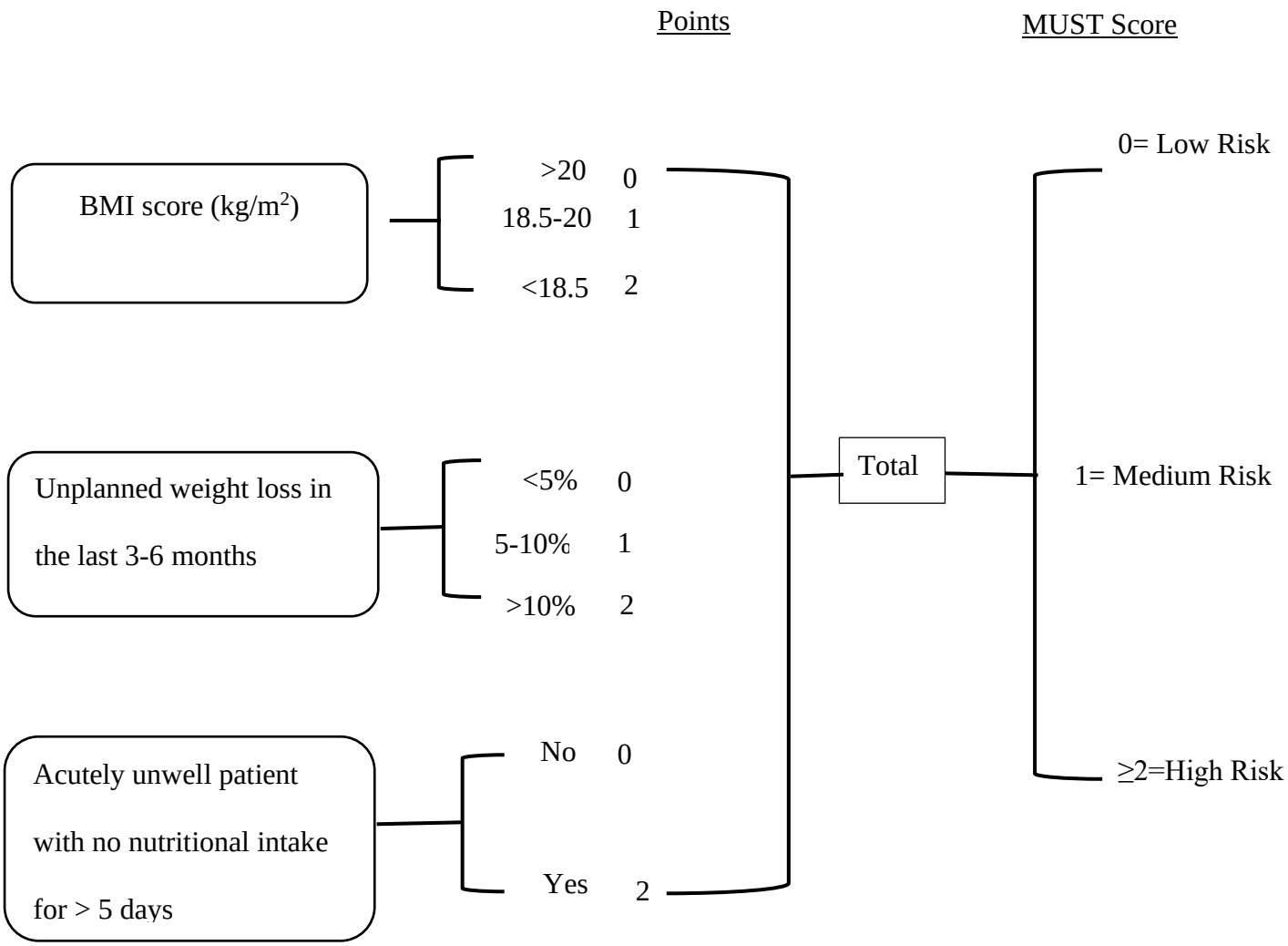


Figure 1.1 The Malnutrition Universal Screening Tool (Elia 2003)

Patients with cancer should be screened for malnutrition (Arends, Bachmann et al. 2017). Primary cancer should be treated to address the drive in catabolic state and prevent progression to severe malnutrition, sarcopenia, refractory cachexia and death (Arends, Bachmann et al. 2017). Malnutrition is an important factor for treatment planning for oncological treatment (Ravasco 2019). Pre-operative nutritional optimization reduces the risk of post-operative septic complications (Li, Ren et al. 2014) in patients with fistulating Crohn's disease and this can be extrapolated to patients with cancer.

Nutritional assessment plays an important role in prognosis of patients with cancer. Patients generally present with two types of cancers. One is early / operable stage and other is advanced / non operable cancer. Among the cancers, colorectal cancer has good prognosis and because of very effective screening modality i.e. colonoscopy, majority of patients are detected at early stage I to III. On the other extreme, lung cancer is more aggressive and has poor prognosis and patients usually are detected at advanced stage and most of the patients undergo palliative treatment including palliative radiotherapy and/ or chemotherapy. These two cancers were studied together to stage the host which will help to determine the treatment targets. The diagnosis of malnutrition and assessment of nutritional status is complex. It involves assessment of patient by experienced dietician. This is modifiable element of patient assessment as can be improved with use of enteral and parenteral nutrition (Dai, Huang et al. 2023).

1.4 FRAILTY ASSESSMENT

Frailty has been defined as “a state of decreased physiological reserve caused by accumulation of aging processes across multiple organ systems, which affect the patient response to stressors.”

Frailty is established to be an important phenotype in geriatrics literature to predict prognosis (Fried, Tangen et al. 2001) and surgeons have taken this concept to use as an “eyeball test” in decision making process and predict prognosis (Katlic and Coleman 2018). Short and long term prognosis in patients with cancer is related to frailty (Boakye, Rillmann et al. 2018). Many surgical societies recommend treatment decisions should be based upon frailty rather than chronological age (Saur, Davis et al. 2022). National Emergency Laparotomy data had found frailty an important risk factor for prognosis in abdominal surgery (Lee, Streid et al. 2020). Frailty was also proposed a decisive factor for deciding critical treatment in patients with COVID-19 infection (Rockwood 2021).

It has been shown that assessment of frailty is quick and can help in preoperative optimisation and provide better outcome (Richardson and Hopker 2016). Modified frailty index is 11 items score which has been validated in surgical and geriatric patients (Ehlert, Najafian et al. 2016). Using this 11items score, patients were classified into 4 groups (see Table 1.1). This score was used because of its simplicity, clinical validity with data available retrospectively in the studied population. It looks at systemic comorbidities and functional status. It was calculated by using information available from electronic medical record (clinical portal).

Nutrition is an important marker of prognosis. Prognostic nutrition index was associated with risk of recurrence in stage II CRC Maruyama, Shimoda et al. (2020). Patients with

cancer should have goal concordant care according to their age, frailty which could be different from standard of care (Berian, Wolf et al. 2022)

Table 1.1 11 items of modified Frailty Index (mFI)

Items	Score
CNS	
Confusion	1
TIA or CVA	1
CVA with neurological deficit	1
CVS	
Hypertension requiring medications	1
Congestive heart failure	1
Myocardial infarction	1
PCI, PCS, or angina	1
Peripheral vascular disease	1
Respiratory	
COPD or recent pneumonia	1
Endocrinology	
Diabetes mellitus	1
ECOG	
ECOG-PS II or above	1
Total	11

CVA (cerebrovascular accident), COPD (chronic obstructive pulmonary disease), PCI (percutaneous coronary intervention), PCS (prior cardiac surgery), TIA (transient ischaemic attack)

Table 1.2. Classification of patients per mFI

Groups	mFI score
Group 1	0
Group 2	1
Group 3	2
Group 4	≥3

Patients with frailty should undergo prehabilitation (Saur, Davis et al. 2022) which has been shown to decrease overall (OR 0.61;95% CI, 0.43-0.86), cardiac (OR 0.46; 95% CI, 0.22-0.98) and pulmonary complications (OR 0.41; 95% CI, 0.25-0.67) (Kamarajah, Bundred et al. 2020). In patients with cancer, individualized assessment of patients with focussing on staging the host and staging the tumour is an important concept to provide best care. This involves use of frailty assessment and not just relying on one component i.e. ASA score (Montroni, Ugolini et al. 2018)

1.5 Systemic inflammation

The systemic inflammatory response plays a key role in staging of the host. Systemic inflammation in the body is mediated by inflammatory mediators. These are of two types i.e. proinflammatory and anti-inflammatory. The examples of pro-inflammatory mediators include interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor (TNF- α) and insulin like growth factor (IGF). The examples of anti-inflammatory mediators include interleukin-10 (IL-10), transforming growth factor- β (TGF- β), prostaglandins and lipoxins. Cancer causes a shift in body haemostasis towards proinflammatory state. These proinflammatory mediators released during cancer, result in decreased appetite, increased catabolism and resulting in malnutrition and cachexia. Cancer related inflammation is a key trigger for low skeletal muscle index (sarcopenia)and strong prognostic factor for survival (Hacker, Hasenclever et al. 2022) . SIR results from tumour and host interaction, as well as influenced by other factors i.e. comorbidities and genetic makeup of host.

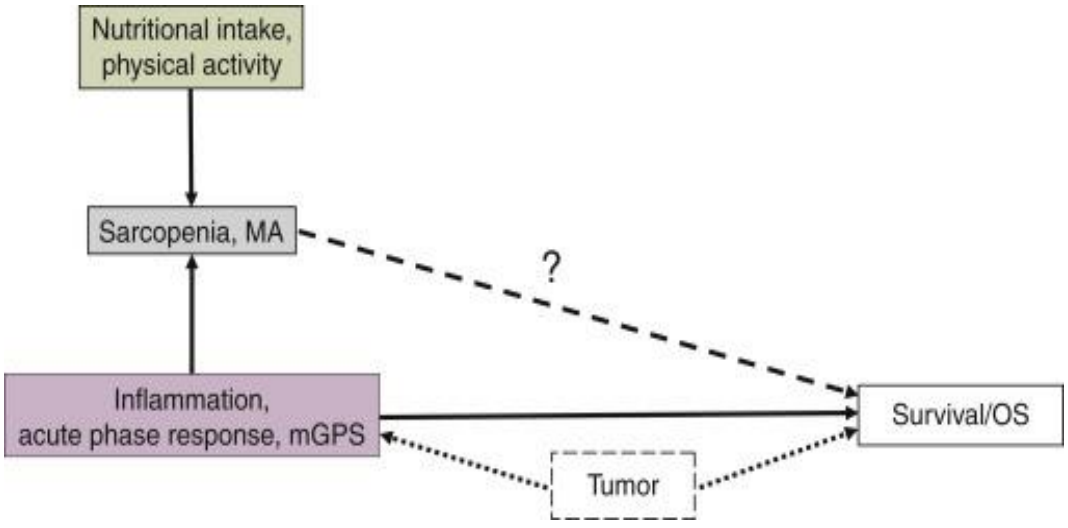


Figure 1.2 Cancer related inflammation is key trigger for sarcopenia and represents a strong prognostic factor for overall survival (Hacker, Hasenclever et al. 2022)

There are various types of inflammatory mediators i.e. interleukin 6 (Scott, McMillan et al. 1996), CRP, albumin, NLR. Inflammation affects the cancer journey in multiple ways

including tumour promotion, gene instability, tumour metastases, inducing angiogenesis, avoiding immune destruction and evading growth suppressors resulting in uncontrolled increase in cancer cells resulting in death (Hanahan and Weinberg 2000, Hanahan and Weinberg 2011)

Figure 1.3 Effect of inflammation on cancer pathway (McAllister and Weinberg 2014)

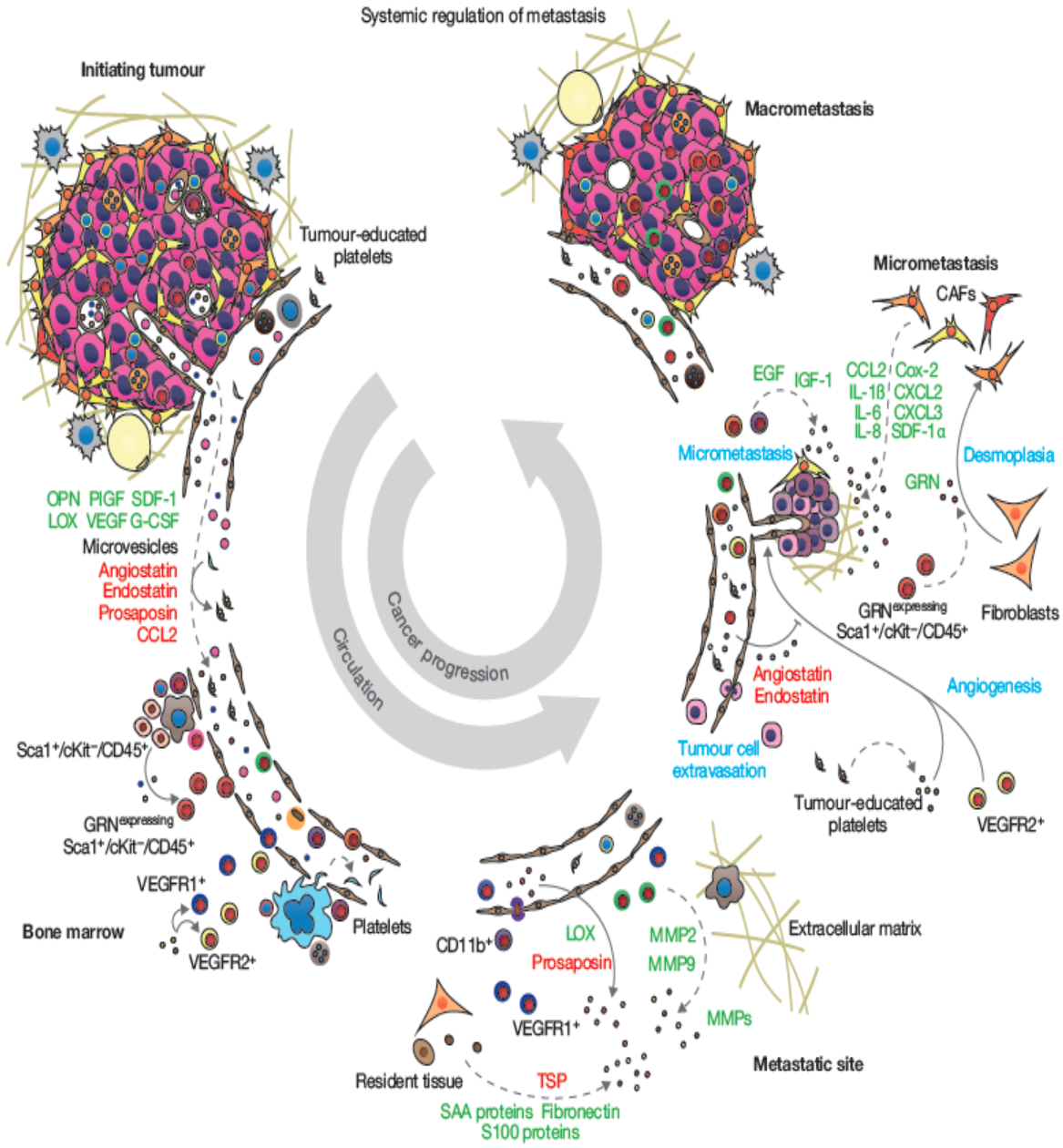


Figure 1.4 Systemic inflammation results in cancer progression by various key mediators as shown below (McAllister and Weinberg 2014)

Biochemical pathway for CRP

CRP is protein produced by hepatocytes and reflects cell mediated immunity and its elevation associated with worse outcomes in several cancers. IL-6 appears to be the ideal marker of chronic systemic inflammation. However, CRP being specifically produced from liver with easy availability in laboratory available tests and is cost effective. CRP is closely

associated with tumour burden and as the tumour progresses, it causes more secretion of IL-6 and other inflammatory mediators from the host which results in increased production of CRP from liver (Hart, Rajab et al. 2020) . Albumin is a marker of nutrition and chronic inflammation and is specifically produced in liver. These two variables combined together provide a score called Glasgow Prognostic score (GPS). This score has been further refined to modified Glasgow Prognostic score (mGPS) (Forrest, McMillan et al. 2003). The difference between these two is shown in Table 1.3

Table 1.3 Difference between GPS and mGPS.

Prognostic marker	Criteria	Score
GPS	CRP ≤10 mg/L and Alb ≥35 g/L	0
	CRP >10 mg/L or Alb <35 g/L	1
	CRP >10 mg/L and Alb <35 g/L	2
mGPS	CRP ≤10 mg/L	0
	CRP >10 mg/L and Alb ≥35 g/L	1
	CRP >10 mg/L and Alb <35 g/L	2

Relationship of mGPS to innate immunity

Tumor related systemic inflammation is part of host innate immunity leading to alteration in tumor microenvironment, promotion of cell division, invasion of basement membrane, mucosa, submucosa, muscularis propria, serosa and metastases to the local and systemic organs, furthermore, inhibition of apoptosis and immunosuppression (Deshmukh, Srivastava et al. 2019, Ferrari, Godio et al. 2022). Other inflammatory mediators produced by bone marrow include neutrophils and platelets. The ratios such as neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are also, used as surrogate markers for inflammation.

1.6 Body composition

Body composition is an important part of host assessment and predicts response to oncological treatment i.e. chemotherapy toxicity (Pin, Couch et al. 2018). Adipose tissue and skeletal muscle are important components for measuring body composition. Skeletal muscle is highly physiologically active organ and constitutes approximately 40-45% of body weight. Low SMI results in loss of independence necessitating the need for home care or discharge to long term care placement or nursing home and it is estimated to cost the US health system approximately $18.5 billion in US dollars per year (Janssen, Shepard et al. 2004).

Various measures of body composition (BC) have been shown to have prognostic value. Body composition is calculated from computerised tomography (CT), magnetic resonance imaging (MRI), Dual energy X-ray absorptiometry (DEXA) and ultrasonography (USG). Computed tomography (CT) has become the gold standard method for analysis of body composition in patients with cancer. CT is widely used as part of staging in patients with cancers and provides easily reproducible modality for measure of body composition without incurring any more radiation, cost or inconvenience. Various semiautomated and manual software packages are available for measurement of body composition using cross sectional imaging i.e. CT. Various thresholds been used for classifying patients to high and low categories using specialized software, various measurements of body composition including total fat area (TFA), subcutaneous fat area (SFA), visceral fat area (VFA), skeletal muscle area (SMA) and skeletal muscle density (SMD) were obtained. Visceral fat is associated with complications i.e. anastomotic leakage in elective colorectal surgery (Verduin, Warps et al. 2021). Pre-operative body mass index (BMI) was obtained from patient clinical record. Various fat and muscle areas obtained from CT were normalized for height in meter square to calculate indices. Low SMI (sarcopenia) and low SMD (myosteatosis)

were considered two most important measures for calculating host body composition. Low SMI or sarcopenia is defined as “loss of skeletal muscle mass irrespective of fat mass” (Fearon, Strasser et al. 2011) and cancer cachexia was defined as “a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.” This clinical syndrome characterised by progressive and global reduction in muscle mass and reduced strength or physical function. Low SMD or myosteatosis is defined as “the amount of fat within muscle tissue.” When fat replaces the muscle tissue, muscle function is said to be reduced which results in muscle attenuation and providing low SMD values in body composition analysis.

Recently, visceral obesity has gained popularity because of its prognostic value. Various measures of body composition are in practice. For the purpose of thesis, the abbreviation SFI (subcutaneous fat index) refers to sex adjusted measurement of subcutaneous fat volume (Ebadi, Martin et al. 2017), VO (visceral obesity/adiposity) refers to sex adjusted measurement of visceral fat area (Doyle, Bennett et al. 2013), SMI (skeletal muscle index) refers to sarcopenia and SMD (skeletal muscle density) refers to myosteatosis. SMI refers to height and /or BMI and sex adjusted measurement of CT derived skeletal muscle area. Whereas, SMD refers to height and /or BMI and sex adjusted measurement of skeletal muscle radiodensity (Martin, Birdsell et al. 2013). SMI is considered to be the most important factor among all measures of body composition for prediction of post operative complications and survival (Paiella, Azzolina et al. 2023). Recently, SMD has attracted attention as well and has been shown to be prognostic for overall survival in patients with non-small cell lung cancer (Sjøblom, Grønberg et al. 2016). Body composition can be measured by using preoperative CT scan. L3 area is identified. For body composition, all skeletal muscles measurement or psoas muscle measurements have been reported (see figures 1.5 and 1.6)

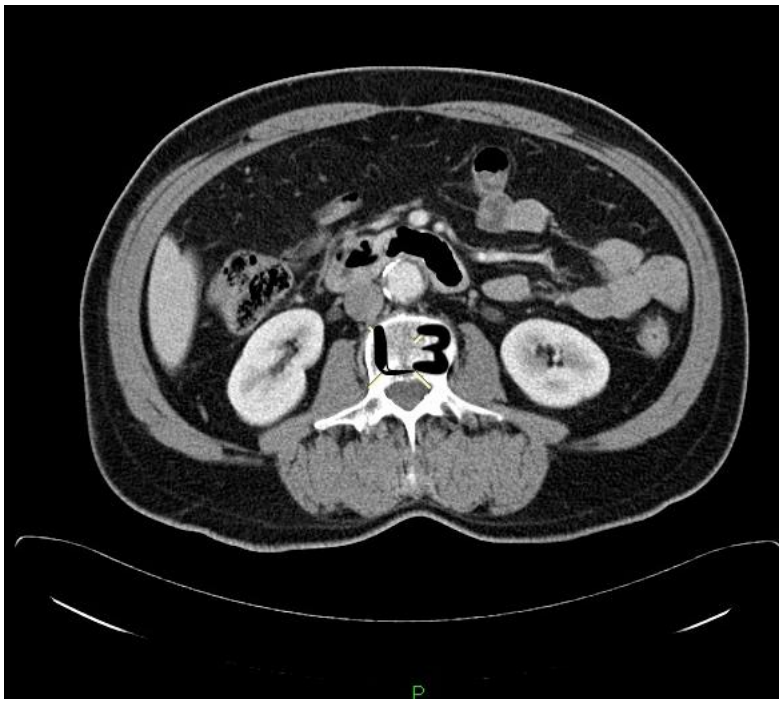


Figure 1.5. Axial L3 image used for calculation of body composition

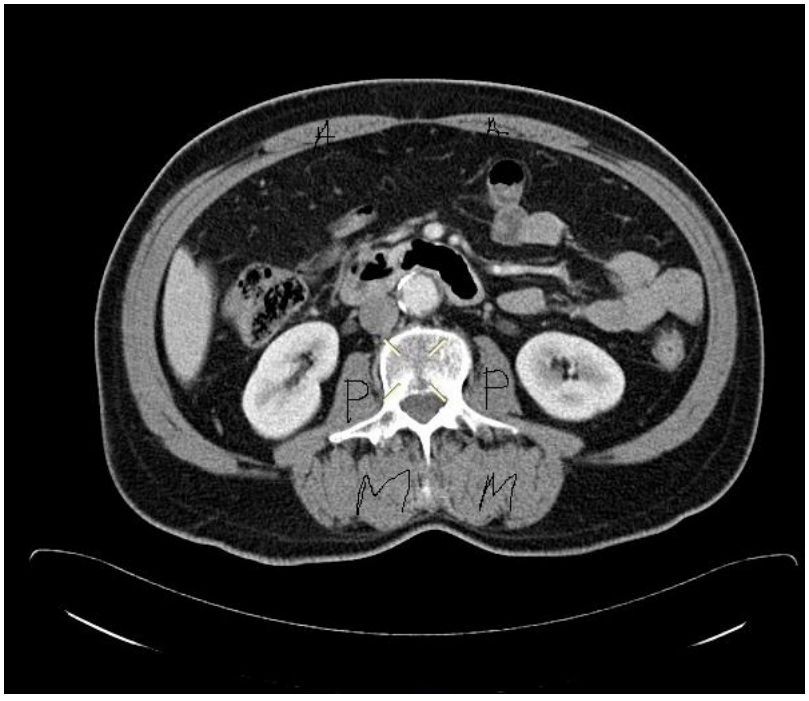


Figure 1.6. Axial L3 image with labelled muscles for calculation of body composition

A. Anterior abdominal muscles (Rectus abdominis)

M. Deep back muscles P. Psoas major muscles

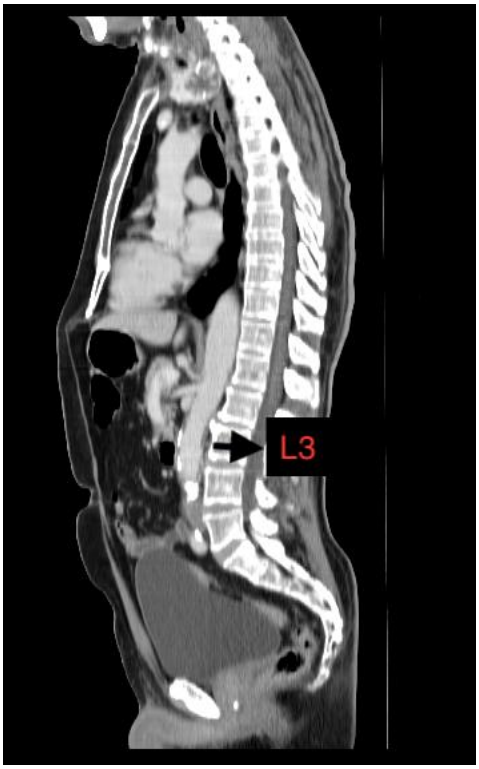


Figure 1.7. Sagittal L3 image used for calculation of body composition

L3 images accuracy was confirmed in axial and sagittal image to ensure correct level selected. Whether this measurement can help to identify patients who have low SMI despite normal BMI (see PMI and SMI chapter). Imaging based body composition using CT, USS, MRI, DEXA and its relationship to SIR was examined.

Assessment of body composition using CT single slice at L3 level is widely accepted measure of body composition. However, it is debatable whether to use all abdominal muscles at L3 level or only psoas muscle to measure SMI and SMD. In patients with operable colorectal cancer, this relationship was studied.

Low SMI had prognostic value in lung cancer. The relationship between MUST, SIR and body composition in advanced lung cancer has not been examined. In this thesis, this relationship was examined to better understand, treat and prognosticate.

As the concept of staging of tumour and staging the host is of fundamental importance to provide the best optimal care for patient with cancer. There is great emphasis on staging the tumour in oncology literature, whereas, staging the host is understudied and undervalued. Although tumour staging varies from tumour type to tumour type, host staging (e.g. body composition and systemic inflammation) is similar irrespective of tumour type and stage of disease. In MDT discussion, radiologist and pathologist mostly, provide data on radiological and pathological tumour staging, whereas host staging is mostly subjective and revolves around performance status. While performance status is very important for planning oncological treatment, there is great need to identify the markers which can better stage the host and provide areas for focussed treatment (Kelly and Shahrokni 2016).

Furthermore, studying various cancers together can provide valuable insight into tumour and host characteristics which can help to identify areas for targeted treatment. There are marked differences in prognosis between colorectal and lung cancers and therefore, they were taken together to identify the areas for targeted treatment by studying two distinct cancers with very different prognosis.

The relationship between MUST, SIR and body composition was examined in large cohort of operable CRC. The majority of patients in CRC cohort had low malnutrition risk. Nutritional status (MUST, frailty) and SIR (mGPS, NLR) have prognostic role in cancer. However, the longitudinal studies are few and essential for understanding this relationship. In this thesis, patient clinicopathological characteristics, systemic inflammatory response and body composition were studied to better identify targeted measures to provide focussed treatment and improve decision making process in patients with operable CRC and advanced lung cancers. The relationship between MUST, SIR and body composition were studied to stage the host. The subjective assessment of the host i.e. frailty and

performance status as well as objective assessment i.e. systemic inflammatory response (SIR) and body composition (BC) provide the holistic approach to staging of the host.

1.7 Aims

The overarching aim/ objective of the thesis was to examine how CT-derived body composition informed the relationship between nutritional status, systemic inflammation and clinical outcomes in patients with common solid tumours and specifically;

1. To examine whether CT derived body composition was ready for application in routine clinical practice and highlight the gaps in our knowledge (see chapter 1.2).

2. To examine the relationship between imaging- based body composition and systemic inflammatory response in patients with cancer (see chapter 1.3).

3. To examine the relationship between skeletal muscle index at L3 and psoas muscle index in patients with primary operable colorectal cancer (see chapter 2).

4. To examine the relationship between malnutrition, body composition, systemic inflammation and clinical outcomes in patients with operable colorectal cancer (see chapter 3).

5. To examine the relationship between malnutrition, body composition, ECOG-PS, systemic inflammation and overall survival in patients with advanced lung cancer (see chapter 4).

6. To examine the relationship between longitudinal changes in malnutrition, body composition, ECOG-PS, systemic inflammation and overall survival in patients with advanced lung cancer (see chapter 5).

7. To examine the relationship between clinicopathological characteristics including malnutrition, body composition, systemic inflammation and overall survival in patients with operable colorectal and advanced lung cancer (see chapter 6).

8. To examine the relationship between tumour metabolic activity, malnutrition, body composition, systemic inflammation, overall survival and tumour metabolic activity in patients with advanced lung cancer (see chapter 7).

1.2 THE CT DERIVED BODY COMPOSITION ANALYSIS IN PATIENTS WITH ADVANCED CANCER: CLINICAL UTILITY AND FUTURE RESEARCH

1.2.1 Introduction

Patients with cancer, in particular advanced cancer, lose weight which is reflected in the loss of adipose tissue and muscle. In those patients of low BMI such loss of body tissue is clear and formed the basis of ancient Greek descriptions of the syndrome of cachexia "The flesh is consumed and becomes water, the abdomen fills with water, the feet and legs swell, the shoulders, clavicles, chest and thighs melt away. This illness is fatal." (Hippocrates 460-377 BC). In normal weight individuals skeletal muscle is the largest tissue in the human body (Pedersen and Febbraio 2012). However, in the modern era many patients with cancer are overweight or obese and the loss of fat and muscle tissue is less obvious. In this context, there has been a continuing clinical interest in measuring adipose tissue and muscle mass in these patients (Martin, Gioulbasanis et al. 2019). Although various imaging techniques including Dual-energy X-ray absorptiometry (DEXA), Magnetic Resonance imaging (MRI) and ultrasound have been used for body composition assessment in patients with cancer, CT derived analysis has been extensively researched given the routine clinical use of CT for tumour staging (Daly, Prado et al. 2018).

Using CT, various components of body composition including subcutaneous fat area (SFA) (Ebadi, Martin et al. 2017), visceral fat area (VFA) (Ebadi, Moctezuma-Velazquez et al. 2020), skeletal muscle index (SMI) (Barret, Antoun et al. 2014, Miyamoto, Baba et al. 2015, Beuran, Tache et al. 2018) and skeletal muscle density (SMD) (Rollins, Tewari et al. 2016, Aleixo, Shachar et al. 2020) have been studied. Over the last decade it has become clear that a CT image at L3 provides a consistent association between CT derived body composition analysis, in particular skeletal muscle index (SMI), and clinical outcomes

(Shachar, Williams et al. 2016, Su, Ruan et al. 2019, Aleixo, Shachar et al. 2020) as shown in Figure 1.8 & 1.9.

Such consistent observations have led for calls to adopt such measurements into routine clinical practice (Thibault and Pichard 2012, Abbass, Dolan et al. 2019). However, before such calls can be met a number of aspects of CT derived body composition analysis need to be better understood. These include (a) methods used to measure fat and muscle tissue (b) adipose tissue and skeletal muscle thresholds used to examine the relationship with clinical outcomes (c) the muscle groups used to measure SMI and SMD (d) the nature of the relationship between SFI, VFI, SMI and SMD and its physiological basis. The aim of the present review was to examine whether CT derived body composition was ready for routine clinical practice and highlights the gaps in our knowledge.

1.2.2 Methods used to measure fat and muscle tissue

There is general acceptance that with reference to the CT image that adipose tissue is measured using thresholds of -190 to -30 and muscle tissue is measured using thresholds of -29 to + 150 Hounsfield units. Slice-O-Matic also uses -150 to -50 HU for VFA. There are two approaches to the analysis of CT images, manual and automatic segmentation of adipose and skeletal muscle, both approaches calculate areas on the CT image. Manual segmentation of adipose tissue and skeletal muscle require knowledge of the CT image and patient anatomy and has been often carried by individuals with specialised knowledge such as radiologists and surgeons (Richards, Roxburgh et al. 2012). An example of selection of CT body composition at L3 using manual software such as image J to outline fat areas is shown in Figure 1.8 and muscles in Figure 1.9 (McSorley, Black et al. 2018). The use of single slice at L3 from CT cross sectional image is considered as reliable marker for CT measurement of body composition (Shen, Punyanitya et al. 2004).

In contrast, semi-automatic and automatic segmentation can be carried out with proprietary software packages and require little specialised knowledge. However, usually such proprietary software contain a function to manually review the segmentation carried out by the software (e.g. Slice-o-Matic). An example of selection of CT body composition fat areas at L3 using semi-automatic software such as Slice-o-Matic is shown in Figure 1.10. Table 1.3.1 shows comparisons of commonly used softwares for body composition analysis.

Surprisingly, few studies have made a direct comparison of the results obtained from manual and automatic segmentation. Recently, Dolan and coworkers (2020) compared manual (Image J) and semi-automatic segmentation (Slice-o-Matic) of adipose and skeletal muscle tissue in 341 patients with primary operable colorectal cancer Dolan, Tien et al. (2020). Bland–Altman analysis was conducted to test agreement of the two segmentation

approaches. The manual segmentation approach, compared with semi-automatic segmentation approach, gave consistently and significantly higher values for both adipose tissue and skeletal muscle. This resulted in fewer patients being classified, using established thresholds, as having low levels of adipose and skeletal muscle tissue using the manual approach. The difference using manual and semi-automated software for SFI (high/low) was +7.9% (5.1cm^2), VFI (high/low) +20.3% (12.9cm^2), SMI (high/low) +2.9% (2.5cm^2) and SMD (high/low) +1.2% (0.4cm^2). Also, Feliciano and co-workers (2020) studied 5990 patients (operable colorectal cancer n=3102, locally invasive breast cancer n=2888) and compared the manual with automatic segmentation with manual segmentation overestimating results with mean difference of + 2.38 cm^2 for SFA (continuous), +1.97 cm^2 for VFA (continuous) and + 2.35 cm^2 for SMA (continuous) (Cespedes Feliciano, Popuri et al. 2020). Therefore, the method of assessment used on the CT images may affect CT derived body composition measurements and classification of patients into low or normal/ high categories. This would suggest that even with semi-automatic segmentation software specialised knowledge will be required to ensure reliable results. Also, that routine clinical reporting would be carried out by trained clinical staff.

Various terms have been used to describe the components of body composition. SFI used to define subcutaneous adiposity, VFI used to define visceral obesity, SMI used to define sarcopenia and SMD used to define myosteatosis or intramuscular adipose tissue. Therefore, for clarity the terms SFI, VFI, SMI and SMD are used in the present review to describe the components of CT-derived body composition analysis. For future research and routine clinical application, it will be important to standardise terminology in the field (Poltronieri, de Paula et al. 2020).

1.2.3 Adipose tissue and skeletal muscle thresholds used to examine the relationship with clinical outcomes

Table 1.5 shows common thresholds used for body composition analysis. Most of the commonly used thresholds for classifying abnormal values in CT derived body composition analysis have been described in last decade years (Doyle, Bennett et al. 2013, Martin, Birdsell et al. 2013, Ebadi, Martin et al. 2017). From the literature, it is clear that the thresholds for areas of adipose and muscle tissue associated with clinical outcomes vary according to age, sex, BMI and would appear to vary with the population studied.

SFA has been normalised for height squared to give subcutaneous fat index (SFI). In n=1762 (61% stage IV) patients a threshold reported used for defining abnormal subcutaneous adiposity associated with clinical outcome was SFI >50 $cm^{2/}m^2$ in males and >42 $cm^{2/}m^2$ in females (Ebadi, Martin et al. 2017). Using this threshold, high subcutaneous adipose tissue was shown to be protective in non-small cell lung cancer (Lee, Lee et al. 2018). Using this threshold, low SFI was associated with increased mortality risk in a cohort of 217 patients with advanced CRC (Charette, Vandeputte et al. 2019) and also 1473 gastrointestinal and bronchogenic cancers (Ebadi, Martin et al. 2017).

VFA has been normalised for height squared to give visceral fat index (VFI). In n=236 patients undergoing gastrointestinal cancer operation, a threshold reported for defining abnormal visceral obesity was VFA >160 cm^2 in males and >80 cm^2 in females (Doyle, Bennett et al. 2013). VFI was shown to have prognostic value with post-operative complications and wound infection in patients with cancer and a low VFI was associated with increased mortality risk in patients with colorectal cancer (Charette, Vandeputte et al. 2019).

SMA has been normalised for height squared to give skeletal muscle index (SMI). There have been various definitions of low SMI (sarcopenia) reported in the literature.

Baumgartner and coworkers defined low SMI as “skeletal muscle mass less than two standard deviation below the mean of a young reference group” (Baumgartner, Koehler et al. 1998). Most studies used 2011 International Consensus definition by Fearon et al. Low SMI was defined as L3 SMI <59 cm^2/m^2 in males and <49 cm^2/m^2 in females (Fearon, Strasser et al. 2011). The Baumgartner definition was based on healthy individuals whereas, Fearon definition was based on 250 obese individuals with gastrointestinal and lung cancer patients with mean age of 64 as described by Prado et al. (Prado, Lieffers et al. 2008). Martin and co-workers derived thresholds based on 1473 patients with gastrointestinal and lung cancer, approximately 50% of whom had TNM stage 4 disease. In males, low SMI was defined as SMI <43 cm^2/m^2 if BMI<25kg/m^2 and <53 when BMI≥25 and in females, low SMI was <41 if BMI<25 or ≥25 (Martin, Birdsell et al. 2013, Daly, ÉB et al. 2018).

From the above it would appear that SFI, VFI and SMI had prognostic value in patients with cancers. However, it is not clear whether the current derived thresholds are abnormal compared with a healthy population or applicable across populations of cancer patients. Therefore, further research is required to establish population and disease specific thresholds for optimal clinical use of CT derived body composition analysis.

1.2.4 Adipose tissue and skeletal muscle density used to examine the relationship with clinical outcome.

Visceral fat density (VFD) has been defined as high ≥ -85 HU. High VFD was associated with an increased risk of adverse events and mortality in 101 patients with hepatocellular carcinoma (47% stage B) treated with radiotherapy (Ebadi, Moctezuma-Velazquez et al. 2020). In 235 advanced CRC, high visceral fat radiodensity was independently associated with mortality (Charette, Vandeputte et al. 2019).

Skeletal muscle density has been defined as <41 HU when BMI was <25 and <33 if BMI ≥25 (Martin, Birdsell et al. 2013) in 1473 patients (50% stage IV) with lung and gastrointestinal cancers. Aleixo and coworkers in a systematic review and meta-analysis recently examined the prognostic value of SMD and reported that, in 21,222 patients with cancer across 40 studies, the prevalence of a low SMD was approximately 50% and was associated with an approximately 75 % greater mortality risk. Specifically, a low SMD was prognostic for poorer overall survival in patients with gynaecological, renal, periampullary/pancreatic, hepatocellular, gastroesophageal, and colorectal cancers (Aleixo, Shachar et al. 2020).

From the above it would appear that SMD has prognostic value in patients with cancers. However, it is not clear whether the current derived thresholds are abnormal compared with a healthy population or applicable across populations of cancer patients. Therefore, further research is required to establish population and disease specific thresholds for optimal clinical use of CT derived body composition analysis. Moreover, unlike the adipose and skeletal muscle area measurements, anatomical and physiological basis of such density measurements is not clear.

1.2.5 The muscle groups used to measure SMI and SMD

Various muscles have been used for body composition analysis. Selective muscles like psoas muscle associated with post-operative complications and survival have been reported in the literature (Park, Yoon et al. 2017, Yaguchi, Kumata et al. 2017, Montalvo, Counts et al. 2018, Herrod, Boyd-Carson et al. 2019). Recently, we studied this relationship at L3 level, in 1002 patients with operable colorectal cancer and found that although total skeletal and psoas muscle area (PMA) were closely related (r=0.7), it was only SMI that had independent prognostic value for post-operative outcomes. SMI measured at L3 level provided better prognostic value when compared to PMI alone (Abbass, Tsz Ho et al.

2020). Psoas muscle may be affected by different musculoskeletal pathologies. Therefore, measurement of all skeletal muscles at L3 level is likely to provide more reliable prognostic information.

Psoas muscle density (PMD) been used alternative to SMD at L3 area and has been prognostic for post-operative complications in operable colorectal cancer (Herrod, Boyd-Carson et al. 2019) and advanced cancer (Sabel, Lee et al. 2011), however, this is not well studied with very few observations and its anatomical basis is not well defined. Therefore, a single muscle group measurement i.e. psoas muscle analysis, although simple to do and readily applied to clinical reporting would not appear to reflect that of total skeletal muscle and not be used as substitute for whole L3 SMI and SMD assessment (Baracos 2017, Rutten, Ubachs et al. 2017, van Dijk, Bakens et al. 2017).

1.2.6 The nature of relationship between SFI, VFI, SMI and SMD and its physiological basis.

Patients with advanced cancer lose adipose tissue and muscle depending upon underlying cancer, the stage of disease and the systemic inflammatory response (Abbass, Dolan et al. 2019). The nature of relationship between SFI, VFI, SMI and SMD is not well characterised. Of these skeletal muscle measurements have been most observations reported (Shachar, Williams et al. 2016, Daly, ÉB et al. 2018) and SMI has had far more observations when compared to SMD (Daly, Prado et al. 2018, Aleixo, Shachar et al. 2020, Lee and Kang 2020). SMI appears to be affected by age, sex, ethnicity and underlying disease processes (Dodds and Sayer 2016) and is prognostic in number of advanced cancers (Bye, Sjøblom et al. 2017, Wagner, Marsoner et al. 2018). Whereas SMD although reported to have prognostic value appears to be affected by various technical factors including patient cardiac output and phase of CT scan. For example, SMD measurement was lowest in non-contrast (Mean ± SD) (29.4 ± 8.9) followed by arterial (32.4 ± 9.3) and then porto- venous phase (34.9 ± 9.4) HU (Rollins, Javanmard-Emamghissi et al. 2017). Moreover, anatomical basis for SMD is not well established. While CT derived SMI and PMI have been compared with similar measurements using a DEXA scan, SMD and PMD can only be derived from CT scan and does not appear to be associated with other measures of skeletal muscle quality and function (Ramage and Skipworth 2018, Rollins, Gopinath et al. 2019). Furthermore, changes in SMI and SMD may occur at different stages in patient journey with cancer. In 123 patients with pancreatic and periampullary cancers, 14 (11.4%) had both low SMI and low SMD, 50 (41%) had low SMI and 31 (25%) had low SMD only, demonstrating that low SMI and low SMD did not occur at the same rate and different body changes occur at different time and suggesting that they were the by-product of two separate biological processes (Stretch, Aubin et al. 2018). Furthermore, Hopkins and co-workers have recently shown that in patients with a low

SMD, 24% were viscerally obese and 10% had a low SMI (Hopkins, Reif et al. 2019).Therefore, their combination in measurements such as skeletal muscle gauge (Weinberg, Shachar et al. 2018) would appear to be premature.

From the above it is clear that SMI has been extensively studied and understood parameter of body composition with prognostic value and with standardisation of its measurement may be usefully incorporated into routine clinical assessment of patients with cancer. In contrast, although SMD has prognostic value the anatomical and physiological basis of this measurement is not clear, and the lack of standardisation would indicate that incorporating into routine clinical assessment is premature (Lee and Kang 2020).

1.2.7 Conclusions and Future Research:

The availability and reliability of CT scanning means that CT defined body composition has the potential to form the basis of the incorporation of body composition analysis into routine clinical practice. CT derived body composition provides important novel prognostic information that can be acquired as part of routine clinical care of patients with advanced cancer. Taken together with comprehensive clinical assessment, CT derived body composition analysis may become an important factor in the clinical decision-making process. However, although SFI, VFI and SMI have clear anatomical and physiological rationale and prognostic value, the rationale and clinical value of VFD and SMD is less clear. For CT derived body composition analysis to reach it its potential there needs to be global efforts to standardise the terminology, methodology and interpretation. Given the number of groups active in this area, it should be possible to standardise the methodology on acquiring and analysing the CT image at L3. This will facilitate the construction of reference ranges according to age, sex and BMI and enable routine clinical reporting of results. In particular, low values and longitudinal losses of adipose tissue and skeletal muscle during cancer could be automatically flagged up to the clinician.

Key Points

- Body composition analysis is of significant clinical importance in patients with cancer
- CT is an objective imaging modality for body composition assessment.
- Lack of standardization in the measurement of body composition analysis (manual, semi-automatic and automated segmentation) and clinical reference ranges according to age, sex and BMI) are major obstacles for routine clinical use.

1.2.8. Tables and Footnotes

Table 1.4: Software comparisons

Soft ware	Advantages	Disadvantages
Image J	Freely available from NIH Updated in real time Easy to define region of interest Apply thresholds	Manual Needs knowledge of anatomy Time consuming One image analysis at one time
Slice- O- Matic	Semi-automated View and edit multiple images at once Excellent company support Easy to use Apply thresholds	Expensive Needs Licence Annual renewal cost
Synapse Vincent	Three dimensional Semi-automated Apply thresholds	Needs Licence
Osirix	Semi-automated Apply thresholds	Needs Licence
Fat Seg	Manual Apply thresholds	Needs Licence
Body Comp Slicer	Semi-automated Quicker than Slice O Matic	Needs Licence

Table 1.5: Most common body composition thresholds used

CT derived Body Composition Measurement
Subcutaneous Adiposity
Increased Subcutaneous fat index (Ebadi threshold) (Ebadi, Martin et al. 2017)
Males : SFI >50 $cm^{2/}m^2$ Females : SFI>42 $cm^{2/}m^2$
Visceral Obesity
Increased Visceral Obesity (Doyle threshold) (Doyle, Bennett et al. 2013)
Males : VFA >160 cm^2 Females : VFA>80 cm^2
Sarcopenia
Low SMI (Martin threshold) (Martin, Birdsell et al. 2013)
Males: BMI<25kg/m^2 and SMI<43 cm^2m^2 or BMI≥25kg/m^2 and SMI<53 cm^2m^2 Females: BMI<25kg/m^2 and SMI<41 cm^2m^2 or BMI≥25kg/m^2 and SMI<41 cm^2m^2
Myosteatosis
Low SMD (Martin threshold) (Martin, Birdsell et al. 2013)
BMI<25kg/m^2 and SMD<41 HU or BMI>25kg/m^2 and SMD<33HU

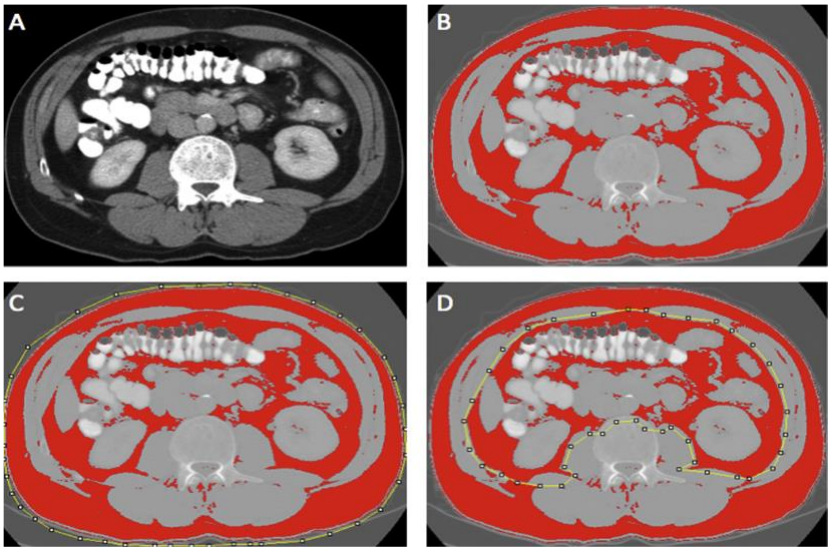


Figure 1.8: How to calculate TFA and VFA. Example of selection of CT body composition fat areas using ImageJ software; (A) mid-L3 vertebra axial slice from portal venous phase CT, (B) threshold selection of adipose tissue using automatic selection of pixels of radiodensity ranging -190 to -30 Hounsfield units (HU), (C) region of interest (ROI) selection for total fat area (TFA, cm^2), (D) ROI selection for visceral fat area (VFA, cm^2). Adapted with permission from (McSorley, Black et al. 2018) .

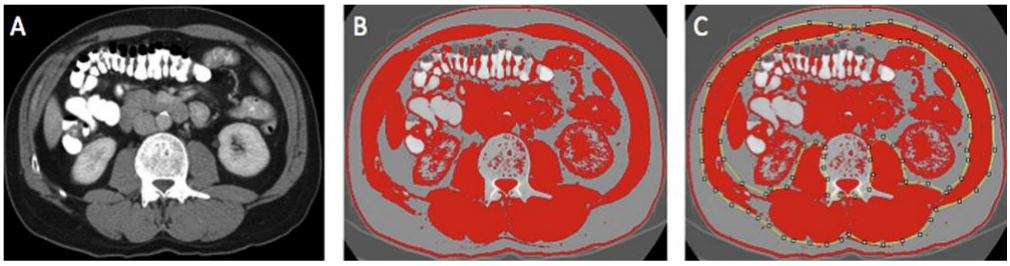


Figure 1.9: How to calculate SMI and SMD Example of selection of CT body composition skeletal muscle area using Image J software; (A) mid-L3 vertebra axial slice from preoperative portal venous phase CT, (B) threshold selection of skeletal muscle tissue using automatic selection of pixels of radiodensity ranging -29 to 150 Hounsfield units (HU), (C) region of interest (ROI) selection for skeletal muscle area (SMA, cm^2). Adapted with permission from (McSorley, Black et al. 2018).

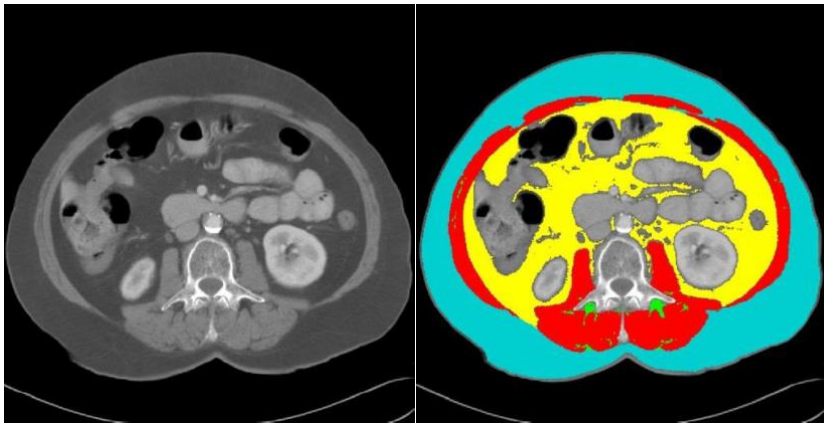


Figure 1.10: How to measure body composition using Slice-O-Matic. Example of selection of CT body composition fat areas using Slice-O-Matic; (A) mid-L3 vertebra axial slice from portal venous phase CT, (B)threshold selection of skeletal muscle density (-190 to -30 Hounsfield units (HU), green), visceral (intra-abdominal) fat area (VFA, -150 to -50 Hounsfield units (HU), yellow), subcutaneous fat area (SFA, -190 to -30 Hounsfield units (HU), blue) and skeletal muscle area (SMA, -29 to +150 Hounsfield units (HU), red) (TomoVision 2020).

1.3 THE RELATIONSHIP BETWEEN IMAGING BASED BODY COMPOSITION ANALYSIS AND THE SYSTEMIC INFLAMMATORY RESPONSE IN PATIENTS WITH CANCER

1.3.1 Introduction

Cancer is the second leading cause of death and has resulted in 9.6 million deaths worldwide in 2018 (WHO 2020) . Patients present with various stages of cancers and the treatment aim is usually classified as curative or palliative, depending on the stage of the disease and patient factors (performance status and co-morbidities). The decision-making process for each patient is complex and involves multidisciplinary team discussions; moreover, using the optimal therapy in the correct patients improves quality of life and survival and has positive implications for health care resources.

As cancer progresses, it is frequently associated with anorexia, weight loss and loss of skeletal muscle mass (termed cancer cachexia) and these are known to be associated with poor outcome. The basis for such changes in body habitus is not clearly understood (Deutz, Ashurst et al. 2019) for example, some tumour types, such as lung and gastrointestinal cancers, are particularly associated with weight and muscle loss; however, in other tumour types (e.g., breast and prostate), this is less common.

While in the past, weight loss and body mass index (BMI) have been used as indicators for malnutrition and cancer cachexia, there have been ongoing attempts to better define body composition in patients with cancer. Various techniques, such as bioelectric impedance analysis, whole body potassium, and air displacement plethysmography, have been used to quantify body composition in the research setting. More recently, imaging-based approaches, such as Dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), ultrasound scan (USS) and computed tomography (CT), have been utilized. These imaging-based body composition measuring modalities have the advantage that they

are readily available and would be readily adopted into clinical practice if shown to be clinically useful. In particular, an excellent agreement between DEXA, CT, and MRI for adipose tissue and skeletal muscle has been reported (Mitsiopoulos, Baumgartner et al. 1998, Shen, Punyanitya et al. 2004, Mourtzakis, Prado et al. 2008, Bredella, Ghomi et al. 2010, Borga, West et al. 2018).

In particular due to its routine use in cancer staging, CT has become the preferred standard for measuring body composition, providing useful new information on body compositional changes associated with cancer cachexia (Mitsiopoulos, Baumgartner et al. 1998, Shen, Punyanitya et al. 2004, Mourtzakis, Prado et al. 2008). In particular, fat and muscle area at Lumbar 3 (L3) vertebra level is highly correlated to other measures of body composition (Shen, Punyanitya et al. 2004, Prado, Birdsell et al. 2009). A Skeletal muscle index (SMI) calculated from image based body composition analysis, provides a reliable objective assessment of skeletal muscle quantity (Mourtzakis, Prado et al. 2008). These imaging-based modalities (DEXA, CT and MRI) have also been investigated in various benign diseases, such as myopathies, malnutrition, chronic respiratory, renal and cardiac illnesses, and these have been found to be reliable tools for the assessment of muscle quantity (Engelke, Museyko et al. 2018).

The basis of the disproportionate loss of skeletal muscle over adipose tissue is not clear. However, it now recognised that systemic inflammatory response is associated with weight and muscle loss and poorer outcomes in patients with cancer (Arends, Baracos et al. 2017) and may be useful in identifying the various stages of cachexia (Douglas and McMillan 2014) (Table 1.3). Therefore, the routine clinical use of radiological imaging offers the opportunity to examine these relationships in more detail. The present review examines the relationship between imaging-based body composition and systemic inflammatory response in patients with cancer.

1.3.2 Methods

Data Sources and Search Strategy

A study protocol was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines (Moher, Liberati et al. 2009) (see Appendix C). A systematic search using Medline, EMBASE, Cochrane databases and Google Scholar was carried out to identify studies assessing the relationship between body composition, systemic inflammation and cancer using MESH Terms "body composition, computed tomography (CT), Dual Energy X-ray Absorptiometry (DEXA), Magnetic resonance imaging (MRI), Ultrasound scan (USS), systemic inflammation, cancer and cachexia." The search was conducted from the start of the relevant database to the date of the last search, which was 31 March 2019.

All relevant studies evaluating the relationship between body composition and systemic inflammatory response in adult patients with cancer were included (see Appendix A). For this systematic review, animal studies, conference abstracts, reviews, non-English studies and those not measuring the topic of interest were excluded**.** The study titles were screened for relevance before a review of abstracts and full texts (TA). Discrepancies were addressed by re-examination and discussion with the senior author (DCM). Reference lists from relevant studies were hand-searched for any other eligible studies. The eligible studies were then assessed for quality using the 22-point STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist, which is a validated methodological quality assessment tool used for submitting studies and to provide feedback by reviewers (von Elm, Altman et al. 2007) (see Appendix B).

1.3.3 Results

Initially, 807 studies were identified, and following subsequent screening of titles, abstracts and then full papers, 23 met the final eligibility criteria (Figure 1.11). Articles were excluded if there was no relationship studied between body composition and systemic inflammation (*n* = 192), animal studies (*n* = 141), duplicates (*n* = 17), non-cancerous (*n* = 16), full articles not available (*n* = 3) and those that were reviews only (*n* = 2). Another 411 studies were excluded following review, as they did not address the topic of interest, namely the relationship between imaging-based body composition and systemic inflammation in patients with cancer.

No study examining the relationship between MRI and USS-derived body composition analysis and markers of the systemic inflammatory response was identified. There were three studies that examined the relationship between DEXA-derived body composition analysis and markers of the systemic inflammatory response and 20 studies that examined this relationship with CT-derived body composition analysis. Of the 20 CT studies, 19 reported body composition analysis using the L3 level of the vertebral column.

All DEXA studies (Ellegard, Ahlen et al. 2009, Wallengren, Iresjö et al. 2015, Chambard, Girard et al. 2018) included in this review used LUNAR DPX-L & LUNAR PRODIGY software (Discovery®, Hologic, Bedford, MA USA) for body composition measurements. Of the 20 CT studies, six studies (Malietzis, Currie et al. 2016, Rollins, Tewari et al. 2016, Feliciano, Kroenke et al. 2017, van Dijk, Bakens et al. 2017, van Dijk, Krill et al. 2018, Xiao, Prado et al. 2019) used Slice-O-Matic software (TomoVision, Montreal, Quebec, Canada), three studies (Richards, Roxburgh et al. 2012, McSorley, Black et al. 2018, Dolan, Almasaudi et al. 2019) used Image J software (NIH Image J version 1.47, https://imagej.nih.gov/ij/), two studies (Kiyotoki, Nakamura et al. 2018, Sueda, Takahasi et al. 2018) used Synapse Vincent software (Fujifilm Medical, Tokyo, Japan**)**, two studies (Zhuang, Huang et al. 2016, Huang, Zhou et al. 2017) used

Infinitt PACS software (INFINITT Healthcare Co., Ltd, Seoul, Korea), one study (Reisinger, Derikx et al. 2016) used OSIRIX software (OSIRIX ®, Version 3.3, downloaded from http://www.osirix-viewer.com), one study (Kim, Kim et al. 2016) used Terrarecon software (Terarecon 3.4.2.11, San Mateo, CA, USA), one study (Serra, Ryan et al. 2018) used Somatom Software (Somatom Sensation, Siemens, Fairfield, CT, USA) and manual CT images analyses was performed in four studies (Itoh, Shirabe et al. 2014, Srdic, Plestina et al. 2016, Okugawa, Toiyama et al. 2018, Basile, Parnofiello et al. 2019). All the 20 CT studies used same thresholds for muscle (−29 to 150 HU) to measure SMA, which were normalized for height in square meter (m^2) to define SMI. Irving et al. compared Slice-O-Matic with Image J in 26 obese subjects with intra- and inter-investigator co-efficient with a reliability of $R^2 = 0.99$ and a mean difference of less than 2% (Irving, Weltman et al. 2007), Richards et al. compared Slice-O-Matic and Image J in a sample of 50 cases with a mean difference of 7.50 cm^2 (Richards, Roxburgh et al. 2012), Van Vugt et al. compared four software packages (Image J, slice-O-matic, OsiriX and FatSeg) in a sample of 50 cases with inter-software an intra-class correlation coefficient of (≥0.999) and a *p*-value of <0.001 (van Vugt, Levolger et al. 2017), and Teigen et al. compared Slice-O-Matic with Image J in 51 cases with an overall mean difference of 1.53cm^2 (Teigen, Kuchnia et al. 2018). Therefore, it appears that there was excellent agreement between the most commonly used software packages. As a result, the study cohorts were considered together in the present review.

Using the STROBE checklist, the breakdown of the quality of these studies is given in Table 1.7. The lowest score achieved was 16 (Serra, Ryan et al. 2018) and the highest was 20 (multiple). Length of follow up was variable. The characteristics of the included studies, the relationship between imaging-based body composition and systemic inflammation are summarized in Table 1.7. The measurement of body composition was carried out in three studies using DEXA and in 20 studies using CT. Therefore, 23 studies met the final inclusion criteria, with 11,474 cancer patients studied (6281 males and 5193 females).

The majority of the studies were single centre (20 studies, *n* = 8,785), prospective (12 studies, *n* = 8,611) and carried out in European countries (12 studies, *n* = 3,272). There were seven studies carried out in Asian countries (*n* = 2,362) and four studies in the USA (*n* = 5,840). The majority of studies were in primary operable cancer (16 studies, *n* = 10,198) and colorectal cancer was the most commonly studied cancer (10 studies, *n* = 8,344).

The skeletal muscle index (SMI) was most commonly measured (21 studies, *n* = 11,277) and C-reactive protein (CRP) and albumin were the most commonly measured markers of the systemic inflammatory response (18 studies, *n* = 8903 and 23 studies, *n* = 11,474 respectively). A significant inverse relationship between SMI and CRP was reported in 13 studies (*n* = 5201), a significant inverse relationship between SMI and mGPS (combination of CRP and albumin) was reported in eight studies (*n* = 1934), a significant inverse relationship between SMI and NLR was reported in eight studies (*n* = 5717) and a direct relationship between SMI and albumin in 15 studies (*n* = 7002).

A low SMI was reported to be associated with shorter overall survival (10 studies, *n* = 5202) and associated with shorter overall survival independent of markers of the systemic inflammatory response (seven studies, *n* = 4481). When both sarcopenia and systemic inflammation were combined, the risk of death was doubled (Feliciano, Kroenke et al. 2017).

Low skeletal muscle density (SMD) and its relationship to systemic inflammation was reported in nine studies (*n* = 6025). A significant inverse relationship between SMD and NLR was reported in seven studies (*n* = 5531), a significant inverse relationship between SMD and mGPS in four studies (*n* = 1509) and a direct relationship between SMD and albumin in six studies (*n* = 1906). A low SMD was reported to be associated with decreased overall survival in four studies (*n* = 1412), cancer-specific survival in two studies (*n* = 533) and disease-free survival in one study (*n* = 211).

A total of 19 of 23 studies were cross-sectional cohort studies. Four studies were longitudinal cohort (1 in DEXA(Wallengren, Iresjö et al. 2015) and three in the CT group (Malietzis, Currie et al. 2016, Feliciano, Kroenke et al. 2017, Basile, Parnofiello et al. 2019). A significant inverse relationship between SMI and CRP was reported in two longitudinal studies (*n* = 2941), and an inverse relationship between SMI and NLR in two longitudinal studies (*n* = 857) and a direct relationship between SMI and albumin in three longitudinal studies (*n* = 3704).

1.3.4 Discussion

The results of the present systematic review show that in approximately 10,000 patients with cancer, there was a consistent association between CT-derived SMI/SMD and systemic inflammation, as evidenced by CRP and albumin (mGPS), and Neutrophil Lymphocyte Ratio (NLR). To our knowledge, this is the first such systematic review. Since this relationship was determined mainly in cross-sectional studies and in primary operable cancers, it is not clear whether a low SMI/SMD results in the presence of systemic inflammation or whether the presence of systemic inflammation results in low SMI/SMD. Nevertheless, given the importance of these respective measures in defining the syndrome of cancer cachexia and cancer progression, it is important to examine this relationship in more detail, particularly in patients with advanced cancer (Douglas and McMillan 2014, Arends, Baracos et al. 2017, Dolan, Lim et al. 2017, Dolan, McSorley et al. 2017). CT abdomen is part of cancer staging in patients with a wide variety of cancers, including gastrointestinal, hepato-biliary, pancreatic, renal, bladder and lung cancers. From CT abdomen, the L3 level can be readily calculated using manual or semi-automated software packages and using muscle and adipose tissue thresholds, all components of body composition can be calculated.

However, the clinical utility of landmarks other than L3 is not clear. There is some debate as to whether the measurement of psoas muscle at lumbar 3 level is less reliable and inferior to measuring all muscles at this level (Baracos 2017, Icard, Iannelli et al. 2018) and therefore, these studies (Hervochon, Bobbio et al. 2017, Okugawa, Toiyama et al. 2019) were considered separately. Using psoas muscle measurement, Hervochon and co-workers, in a cohort of 161 patients with operable NSCLC, reported that low SMI (total psoas area $\leq 33^{rd}$ percentile) was significantly associated with elevated CRP (Hervochon, Bobbio et al. 2017). Furthermore, Okugawa and co-workers, in a cohort of 308 patients with operable CRC, reported that low SMI (using sex-specific median values of psoas muscle index, male: 286.8 mm^2/m^2, female:

210.6 mm^2/m^2) was significantly associated with elevated CRP and low albumin (Okugawa, Toiyama et al. 2019). Therefore, it would appear that skeletal muscle, however, assessed from CT scans, is consistently associated with measures of the systemic inflammatory response.

Since there is little evidence that increasing skeletal muscle mass is associated with a reduction in cancer-associated systemic inflammation, a plausible hypothesis explaining this relationship is that a pro-inflammatory state is the main etiological factor in progressive muscle loss and this underpins the nutritional and functional decline associated with cancer cachexia. For example, comparing inoperable cancer with operable cancer, the former is consistently associated with greater tumour bulk and greater elevation of the mGPS and NLR (Dolan, Lim et al. 2017, Dolan, McSorley et al. 2017) and weight and skeletal muscle loss is a feature of the cachexia of advanced disease. Furthermore, a greater elevation of the mGPS is associated with more aggressive tumours, such as lung and pancreatic cancer (Proctor, Morrison et al. 2011, MacDonald 2012, Dolan, McSorley et al. 2017), and these tumours are characterized as the tumour types most commonly associated with cachexia.

Therefore, it is of interest that there is good evidence that elevated circulating concentrations of key pro-inflammatory cytokines (e.g., Interleukin 6 [IL-6], Interleukin 1 [IL-1]) link the presence and aggressiveness of the tumour to the loss of skeletal muscle mass (Zimmers, Fishel et al. 2016, McDonald, McMillan et al. 2018) and elevated markers of the systemic inflammatory response (Guthrie, Charles et al. 2013). If this was the case, the pro-inflammatory state could be expected to be a catabolic event and would predate the significant loss of skeletal muscle mass. Indeed, of the longitudinal studies reviewed, the presence of a systemic inflammatory response at baseline was associated with lower SMI on follow-up independent of tumour stage in patients with primary operable cancer (Malietzis, Currie et al. 2016, Feliciano, Kroenke et al. 2017). Furthermore, it is recognized that an elevated CRP and low albumin concentration are risk factors for the development of cancer (Izano, Wei et al.

2016, Demb, Wei et al. 2019). Taken together, these observations directly link the loss of skeletal muscle mass and the presence of a systemic inflammatory response. If this hypothesis were to prove to be the case, it would have profound implications for how cachexia is defined and how it is treated in cancer patients.

With reference to the definition of cancer cachexia, it has been currently defined as weight loss > 5% or BMI < 20kg/m^2 with weight loss > 2% or sarcopenia with weight loss > 2% (Fearon, Strasser et al. 2011). However, the present review and the above rationale make a powerful argument for the definition of cancer cachexia to be based on the presence of a systemic inflammatory response, the mGPS, given its consistent thresholds (Arends, Baracos et al. 2017) . This can be clarified using a quote by MacDonald in his 2012 review article. 'The seminal observation by McMillan and colleagues that the presence of dysregulated state as evidenced by a high CRP connotes a dire prognosis has generally been ignored to date and not used to stratify patients in oncology clinical trials. Particularly in the more aggressive tumour types (e.g., pancreas and lung), the future of patients with elevated mGPS is so grim that they should be given precachexia status and offered multimodal therapy which may delay the onset of cachexia and/ or death (MacDonald 2012).' More recently, Baracos et al, proposed that the cardinal feature of cachexia was the loss of skeletal muscle (Baracos, Mazurak et al. 2018). Given that the systemic inflammatory response is a major driver of this loss (supported by the present review), it can readily be argued that the systemic inflammatory response forms the basis of definition of cancer cachexia. Indeed, there is increasing data to support such an approach (Silva, Wiegert et al. 2019). Clearly in light of the present review, the systemic inflammation may be combined with a low SMI (Dolan, Almasaudi et al. 2019) and/ or combined with performance status (Laird, Kaasa et al. 2013, on behalf of the, Simmons et al. 2019) to better define cachexia.

With reference to the treatment of cancer cachexia, the present review suggests that systemic inflammatory response should be primarily targeted. Unfortunately, to date, few attempts have been made to use systemic inflammation as a therapeutic end-point (Solheim, Fearon et al. 2013). More recently, an early phase clinical trial using a multimodal intervention with an anti-inflammatory agent (Ibuprofen, Trondheim, Norway) had a positive effect on the weight and lean body mass and this is now being examined in a phase 3 trial (Trial registration number NCT02330926) in advanced cancer patients (Solheim, Laird et al. 2018). Using a more potent anti-inflammatory, another randomized controlled trial is underway, using bermekimab, which is a humanized antibody to IL-1α (McDonald, McMillan et al. 2018) and examining its effects on muscles, physical function and appetite in patients with lung, pancreatic or ovarian cancer (MICA trial). If anti-inflammatory treatment given to patients that had evidence of a systemic inflammatory response were proven to prevent further loss of skeletal muscle, this would be a major step forward for the definition and treatment of patients with cancer cachexia.

A potential management algorithm is shown in Figure 1.12. On the CT staging of the tumour, there should also be assessment of body composition and laboratory assessment of the systemic inflammatory response. In particular, assessment of SMI and mGPS should be carried out. Such staging of the tumour and host would provide the basis for patient optimization, providing nutritional support and anti-inflammatory agents (Miller and Skipworth 2019).

This systematic review has some limitations. Firstly, included studies were mainly retrospective and cross sectional. Secondly, the studies were heterogeneous, with various markers of systemic inflammation across a range of various cancers. Thirdly, most of the studies were from single institutions. Large prospective multi-centre follow-up studies involving collaborations among researchers, clinicians, dieticians, physiotherapists, nurses

and the pharmaceutical industry are required to generalize the findings of this systematic review and to provide the best patient care. Moreover, how an algorithm could be routinely incorporated into standard radiological imaging software to capture SMI and SMD for clinical reporting remains to be established. At present, it is not clear whether muscle loss from cancer can be differentiated from purposeful weight loss using CT.

The present systematic review shows low SMI and low SMD to be consistently associated with measures of systemic inflammatory response, including CRP, albumin, mGPS and NLR, in patients with cancer. These observations have implications for the definition and treatment of cancer cachexia which should include measures of the systemic inflammatory response. Once the technical hurdles can be overcome, reporting of SMI should be considered as a routine part of radiology reporting because of its clinical significance.

1.3.5 Tables

Table 1.6 Framework based on modified Glasgow Prognostic score (mGPS).

mGPS	Biochemical Markers		Cachexia Stage
	CRP (mg/L)	Albumin (g/L)	
0	<10	≥35	No cachexia
0	<10	<35	Undernourished
1	>10	≥35	Pre-cachexia
2	>10	<35	Refractory cachexia

CRP = C-reactive protein.

Table 1.7 Characteristics of included studies.

Authors (Year)	Reported STROBE Checklist Points	Type of Study	*n* (F/M)	Country	Cancer Studied	Cancer Stage	Level of Analysis	Systemic Inflammation	Comments
DEXA									
Ellega°rd et al, 2009 [101]	20	Prospective cross-sectional	132 (46/86)	Sweden & New Zealand	Gastrointestinal	Advanced inoperable	Whole body	CRP, Albumin	Low SMI directly associated with elevated CRP and low albumin ($p < 0.05$).
Wallengren et al, 2014 [102]	19	Prospective longitudinal	471 (212/259)	Sweden	Gastrointestinal, pancreatic-biliary	Advanced inoperable	Whole body	CRP, Albumin	Low SMI directly associated with elevated CRP ($p < 0.001$).
Chambard et al, 2018 [103]	20	Prospective cross-sectional	64 (16/48)	France	Non-small cell Lung	Advanced inoperable	Whole body	CRP, Albumin, WCC	Low SMI directly associated with elevated CRP ($p < 0.05$) & WCC ($p < 0.001$).
CT									
Richards et al, 2012 [108]	20	Prospective cross-sectional	174 (79/95)	United Kingdom	Colo-rectal	Primary operable	L3	CRP, Albumin, mGPS, NLR	Low SMI (34%) directly associated with elevated mGPS (32%) ($p < 0.001$)
Itoh et al, 2013 [117]	19	Retrospective cross-sectional	190 (44/146)	Japan	Hepatocellular	Primary operable	L3	Albumin	Low visceral fat area associated with sarcopenia ($p < 0.001$) and low albumin ($p < 0.005$)
Reisinger et al,2016 [114]	17	Prospective cross-sectional	87 (31/56)	Netherlands	Colo-rectal	Primary operable	L3	CRP, mGPS	Low SMI associated with elevated CRP ($p = 0.05$).
Rollins et, al,2016 [53]	18	Retrospective cross-sectional	229 (105/124)	United Kingdom	Pancreatic-biliary	Advanced inoperable	L3	CRP, Albumin, mGPS, NLR	Low SMI and SMD associated with elevated CRP ($p < 0.05$), low albumin ($p < 0.001$) and elevated NLR ($p < 0.01$).

Malietz et al, 2016 [104]	19	Prospective longitudinal	763 (306/457)	United Kingdom	Colo-rectal	Primary operable	L3	Albumin, NLR	Low SMI (65%) and low SMD (84%) associated with NLR > 3 (61% & 57%) ($p < 0.001$) and low albumin (28% each) ($p = 0.01$).
Kim et al, 2016 [115]	20	Retrospective cross-sectional	186 (30/156)	South Korea	Small cell lung	Primary operable	L3	CRP, Albumin, mGPS, NLR	Low SMI associated with elevated CRP ($p < 0.05$), low albumin ($p < 0.05$) and elevated NLR ($p < 0.01$).
Zhuang et al, 2016 [112]	19	Retrospective cross-sectional	937 (207/730)	China	Gastric	Primary operable	L3	Albumin	Low SMI associated with low albumin ($p < 0.001$).
Huang, et al, 2016 [113]	20	Prospective cross-sectional	470 (364/106)	China	Gastric	Primary operable	L3	Albumin	Low SMI associated with low albumin ($p < 0.001$).
Van Di Jik et al, 2017 [76]	19	Prospective cross-sectional	186 (84/102)	Netherlands	Pancreatic	Both operable and inoperable	L3	CRP, Albumin, mGPS	Low SMD associated with low albumin ($p < 0.01$)
Feliciano et al, 2017 (C-SCANS study) [105]	20	Retrospective longitudinal	2470 (1219/1251)	United States, Canada	Colo-rectal	Primary operable	L3	CRP, Albumin, NLR, IL-6	Low SMI associated with elevated CRP ($p < 0.05$), low albumin ($p < 0.01$) and elevated IL-6 ($p < 0.05$)
Srdic et al, 2017 [118]	20	Prospective cross-sectional	100 (33/67)	Croatia	Non-small cell lung	Advanced inoperable	L3	CRP, albumin, mGPS	Low SMI (15% loss of skeletal muscle mass) associated with low albumin ($p < 0.01$)
Kiyotoki et al, 2017 [110]	20	Retrospective cross-sectional	60 All females	Japan	Cervical	Primary operable	L3	CRP, Albumin	Low SMI associated with low albumin ($p < 0.01$).
Serra et al, 2017 [116]	16	Prospective cross-sectional	11 All females	United States	Breast	Primary operable	L4-L5	CRP, Albumin	Significant improvement in muscle strength with resistance training with reduction in inflammatory mediators including CRP.

McSorley et al, 2017 [58]	20	Retrospective cross-sectional	322 (148/174)	United Kingdom	Colo-rectal	Primary operable	L3	CRP, Albumin, mGPS, NLR	Low SMI (47%) and SMD (58%) associated with elevated mGPS (23%) and NLR > 3 (44%) ($p < 0.01$).
Van DiJik et al,2018 [106]	20	Prospective cross-sectional	97 (30/67)	Canada	Colo-rectal	Primary & metastatic both operable	L3	CRP, Albumin	Low SMI (65%) associated with elevated CRP > 5 mg/dL (74%) ($p < 0.05$).
Okugawa et al, 2018 [119]	20	Prospective cross-sectional	308 (125/183)	Japan	Colo-rectal	Primary operable	L3	CRP, Albumin, NLR, PLR	Low SMI and SMD associated with elevated CRP ($p < 0.0001$) and low albumin ($p < 0.05$).
Dolan et al, 2018 [109]	19	Retrospective cross-sectional	650 (296/354)	United Kingdom	Colo-rectal	Primary operable	L3	CRP, Albumin, mGPS, NLR	Low SMI (44%) and SMD (60%) associated with elevated mGPS (23%) ($p < 0.001$) and NLR > 3 (43%) ($p < 0.05$).
Sueda et al, 2018 [111]	20	Retrospective cross-sectional	211 (77/134)	Japan	Colo-rectal	Primary operable	L3	Albumin, NLR	Low SMI (48%) and SMD (49%) associated with NLR > 3 (41%) with ($p < 0.05$) and $p < 0.01$ respectively.
Basile et al, 2019 [120]	20	Retrospective longitudinal	94 (42/52)	Italy	Pancreatic	Advanced inoperable	L3	CRP, Albumin, NLR	Low SMI & SMD associated with NLR > 5($p < 0.001$).
Xiao et al, 2019 [107]	20	Retrospective cross-sectional	3262 (1628/1624)	United States	Colo-rectal	Primary Operable	L3	CRP, Albumin, NLR	Low SMI & SMD associated with raised NLR ≥ 5 ($p < 0.001$).

L3 = Lumbar 3 vertebral level, SM I= Skeletal muscle index, SMD = Skeletal muscle density, mGP S= modified Glasgow prognostic score, NLR = Neutrophil lymphocyte ratio

1.3.6 Figures

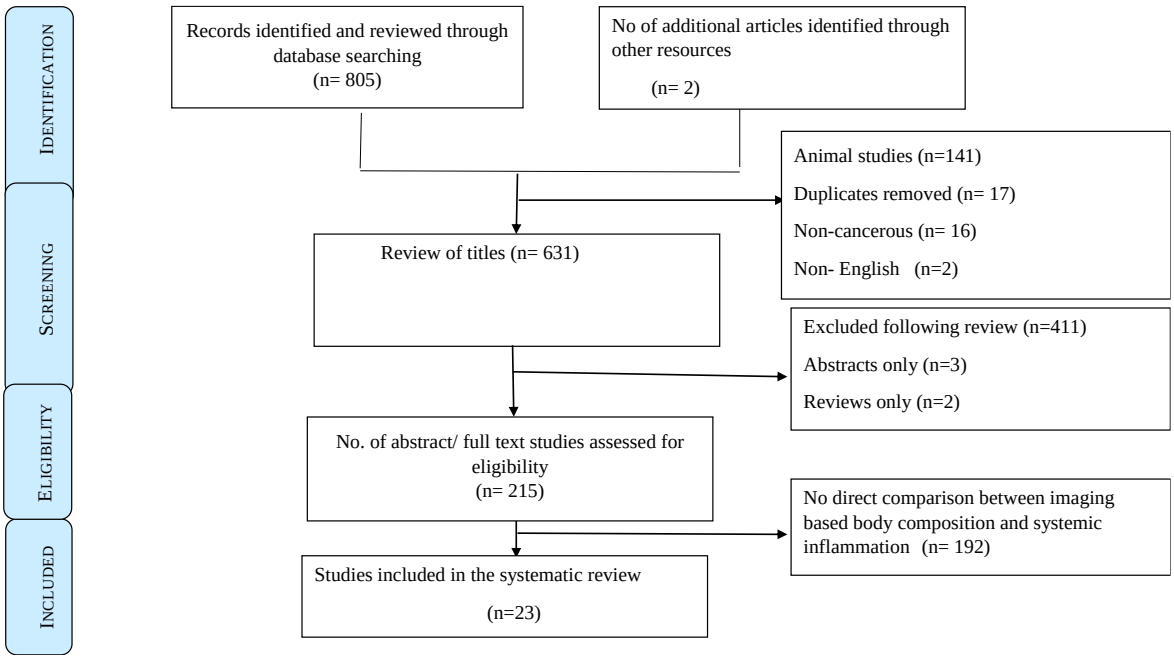


Figure 1.11. Preferred reporting items for systematic review protocol flow diagram.

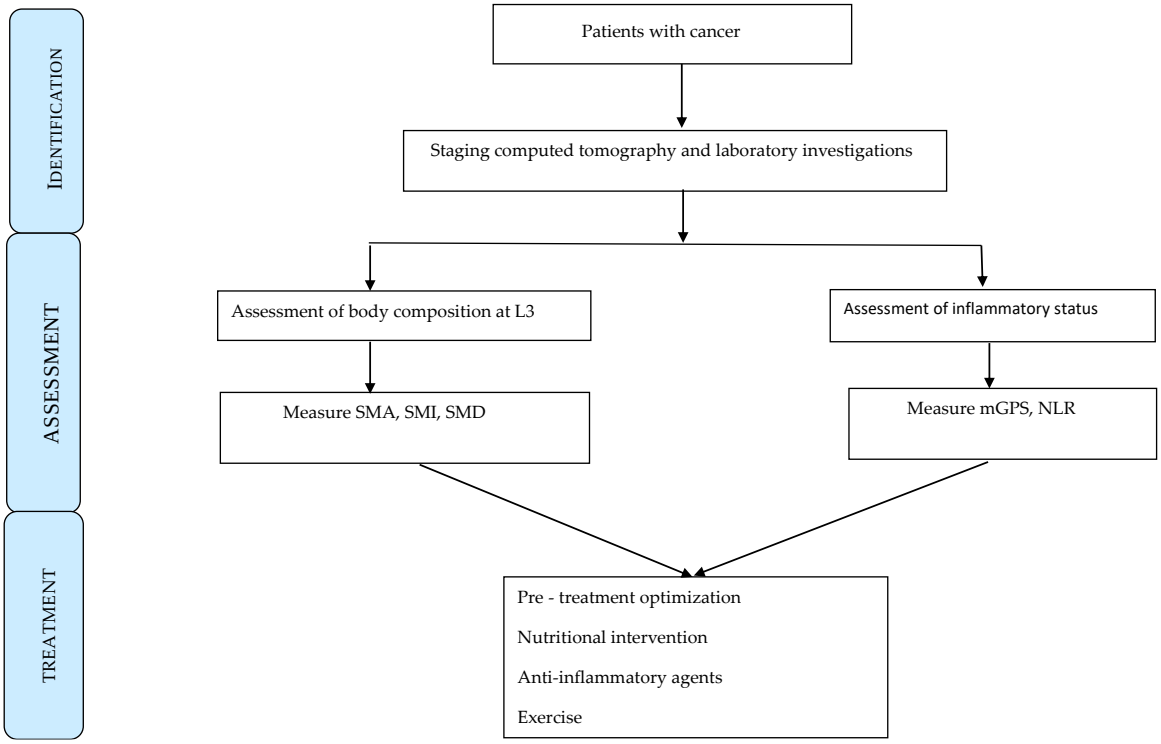


Figure 1.12. Management algorithm of pre-treatment assessment in patients with cancer. SMA = Skeletal muscle area, SMI = Skeletal muscle index, SMI = Skeletal muscle density, mGPS = modified Glasgow prognostic score, NLR = neutrophil lymphocyte ratio.

2 THE RELATIONSHIP BETWEEN COMPUTED TOMOGRAPHY DERIVED SKELETAL MUSCLE INDEX, PSOAS MUSCLE INDEX AND CLINICAL OUTCOMES IN PATIENTS WITH OPERABLE COLORECTAL CANCER

2.1 Introduction

Colorectal cancer (CRC) is the third most common cancer and is the fourth leading cause of cancer related deaths worldwide. Incidence of CRC is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030 (Bray, Ferlay et al. (2018)**.** Colorectal cancer surgery is associated with high risk of adverse events. This is a key area of quality improvement in colorectal surgery. Despite improvements in tumour staging and use of the multidisciplinary team (MDT) based approach, post-operative complications and mortality persist, leading to poor survival. Therefore, staging the tumour and staging the host are important steps towards treatment of colorectal cancer and accurately prognosticate clinical outcomes (Park, Ishizuka et al. (2018).

Sarcopenia as evidenced by CT derived low skeletal muscle index (SMI) and low psoas muscle index (PMI) have both been identified as poor prognostic factors for patients with operable CRC in terms of both short and long term clinical outcomes (see Table 2.1 and Table 2.2) (Jones, Doleman et al. 2015, Miyamoto, Baba et al. 2015, Reisinger, van Vugt et al. 2015, Feliciano, Kroenke et al. 2017, Hanaoka, Yasuno et al. 2017, Cespedes Feliciano, Avrutin et al. 2018, Deng, Lin et al. 2018, Nakanishi, Oki et al. 2018, Okugawa, Toiyama et al. 2018, Tamagawa, Aoyama et al. 2018, van Vugt, Coebergh van den Braak et al. 2018, Dolan, Knight et al. 2019, Nakata, Furuya et al. 2019).

However, it is not clear whether, these measures reflect the same muscular entity. For example, SMA reflects a number of muscle types i.e. paraspinal, lateral and anterior abdominal wall muscles. In contrast, psoas muscle, a paraspinal muscle, is a primary flexor of hip and originates from lumbar vertebrae and inserts on lesser trochanter of femur. The

PMA measurement is less complex and less time consuming. Being easily identifiable next to the L3 vertebra level, psoas muscle cross-sectional area has been used in recent studies to evaluate the relationship between skeletal muscle mass and outcome (Jones, Doleman et al. 2015). However, its value as sentinel muscle for skeletal muscle loss has been questioned (Baracos 2017).

Jones *et al.* reported that in 100 patients with operable CRC, SMA and PMA were highly correlated (r=0.9) (Jones, Doleman et al. 2015). However, Rutten et al, reported in 150 patients with advanced ovarian cancer, a weaker correlation (r=0.5) (Rutten, Ubachs et al. 2017). Furthermore, Rollins et al. reported that, in 150 non-cancerous, non-emergency patients, SMA and PMA were moderately correlated (r=0.7) (Rollins, Gopinath et al. 2019). Therefore, it is not clear whether the prognostic value of SMA reflects that of PMA.

The aim of the present study was to examine the relationship between SMI and PMI and clinical outcomes in a large cohort of patients with primary operable colorectal cancer.

2.2 Patients and Methods

Clinical and pathological data were collected retrospectively from prospectively maintained colorectal cancer database at the Academic Department of Surgery at Glasgow Royal Infirmary from March 2008 to March 2018. Owing to retrospective nature of study, local Ethics Board waived the need for formal ethics approval. The flow diagram of included patients is shown in Figure 2.1. Pre-operative CT scans of n=1047 patients were analysed, 45 patients with stage IV disease were excluded, giving final total of 1002 patients for subsequent analysis. Only patients with an available staging CT scan (within 3 months of surgery, median 1.5 months) were included in this study. Patient data were collected for age, sex, ASA scores, BMI, TNM stage and modified Glasgow prognostic (mGPS) scores preoperatively.

Methods

Body composition was assessed using pre-operative staging CT scans obtained from Picture Archiving and Communication System (PACS) and body composition measurement was performed at third lumbar level which is shown to be strongly correlated to whole body muscle and adipose tissue in healthy adults (Shen, Punyanitya et al. 2004) and patients with cancer (Mourtzakis, Prado et al. 2008). Images were analysed using NIH image software image J (https://imagej.nih.gov.ij/) by using skeletal muscle thresholds of -29 to 150 HU. Both left and right psoas muscle areas were outlined as shown in Figure 2.2 and added for total psoas muscle area (van den Berg, Kok et al.) and this was normalized by height in square meters for PMI. Whole L3 Skeletal muscles i.e. anterior abdominal wall, paravertebral and psoas muscles were outlined as shown in Figure 2.2 and skeletal muscle area (SMA) was normalized for height square meters for SMI. Measurements were performed by two individuals (YTH and TA) for 30 test scans to ensure inter observer

reliability with Intraclass correlation coefficient (ICC) of 0.987 for PMI and 0.996 for SMI. Observers were blinded to patient clinical details and outcomes.

The receiver operating characteristics (ROC) curve was plotted for SMI and PMI, the optimal thresholds for mortality in this population were calculated. SMI threshold values obtained were identical to previous thresholds described by Dolan et al (Dolan, Almasaudi et al. 2019) and therefore, were used for subsequent analysis and classification of patients into high and low SMI. For males, low SMI was defined as SMI<45 cm^2m^2 if BMI<25kg/m^2 and SMI<53 cm^2m^2 if BMI≥25kg/m^2 and for females, low SMI was defined as SMI<39 cm^2m^2 if BMI<25kg/m^2 and SMI<41 cm^2m^2 if BMI≥25kg/m^2.

For PMI, area under curve (AUC) provided most specificity at threshold of 7.4 cm^2/m^2 (p=0.002) for males, however, this AUC was not significant for females. Therefore, optimal threshold was calculated for all included cases (n=1002) with operable CRC in this patient population and was set at 6.1cm^2/m^2 (p=0.027).

Statistical Analysis

The correlation between total SMA and PMA was calculated using Pearson correlation coefficient. Chi square test was used for analysis of categorical variables. Logistic regression analysis was used to calculate OR and 95% CIs for post-operative complications and length of hospital stay while Cox proportional hazard model was used to calculate HR and 95% CI for overall survival. Variables with p<0.1, on univariate analysis were entered in a backward conditional multivariate analysis. P-value of <0.05 was considered significant. Patients were followed up till death or October 1, 2019 which was used as censor date. Median duration of follow up was 52 months.

The relationship between clinico-pathological characteristics and clinical outcomes as stratified by SMI (Table 2.3) and PMI (Table 2.4) were shown. Complications were

divided into infective, non-infective and further classified according to Clavien-Dindo grade. Length of hospital stay was divided into ≤ 7 days or > 7 days as usual discharge for these patients is around 4 to 5 days. Overall survival was defined as time in months from date of surgery to time of death or time to end of study or loss to follow up.

Scatterplot relationship between SMA and PMA according to age (Figure 2.3), sex (Figure 2.4), ASA score (see Figure 2.5), TNM stage (see Figure 2.6) and mGPS (see Figure 2.7) respectively. All of the statistical analysis was performed using SPSS version 25 (IBM Corporation, 2017, Armonk, NY).

2.3 Results

The relationship between clinico-pathological characteristics and clinical outcomes in patients with primary operable CRC as stratified by SMI is shown in Table 2.3. Half of patients had low SMI (n=504) with two third of patients being ≥65 years old (n=380), males (n=298, 59%) and ASA ≥ II (n=414, 82%). A low SMI was associated with old age ($p<0.001$), male sex ($p<0.05$), higher ASA score ($p<0.05$), low BMI ($p<0.001$), higher TNM stage ($p<0.001$), Clavien-Dindo grade 3 to 5 post-operative complications ($p<0.05$), prolonged length of hospital stay ($p=0.002$), 90 day mortality ($p<0.01$) and reduced 3 years overall survival ($p<0.001$). Low SMI remained a significant predictor of 3 year overall survival ($p=0.002$) after adjustment for age.

The relationship between clinico-pathological characteristics and clinical outcomes in patients with primary operable CRC as stratified by PMI is shown in Table 2.4. 41% of patients had low PMI (n=406) with 67% being ≥65 years old (n=271), females (n=256, 63%) and ASA ≥ II (n=332, 82%). A low PMI was associated with female sex ($p<0.001$), low BMI ($p<0.001$), non-infective complications ($p<0.05$), prolonged length of hospital stay ($p<0.05$) and reduced 3 y overall survival ($p<0.01$).

The overall correlation between total SMA and PMA was moderate (r=0.70). The correlation between total SMA and PMA according to age groups (<65/65-74/>74) was moderate (r=0.70) as shown in Figure 2.3 and was especially significant at <65 (r=0.72) and 65-74 (r=0.68) years group respectively. The correlation between total SMA and PMA according to sex was moderate (r=0.69) as shown in Figure 2.4. The correlation between total SMA and PMA according to ASA was moderate (r=0.69) as shown in Figure 2.5 and was especially significant at ASA class II (r=0.74) and III (r=0.71) respectively. The correlation between total SMA and PMA according to TNM stage was moderate (r= 0.70)

as shown in Figure 2.6 and this did not differ significantly with TNM stage I to III. There was also moderate correlation between total SMA and PMA according to pre-operative mGPS (r=0.70) as shown in Figure 2.7 and this did not differ significantly across all three categories (mGPS= 0/1/2).

The relationship between clinicopathological characteristics, body composition and postoperative complications is shown in Table 2.5. On univariate logistic regression analysis, patient sex (OR 1.40; 95%CI, 1.08-1.81, p=0.011), ASA (OR 1.29; 95% CI, 1.10-1.52, p= 0.002), mGPS (OR 1.23; 95% CI, 1.04-1.45, p=0.015) were significantly associated with risk of postoperative complications. On multivariate analysis, sex (OR 1.38; 95% CI, 1.06 -1.79, p=0.015), ASA (OR 1.26; 95% CI, 1.07 -1.49, p=0.007), mGPS (OR 1.19; 95% CI, 1.00 -1.40, p=0.048) were independently associated with postoperative complications.

The relationship between clinicopathological characteristics, body composition and length of hospital stay is shown in Table 2.6. On univariate logistic regression analysis, patient age (OR 1.01; 95% CI, 1.00-1.03, p=0.021), ASA (OR 1.50; 95% CI, 1.27 -1.77, p<0.001), TNM stage (OR 1.24; 95% CI, 1.05-1.46, p=0.011), mGPS (OR 1.53; 95% CI, 1.29 -1.83, p<0.001), low SMI (OR 1.47; 95% CI, 1.15-1.89, p=0.002) and low PMI (OR 1.34, 95% CI; 1.04-1.73, p=0.025) were significantly associated with prolonged length of hospital stay. On multivariate analysis, ASA (OR 1.42; 95% CI, 1.20 -1.68, p<0.001), mGPS (OR 1.41; 95% CI, 1.18 -1.69, p<0.001), low SMI (OR 1.32; 95% CI, 1.02-1.70, p=0.037) were independently associated with prolonged hospital stay. When SMI was excluded from the multivariate model, low PMI (OR 1.28; 95% CI, 0.87-1.88, p=0.205) was not independently associated with prolonged hospital stay.

The relationship between clinicopathological characteristics, body composition and overall survival is shown in Table 2.7. On univariate Cox-regression analysis, patient age (HR

1.06; 95% CI, 1.04 -1.09, p<0.001), Sex (HR 1.27; 95% CI, 0.97-1.66, p=0.079), ASA (HR 1.69; 95% CI,1.43-2.01, p<0.001), BMI (HR 0.17; 95% CI, 0.61-0.83, p<0.001), TNM stage (HR 1.55; 95% CI 1.16-2.08, p=0.003), mGPS (HR 1.63; 95% CI, 1.40 -1.90, p<0.001), low SMI (HR 2.29; 95% CI, 1.47-3.58, p<0.001) and low PMI (HR 1.43; 95% CI, 1.10 -1.86, p=0.007) were significantly associated with overall survival. On multivariate analysis, patient age (HR 1.41; 95% CI, 1.19-1.66, p<0.001), ASA (HR 1.41; 95% CI,1.19-1.66, p<0.001), BMI (HR 0.75; 95% CI, 0.66-0.86, p<0.001),TNM stage (HR 1.61; 95% CI,1.36 -1.91, p<0.001) and mGPS (HR 1.32; 95% CI, 1.14 -1.52, p<0.001) were independently associated with overall survival .

2.4 Discussion

The present study is one of the few studies that has directly compared the prognostic value of SMI and PMI at L3 in patients with primary operable CRC. The results of the present large study showed that although they were moderately correlated (r=0.70), both had prognostic value in terms of clinical outcomes including length of hospital stay and overall survival. However, only SMI had independent prognostic value. Therefore, the present results are consistent with low muscle mass, as evidenced by either low total SMI or low PMI, being important in patients with primary operable CRC.

In the present study, psoas muscle constituted approximately 10-15% of total SMA and this value was consistent with the 10% reported by Rutten et al. Rutten, Ubachs et al. (2017) . The present results were consistent with the literature (Tables 2.1 and 2.2) [52,106,115,148-157], however, there have been far more observations of SMI (approximately 5248) compared with PMI (approximately 982). This is perhaps due to the fact that psoas muscle had been considered as a specialized muscle and that it may waste at a different rate compared with other skeletal muscles. Indeed, some authors have concluded that PMI was not suitable measure of skeletal muscle loss (Baracos 2017).

The present study is one of the few studies (and the largest to date) that has directly compared the prognostic value of SMI and PMI at L3 in patients with primary operable CRC. Given the large cohort the present results showed definitively that although SMI and PMI were moderately correlated (r=0.70), both had prognostic value in terms of clinical outcomes including length of hospital stay and overall survival. Moreover, the results definitively showed that only SMI had independent prognostic value. Therefore, the present results are consistent with low muscle mass, as evidenced by either low total SMI or low PMI, being important in patients with primary operable CRC.

The present results showed that, using ROC analysis, 50% of the 1002 had low SMI and 41% had low PMI. Therefore, in addition to having a moderate correlation, both had similar relationship with survival. This was despite that PMA was affected by different degenerative spinal pathologies (Rutten, Ubachs et al. (2017). Indeed, there was a moderate correlation between SMA and PMA (r=0.70) in non-cancer patients (Rollins, Gopinath et al. 2019). Therefore, PMA is a reasonable substitute, and had been reported to be associated with greater postoperative complications in patients with CRC (see Table 2.2) (Jones, Doleman et al. 2015, Hanaoka, Yasuno et al. 2017, Okugawa, Toiyama et al. 2018, Tamagawa, Aoyama et al. 2018, Dolan, Knight et al. 2019, Herrod, Boyd-Carson et al. 2019, Nakata, Furuya et al. 2019). However, the threshold may be variable. For example, when the Prado threshold for PMA, (Prado, Lieffers et al. 2008) was applied in the present cohort, only 14% of patients were classified as low PMA compared with 41% using threshold value derived from the present cohort. However, the Prado cohort (n=250) was Canadian patients with lung and gastrointestinal cancer. Therefore, similar to SMI, it is important to derive threshold values for the patient population under study (Dolan, Almasaudi et al. 2019).

In the present study, it was of interest that low SMI was associated with male sex whereas low PMI was associated with female sex such that there was a consistent sex associated difference in the relationship between SMI and PMI (see Figure 2.4). The basis of this observation is not clear. However, a possible explanation is that there is differential wasting of psoas and other core muscles in male and female patients with colorectal cancer. Further longitudinal studies will be required to better understand this relationship.

In current practice, surgeons will take into account host factors like age, performance status and systemic inflammatory status and tumour factors including TNM stage into the decision-making process (Kuipers, Grady et al. 2015, Park, Ishizuka et al. 2018).

Determining skeletal muscle status may also be useful for surgeons prior to surgery. This will allow them to assess whether the patient is sarcopenic despite a normal BMI.

There are some limitations for this study. First, this was single centre study and therefore may be subject to a certain degree of selection bias. Secondly, this is retrospective cohort study and comes with limitations associated with this study design. Future work should determine whether there is differential effect on SMI and PMI in longitudinal studies.

In the present study neither skeletal muscle density nor psoas muscle density were included. Using CT-derived body composition measurements, muscle density is critically dependent on the phase of the scan at which the image is collected. To date although there have been reports that muscle density has prognostic value, it is not a well standardised measurement (Rollins, Gopinath et al. 2019). For example, muscle radiodensities on CT scanning are dependent on cardiac output at the time of scan and varied proportions of intramuscular blood supply to the individual muscles in accordance with pathophysiological and health status. Indeed, it may be MRI may be a better modality to assess skeletal muscle quality in patients with cancer (Rollins, Gopinath et al. 2019). Lastly, further work is required to determine the anatomical basis for CT-derived muscle density measurements (Aubrey, Esfandiari et al. 2014, Ramage, Johns et al. 2018).

In summary, though both total skeletal muscle index and psoas muscle index had prognostic value, total skeletal muscle index was independently associated with clinical outcomes in patients with primary operable colorectal cancer.

2.5 Tables and Footnotes

Table 2.1: The relationship of total skeletal muscle index and clinical outcomes in operable colorectal cancer n=5248

Authors (year)	**n**	**Level of analysis**	**Clinical outcomes**	**OR/ HR (p-value)**
Reisinger *et al.* (2015) [114]	340	L3SMI	OS	OR=43.40 (p=0.007)
Miyamoto *et al.* (2015)[51]	220	L3SMI	RFS OS	HR=2.176 (p=0.015) HR=2.270 (p=0.019)
Feliciano *et al.* (2017)[105]	2470	L3SMI	OS CRC related death	HR=1.28* HR=1.42*
Nakanishi *et al.* (2018)[147]	494	L3SMI	Postoperative complications	OR=1.82 (p=0.01)
Deng *et al.* (2018)[148]	101	L4 SMI	OS Progression-free s0urvival	HR=1.54 (p<0.05) HR=1.23 (p<0.05)

Van Vugt *et al.* (2018)[149]	816	L3SMI	Postoperative complications	OR=1.91 (p=0.018)
Feliciano et al (2018)[150]	807	L3SMI	OS	HR=1.66*

L3= 3rd Lumbar vertebra, OS=overall survival, RFS= Recurrence-free survival, SMI= Skeletal muscle index,

*p-value was not given

Table 2.2. The relationship of psoas muscle index and clinical outcomes in operable colorectal cancer n=982

Authors (year)	**n**	**Level of analysis**	**Clinical outcomes**	**OR/ HR (p-value)**
Jones *et al.* (2015)[151]	100	L3PMI	Postoperative complications	OR=5.41 (p=0.01)
Hanaoka *et al.* (2017)[152]	133	Ratio of short to long axis of PM	Postoperative complications Infectious complications	OR=2.71 (p=0.032) OR=4.26 (p=0.012)
Tamagawa *et al.* (2018)[153]	82	L3PMI	Postoperative complications	OR=3.508 (p=0.027)
Okugawa *et al.* (2018)[154]	308	L4PMI	Cancer-specific survival Disease-free survival Infectious complications	HR=2.75 (p=0.001) HR=3.15 (p=0.0001) OR=2.03 (p=0.013)

Dolan *et al.* (2019)[155]	163	L3PMI	1-year mortality	HR=2.233 (p=0.194)
Nakata *et al.* (2019)[156]	196	L3PMI	OS	HR=2.05 (p<0.01)

PM= psoas muscle, OS= overall survival

Table 2.3: The relationship between clinicopathological characteristics and clinical outcomes in patients with primary operable CRC as stratified by skeletal muscle index (n=1002).

Characteristics	All, n (%) n=1002	High SMI n (%) 498 (49.7)	Low SMI n (%) n=504 (50.3)	P-value
Age, years				<0.001*
<65	345 (34.4)	221 (44.4)	124 (24.6)	
65-74	367 (36.6)	175 (35.1)	192 (38.1)	
>74	290 (28.9)	102 (20.5)	188 (37.3)	
Sex				0.014*
Male	554 (55.3)	256 (51.4)	298 (59.1)	
Female	448 (44.7)	242 (48.6)	206 (40.9)	
ASA				0.040*
I	196 (19.6)	106 (21.3)	90 (17.9)	
II	456 (45.5)	230 (46.2)	226 (44.8)	
III	316 (31.5)	150 (30.1)	166 (32.9)	
IV	34 (3.4)	12 (2.4)	22 (4.4)	
BMI, kg/m^2				<0.001*
<20	64 (6.4)	18 (3.6)	46 (9.1)	
20-24.9	297 (29.6)	132 (36.5)	165 (32.7)	

25-29.9	336 (33.5)	131 (26.3)	205 (40.7)	
≥30	305 (30.4)	217 (43.6)	88 (17.5)	
TNM stage				<0.001*
I	240 (24.0)	143 (28.7)	97 (19.2)	
II	404 (40.3)	174 (34.9)	230 (45.6)	
III	358 (35.7)	181 (36.3)	177 (35.1)	
Any complications				0.252
Yes	388 (38.7)	184 (36.9)	204 (40.5)	
No	614 (61.3)	314 (63.1)	300 (59.5)	
Non-infective complications				0.164
Yes	138 (13.8)	61 (12.2)	77 (15.3)	
No	864 (86.2)	437 (87.8)	427 (84.7)	
Infective complications				0.855
Yes	250 (25.0)	123 (24.7)	127 (25.2)	
No	752 (75.0)	375 (75.3)	377 (74.8)	
Clavien Dindo (3-5) complications				0.047*
Yes	95 (9.5)	38 (7.6)	57 (11.3)	
No	907 (90.5)	460 (92.4)	447 (88.7)	

Length of hospital stay				0.002*
≤7 days	455 (45.4)	250 (50.2)	205 (40.7)	
>7 days	547 (54.6)	248 (49.8)	299 (59.3)	
90 day mortality				0.006*
Yes	26 (2.6)	6 (1.2)	20 (4.0)	
No	976 (97.4)	492 (98.8)	484 (96.0)	
Survival				<0.001*
3-yr survival % (SE)	-	87 (2)	81 (2)	
Age adjusted (<65,65-74,>74)	91 (1)	90 (2)	84 (2)	0.002*

Table 2.4. The relationship between clinico-pathological characteristics and clinical outcomes in patients with primary operable CRC as stratified by psoas muscle index (n=1002)

Characteristics	All, n (%) n=1002	High PMI n (%) N=596 (59.5%)	Low PMI n (%) n=406 (40.5%)	P-value
Age, years				0.100
<65	345 (34.4)	210 (35.2)	135 (33.3)	
65-74	367 (36.6)	229 (38.4)	138 (34.0)	
>74	290 (28.9)	157 (26.3)	133 (32.8)	
Sex				<0.001*
Male	554 (55.3)	404 (67.8)	150 (36.9)	
Female	448 (44.7)	192 (32.2)	256 (63.1)	
ASA				0.256
I	196 (19.6)	122 (20.5)	74 (18.2)	
II	456 (45.5)	272 (45.6)	184 (45.3)	
III	316 (31.5)	184 (30.9)	132 (32.5)	
IV	34 (3.4)	18 (3.0)	16 (3.9)	

BMI, kg/m^2				<0.001*
<20	64 (6.4)	21 (3.5)	43 (10.6)	
20-24.9	297 (29.6)	144 (24.2)	153 (37.7)	
25-29.9	336 (33.5)	209 (35.1)	127 (31.3)	
≥30	305 (30.4)	222 (37.2)	83 (20.4)	
TNM stage				0.173
I	240 (24.0)	155 (26.0)	85 (20.9)	
II	404 (40.3)	232 (38.9)	172 (42.4)	
III	358 (35.7)	209 (35.1)	149 (36.7)	
Any complications				0.617
Yes	388 (38.7)	227 (38.1)	161 (39.7)	
No	614 (61.3)	369 (61.9)	245 (60.3)	
Non-infective complications				0.024*
Yes	138 (13.8)	70 (11.7)	68 (16.7)	
No	864 (86.2)	526 (88.3)	338 (83.3)	
Infective complications				0.217
Yes	250 (25.0)	157 (26.3)	93 (22.9)	
No	752 (75.0)	439 (73.7)	313 (77.1)	

Clavien-Dindo (3-5) complications				0.487
Yes	95 (9.5)	80 (9.2)	15 (11.1)	
No	907 (90.5)	787 (90.8)	120 (88.9)	
Length of hospital stay				0.025*
≤7 days	455 (45.4)	288 (48.3)	167 (41.1)	
>7 days	547 (54.6)	308 (51.7)	239 (58.9)	
90 day mortality				0.384
Yes	26 (2.6)	21 (2.4)	5 (3.7)	
No	976 (97.4)	846 (97.6)	130 (96.3)	
Survival				0.007*
3-yr survival % (SE)	-	87 (1)	83 (2)	

*p<0.05

Table 2.5: The relationship between clinicopathological characteristics, body composition and postoperative complications in patients with operable CRC (n=1002)

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	P-value	OR (95% CI)	P-value
Clinico-pathological				
Age (≤65/65-74/≥74)	1.00 (0.99 -1.02)	0.590		
Sex (male/ female)	1.40 (1.08-1.81)	0.011	1.38 (1.06-1.79)	0.015
ASA I/II/III/IV	1.29 (1.10-1.52)	0.002	1.26 (1.07-1.49)	0.007
BMI (<20/20-24/25-29/≥30)	1.01 (0.99-1.03)	0.262		
TNM stage (I/II/III)	1.08 (0.91-1.27)	0.381		
mGPS (0/1/2)	1.23 (1.04-1.45)	0.015	1.19 (1.00-1.40)	0.048
Body Composition				
Low SMI	1.16 (0.90-1.50)	0.252		
Low PMI	1.07 (0.83-1.38)	0.617		

Table 2.6: The relationship between clinicopathological characteristics, body composition and length of hospital stay in patients with operable CRC (n=1002)

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	P-value	OR (95% CI)	P-value
Clinico-pathological				
Age (≤65/65-74/≥74)	1.00 (0.99 -1.02)	0.590		
Sex (male/ female)	1.40 (1.08-1.81)	0.011	1.38 (1.06-1.79)	0.015
ASA I/II/III/IV	1.29 (1.10-1.52)	0.002	1.26 (1.07-1.49)	0.007
BMI (<20/20-24/25-29/≥30)	1.01 (0.99-1.03)	0.262		
TNM stage (I/II/III)	1.08 (0.91-1.27)	0.381		
mGPS (0/1/2)	1.23 (1.04-1.45)	0.015	1.19 (1.00-1.40)	0.048
Body Composition				
Low SMI	1.16 (0.90-1.50)	0.252		
Low PMI	1.07 (0.83-1.38)	0.617		

Table 2.7: The relationship between clinicopathological characteristics, body composition and overall survival in patients with operable CRC (n=1002)

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Clinico-pathological				
Age (≤65/65-74/≥74)	1.06 (1.04 -1.09)	<0.001	1.41 (1.19-1.66)	<0.001
Sex (male/ female)	1.27 (0.97-1.66)	0.079	1.26 (0.99-1.59)	0.060
ASA I/II/III/IV	1.69 (1.43-2.01)	<0.001	1.41 (1.19-1.66)	<0.001
BMI (<20/20-24/25-29/≥30)	0.17 (0.61-0.83)	<0.001	0.75 (0.66-0.86)	<0.001
TNM stage (I/II/III)	1.55 (1.16-2.08)	0.003	1.61 (1.36-1.91)	<0.001
mGPS (0/1/2)	1.63 (1.40-1.90)	<0.001	1.32 (1.14-1.52)	<0.001
Body Composition				
Low SMI	2.29 (1.47-3.58)	<0.001	1.29 (0.97-1.71)	0.082
Low PMI	1.43 (1.10-1.86)	0.007		0.569
Adjuvant therapy	1.38 (1.15-1.65)	<0.001		0.351

2.6 **Figures and Legends**

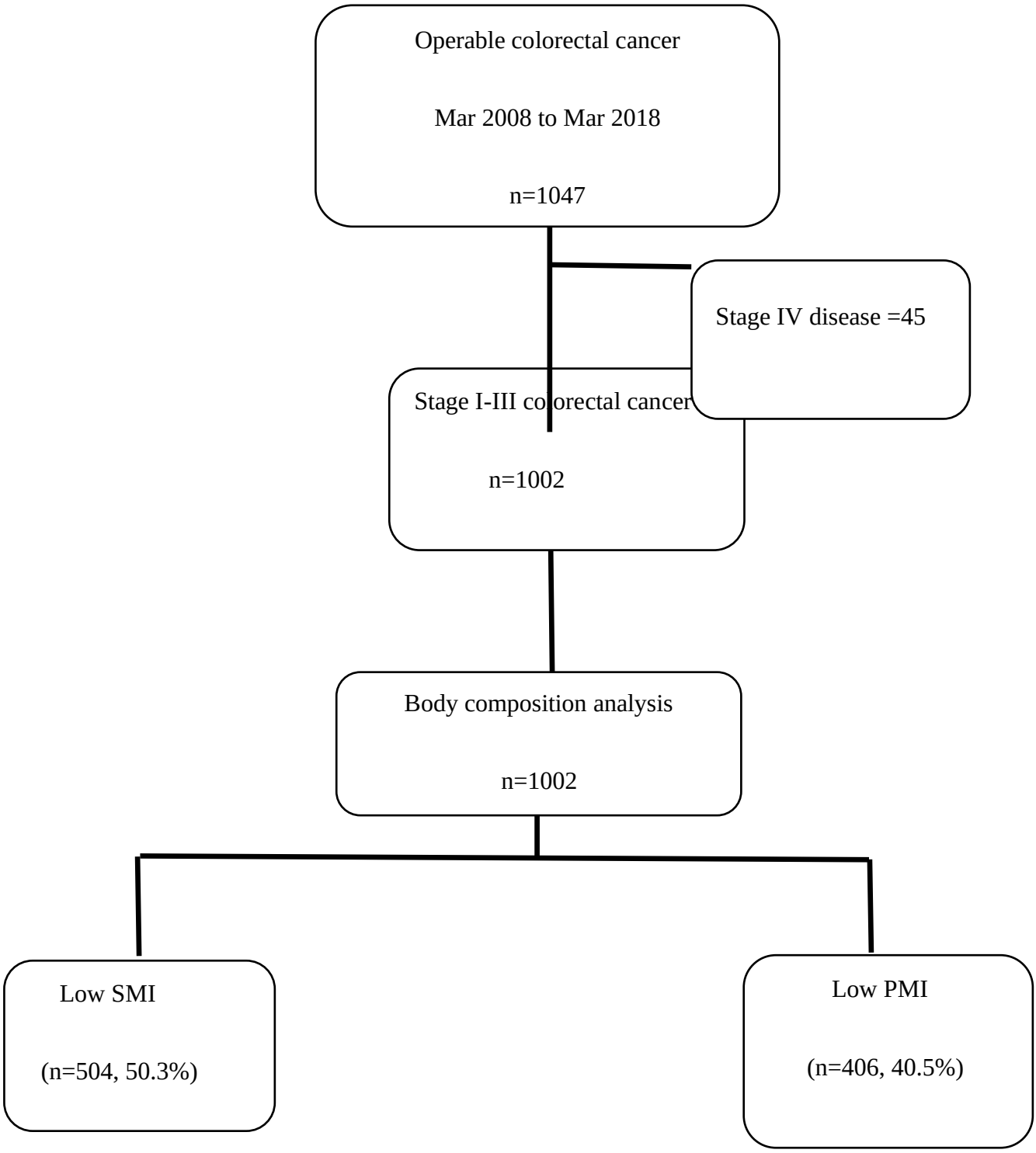


Figure 1. Flow diagram of included patients with operable colorectal cancer.

PMI=psoas muscle index, SMI= Skeletal muscle index

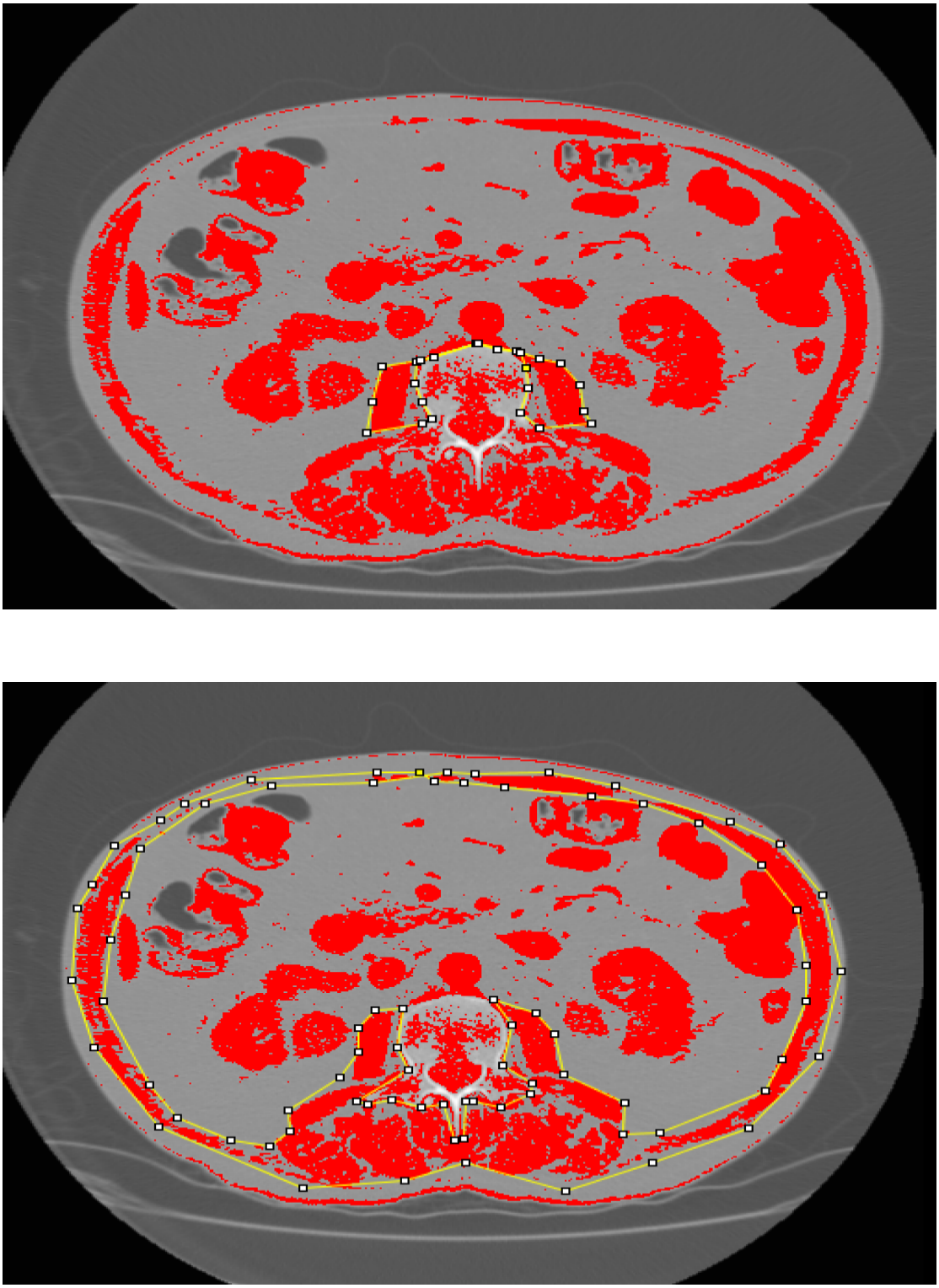


Figure 2.2. L3 axial CT scans with muscles highlighted red between two marked yellow lines using image J, with total skeletal muscles (above) and psoas muscles (below).

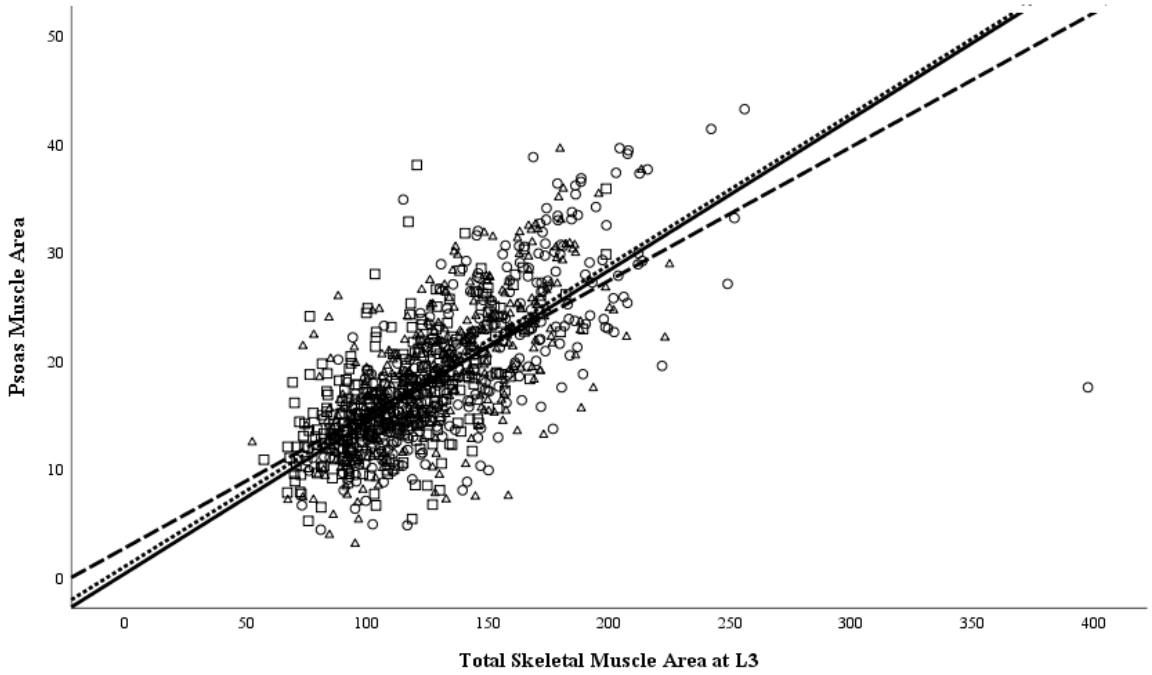


Figure 2.3. Scatterplot of the relationship between total skeletal muscle area and psoas muscle area at L3 according to age groups (n=1002, <65y n=345, r_s=0.72, p<0.001 (Dotted line), 65-74y n=367, r_s=0.68, p<0.001 (Solid line), >74y n=290, r_s=0.60, p<0.001 (Dashed line).

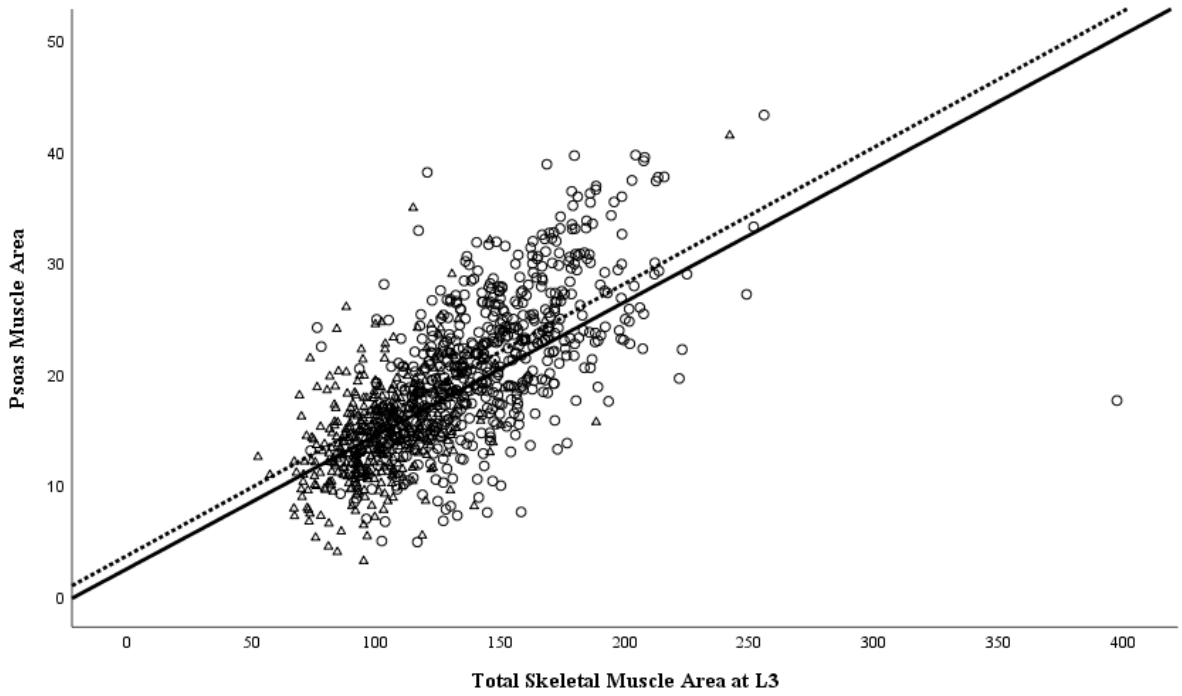


Figure 2.4. Scatterplot of the relationship between total skeletal muscle area and psoas muscle area at L3 according to sex (n=1002, Males n=554, r_s=0.56, p<0.001 (Dotted line), Females n=448, r_s=0.53, p<0.001 (Solid line).

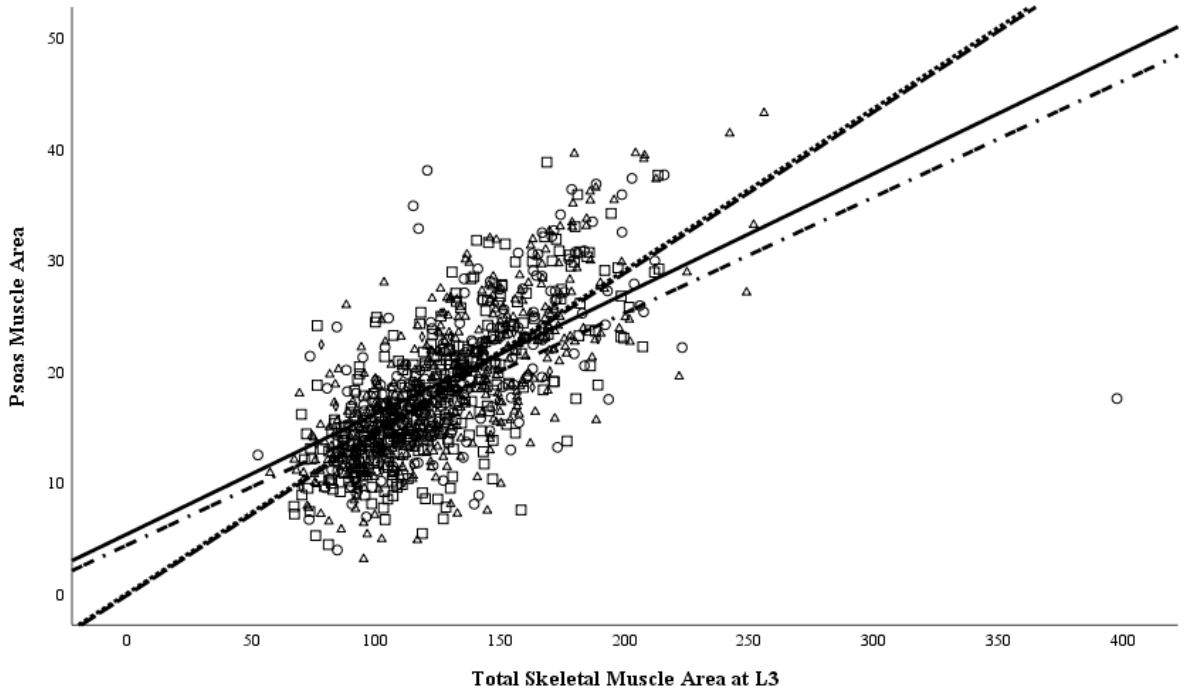


Figure 2.5. Scatterplot of the relationship between total skeletal muscle area and psoas muscle area at L3 according to ASA score (n=1002, ASA I n=196, r_s=0.60, p<0.001 (Solid line), ASA II n=456, r_s =0.74, p<0.001 (Dotted line), ASA III n=316, r_s= 0.71 p<0.001(Dashed line), ASA IV n=34, r_s= 0.64, p<0.001 (Dotted dashed line).

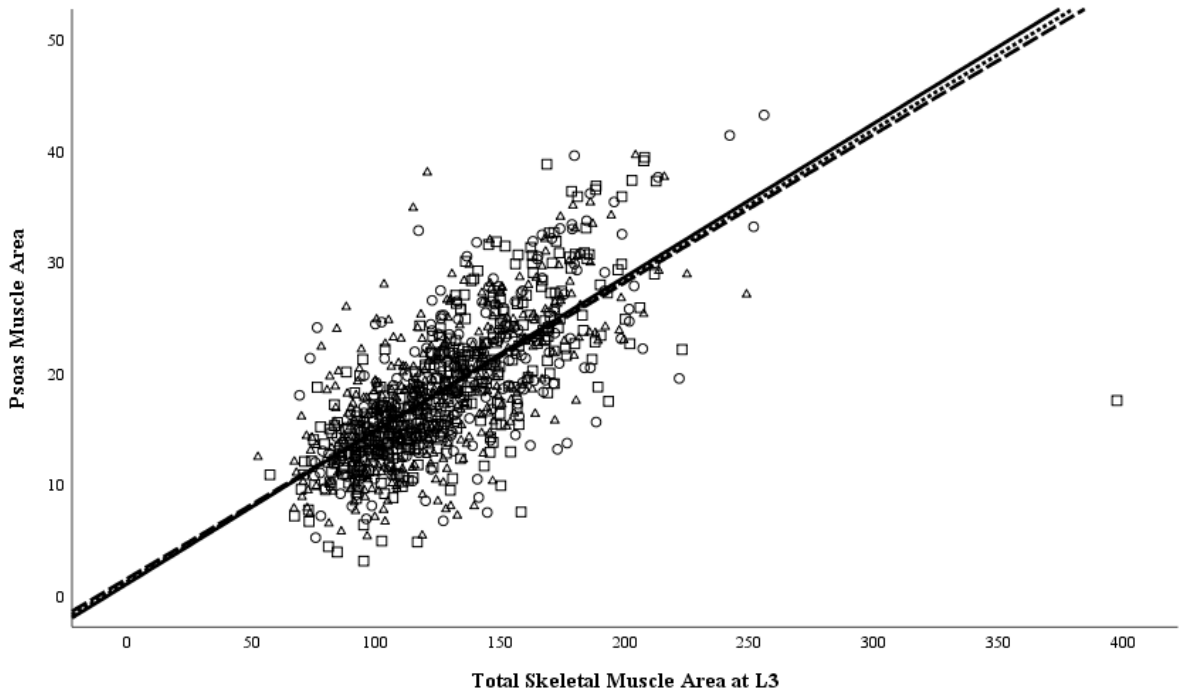


Figure 2.6. Scatterplot of the relationship between total skeletal muscle area and psoas muscle area at L3 according to TNM stage (n=1002, TNM I n=240, r_s=0.70, p<0.001 (Dotted line), TNM II n= 404, r_s =0.68, p<0.001 (Solid line), TNM III n= 358, r_s= 0.70, p<0.001 (Dashed line).

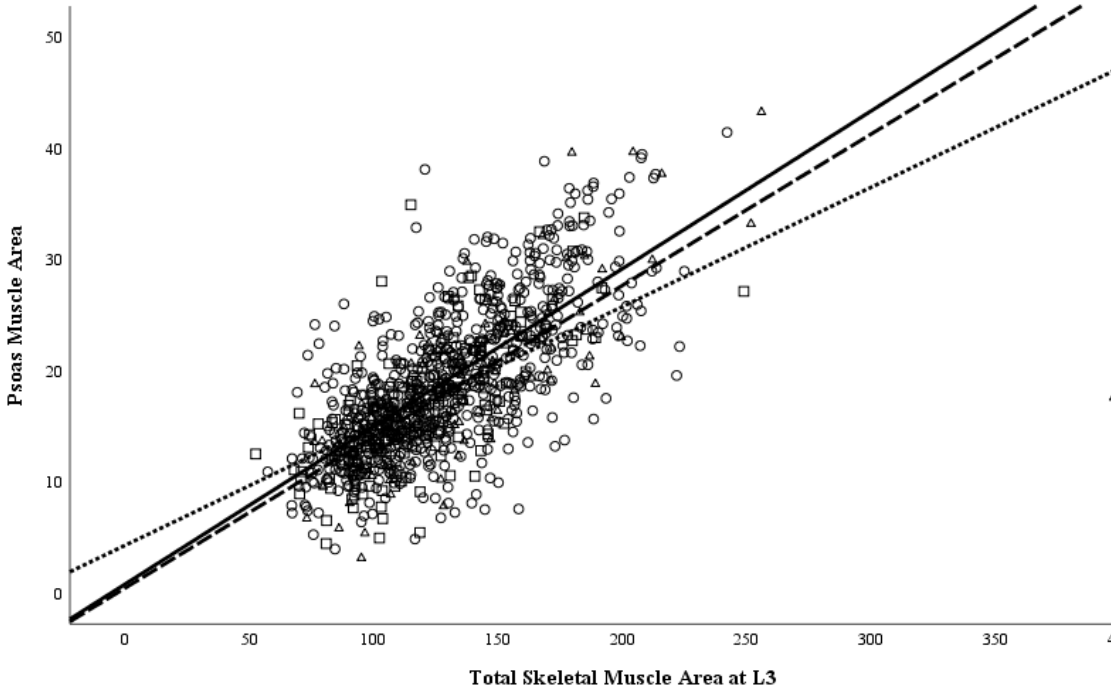


Figure 2.7. Scatterplot of the relationship between total skeletal muscle area and psoas muscle area at L3 according to mGPS stage (n=1002, mGPS 0 n=731, r_s=0.70, p<0.001 (Solid line), mGPS 1 n=109, r_s=0.66, p<0.001 (Dotted line), mGPS 2 n=162, r_s= 0.68, p<0.001 (Dashed line).

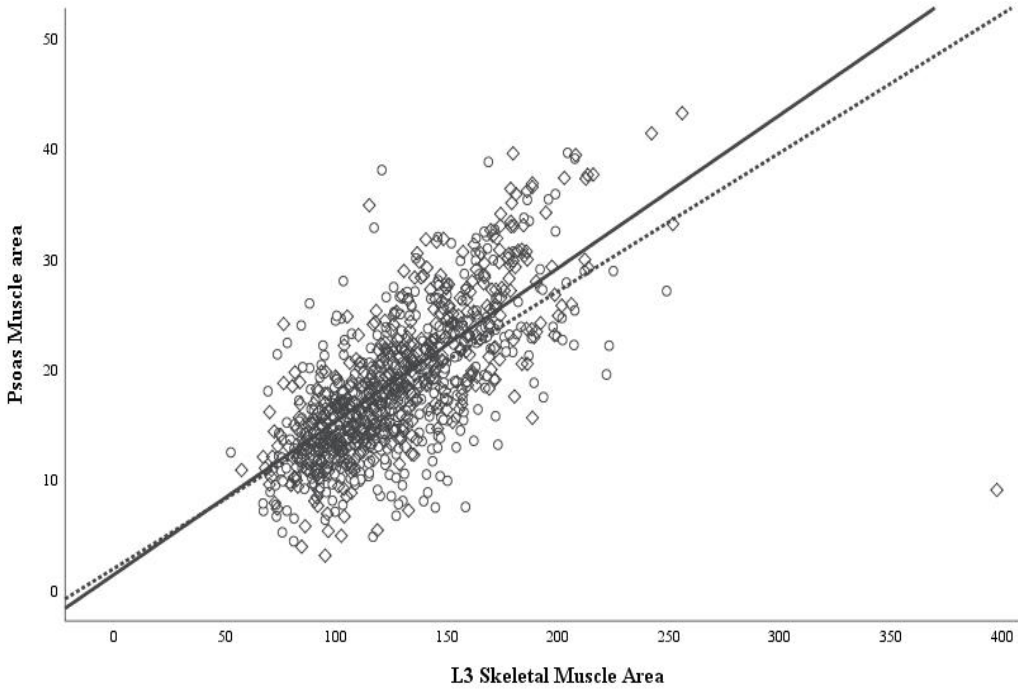


Figure 2.8. Scatterplot of the relationship between total skeletal muscle area and psoas muscle area at L3 according to contrast phase of CT (n=991, Portal venous n=492, r_s=0.72, p<0.001 (Solid line), Arterial n=499, r_s=0.64, p<0.001 (Dotted line).

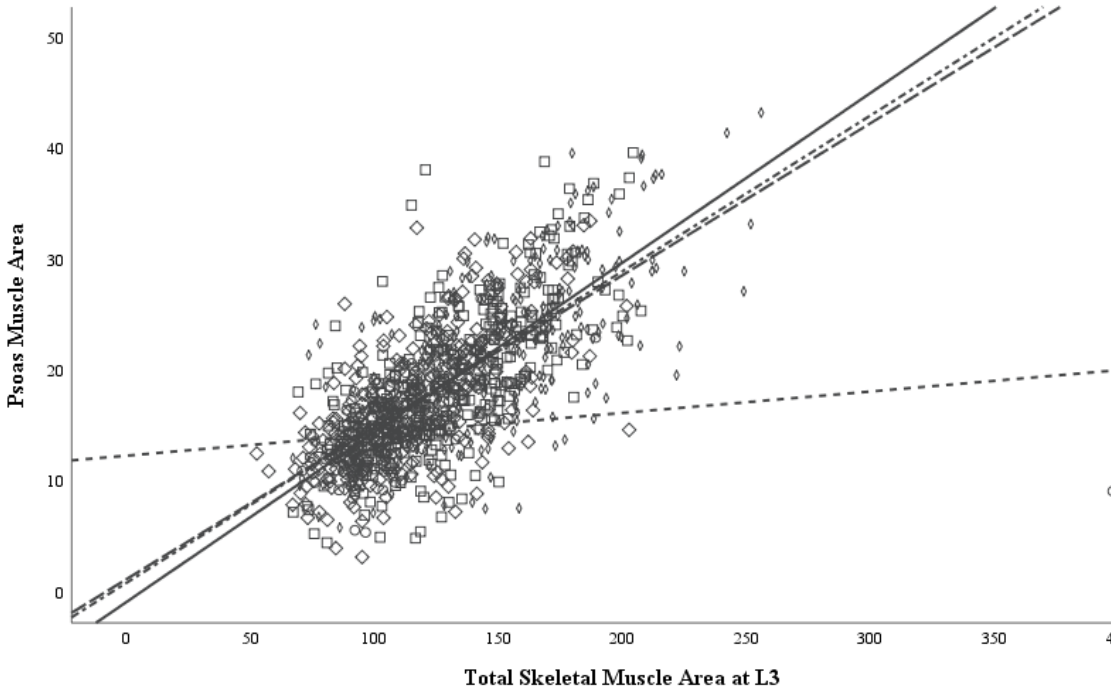


Figure 2.9. Scatterplot of the relationship between total skeletal muscle area and psoas muscle area at L3 according to BMI categories (Total n=1002, <20 n=64, r_s=0.18, p<0.001 (dotted line), 20-24 n=297, r_s=0.66, p<0.001 (Dashed line), 25-30 n=336, r_s=0.70, p<0.001 (Solid line), >30 n=305, r_s=0.70, p<0.001 (Dotted dashed line).

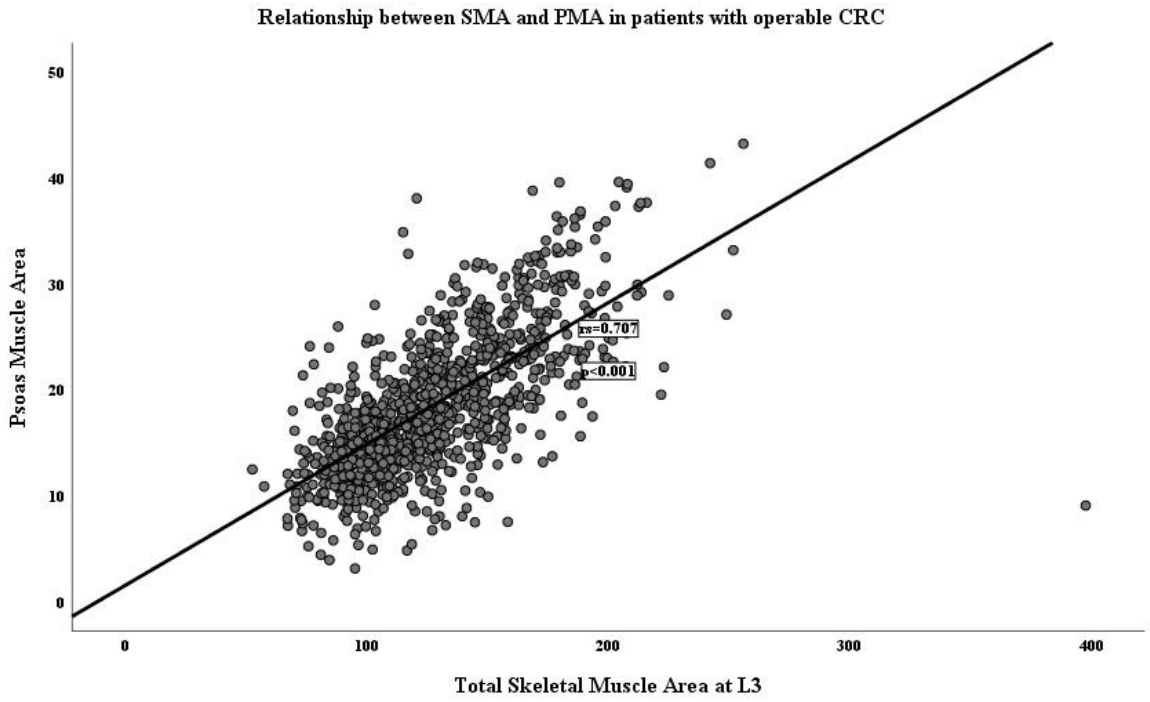


Figure 2.10. Scatterplot of the relationship between total skeletal muscle area and psoas muscle area at L3 (Total n=1002, r_s=0.707, p<0.001).

3 THE RELATIONSHIP BETWEEN SYSTEMIC INFLAMMATION, BODY COMPOSITION AND CLINICAL OUTCOMES IN PATIENTS WITH OPERABLE COLORECTAL CANCER AT LOW TO MEDIUM / HIGH NUTRITION RISK

3.1 Introduction

As cancer is a leading cause of death worldwide. Colorectal cancer (CRC) is the third most common cancer and is the fourth leading cause of cancer related deaths worldwide. Incidence of CRC is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030 (Bray, Ferlay et al. 2018) . In the United Kingdom, CRC is the common cancer with around 42,000 new cases diagnosed annually and is the second most common cause of cancer death (Cancer Research 2019). Despite improvements in tumour staging and use of the multidisciplinary team (MDT) based approach, post-operative complications and mortality persist, leading to poor survival. Therefore, staging the tumour and staging the host are important steps in moving forward in treatment of colorectal cancer (Park, Ishizuka et al. 2018).

Malnutrition plays an important role in patients undergoing surgery for colorectal cancer (CRC). Various nutritional assessment methods are routinely used and, in the UK, Malnutrition Universal Screening Tool (MUST) has been adopted by the British Association of Parenteral and Enteral Nutrition (BAPEN) (Elia 2003). MUST score is a five-step process to categorize patients in low, medium and high nutritional risk groups as shown in Figure 1.1 and in accordance with international nutritional guidelines (Arends, Baracos et al. 2017). MUST score is widely used in National Health Service (NHS) in the UK and nursing and medical staff are familiar with its use and is included in the admission

checklist. Its use in patients with cancer has been validated (Boleo-Tome, Monteiro-Grillo et al. 2012).

Systemic inflammation measured by modified Glasgow Prognostic score (mGPS) and neutrophil lymphocyte ratio (NLR) has been shown to have prognostic value in patients undergoing surgery for CRC (Dolan, Lim et al. 2017). Recently in a cohort of 363 patients undergoing surgery for CRC, it was reported that MUST was directly associated with mGPS and NLR and a low skeletal muscle index (SMI) measured using CT (Almasaudi, McSorley et al. 2019). However, it was of interest that approximately 80% of patients were at low nutritional risk, as defined by MUST, and in these patients approximately 20% were systemically inflamed and approximately 45% had a low skeletal muscle index. Given that systemic inflammation and low SMI are directly related (Abbass, Dolan et al. 2019), it was of interest to examine their relationship and prognostic value in patients at low and medium/ high nutrition risk.

The aim of the present study was to examine the relationship between malnutrition, systemic inflammation, body composition and clinical outcomes in patients with operable CRC at low and medium/ high nutritional risk.

3.2 Patients and methods

Data were collected from prospectively maintained colorectal cancer data base at academic department of surgery, Glasgow Royal Infirmary from March 2008 to March 2018. The flow diagram of included patients was shown in Figure 3.1. From initial sample of 1060 patients, patients with stage IV disease, non-colorectal cancers were excluded giving 1002 with stage I to III operable colorectal cancer patients. 984 patients had MUST scores available in this cohort and these patients were entered into the study.

MUST score was calculated from pre-treatment admission record and the relationship between MUST, clinicopathological characteristics, systemic inflammation, body composition and clinical outcomes in patients with primary operable CRC was shown in Table 3.1. Systemic inflammation was measured using modified Glasgow prognostic score (mGPS) and Neutrophil lymphocyte ratio (NLR). Pre op mGPS and NLR were analysed from serum samples performed prior to surgery.

Body composition was assessed from the staging CT scan and L3 slices were retrieved from Picture archiving and communication system (PACS). Body composition was analysed using image J software (https://imagej.nih.gov/ij/) by applying validated thresholds (Martin, Birdsell et al. 2013, Ebadi, Martin et al. 2017, Dolan, Almasaudi et al. 2019) for colorectal cancer patients. Established thresholds of -29 to 150 HU for skeletal muscle and -190 to -30 HU for adipose tissue were used as previously described (Dolan, McSorley et al. 2017).

The CT scans were analysed for total fat area (TFA), visceral fat area (VFA), subcutaneous fat area (SFA), skeletal muscle area (SMA) and skeletal muscle density (SMD). Measurements were performed by two individuals (TA and RD) on a sample of 40 patients. The interrater reliability was assessed using inter-class correlation coefficients

(ICCs). The ICCC values were as follows TFA and VFA = 0.999; SMA = 0.996 and SMD = 0.993). The cross-sectional area of fat and muscles was normalized for height (m^2) to calculate fat and skeletal muscle indices.

Visceral obesity was defined as VFA>160cm^2 in males and >80cm^2 in females (Doyle, Bennett et al. 2013). Sarcopenia (low SMI) was defined per Martin threshold as SMI <43 cm^2/m^2 in BMI<25$kg/m^2$and SMI <53 cm^2/m^2 in BMI ≥25 kg/ m^2 males and SMI<39 cm^2/m^2 in BMI <25 kg/m^2 and SMI<41cm^2/m^2 with BMI ≥25kg/m^2. Myosteatosis (low SMD) was defined as SMD <41HU in patients with BMI<25kg/m^2 and SMD<33HU in patients with BMI≥25kg/m^2 (Martin, Birdsell et al. 2013)

Statistical Analysis

Independent sample t test and χ^2 test were used in the analysis of continuous and categorical variables respectively. Binary logistic regression analysis was carried out on patients with low nutritional risk (MUST=0) group with relationship to any post-operative complications, length of hospital stay and overall survival. Logistic regression analysis was used to calculate OR and 95% CIs for post-operative complications and length of hospital stay while Cox proportional hazard model was used to calculate HR and 95% CI for overall survival. The Kaplan–Meier method and log rank test were used for survival analysis. P-value of <0.05 was considered significant.

The enrolled patients were followed up till death or October 1, 2019 whichever came first. Median duration of follow up was 52 months, 3 patients were lost to follow up. Post-operative complications within a month of surgery with their relationship to MUST were evaluated. Hospital stay was divided into ≤ 7 days and > 7 days as most of the patients undergoing CRC will be discharged by day 4 to 5. Overall survival was defined as time in months from date of surgery to time of death from any cause or time to end of study or loss

to follow up. Patients were followed up as per colorectal cancer guidelines with tumour markers i.e. carcinoembryonic antigen (CEA) check every 3 months for first 2 years and 6 months in years 3 to 5, CT follow up yearly and colonoscopy at year 1 and 3 (Hardiman, Felder et al. 2021). Of the 131 patients who died in this sample of 810 low nutritional risk patients, 115 died of colorectal cancer (16 other causes). All of the statistical analysis was performed using SPSS version 25 (IBM Corporation, 2017, Armonk, NY).

3.3 Results

In 1002 patients with stage I to III colorectal cancer, 984 had MUST scores available. 810 patients (82%) were at low nutritional risk (MUST=0), 174 patients (18%) were at medium to high nutritional risk (MUST1- ≥2). Mean age of patients was 68 years (range, 23-93). 55% of patients were males (n=544). The relationship between MUST and clinicopathological factors were shown in Table 3.1. Compared with low MUST, moderate to high MUST was associated with older age ($p<0.001$), female sex ($p<0.05$), higher ASA ($p<0.01$), emergency presentation ($p<0.05$), colon cancer ($p<0.01$), higher mGPS ($p<0.001$) and NLR ($p<0.001$), lower subcutaneous and visceral obesity (both $p<0.001$), low SMI ($p<0.001$) , longer hospital stay ($p<0.001$) and poorer 3 year survival ($p<0.001$).

In those patients at low nutrition risk (n=810, 82%), the relationship between mGPS and clinicopathological factors were shown in Table 3.2.1. Compared with mGPS 0, mGPS 1/2 was associated with higher ASA ($p<0.01$), higher NLR ($p<0.001$), low SMI ($p<0.001$), greater length of hospital stay ($p<0.001$) and poorer 3-year survival ($p<0.05$).

In those patients at medium to high nutritional risk (n=174, 18%), the relationship between mGPS and clinicopathological factors were shown in Table 3.2.2. Compared with mGPS 0, mGPS 1/2 was associated with higher ASA ($p<0.05$), higher NLR ($p<0.05$), low SMI ($p=0.05$), low SMD ($p<0.05$), longer hospital stay ($p<0.05$) and poorer 3 years survival ($p<0.05$).

The variables associated with post-operative complications in patients with operable CRC in low risk MUST (MUST=0) were presented in Table 3.3a. On univariate logistic regression, age ($p=0.014$), sex ($p=0.052$), ASA ($p=0.014$), mGPS ($p=0.018$), NLR ($p=0.083$) were significantly associated with post-operative complications. On multivariate analysis, age (OR 1.22; 95% CI: 1.02-1.48; $p=0.034$), ASA (OR 1.22; 95% CI: 1.01-1.47;

p=0.035), mGPS (OR 1.25; 95% CI: 1.01-1.54; p=0.037) were independently associated with post-operative complications.

The variables associated with post-operative complications in patients with operable CRC in medium to high nutrition risk (MUST=1-≥2) were presented in Table 3.3b. On univariate logistic regression, age (p=0.098) and sex (p=0.040) were significantly associated with post-operative complications. On multivariate analysis, only sex (OR 2.03; 95% CI: 1.04-3.99; p=0.039) was independently associated with post-operative complications.

The variables associated with length of hospital stay in patients with operable CRC in low risk MUST (MUST=0) were presented in Table 3.4a. On univariate logistic regression analysis, age (p=0.001), ASA (p<0.001), TNM stage (p=0.019), mGPS (p<0.001), NLR (p<0.001), low SMI (p=0.010) were significantly associated with prolonged hospital stay >7 days. On multivariate analysis, ASA (OR 1.28; 95% CI: 1.05-1.56; p=0.014), mGPS (OR 1.30; 95% CI: 1.04-1.63; p=0.022), NLR (OR 1.65; 95% CI: 1.35-2.03; p<0.001) were independently associated with prolonged hospital stay >7 days.

The variables associated with length of hospital stay in patients with operable CRC in medium to high nutrition risk (MUST=1-≥2) were presented in Table 3.4b. On univariate logistic regression analysis, ASA (p<0.05), mGPS (p=0.075), elevated SFI (p=0.060) were significantly associated with prolonged hospital stay >7 days. On multivariate analysis, only ASA (OR 1.66; 95% CI: 1.09-2.52; p=0.017) was independently associated with prolonged hospital stay >7 days.

The variables associated with overall survival in patients with operable CRC in low risk MUST (MUST=0) were shown in Table 3.5a. A total of 679 patients (84%) were alive at censor date in MUST=0 group. Death due to any cause occurred in 131 (16%) patients.

The median survival was 58 months (range 0-139 months). After exclusion of 30 days mortality, 6 patients (0.7%), there was significant association between MUST score and overall survival ($p<0.001$).

On univariate Cox regression survival analysis, age ($p<0.001$), sex ($p=0.021$), ASA ($p<0.001$), TNM stage ($p<0.001$), mGPS ($p=0.003$), NLR ($p=0.023$), low SMI ($p=0.076$), low SMD ($p=0.005$) were significantly associated with overall survival. On multivariate analysis, age (HR 1.41; 95% CI : 1.21-1.79; $p=0.004$), sex (HR 1.49 ;95%CI: 1.04-2.15; $p=0.031$), ASA (HR 1.44; 95%CI:1.13-1.83; $p=0.003$), TNM stage (HR 1.80; 95% CI:1.40-2.31; $p<0.001$), mGPS (HR 1.29; 95%CI: 1.03-1.62; $p=0.026$) were independently associated with overall survival .

The variables associated with overall survival in patients with operable CRC medium to high nutrition risk (MUST=1-≥2) were presented in Table 3.5b. On univariate Cox regression survival analysis, ASA ($p<0.001$), TNM stage ($p<0.002$), mGPS ($p=0.006$), NLR ($p=0.057$), low SMD ($p=0.080$) were significantly associated with overall survival. On multivariate analysis, ASA (HR 1.60; 95%CI:1.22-2.11; $p<0.001$), TNM stage (HR 1.67; 95% CI:1.20-2.31; $p=0.002$) and mGPS (HR 1.29; 95%CI: 1.03-1.62; $p=0.026$) were independently associated with overall survival.

3.4 Discussion

The results of the present study in almost 1000 patients with primary operable colorectal cancer shows that approximately 80% of patients were at low nutritional risk. In those patients, at low nutrition risk (MUST 0), the systemic inflammatory response, as evidenced by an elevated mGPS 1/2, was associated with low SMI, greater length of hospital stay and poorer overall survival. Similarly, in those patients at moderate/ high nutritional risk (MUST 1/2) an elevated mGPS was associated with low SMI, greater length of hospital stay and poorer overall survival. Therefore, the combined assessment of MUST and mGPS has complementary value and may form the basis of a routine disease related malnutrition assessment in patients with primary operable colorectal cancer.

The MUST tool is simple to use and provides recommendation for health care professionals to improve nutritional status of patients. MUST has been validated in terms of predicting clinical outcomes and compares favourably with other nutritional risk assessments (Stratton, King et al. 2006, Henderson, Moore et al. 2008). Similarly, the mGPS is simple and objective to use, has been extensively validated in predicting clinical outcomes and compares favourably with other systemic inflammation based prognostic scores (Dolan, Lim et al. 2017, Dolan, McSorley et al. 2017). Therefore, the combined use in cancer patients undergoing nutritional assessment is worthy of further study.

The results of the present study are consistent with the recommendations of a recent task force commissioned by 4 major international clinical nutrition societies (ESPEN, ASPEN, PENSA and FELANPE). They proposed that the diagnosis of malnutrition was based on 3 phenotypic criteria (unintentional weight loss, low BMI and low muscle mass) and 2 etiologic criteria (low food intake or low food assimilation and inflammation or disease

burden) and that to diagnose malnutrition at least 1 phenotypic and 1 etiologic criteria should be present. Therefore, when malnutrition is caused by an underlying chronic disease it may be termed disease related malnutrition and in the presence of a systemic inflammatory response may be considered to be cachexia (Muscaritoli, Arends et al. 2019).

The strengths of the present study include a large sample size and detailed phenotypic characterisation of patients with primary operable colorectal cancer. However, there are a number of limitations. The present study is from a single institution and therefore may not be representative of all patients with primary operable colorectal cancer. Also, the MUST defined cohort of moderate/ high risk patients was relatively small. Therefore, confirmatory studies are required. However, given the simplicity of our study approach it is likely that this work will be readily repeated.

It will be interesting to longitudinally study this relationship between MUST, systemic inflammation and body composition in CRC cohort. Improving fitness of patient by addressing malnutrition with muscle mass and function coupled with decrease in stress of surgery (inflammatory response) will help in reducing adverse post-operative outcome and achieve best possible outcome for patient. Reducing catabolism and improving anabolic response by addressing nutrition, inflammation, muscle mass and function are important components in treatment of patients with CRC.

Conclusion:

The combination of MUST and mGPS would appear to provide a reliable objective assessment tool for risk stratification of length of hospital stay and survival in patients with primary operable CRC.

1.3 Tables

Table 3.1: The relationship between MUST, clinico-pathological characteristics, systemic inflammation, body composition and clinical outcomes in patients with primary operable CRC

	Total n=984	Low nutritional risk MUST= 0 n=810 (82.3%)	Medium to high nutritional risk MUST 1- ≥2 n=174 (17.7%)	p-value
Clinico-pathological				
Age, y				<0.001
<65	342 (34.8)	298 (36.8)	44 (25.3)	
65-74	362 (36.8)	309 (38.1)	53 (30.1)	
>74	280 (28.5)	203 (25.1)	77 (44.3)	
Sex				0.017
Male	544 (55.3)	462 (57)	82 (47.1)	
Female	440 (44.7)	348 (43)	92 (52.9)	
ASA				0.005
I	193 (19.6)	167 (20.6)	26 (14.9)	
II	450 (45.7)	374 (46.1)	76 (43.7)	
III	308 (31.3)	248 (30.6)	60 (34.5)	
IV	33 (3.4)	21 (2.6)	12 (6.9)	
Presentation				<0.001
Elective	922 (93.7)	770 (95.1)	152 (87.4)	
Emergency	62 (6.3)	40 (4.9)	22 (12.6)	
TNM				0.140

1	235 (23.9)	204 (25.2)	31 (17.8)	
2	398 (40.4)	320 (39.5)	78 (44.8)	
3	351 (35.7)	286 (35.3)	65 (37.4)	
Primary cancer				0.006
Colon	588 (59.8)	468 (57.8)	120 (69)	
Rectum	396 (40.2)	342 (42.2)	54 (31)	
Adjuvant treatment				0.245
No	464 (47.2)	375 (46.3)	89 (51.1)	
Yes	520 (52.8)	435 (53.7)	85 (48.9)	
Systemic Inflammation				
mGPS				<0.001
0	722 (73.4)	623 (76.9)	99 (56.9)	
1	107 (10.9)	93 (11.5)	14 (8)	
2	155 (15.8)	94 (11.6)	61 (35.1)	
NLR				<0.001
<3	515 (52.3)	451 (55.7)	64 (36.8)	
3-5	303 (30.8)	236 (29.1)	67 (38.5)	
>5	166 (16.9)	123 (15.2)	43 (24.7)	
Body composition				
Subcutaneous adiposity (Ebadi threshold) [38]				<0.001
No	197 (20)	122 (15.1)	75 (43.1)	

Yes	787 (80)	688 (84.9)	99 (56.9)	
Visceral obesity (Doyle threshold) [39]				<0.001
No	267 (27.1)	171 (21.1)	96 (55.2)	
Yes	717 (72.9)	639 (78.9)	78 (44.8)	
Low SMI (Martin threshold) [40]				<0.001
No	491 (49.9)	433 (53.5)	58 (33.3)	
Yes	493 (50.1)	377 (46.5)	116 (66.7)	
Low SMD (Martin threshold) [40]				0.015
No	326 (33.1)	282 (34.8)	44 (25.3)	
Yes	658 (66.9)	528 (65.2)	130 (74.7)	
Postoperative outcome				
Any complications				0.410
No	604 (61.4)	502 (62)	102 (58.6)	
Yes	380 (38.6)	308 (38)	72 (41.4)	
Infective complication				0.500
No	738 (75)	611 (75.4)	127 (73)	
Yes	246 (25)	199 (24.6)	47 (27)	
Clavien-Dindo grade				0.145
0	604 (61.4)	502 (62)	102 (58.6)	

1-2	288 (29.3)	239 (29.5)	49 (28.2)	
3-5	92 (9.3)	69 (8.5)	23 (13.2)	
Length of hospital stay				<0.001
≤7 d	448 (45.5)	394 (48.6)	54 (31)	
>7 d	536 (54.5)	416 (51.4)	120 (69)	
Survival				<0.001
3 yr. survival % (SE)	85 (1)	90 (1)	67 (4)	

Table 3.1.1: The relationship between clinico-pathological characteristics, systemic inflammation, body composition and clinical outcomes in patients with primary operable CRC at low nutritional risk patients (MUST=0)

	Total n=810	Low nutritional risk (MUST=0) with mGPS=0 n=623 (76.9%)	Low nutritional risk (MUST=0) with mGPS=1/2 n=187 (23.1%)	p-value
Clinico-pathological				
Age, y				0.166
<65	298 (36.8)	234 (37.6)	64 (34.2)	
65-74	309 (38.1)	241 (38.7)	68 (36.4)	
>74	203 (25.1)	148 (23.8)	55 (29.4)	
Sex				0.821
Male	462 (57)	354 (56.8)	108 (57.8)	
Female	348 (43)	269 (43.2)	79 (42.2)	
ASA				0.004
I	167 (20.6)	134 (21.5)	33 (17.6)	
II	374 (46.1)	298 (47.8)	76 (40.6)	
III	248 (30.6)	180 (28.9)	68 (36.4)	
IV	21 (2.6)	11 (1.8)	10 (5.3)	
Presentation				0.148
Elective	770 (95.1)	596 (95.7)	174 (93)	
Emergency	40 (4.9)	27 (4.3)	13 (7)	
TNM				0.013
1	204 (25.2)	181 (29.1)	23 (12.3)	
2	320 (39.5)	221 (35.5)	99 (52.9)	
3	286 (35.3)	221 (35.5)	65 (34.8)	

Primary cancer				<0.001
Colon	468 (57.8)	332 (53.3)	136 (72.7)	
Rectum	342 (42.2)	291 (46.7)	51 (27.3)	
Adjuvant treatment				0.667
No	375 (46.3)	291 (46.7)	84 (44.9)	
Yes	435 (53.7)	332 (53.3)	103 (55.1)	
Systemic Inflammation				
NLR				<0.001
<3	451 (55.7)	376 (60.4)	75 (40.1)	
3-5	236 (29.1)	176 (28.3)	60 (32.1)	
>5	123 (15.2)	71 (11.4)	52 (27.8)	
Body composition				
Subcutaneous adiposity (Ebadi threshold) [38]				0.669
No	122 (15.1)	92 (14.8)	30 (16)	
Yes	688 (84.9)	531 (85.2)	157 (84)	
Visceral obesity (Doyle threshold) [39]				0.915
No	171 (21.1)	131 (21)	40 (21.4)	
Yes	639 (78.9)	492 (79)	147 (78.6)	
Low SMI (Martin threshold) [40]				<0.001
No	434 (53.5)	355 (57)	78 (41.7)	
Yes	377 (46.5)	268 (43)	109 (58.3)	
Low SMD (Martin threshold) [40]				0.003

No	282 (34.8)	234 (37.6)	48 (25.7)	
Yes	528 (65.2)	389 (62.4)	139 (74.3)	
Clinical outcomes				
Any complications				0.030
No	501 (62)	398 (64)	103 (55.1)	
Yes	309 (38)	225 (36)	84 (44.9)	
Infective complication				0.187
No	610 (75.3)	476 (76.4)	134 (71.7)	
Yes	200 (24.7)	147 (23.6)	53 (28.3)	
Clavien-Dindo grade				0.058
0	501 (61.9)	398 (63.9)	103 (55.1)	
1-2	240 (29.6)	174 (27.9)	66 (35.3)	
3-5	69 (8.5)	51 (8.2)	18 (9.6)	
Length of hospital stay				<0.001
≤7 d	394 (48.6)	324 (52)	70 (37.4)	
>7 d	416 (51.4)	299 (48)	117 (62.6)	
Survival				0.048
3 yr. survival % (SE)	90% (1)	91% (1)	87% (3)	

Table 3.2.2: The relationship between clinico-pathological characteristics, systemic inflammation, body composition and clinical outcomes in patients with primary operable CRC at medium to high risk of malnutrition (MUST 1-≥2)

	Total n=174	Medium to high nutrition risk MUST 1- ≥2 with mGPS=0 n=99 (56.9%)	Medium to high nutrition risk MUST 1- ≥2 with mGPS=1/2 n=75 (43.1%)	p-value
Clinico-pathological				
Age, y				0.676
<65	44 (25.3)	24 (24.2)	20 (26.7)	
65-74	53 (30.5)	30 (30.3)	23 (30.7)	
>74	77 (44.3)	45 (45.5)	32 (42.7)	
Sex				0.155
Male	82 (47.1)	42 (42.4)	40 (53.3)	
Female	92 (52.9)	57 (57.6)	35 (46.7)	
ASA				0.024
I	26 (14.9)	22 (22.2)	4 (5.3)	
II	76 (43.7)	40 (40.4)	36 (48)	
III	60 (34.5)	31 (31.3)	29 (38.7)	
IV	12 (6.9)	6 (6.1)	6 (8)	
Presentation				0.248
Elective	152 (87.4)	89 (89.9)	63 (84)	
Emergency	22 (12.6)	10 (10.1)	12 (16)	
TNM				0.075
1	31 (17.8)	26 (26.3)	5 (6.7)	
2	78 (44.8)	36 (36.4)	42 (56)	
3	65 (37.4)	37 (37.4)	28 (37.3)	

Primary cancer				0.002
Colon	120 (69)	59 (59.6)	61 (81.3)	
Rectum	54 (31)	40 (40.4)	14 (18.7)	
Adjuvant treatment				0.102
No	89 (51.1)	56 (56.6)	33 (44)	
Yes	85 (48.9)	43 (43.4)	42 (56)	
Systemic Inflammation				
NLR				0.006
<3	64 (36.8)	45 (45.5)	19 (25.3)	
3-5	67 (38.5)	35 (35.4)	32 (42.7)	
>5	43 (24.7)	19 (19.2)	24 (32)	
Body composition				
Subcutaneous adiposity (Ebadi threshold) [38]				0.473
No	75 (43.1)	45 (45.5)	30 (40)	
Yes	99 (56.9)	54 (54.5)	45 (60)	
Visceral obesity (Doyle threshold) [39]				0.300
No	96 (55.2)	58 (58.6)	38 (50.7)	
Yes	78 (44.8)	41 (41.4)	37 (49.3)	
Low SMI (Martin threshold) [40]				0.052
No	58 (33.3)	39 (39.4)	19 (25.3)	
Yes	116 (66.7)	60 (60.6)	56 (74.7)	
Low SMD (Martin threshold) [40]				0.036
No	44 (25.3)	31 (31.3)	13 (17.3)	

Yes	130 (74.7)	68 (68.7)	62 (82.7)	
Postoperative outcome				
Any complications				0.358
No	102 (58.6)	61 (61.6)	41 (54.7)	
Yes	72 (41.4)	38 (38.4)	34 (45.3)	
Infective complication				0.003
No	127 (73)	81 (81.8)	46 (61.3)	
Yes	47 (27)	18 (18.2)	29 (38.7)	
Clavien-Dindo grade				0.515
0	102 (58.6)	61 (61.6)	41 (54.7)	
1-2	49 (28.2)	25 (25.3)	24 (32)	
3-5	23 (13.2)	13 (13.1)	10 (13.3)	
Length of hospital stay				0.038
≤7 d	54 (31)	37 (37.4)	17 (22.7)	
>7 d	120 (69)	62 (62.6)	58 (77.3)	
Survival				0.003
3 yr. survival % (SE)	67 (4)	73 (5)	58 (6)	

Table 3.3a: The relationship between clinico-pathological characteristics, systemic inflammation, body composition and any post-operative complications patients with primary operable CRC, at low risk MUST (MUST=0)

	Univariate analysis		Multivariate analysis	
Variables	OR (95%CI)	p-value	OR (95%CI)	p-value
Clinico-pathological				
Age (<65/65-74/>74)	1.27 (1.05-1.52)	0.014	1.22 (1.02-1.48)	0.034
Sex (Male/Female)	1.33 (1.00-1.78)	0.052	1.31 (0.98-1.74)	0.073
ASA (I-IV)	1.26 (1.05-1.52)	0.014	1.22 (1.01-1.47)	0.035
TNM stage (I-III)	1.08 (0.90-1.30)	0.408	-	-
Systemic inflammation				
mGPS (0/1/2)	1.28 (1.04-1.57)	0.018	1.25 (1.01-1.54)	0.037
NLR (<3/3-5/>5)	1.18 (0.98-1.43)	0.083		0.303
Body Composition				
Subcutaneous adiposity (Ebadi threshold) [38]	1.15 (0.77-1.72)	0.493	-	-
Visceral adiposity (Doyle threshold) [39]	1.14 (0.80-1.61)	0.476	-	-
Low SMI (Martin threshold) [40]	1.10 (0.83-1.47)	0.500	-	-
Low SMD (Martin threshold) [40]	1.08 (0.80-1.45)	0.624	-	-

Binary logistic regression, variables with p<0.1 on univariate analysis were entered into backward conditional multi variate analysis. P-value <0.05 was considered significant. ASA, American Society of Anaesthesiologists; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil lymphocyte ratio; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; TNM, tumor, node, metastasis.

Table 3.3b: The relationship between clinico-pathological characteristics, systemic inflammation, body composition and post-operative complications in patients with primary operable CRC, at medium to high nutrition risk (MUST=1-≥2)

	Univariate analysis		Multivariate analysis	
Variables	OR (95%CI)	p-value	OR (95%CI)	p-value
Clinico-pathological				
Age (<65/65-74/>74)	0.70 (0.46-1.07)	0.098	-	0.114
Sex (Male/Female)	2.03 (1.05-3.99)	0.040	2.03 (1.04-3.99)	0.039
ASA (I-IV)	1.31 (0.88-1.96)	0.189	-	-
TNM stage (I-III)	0.93 (0.59-1.49)	0.771	-	-
Systemic inflammation				
mGPS (0/1/2)	1.26 (0.86-1.86)	0.230	-	-
NLR (<3/3-5/>5)	1.22 (0.79-1.89)	0.366	-	-
Body Composition				
Subcutaneous adiposity (Ebadi threshold) [38]	0.85 (0.43-1.66)	0.630	-	-
Visceral adiposity (Doyle threshold) [39]	0.80 (0.41-1.57)	0.524	-	-
Low SMI (Martin threshold) [40]	0.71 (0.36-1.41)	0.323	-	-
Low SMD (Martin threshold) [40]	1.23 (0.57-2.66)	0.597	-	-

Binary logistic regression, variables with p<0.1 on univariate analysis were entered into backward conditional multi variate analysis. P-value <0.05 was considered significant. ASA, American Society of Anaesthesiologists; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil lymphocyte ratio; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; TNM, tumor, node, metastasis.

Table 3.4a: The relationship between clinico-pathological characteristics, systemic inflammation, body composition and length of hospital stay (≤7 or >7 days) in patients with primary operable CRC, at low nutrition risk (MUST=0)

	Univariate analysis		Multivariate analysis	
Variables	OR (95%CI)	p-value	OR (95%CI)	p-value
Clinico-pathological				
Age (<65/65-74/>74)	1.36 (1.14-1.63)	0.001	1.21 (1.00-1.47)	0.055
Sex (Male/Female)	1.12 (0.85-1.48)	0.416	-	-
ASA (I-IV)	1.42 (1.19-1.71)	<0.001	1.28 (1.05-1.56)	0.014
TNM stage (I-III)	1.24 (1.04-1.49)	0.019	1.19 (0.98-1.43)	0.074
Systemic inflammation				
mGPS (0/1/2)	1.54 (1.24-1.91)	<0.001	1.30 (1.04-1.63)	0.022
NLR (<3/3-5/>5)	1.78 (1.47-2.17)	<0.001	1.65 (1.35-2.03)	<0.001
Body Composition				
Subcutaneous adiposity (Ebadi threshold) [38]	1.03 (0.70-1.50)	0.897	-	-
Visceral adiposity (Doyle threshold) [39]	1.15 (0.82-1.62)	0.406	-	-
Low SMI (Martin threshold) [40]	1.44 (1.09-1.90)	0.010	-	0.200
Low SMD (Martin threshold) [40]	1.32 (0.99-1.77)	0.059	-	0.965

Binary logistic regression, variables with p<0.1 on univariate analysis were entered into backward conditional multi variate analysis. P-value <0.05 was considered significant. ASA, American Society of Anaesthesiologists; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil lymphocyte ratio; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; TNM, tumor, node, metastasis.

Table 3.4b: The relationship between clinico-pathological characteristics, systemic inflammation, body composition and length of hospital stay (≤7 or >7 days) in patients with primary operable CRC, at medium to high nutrition risk (MUST=1-≥2)

	Univariate analysis		Multivariate analysis	
Variables	OR (95%CI)	p-value	OR (95%CI)	p-value
Clinico-pathological				
Age (<65/65-74/>74)	0.82 (0.55-1.23)	0.338	-	-
Sex (Male/Female)	1.61 (0.84-3.10)	0.154	-	-
ASA (I-IV)	1.66 (1.09-2.52)	0.017	1.66 (1.09-2.52)	0.017
TNM stage (I-III)	0.98 (0.62-1.53)	0.918	-	-
Systemic inflammation				
mGPS (0/1/2)	1.34 (0.97-1.99)	0.075	-	0.187
NLR (<3/3-5/>5)	1.41 (0.92-2.15)	0.115	-	-
Body Composition				
Subcutaneous adiposity (Ebadi threshold) [38]	1.87 (0.98-3.57)	0.060	-	0.134
Visceral adiposity (Doyle threshold) [39]	1.59 (0.82-3.07)	0.167	-	-
Low SMI (Martin threshold) [40]	1.00 (0.51-1.98)	1.000	-	-
Low SMD (Martin threshold) [40]	1.21 (0.58-2.50)	0.612	-	-

Binary logistic regression, variables with p<0.1 on univariate analysis were entered into backward conditional multi variate analysis. P-value <0.05 was considered significant. ASA, American Society of Anaesthesiologists; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil lymphocyte ratio; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; TNM, tumor, node, metastasis.

Table 3.5a: The relationship between clinico-pathological characteristics, systemic inflammation, body composition and overall survival in patients with primary operable CRC, at low nutrition risk (MUST=0)

	Univariate analysis		Multivariate analysis	
Variables	HR (95%CI)	p-value	HR (95%CI)	p-value
Clinico-pathological				
Age (<65/65-74/>74)	1.59 (1.27-1.99)	<0.001	1.41 (1.21-1.79)	0.004
Sex (Male/Female)	1.52 (1.06-2.18)	0.021	1.49 (1.04-2.15)	0.031
ASA (I-IV)	1.67 (1.33-2.09)	<0.001	1.44 (1.13-1.83)	0.003
TNM stage (I-III)	1.80 (1.41-2.29)	<0.001	1.80 (1.40-2.31)	<0.001
Systemic inflammation				
mGPS (0/1/2)	1.43 (1.15-1.79)	0.003	1.29 (1.03-1.62)	0.026
NLR (<3/3-5/>5)	1.30 (1.04-1.62)	0.023		0.275
Body Composition				
Subcutaneous adiposity (Ebadi threshold) [38]	0.85 (0.54-1.35)	0.505	-	-
Visceral adiposity (Doyle threshold) [39]	1.05 (0.69-1.60)	0.821	-	-
Low SMI (Martin threshold) [40]	1.36 (0.97-1.92)	0.076		0.859
Low SMD (Martin threshold) [40]	1.69 (1.15-2.48)	0.005		0.235

Cox regression analysis, variables with p<0.1 on univariate analysis were entered into backward conditional multi variate analysis. P-value <0.05 was considered significant. ASA, American Society of Anaesthesiologists; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil lymphocyte ratio; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; TNM, tumor, node, metastasis.

Table 3.5b: The relationship between clinicopathological characteristics, systemic inflammation, body composition and overall survival in patients with primary operable CRC, at medium to high nutrition risk (MUST=1-≥2).

	Univariate analysis		Multivariate analysis	
Variables	HR (95%CI)	p-value	HR (95%CI)	p-value
Clinico-pathological				
Age (<65/65-74/>74)	1.26 (0.95-1.67)	0.105	-	-
Sex (Male/Female)	1.34 (0.87-2.06)	0.178	-	-
ASA (I-IV)	1.62 (1.24-2.12)	<0.001	1.60 (1.22-2.11)	<0.001
TNM stage (I-III)	1.66 (1.21-2.28)	<0.002	1.67 (1.20-2.31)	0.002
Systemic inflammation				
mGPS (0/1/2)	1.37 (1.09-1.70)	0.006	1.29 (1.03-1.62)	0.026
NLR (<3/3-5/>5)	1.29 (0.99-1.69)	0.057	-	0.238
Body Composition				
Subcutaneous adiposity (Ebadi threshold) [12]	0.96 (0.63-1.48)	0.864	-	-
Visceral adiposity (Doyle threshold) [11]	0.94 (0.62-1.44)	0.794	-	-
Low SMI (Martin threshold) [10]	1.37 (0.86-2.19)	0.180	-	-
Low SMD (Martin threshold) [10]	1.62 (0.94-2.79)	0.080	-	0.381

Cox regression analysis, variables with p<0.1 on univariate analysis were entered into backward conditional multi variate analysis. P-value <0.05 was considered significant. ASA, American Society of Anaesthesiologists; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil lymphocyte ratio; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; TNM, tumor, node, metastasis.

3.5 Figures and Legends

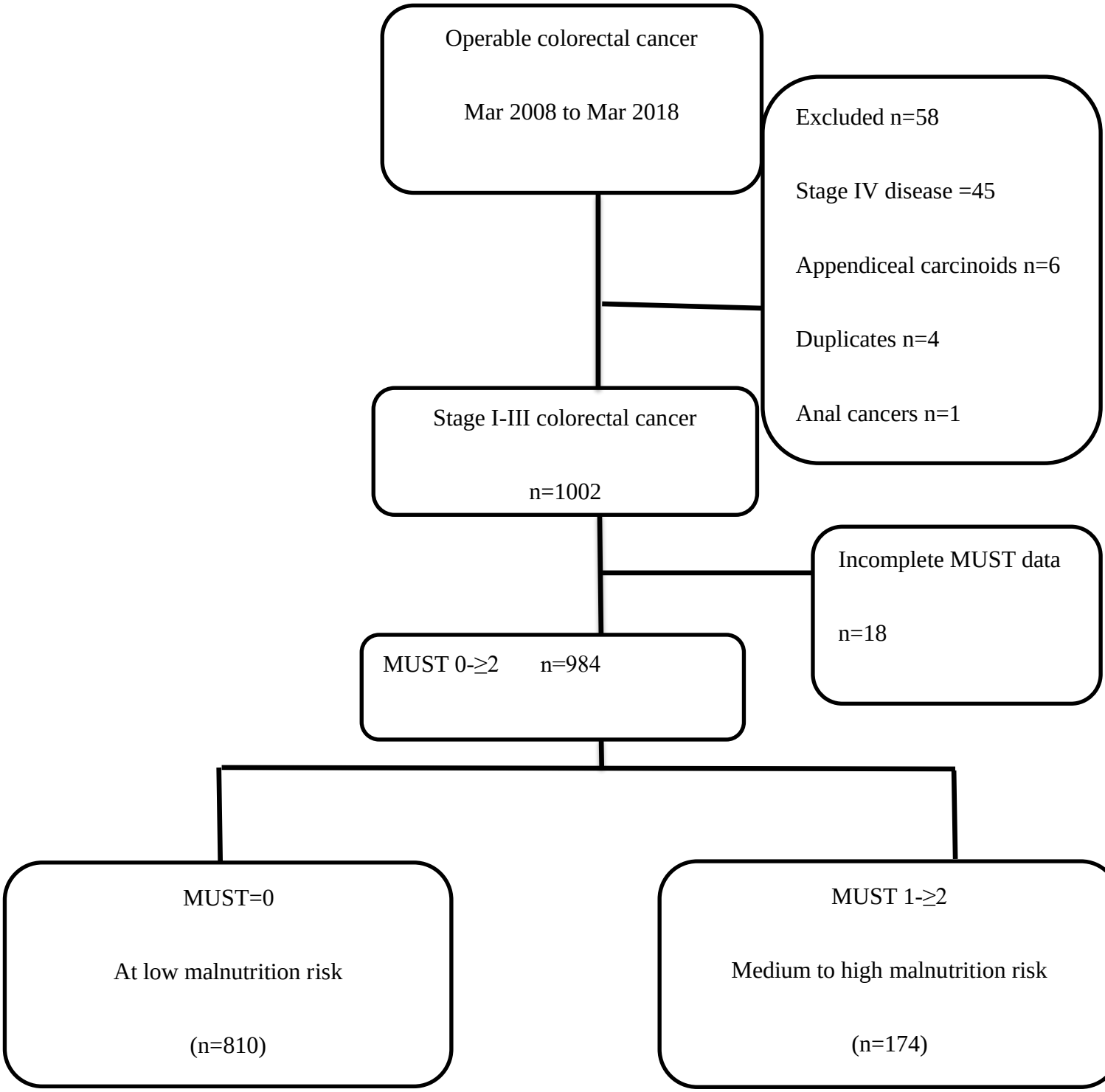


Figure 3.1. Flow diagram of included patients with operable colorectal cancer.

4 THE RELATIONSHIP BETWEEN MUST, ECOG-PS, mGPS and CT DERIVED BODY COMPOSITION ANALYSIS IN PATIENTS WITH ADVANCED LUNG CANCER

4.1 Introduction

Although the treatment options for patients with advanced lung cancer have increased over the last decade, prognosis remains relatively poor compared with other advanced cancers, in part due to the presence of cachexia. The definition of cancer cachexia has been the subject of ongoing discussion and there have been considerable efforts to rationalize its definition. The starting point for much of this work was an international consensus in 2011 (Fearon, Strasser et al. 2011) and cancer cachexia was defined as "a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment." In the intervening years, the importance of systemic inflammatory responses in the progressive nutritional and functional decline of patients with cancer has been increasingly recognized and is now integral to the definition and treatment of cancer cachexia (Laird, Kaasa et al. 2013, Diakos, Charles et al. 2014, Arends, Baracos et al. 2017, Simmons, McMillan et al. 2017, Baracos 2018). This more nuanced definition reflects the evolution of criteria in the definition of malnutrition in which cancer cachexia is considered as part of disease related malnutrition with inflammation (Cederholm, Barazzoni et al. 2017, Cederholm, Jensen et al. 2019).

The Global Leadership Initiative on Malnutrition (Cederholm, Jensen et al. 2019) has proposed that malnutrition be defined by using at least one phenotypic criteria (weight loss, low BMI or low muscle mass) and at least one aetiologic criteria (low food intake or assimilation and inflammation or disease burden). With reference to such work there are established clinical tools that include such phenotypic and aetiologic criteria. For example,

the malnutrition universal screening tool (MUST) includes weight loss, BMI and nutritional intake (Figure 1.1), ECOG-performance status includes muscle mass and function and the modified Glasgow Prognostic Score (mGPS) includes systemic inflammation. More recently, CT derived body composition analyses have enabled accurate determination of muscle mass (Daly, Prado et al. 2018). To date, data on the interaction between these tools and their comparative use to predict clinical outcome in patients with cancer has been limited. Recently, in patients with operable colorectal cancer, approximately 20% of patients were considered at medium or high nutritional risk by MUST and of these approximately 40% also had evidence of systemic inflammation (CRP>10 mg/L) and both had independent prognostic value (Almasaudi, McSorley et al. 2019). Therefore, the aim of the present study was to examine the relationship between MUST, ECOG, SIR and body composition in patients with advanced lung cancer.

4.2 Patients and Methods

Clinicopathological characteristics including MUST, ECOG-PS, mGPS and body composition data were collected prior to radiotherapy into a prospectively maintained database of patients with advanced lung cancer undergoing radiotherapy at The Beatson West of Scotland Cancer Institute from Jan 2009 to Feb 2017 (n=643). This included patients with available pre-treatment MUST, systemic inflammatory scores and cross-sectional CT with available L3 image. Only patients with TNM stage III/IV disease were included in the analysis and 19 patients with TNM stage II were excluded. This study was approved by Health Research Authority Ethics Committee (17/NW/0190) of Greater Glasgow and Clyde NHS Health Board.

Malnutrition Universal Screening Tool (MUST) is included as a part of admission checklist prior to commencing oncology treatment and is performed by admitting nursing staff. MUST is a bed side assessment of patient weight loss, BMI and nutritional intake as shown in Figure 1.1 (Elia 2003). Using MUST, patients were classified into low (MUST=0, n=189), medium (MUST=1, n=341) and high malnutrition risk (MUST≥2, n=113) as shown in Figure 4.6.

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.

Plasma 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 ≤ 10 mg/L = 0, CRP>10mg/L=1, CRP>10mg/L and albumin<35g/L=2.

Body composition was assessed from the pre-radiotherapy CT scans using image J software (https://imagej.nih.gov/ij/). The CT scan L3 DICOM image was analysed for total fat area (TFA), visceral fat area (VFA), subcutaneous fat area (SFA), skeletal muscle area (SMA) and skeletal muscle density (SMD). Measurements were performed by two individuals (TA and RD) blinded to the patients' clinical data on a sample of 40 patients to reduce the risk of observer bias and ensure accuracy. The interrater reliability was assessed using inter-class correlation coefficients (ICCs). The ICCC values were as follows; TFA and VFA = 0.999; SMA = 0.996 and SMD = 0.993. The cross-sectional area of fat and muscles was normalized for height (m^2) to calculate fat and skeletal muscle indices. The thresholds used for subcutaneous adiposity (Ebadi, Martin et al. 2017), visceral obesity (Doyle, Bennett et al. 2013), low SMI and low SMD (Martin, Birdsell et al. 2013) were shown in Table 4.1.

The relationship between the MUST score (Figure 4.2) and its relationship with clinicopathological factors including ECOG-PS, mGPS and body composition analysis (in particular SMI) and survival was examined using univariate and multivariate analyses. χ^2 test was used for analysis of categorical variables.

Overall survival was calculated in months and defined as the time from study entry until death or censored if alive at follow-up date (1st October 2019). Median duration of follow up was 10 months. Cox proportional hazard model was used to calculate HR and 95% CI for overall survival. Significant variables identified on univariate analysis ($p<0.1$) were entered into multivariate analysis in backward conditional manner and adjustment was performed for patient age and sex. Survival curves were obtained using Kaplan Meier analysis and 3-year survival rates were calculated by life table analysis. P-value of <0.05 was considered significant. The statistical analysis was performed using SPSS version 25 (IBM Corporation, 2017, Armonk, NY).

The study has been conducted and adheres to the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines (McShane, Altman et al. 2005).

4.3 Results

All patients included in this study were discussed in multi-disciplinary meeting (MDM) and an informed decision was made by considering tumour and patient characteristics and patient wishes. All patients received radiotherapy. 54% of patients in this cohort also received concurrent systemic chemotherapy. Platinum compounds (cisplatin and carboplatin) being the first line chemotherapeutic agents. 8 (1.2%) patients also received immunotherapy with programmed cell death (PD-1) inhibitors e.g. Nivolumab. Patients with high malnutrition risk received less chemotherapy (see Table 4.2).

Nutritional status was determined using MUST score prior to commencing radiotherapy. 640 (99.5%) patients received radiotherapy to the chest. Careful marking of the patients receiving radiotherapy was carried out prior to treatment to limit toxicity to the surrounding structures. Because of advanced stage of these patients, various other regions of body were also radiated, brain n=31 (4.8%), spinal n=18 (2.8%), bone n=16 (2.5%) and neck n=3 (0.5%). Distant metastases were common. Common regions of metastases were skeletal (109, 17%), liver (83, 13%), adrenal (68, 11%), brain (64, 10%), spine (34, 5%), pancreas (7, 1%) and kidneys (7, 1%). Patients with symptomatic brain metastases (n=16) and those with advanced stage small cell lung cancer (n=15) received cranial radiotherapy.

Only patients receiving radiotherapy as principal mode of treatment were included in the study. However, 12 of these patients (2%) had prior lobectomy and 1 had previous pneumonectomy, these patients developed post-operative recurrence and had advanced lung cancer.

Comorbidities were assessed systematically and were documented using body systems as shown (Table 1.1). These were grouped into 11 point scoring system called as modified frailty index which is validated screening tool in oncological and geriatric population

(Ehlert, Najafian et al. 2016, Al-Khamis, Warner et al. 2019, Shahrokni, Vishnevsky et al. 2019). These comorbidities scores were added and classified into 4 groups (supplementary Table 1.2). Relationship of the MUST and mFI were examined in Table 4.2. Comorbidities were strongly associated with MUST categories and this was independent of ASA class ($p<0.001$).

Of the 643 lung cancer patients studied, the majority of patients were >65 years old (70%), had ASA III (67%), had NSCLC (81%), had TNM stage IV (63%), had ECOG 0-1 (62%), had systemic inflammation (mGPS>0, 74%) and had MUST ≥1 (71%). The majority of patients had subcutaneous adiposity (78%), visceral obesity (76%), had normal SMI (58%) and had low SMD (67%). The majority of patients received radiotherapy with palliative intent (82%). On follow-up 593 died (95% cancer related and 5% of non-cancerous causes).

The relationship between MUST, clinicopathological characteristics and body composition was shown in Table 6.2. A higher MUST was significantly associated with elevated mFI ($p<0.001$), poorer ECOG-PS ($p=0.001$), elevated mGPS ($p<0.001$), less subcutaneous adiposity ($p<0.01$), less visceral obesity ($p<0.01$), low SMI ($p<0.001$) and poorer 12-month survival rate ($p=0.001$).

The relationship between clinicopathological characteristics, body composition and overall survival was shown in Table 4.3. On univariate analysis, higher TNM stage ($p<0.001$), MUST ($p<0.001$), ECOG-PS ($p<0.001$), mGPS ($p<0.001$) and low SMI ($p<0.05$) were significantly associated with poorer overall survival. On multivariate analysis, TNM stage (HR 1.64, 95%CI 1.38-1.94, $p<0.001$), MUST (HR 1.16, 95%CI 1.03-1.31, $p<0.05$), ECOG-PS (HR 1.23, 95%CI 1.10-1.39, $p<0.001$) and mGPS (HR 1.20, 95%CI 1.09-1.33, $p<0.001$) were independently associated with overall survival. The relationship between

MUST, ECOG-PS, mGPS and overall survival was shown in Figures 4.2, 4.3 and 4.4 respectively.

The relationship between TNM stage, MUST, ECOG-PS, mGPS and overall survival in patients with advanced lung cancer (stage III-IV) was shown in Tables 4.4a, 4b, 4c and 4d. In all patients (Table 4a, n=643) on multivariate Cox regression analysis, TNM stage (HR 1.70, 95%CI 1.43-2.01, p<0.001), MUST (HR 1.17, 95%CI 1.04-1.31, p=0.011), ECOG-PS (HR 1.25, 95%CI 1.11-1.40, p<0.001) and mGPS (HR 1.24, 95%CI 1.13-1.37, p<0.001) were independently associated with overall survival.

In patients with MUST=0, the relationship between TNM stage, ECOG-PS, mGPS and overall survival was shown in Table 4b (n=189). On multivariate Cox regression analysis, TNM stage (HR 2.49, 95%CI 1.74-3.58, p<0.001) and ECOG-PS (HR 1.22, 95% CI 0.94-1.57, p=0.013) were independently associated with overall survival.

In patients with MUST=1, the relationship between ECOG-PS, mGPS and overall survival was shown in Table 4c (n=341). On multivariate Cox regression analysis, TNM stage (HR 1.67, 95%CI 1.33-2.09, p<0.001), ECOG-PS (HR 1.17, 95% CI 0.99-1.37, p=0.060) and mGPS (HR 1.25, 95%CI 1.08-1.45, p=0.002) were independently associated with overall survival.

In patients with MUST>2, the relationship between TNM stage, ECOG-PS, mGPS and overall survival was shown in Table 4d (n=113). On multivariate Cox regression analysis, ECOG-PS (HR 1.32, 95% CI 1.02-1.71, p=0.033) and mGPS (HR 1.61, 95%CI 1.24-2.09, p<0.001) were independently associated with overall survival.

Therefore, TNM stage had independent prognostic value in low and medium risk MUST which was maintained after adjustment for age and sex. Tumour characteristics and host phenotype both were important for lung cancer treatment.

The relationship between MUST, ECOG-PS, mGPS and overall survival in patients with TNM stage IV disease was examined (n=403). In these patients, MUST and ECOG-PS were not independently associated with overall survival (p=0.343 and p=0.057), while mGPS had independent prognostic value (HR 1.26, 95%CI 1.10-1.43, p=0.003).

4.4 Discussion

The results of the present study show that, in patients with advanced lung cancer, nutritional risk (MUST) was associated with poor performance status (ECOG-PS), systemic inflammation and lower fat (SFI and VFA) and muscle mass (SMI). Moreover, together with performance status and systemic inflammation, MUST had independent prognostic value whereas body composition measures did not. Taken together, the present study shows, for the first time, the optimal combination of routine clinical phenotypic and aetiologic criteria of malnutrition to predict survival in patients with advanced lung cancer.

Antoun and coworkers (2019) reported that, in 531 patients with non-small cell lung cancer, higher cachexia stage as defined by the original criteria of Fearon and coworkers (Fearon, Strasser et al. 2011, Martin, Senesse et al. 2015) was associated with poorer functional items of quality of life and activity levels but not low SMI. In this study, approximately 70% of patients were defined at nutritional risk and none of these parameters was examined in relation to survival. (Antoun, Morel et al. 2019). Also, Daly and coworkers (2020) in 1027 patients with advanced cancer and using Fearon criteria to define BMI adjusted weight loss grading system (Martin, Senesse et al. 2015) reported that higher WLGS was associated with poorer functional and symptom scales of quality of life questionnaires. Furthermore, higher WLGS (grade 4) was associated with poorer overall survival. In this study approximately 40% of patients were defined at nutritional risk (Daly, Dolan et al. 2020). Recently, Dolan and coworkers reported that, in 730 patients with advanced cancer, when WLGS was directly compared with ECOG-PS and mGPS, all 3 were independently associated with overall survival. In this study, 40 % of patients were defined at nutritional risk. In those patients not at nutritional risk (WLGS 0/1), ECOG-PS and mGPS retained prognostic value (Dolan, Daly et al. 2019) In the present study, using MUST, approximately 70% of patients were considered at nutritional risk and of these

approximately 80% also had evidence of systemic inflammation (CRP>10 mg/L) and both had independent prognostic value. Therefore, given the present and these previous results MUST and WLGS are useful prognostic adjuncts to the ECOG-PS/ mGPS framework. It remains to be determined whether existing measures of nutritional risk such as MUST or new measures such as WLGS have most clinical utility in patients with advanced cancer.

In Europe, Malnutrition Universal Screening Tool (MUST) developed by task force established by BAPEN (Elia 2003) is commonly used and medical and nursing staff are familiar with its use and clinical applicability. MUST reliably assesses host factors (BMI), weight loss and food intake and has been shown to provide a validated scoring system to reliably assess nutritional status (Boleo-Tome, Monteiro-Grillo et al. 2012). Therefore, since MUST is already part of routine clinical assessment, WLGS would have to be shown to be superior to MUST to enter routine clinical practice. Similarly, globally where other nutritional risk screening tools are used in clinical practice (Chen, Zhang et al. 2020), WLGS would have to show superior prognostic value.

It has now been established that the systemic inflammatory response has prognostic value in localised and advanced cancer patients. In the present study the mGPS was used to assess the systemic inflammatory response as it is routinely clinically available, has standardised thresholds and has been extensively validated (Dupre and Malik 2018).

The results of the present study clearly support the GLIM recommendations on the assessment of disease related malnutrition and multimodal approach to the treatment of cancer cachexia such as the MENAC trials (Solheim, Laird et al. 2018). Moreover, given the simplicity of MUST, ECOG-PS and mGPS assessments, this framework should be applied to existing advanced cancer datasets and clinical trials to identify important patient subgroups amenable to targeted treatment.

In the present study validated prognostic tools were compared to examine whether they had complementary value in patients with advanced lung cancer and the combination of MUST, ECOG-PS and mGPS provided a routine clinically available assessment that is compatible with GLIM guidelines and predicts overall survival. Indeed, some the components of MUST and the mGPS are captured in the new GLIM criteria. These include the phenotypic criteria such as weight loss and low BMI and etiologic criteria such as compromised dietary intake and inflammation. Therefore, in the present analysis it would appear that some of the GLIM criteria do indeed have complementary prognostic value. However, in contrast to the validated prognostic tools used in the present study, it remains to be established how the GLIM criteria are to be measured and combined for optimal prognostic value. Furthermore, the GLIM criteria do not include a measure of physical activity and performance status which were shown to have independent prognostic value in the present study.

A number of studies have shown that approximately 50% of patients with terminal lung cancer did not have a discussion of hospice and end of life care, two months before death (Huskamp, Keating et al. 2009). By taking into consideration objective tumour and host characteristics it may be possible to have such discussions on an evidence based basis and therefore better palliation of symptoms and end of life care.

The present study has some limitations. This is a retrospective cohort study and has limitations seen with this study design. However, data were collected using a prospective proforma and thus the study had well documented clinicopathological data reducing the risk of bias. Further prospective and longitudinal studies on examining relationship between MUST, ECOG-PS, SIR and body composition in patients with advanced cancer are warranted.

In summary, there was a strong association between MUST, ECOG-PS, mGPS and low SMI in patients with advanced lung cancer. However, only MUST, ECOG-PS and mGPS were independently associated with overall survival. The combination of MUST, ECOG-PS and mGPS provides a routine clinically available assessment that is compatible with GLIM guidelines and predicts overall survival.

4.5 Tables and Footnotes

Table 4.1: Body composition thresholds used in patients with advanced lung cancer.

CT derived Body Composition Measurement
Subcutaneous Adiposity
Increased Subcutaneous fat index (Ebadi, Martin et al. 2017**)**
Males : SFI >50 cm^2m^2 Females : SFI>42 cm^2m^2
Visceral Obesity
Increased Visceral Obesity (Doyle, Bennett et al. 2013**)**
Males : VFA >160 cm^2 Females : VFA>80 cm^2
Sarcopenia
Low SMI (Martin) (Martin, Birdsell et al. 2013**)**
Males: BMI<25kg/m^2 and SMI<43 cm^2m^2 or BMI≥25kg/m^2 and SMI<53 cm^2m^2 Females: BMI<25kg/m^2 and SMI<41 cm^2m^2 or BMI≥25kg/m^2 and SMI<41 cm^2m^2
Myosteatosis
Low SMD (Martin) (Martin, Birdsell et al. 2013**)**
BMI<25kg/m^2 and SMD<41 HU or BMI>25kg/m^2 and SMD<33HU

Table 4.2: The relationship between MUST, clinicopathological characteristics, CT derived body composition and overall survival in patients with advanced lung cancer (n=643)

Characteristics	Total n=643	MUST=0 n=189 (29%)	MUST=1 n=341 (53%)	MUST- ≥2 n=113 (18%)	p-value
Age, y					0.854
<65	195 (30.3)	57 (30.2)	107 (31.4)	31 (27.4)	
65-74	249 (38.7)	78 (41.3)	119 (34.9)	52 (46.0)	
>74	199 (30.9)	54 (28.6)	115 (33.7)	30 (26.5)	
Sex					0.815
Male	330 (51.3)	94 (49.7)	179 (52.5)	57 (50.4)	
Female	313 (48.7)	95 (50.3)	162 (47.5)	56 (49.6)	
ASA					0.125
II	60 (9.3)	23 (12.2)	26 (7.6)	11 (9.7)	
III	434 (67.5)	127 (67.2)	236 (69.2)	71 (62.8)	
IV	149 (23.2)	39 (20.6)	79 (23.2)	31 (27.4)	
mFI					<0.001
Group I	31 (4.8)	19 (10.1)	10 (2.9)	2 (1.8)	
Group II	122 (19)	50 (26.5)	58 (17)	14 (12.4)	
Group III	237 (36.9)	51 (27)	138 (40.5)	48 (42.5)	
Group IV	253 (39.3)	69 (36.5)	135 (39.6)	49 (43.4)	
Cancer Type					0.386
NSCLC	521 (81)	148 (78.3)	283 (83)	90 (79.6)	
SCLC	122 (19)	41 (21.7)	58 (17)	23 (20.4)	
TNM					0.684
3	240 (37.3)	64 (33.9)	137 (40.2)	39 (34.5)	
4	403 (62.7)	125 (66.1)	204 (59.8)	74 (65.5)	
ECOG					0.001
0-1	402 (62.5)	131 (69.3)	213 (62.5)	58 (51.3)	
2	174 (27.1)	45 (23.8)	92 (27)	37 (32.7)	
3	67 (10.4)	13 (6.9)	36 (10.6)	18 (15.9)	

mGPS					<0.001
0	169 (26.3)	82 (43.4)	65 (19.1)	22 (19.5)	
1	175 (27.2)	51 (27)	104 (30.5)	20 (17.7)	
2	299 (46.5)	56 (29.6)	172 (50.4)	71 (62.8)	
Body composition					
Subcutaneous adiposity (Ebadi threshold)[38]					0.002
No	140 (22.2)	30 (16.9)	73 (21.5)	37 (32.7)	
Yes	490 (77.8)	148 (83.1)	266 (78.5)	76 (67.3)	
Visceral obesity (Doyle threshold)[39]					0.009
No	154 (24.4)	36 (20.2)	79 (23.3)	39 (34.5)	
Yes	476 (75.6)	142 (79.8)	260 (76.7)	74 (65.5)	
Low SMI (Martin threshold)[40]					<0.001
No	374 (58.2)	128 (67.7)	194 (56.9)	52 (46)	
Yes	269 (41.8)	61 (32.3)	147 (43.1)	61 (54)	
Low SMD (Martin threshold)[40]					0.086
No	213 (33.1)	71 (37.6)	110 (32.3)	32 (28.3)	
Yes	430 (66.9)	118 (62.4)	231 (67.7)	81 (71.7)	
Concurrent Chemotherapy					0.009
Yes	344 (53.5)	114 (60.3)	179 (52.5)	51 (45)	
No	299 (46.5)	75 (39.7)	162 (47.5)	62 (55)	
Radiotherapy Intent					0.236
Radical	117 (18.2)	31 (16.4)	70 (20.5)	16 (14.2)	
Palliative	526 (81.8)	158 (83.6)	271 (79.5)	97 (85.8)	
Survival					0.001
12 months survival % (SE)	45 (2)	57 (4)	43 (3)	34 (4)	

Table 4.3: The relationship between clinicopathological characteristics and overall survival in patients with advanced lung cancer: Univariate and multivariate analysis (n=643).

	Univariate analysis		Multivariate analysis	
Variables	HR (95%CI)	p-value	HR (95%CI)	p-value
Clinico-pathological				
Age (<65/65-74/>74)	0.93 (0.84-1.03)	0.147		
Sex (Male/Female)	0.97 (0.83-1.14)	0.710		
ASA (II-IV)	0.96 (0.83-1.11)	0.541		
TNM stage (III-IV)	1.65 (1.40-1.95)	<0.001	1.64 (1.38-1.94)	<0.001
MUST (0/1/≥2)	1.25 (1.11-1.40)	<0.001	1.16 (1.03-1.31)	0.012
ECOG-PS (0-1/2/3)	1.29 (1.15-1.45)	<0.001	1.23 (1.10-1.39)	<0.001
mGPS (0/1/2)	1.28 (1.16-1.41)	<0.001	1.20 (1.09-1.33)	<0.001
Body Composition				
Subcutaneous adiposity (Ebadi threshold)[38]	0.98 (0.81-1.19)	0.856	-	-
Visceral adiposity (Doyle threshold)[39]	0.98 (0.82-1.18)	0.838	-	-
Low SMI (Martin threshold)[40]	1.22 (1.04-1.43)	0.014	1.17 (1.00-1.38)	0.055
Low SMD (Martin threshold)[40]	1.11 (0.94-1.31)	0.217		

Cox regression analysis, variables with p<0.1 on univariate analysis were entered into backward conditional multi variate analysis. P-value <0.05 was considered significant. ASA, American Society of Anaesthesiologists score; TNM, tumor, node, metastasis.; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil lymphocyte ratio; SMI, skeletal muscle index; SMD, skeletal muscle radiodensity

Table 4.4: The relationship between TNM stage, MUST, ECOG-PS, mGPS and overall survival in patients with advanced cancer (n=643)

Characteristics	**Univariate**	**p-value**	**Multivariate**	**p-value**	**Multivariate Adjusted for Age and Sex**	**p-value**
Table 4a MUST 0-	n=643					
TNM (III-IV)	1.74 (1.47- 2.06)	<0.001	1.70 (1.43–2.01)	<0.001	1.70 (1.44-2.02)	<0.001
MUST 0-≥2	1.25 (1.11-1.40)	<0.001	1.17 (1.04-1.31)	0.011	1.17 (1.04-1.32)	0.008
ECOG-PS (0-	1.29 (1.15-1.45)	<0.001	1.25 (1.11-1.40)	<0.001	1.28 (1.14-1.44)	<0.001
mGPS (0/1/2)	1.28 (1.16-1.41)	<0.001	1.24 (1.13-1.37)	<0.001	1.25 (1.13-1.38)	<0.001
Table 4b MUST	**n=189**					
Characteristics	**Univariate**	**p-value**	**Multivariate**	**p-value**	**Multivariate Adjusted**	**p-value**
TNM (III-IV)	2.35 (1.65- 3.35)	<0.001	2.49 (1.74–3.58)	<0.001	2.35 (1.65-3.35)	<0.001
ECOG-PS	1.29 (1.01-1.67)	0.045	1.22 (0.94-1.57)	0.013	1.24 (0.96-1.60)	0.098
mGPS	1.10 (0.92-1.30)	0.294				
Table 4c MUST =1	**n=341**					
Characteristics	**Univariate**	**p-value**	**Multivariate**	**p-value**	**Multivariate Adjusted**	**p-value**
TNM (III-IV)	1.77 (1.42- 2.22)	<0.001	1.67 (1.33- 2.09)	<0.001	1.70 (1.35-2.14)	<0.001
ECOG-PS	1.22 (1.04-1.43)	0.015	1.17 (0.99-1.37)	0.060	1.19 (1.02-1.40)	0.031
mGPS	1.27 (1.10-1.46)	0.001	1.25 (1.08-1.45)	0.002	1.26 (1.09-1.45)	0.002
Table 4d MUST	**n=113**					
Characteristics	**Univariate**	**p-value**	**Multivariate**	**p-value**	**Multivariate Adjusted**	**p-value**
TNM (III-IV)	1.35 (0.91-2.00)	0.140				
ECOG-PS	1.33 (1.03-1.71)	0.029	1.32 (1.02-1.71)	0.033	1.40 (1.08-1.83)	0.012
mGPS	1.62 (1.24-2.10)	<0.001	1.61 (1.24-2.09)	<0.001	1.60 (1.24-2.08)	<0.001

4.6 Figures

Figure 4.1: Flow diagram of included patients with advanced lung cancer.

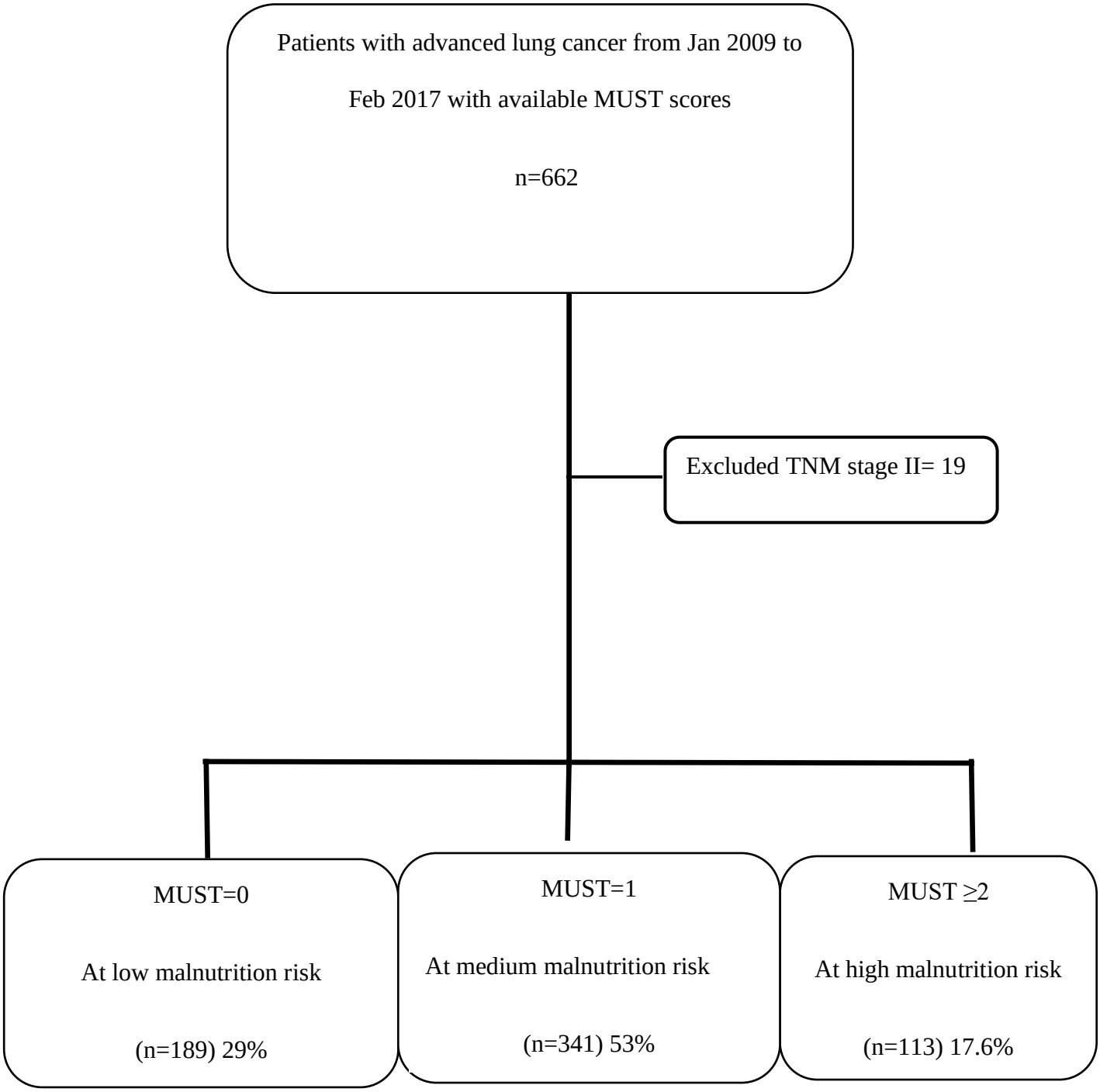


Figure 4.1. Flow diagram of included patients with advanced lung cancer.

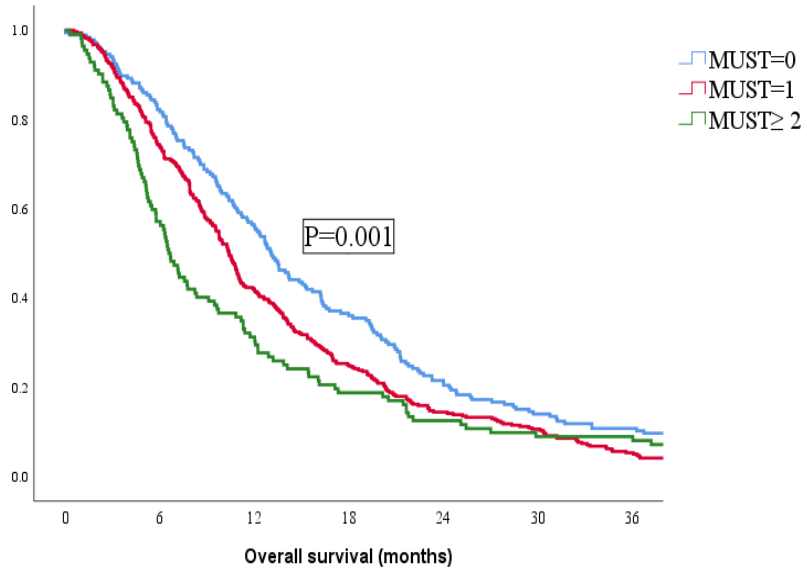


Figure 4.2: The relationship between the MUST and OS in patients with advanced lung cancer.

(Median Survival in months: MUST 0: 13, MUST 1: 10, MUST ≥ 2: 6.0)

MUST=0	186	153	105	68	40	26	20
MUST=1	340	252	143	85	49	36	18
MUST≥2	112	64	35	21	14	10	10

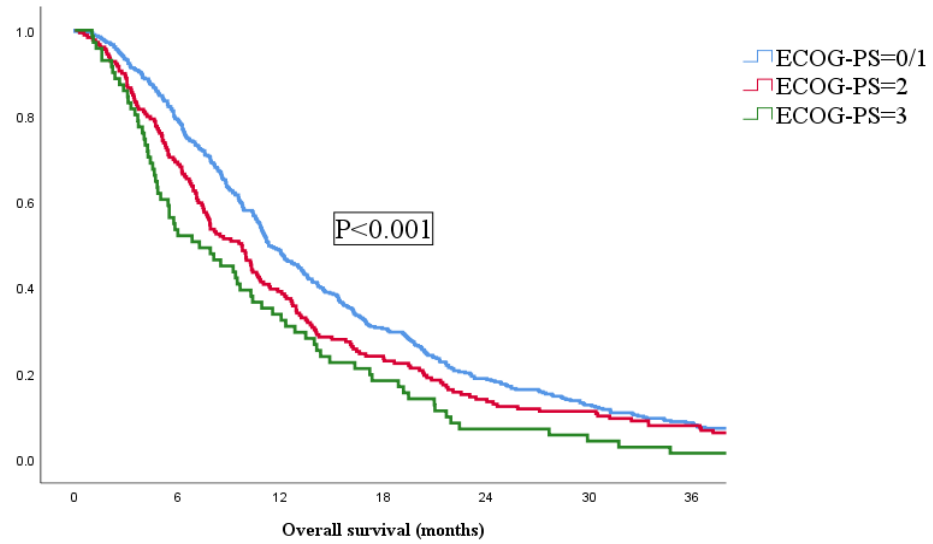


Figure 4.3: The relationship between the ECOG-PS and OS in patients with advanced lung cancer.

(Median Survival in months ECOG-PS 0-1: 11, ECOG-PS 2: 10 ECOG-PS 3: 7)

ECOG=0/1	388	307	189	118	73	49	33
ECOG =2	179	124	70	43	25	20	14
ECOG =3	71	38	24	13	5	3	1

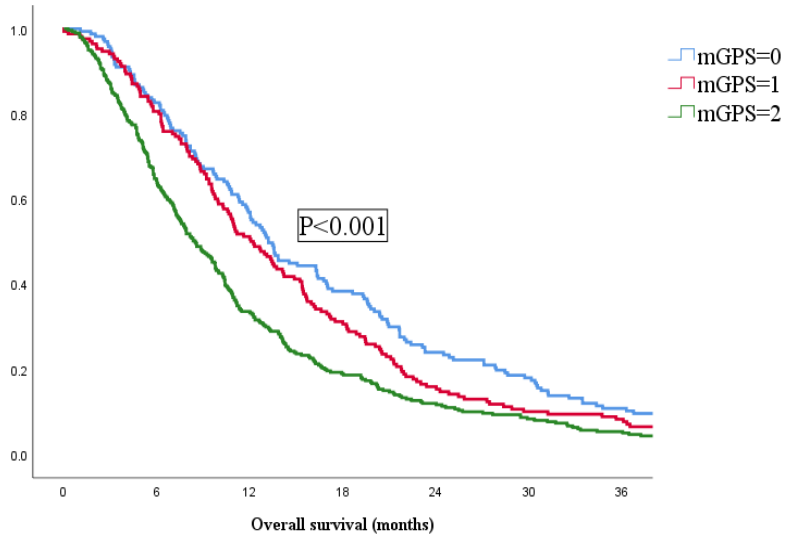


Figure 4.4: The relationship between the mGPS and OS in patients with advanced lung cancer.

(Median Survival in months: mGPS 0: 13, mGPS 1: 12, mGPS 2: 8)

mGPS=0	167	138	95	64	40	30	18
mGPS=1	170	137	87	53	27	17	14
mGPS=2	301	194	101	57	36	25	16

5 THE LONGITUDINAL CHANGES IN CT CT-DERIVED BODY COMPOSITION AND RELATIONSHIP WITH CLINICOPATHOLOGICAL CHARACTERISTICS IN PATIENTS WITH ADVANCED LUNG CANCER

5.1 Introduction

Lung cancer is the second most common cause of death (WHO 2020) and is associated with progressive nutritional and functional decline, resulting in poor response to treatment and poor overall survival (Aapro, Arends et al. 2014) . Therefore, while staging the tumour is an important part of oncological treatment, staging the host has been considered of less importance. CT derived body composition (using the tumour staging CT) has been used for fat and muscle measurements such as subcutaneous fat index (SFI), visceral fat index (VFI), skeletal muscle index (SMI) and skeletal muscle density (SMD) have been reported to be important independent measures to predict complications and survival in patients with cancer (Antoun, Lanoy et al. 2013, Ebadi, Martin et al. 2017, Almasaudi, Dolan et al. 2019, Lee, Lin et al. 2019, Ebadi, Moctezuma-Velazquez et al. 2020)

To date, the large majority of such studies have been cross sectional in nature and therefore to better understand the basis of the relationship between CT-derived body composition and clinical outcomes, longitudinal studies are required. However, few longitudinal CT-derived body composition studies have been reported. The majority have been in patients with operable colorectal cancer where the changes observed were relatively small and significant changes applied to small proportion of patients (<10%) and therefore of limited clinical significance (Brown, Caan et al. 2018, Dolan, Abbass et al. 2021, Beaudart, Drost et al. 2022) . Fewer longitudinal studies have been carried out in patients with advanced lung cancer where changes in body composition may be of greater clinical significance. Therefore, the aim of the study was to examine the relationship between malnutrition,

systemic inflammation and body composition in patients with advanced lung cancer undergoing radiotherapy over a 3 month period.

5.2. Patients and Methods

The present retrospective longitudinal study in patients with advanced lung cancer undergoing radiotherapy was taken from prospectively maintained database at West of Scotland Beatson Cancer Institute between January 2009 and February 2017. In total, we identified 662 patients with lung cancer, who received radiotherapy. Of those, 13 patients with stage II disease were excluded since they did not have advanced disease. Of the available 643 patients, 494 patients had available longitudinal CT scans and 149 did not. The 3 months interval reflected the routine CT protocol in these patients. 117 patients received radiotherapy with radical and 526 with palliative intent. This study was approved by the Health Research Authority Ethics Committee (17/NW/0190) of Greater Glasgow and Clyde NHS Health Board.

MUST was calculated by using Malnutrition universal screening tool (Elia 2003) and frailty was calculated using modified frailty index (Al-Khamis, Warner et al. 2019). Eastern Cooperative Oncology Group (ECOG) score was used to predict the performance status of the patients (Oken, Creech et al. 1982). Serum concentration of inflammatory markers were measured at two stages at baseline and at 3 months intervals. The modified Glasgow Prognostic score (mGPS) was calculated from a combination of CRP and albumin (Douglas and McMillan 2014) . Neutrophil lymphocyte ratio (NLR) >3 was considered raised (Malietzis, Giacometti et al. 2014).

Longitudinal 3 months clinicopathological characteristics were available for MUST, ECOG, mGPS and NLR. Body composition data were collected from CT scans performed at baseline and 3 months following radiotherapy treatment.

Body composition

Body composition data were collected for total fat area (TFA), visceral fat area (VFA), subcutaneous fat area (SFA), skeletal muscle area (SMA) and density (SMD) at 3 months interval following radiotherapy. Two researchers (TA & RD) performed body composition analysis on 40 test scans with assessment of interclass correlation coefficient (ICC) of 0.999 for TFA, VFA, 0.996 for SMA and 0.993 for SMD respectively. We used widely accepted thresholds studied in lung cancer patients for subsequent analysis as shown in supplementary Table 1.3.2. Ebadi et al (Ebadi, Martin et al. 2017) for subcutaneous adiposity, Doyle et al, (Doyle, Bennett et al. 2013) for visceral adiposity, Martin et al, (Martin, Birdsell et al. 2013) for muscle area and density were used for subsequent analysis. The clinicopathological characteristics of patients undergoing radiotherapy for advanced lung cancer with (n=494) and without follow up scans at 3 months (n=149) were shown in Table 5.1. The longitudinal changes in CT derived body composition measurements in 494 patients with advanced lung cancer with available baseline and 3/12 longitudinal CT were shown in Table 5.2.

Patients were followed up to death or censor date of 1st March 2020. The median duration of follow up was 10 months with a range of 0-96 months. Cause of death was confirmed from death certificates or discharge letters to GP.

Statistical tests:

Categorical variables were compared using chi square test. Clinicopathological characteristics and body composition measurements were presented as median and range and were compared using paired Wilcoxson signed rank test. This test was used as these variables were measured on two occasions (pre and post DXT). This test converts scores to ranks and compares at time 1 and time 2. Subcutaneous adiposity, visceral adiposity, SMI

and SMD were categorised into two categories using established thresholds. Matched values pre-radiotherapy and post-radiotherapy were compared using McNemar's test. Changes in clinicopathological characteristics and body composition were presented as median and ranges and compared using paired Kruskal – Wallis tests. Multiple linear logistic regression analysis was used to predict changes in SMI by various clinicopathological variables.

The time between date of initial CT and death from any cause was used to define overall survival (OS). Survival data were analysed using univariate Cox regression analysis. SFI, VFA, SMI and SMD were used as continuous variables while MUST, ECOG, mGPS, NLR, high SFI, high VFA, high SMI and high SMD were used as categorical variables and analysed using categorical Cox regression survival analysis (see Table 5.2). Missing data were excluded from analysis on a variable by variable basis. Two tailed p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 21.0. SPSS Inc., Chicago, IL, USA) .

Water fall plot analysis was carried out to access the longitudinal changes in body composition with regards to age, sex, TNM stage, and mGPS over the 3 month period (see Fig 5.2-5.5).

5.3 Results

The relationship between patients with advanced lung cancer with follow up 3 months CT scans available (n=494) and not available (n=149) was shown in Table 5.1. At baseline, patients with no available follow up CT scans were younger ($p<0.01$), had more advanced stage ($p<0.001$), had poor performance status ($p<0.05$) and were more systemically inflamed (NLR $p<0.01$).

Also, patients with no available follow-up scan had less subcutaneous adiposity (SFI $p<0.01$) and visceral obesity (VFA $p<0.001$) but had more sarcopenia (low SMI $p<0.05$). Patients with no available follow-up CT scan were less likely to receive concurrent chemotherapy ($p<0.05$) and more likely to receive radiotherapy with palliative intent only and had poorer 1 year survival with (both $p<0.001$).

In those, 494 patients with follow-up CT scans (Table 5.2), malnutrition increased (MUST $p<0.001$), performance status decreased (ECOG $p<0.001$) and systemic inflammation increased (NLR $p<0.001$, mGPS $p<0.001$). Also, on follow-up, the patients with high subcutaneous and visceral adiposity decreased (SFI and VFA both $p<0.001$) and sarcopenia increased (SMI and SMD both $p<0.001$). Specifically, on follow-up, the patients with high SF1 decreased from n=398 (81%) to n=330 (67%), patients with high VFA decreased from n=391(79%) to n=313 (63%), patients with high SMI decreased from n=298 (60%) to n=l50 (30%) and patients with high SMD decreased from n=158 (32%) to n=95 (19%). The changes in SFI, VFA, SMI and SMD were not significantly associated with overall survival.

Waterfall plot analysis for the changes in body composition according to age < 74 and ≥ 74 y) was shown in Figure 5.2A-H. The percentage change in SF1, VFA, SMI and SMD were similar according to age.

Waterfall plot analysis for the changes in body composition according to sex (male and female) was shown in Figure 5.3A-H. The percentage change in SF1, VFA and SMI were similar according to sex. There was a significant difference in SMD ($p<0.01$).
Waterfall plot analysis for the changes in body composition according to TNM stage was shown in Figure 5.4A-H. The percentage change in VFA, SMI and SMD were similar according to TNM stage III-IV.
Waterfall plot analysis for the changes in body composition according to baseline mGPS (0 and 2) was shown in Figure 5.5A-H. The percentage change in SF1, VFA, SMI and SMD were similar according to mGPS.

Among 494 patients with longitudinal CT scans available, malnutrition increased with MUST ≥ 2 increased from 91 patients (18.4%) to 356 (72.1%) over 3/12 longitudinal post radiotherapy analysis. Also, patients with MUST =0 decreased from n=136 (27.5%) to n=26 (5.3%) in longitudinal analysis with $p<0.001$. Wilcoxson signed rank test revealed a statistically significant increase in MUST score following radiotherapy, $z= -17.31$, $p<0.001$, with a large effect size ($r=0.55$). The median MUST score increased from pre radiotherapy (MUST =1) to post radiotherapy (MUST=2). On Cox regression when taken as categorical variable, post radiotherapy MUST score was associated with worsened overall survival.

Among 494 patients with longitudinal CT scans available, ECOG increased with ECOG=3 increased from 47 patients (9.5%) to 99 (20%) over 3/12 longitudinal post radiotherapy analysis. Also, patients with ECOG 0/1 decreased from n=319 (64.6%) to n=71 (14.6%) in longitudinal analysis with $p<0.001$. Wilcoxson signed rank test revealed a statistically significant increase in ECOG score following radiotherapy, $z= -16.29$, $p<0.001$, with a large effect size ($r=0.52$). The median ECOG score increased from pre radiotherapy

(ECOG =1) to post radiotherapy (ECOG=2). On Cox regression when taken as categorical variable, post radiotherapy ECOG was associated with worsened overall survival.

Among 494 patients with longitudinal CT scans available, mGPS increased with mGPS =2 increased from 222 patients (44.9%) to 388 (79%) over 3/12 longitudinal post radiotherapy analysis. Also, patients with mGPS =0 decreased from n=130 (26.3%) to n=30 (6.1%) in longitudinal analysis with $p<0.001$. Wilcoxson signed rank test revealed a statistically significant increase in mGPS score following radiotherapy, $z= -11.65$, $p<0.001$, with a medium effect size ($r=0.37$). The median mGPS score increased from pre radiotherapy (mGPS =1) to post radiotherapy (mGPS =2). On Cox regression when taken as categorical variable, pre radiotherapy and post radiotherapy elevation in mGPS was associated with worsened overall survival.

Among 494 patients with longitudinal CT scans available, systemic inflammation increased with NLR >5 increased from 162 patients (32.8%) to 387 (78.7%) over 3/12 longitudinal post radiotherapy analysis. Also, patients with NLR<3 decreased from n=181 (36.6%) to n=33 (6.7%) in longitudinal analysis with $p<0.001$. Wilcoxson signed rank test revealed a statistically significant increase in NLR following radiotherapy, $z= -13.71$, $p<0.001$, with a medium effect size ($r=0.44$). The median NLR increased from pre radiotherapy (NLR =1) to post radiotherapy (NLR=2). On Cox regression when taken as categorical variable, post radiotherapy elevation in NLR was associated with worsened overall survival.

Body composition:

Among 494 patients with longitudinal CT scans available, subcutaneous adiposity decreased from median 92.41 cm^2/m^2 to 67.32 cm^2/m^2 over 3/12 longitudinal post radiotherapy analysis. Also, patients with high SFI decreased from n=398 (81%) to n=330 (67%) in longitudinal analysis with $p<0.001$. Wilcoxson signed rank test revealed a

statistically significant reduction in subcutaneous adiposity following radiotherapy, z= -12.80, p<0.001, with a medium effect size (r=0.41). On Cox regression when taken as continuous or categorical variable, no measurement of SFI was associated with improved overall survival.

Among 494 patients with longitudinal CT scans available, visceral obesity decreased from median 223.14 cm^2 to 164.30 cm^2/m^2 over 3/12 longitudinal post radiotherapy analysis. Also, patients with high VFA decreased from n=391 (79%) to n=313 (63%) in longitudinal analysis with p<0.001. Wilcoxson signed rank test revealed a statistically significant reduction in visceral adiposity following radiotherapy, z= -9.91, p<0.001, with a medium effect size (r=0.32). On Cox regression when taken as continuous or categorical variable, no measurement of VFA was associated with improved overall survival.

Among 494 patients with longitudinal CT scans available, skeletal muscle index (SMI) decreased from median 46.11 cm^2/m^2 to 39.39 cm^2/m^2 over 3/12 longitudinal post radiotherapy analysis. Also, patients with high SMI decreased from n=298 (60%) to n=150 (30%) in longitudinal analysis with p<0.001. This shows that the patients with lung cancer continue to lose muscle mass during the course of illness and patients with low SMI doubled in longitudinal analysis. Wilcoxson signed rank test revealed a statistically significant reduction in SMI following radiotherapy, z= -16.65, p<0.001, with a large effect size (r=0.53). On Cox regression when taken as continuous or categorical variable, no measurement of SMI was associated with improved overall survival.

Among 494 patients with longitudinal CT scans available, skeletal muscle density (SMD) decreased from median 32.30 HU to 28.43 HU in post radiotherapy analysis. Also, patients with high SMD decreased from n=158 (32%) to n=95 (19%) in longitudinal analysis with p<0.001. This shows that the patients with lung cancer continue to lose muscle density

during the course of illness. Wilcoxson signed rank test revealed a statistically significant reduction in SMD following radiotherapy,

$z= -8.11$, $p<0.001$, with a small effect size ($r=0.26$). On Cox regression when taken as continuous or categorical variable, no measurement of SMD was associated with improved overall survival.

When multiple linear regression analysis was carried out for the changes in SMI against pre DXT clinicopathological characteristics, including age, sex, ASA, MUST, mFI, TNM stage, ECOG-PS, mGPS and NLR, only age ($r=-0.098$, $p<0.036$) was significantly associated with the changes in SMI (see Table 5.3).

Longitudinal changes in body composition in patients with lung cancer according to sex and their relationship to inflammatory markers in pre and post treatment period was shown in Appendix D.

5.4 Discussion

To our knowledge, this is the first study to evaluate the longitudinal relationship between malnutrition risk, systemic inflammation and body composition in patients with advanced lung cancer. The results of the present longitudinal study show that, over a 3 month period, patients undergoing radiotherapy for advanced lung cancer developed greater nutritional risk, poorer performance status and more systemic inflammation and this was accompanied by a loss of both body fat and skeletal muscle. However, such loss of fat and muscle was not associated with overall survival whereas changes in malnutrition risk, performance status and systemic inflammation were associated with overall survival. Therefore, the loss of body mass should be considered in the context of malnutrition risk, performance status and systemic inflammation. The present study results are in contrast to those, using a similar methodological approach, previously reported in a longitudinal study of patients with primary operable colorectal cancer (Dolan, Abbass et al. 2021). Over a 12 month period, there were small changes in SF1 (+3%), VFA (-1%), SMI (+8%) and SMD (-2%) whereas in the present study, over a 3 month period, there were larger changes in SF1 (-14%), VFA (-16%), SMI (-30%), SMD (-13%). This was despite the present lung cancer cohort having similar baseline SF1, VFA, SMI and SMD. From these objective body composition results, it would appear that the effect of tumour type and stage of disease has a profound effect on body composition. However, although both cohorts had a similar age profile there were large differences in the systemic inflammatory responses between the cohorts. In the colorectal cohort, at baseline, approximately 35% of patients were systemically inflamed (mGPS 25%, NLR 47%) whereas in the present study approximately 70% of patients were systemically inflamed (mGPS 74%, NLR (63%) and increased over the 3 month period. Therefore, it is of interest that, in the present study, such relatively large changes in body composition can occur over a

relatively short period of time and would question the relative importance of tumour type, tumour burden and systemic inflammation in promoting such changes in body composition. Indeed, the GLIM criteria give tumour burden and systemic inflammation as equivalent etiologic factors. The present study results would suggest that systemic inflammatory response is the dominant etiologic factor confirming the hypothesis proposed by McGovern and co-workers (McGovern, Dolan et al. 2021, McGovern, Dolan et al. 2022). In the present study it was of interest that the change in malnutrition risk, performance status and systemic inflammation were independent predictors of survival whereas CT-derived body composition measures were not. These results confirm the results of a large cross sectional study (n>5000) by Martin and co-workers (Martin, Muscaritoli et al. 2021). Of course, patients with advanced lung cancer have additional issues such as pain, fatigue, and depression, which can contribute to nutritional risk. Although the progressive nutritional and functional decline of patients with advanced cancer has until recently been considered multifactorial and as such requires a multimodal treatment. It is compelling that the systemic inflammatory response is associated with many of the issues experienced by patients with advanced cancer (McGovern, Dolan et al. 2022). However, the efficacy of anti-inflammatory treatment in patients with advanced cancer remains to be determined.

These study findings complement recent work by Al-Sawaf et al (Al-Sawaf, Weiss et al. 2023) who examined body composition in early stage lung cancer. They showed that low SFA, VFA and SMI were associated with decreased lung cancer specific survival and overall survival. They highlighted that this was associated with specific inflammatory pathways i.e. (insulin -like growth factor 1, sematophorin-3A). This TRACERx study did not have data on nutritional assessment or routinely available biomarkers (e.g., CRP), so a direct comparison was not possible. Nevertheless, they showed at clinical level what was demonstrated at cellular level. In the TRACERx

cohort, it was also confirmed that in terms of prognostic recovery, body composition may be less important in the face of other factors.

The limitations of the present study include its retrospective nature and those only patients with an electronically available CT scan were included in the analysis. Moreover, not all patients had follow-up CT scans at 3 months and those patients who did not have a follow-up CT scan were older, had TNM stage 4 disease, had poorer performance status, had a higher NLR, had less subcutaneous and visceral obesity, had a lower SMI and had a higher mortality. However, the study population was relatively large, most patients had follow-up scans and were well-documented in terms of clinicopathological characteristics, body composition. and measures of the systemic inflammatory response.

Conclusions

The present study shows that, using CT body composition analysis, there was a significant loss of fat and muscle in patients with advanced lung cancer. However, such loss of body mass was not associated with overall survival whereas changes in malnutrition risk, performance status and systemic inflammation were associated with overall survival. Therefore, the loss of body mass should be considered in the context of malnutrition risk, performance status and systemic inflammation.

5.5 Tables and Footnotes

Table 5.1: The clinicopathological characteristics of patients undergoing radiotherapy for advanced lung cancer with and without follow up scan at 3 months

Characteristics	Follow up scan available n= 494	Follow up scan not available n=149	p-value
Age, y			<0.004
<65	141 (28.5)	54 (36.2)	
65-74	185 (37.4)	64 (43)	
>74	168 (34)	31 (20.8)	
Sex			
Female	240 (48.6)	73 (49)	0.930
Male	254 (51.4)	76 (51)	
ASA			0.460
II	54 (10.9)	6 (4)	
III	322 (65.2)	112 (75.2)	
IV	118 (23.9)	31 (20.8)	
***MUST**			0.064
0	136 (27.5)	53 (35.6)	
1	267 (54)	74 (49.7)	

≥2	91 (18.4)	22 (14.8)	
mFI			0.004
Group I	18 (3.6)	13 (8.7)	
Group II	88 (17.8)	34 (22.8)	
Group III	184 (37.2)	53 (35.6)	
Group IV	204 (41.3)	49 (32.9)	
Cancer Type			0.949
NSCLC	400 (81)	121 (81.2)	
SCLC	94 (19)	28 (18.8)	
TNM			<0.001
3	215 (43.5)	25 (16.8)	
4	279 (56.5)	124 (83.2)	
***ECOG**			0.044
0-1	319 (64.6)	83 (55.7)	
2	128 (25.9)	46 (30.9)	
3	47 (9.5)	20 (13.4)	
***mGPS**			0.375

0	130 (26.3)	39 (26.2)	
1	142 (28.7)	33 (22.1)	
2	222 (44.9)	77 (51.7)	
***NLR**			0.007
<3	181 (36.6)	33 (28)	
3-5	151 (30.6)	29 (24.6)	
>5	162 (32.8)	56 (47.5)	
Body composition			
***Subcutaneous adiposity (Ebadi threshold)**			0.001
No	96 (19.4)	44 (32.4)	
Yes	398 (80.6)	92 (67.6)	
***Visceral obesity (Doyle threshold)**			<0.001
No	103 (20.9)	51 (37.5)	
Yes	391 (79.1)	85 (62.5)	
***Low SMI (Martin threshold)**			0.043
No	298 (60.3)	76 (51)	
Yes	196 (39.7)	73 (49)	

***Low SMD (Martin threshold)**			0.263
No	158 (32)	55 (36.9)	
Yes	336 (68)	94 (63.1)	
Concurrent Chemotherapy			0.035
Yes	253 (51.2)	91 (61.1)	
No	241 (48.8)	58 (38.9)	
Radiotherapy Intent			<0.001
Radical	117 (23.7)	0	
Palliative	377 (76.3)	149 (100)	
Survival			<0.001
Alive	12 (2.4)	0	
Dead	482 (97.6)	149 (100)	
12 months survival % (SE)	51 (2)	26 (4)	

*longitudinal data available

Table 5.2. The longitudinal changes in clinicopathological and CT derived body composition measurements in patients undergoing radiotherapy for advanced lung cancer

Body Composition Measurement Total Cohort	**Pre DXT CT scan (n=494)**	**Post DXT CT scan (n=494)**	**P-value**	**Changes in Median**	**Overall survival HR 95% CI**	**P-value**
Clinicopathological						
MUST 0,1≥2	MUST 0: 136 (27.5) MUST 1: 267 (54) MUST ≥2: 91 (18.4) Median pre DXT MUST score =1	MUST 0: 26 (5.3) MUST 1: 112 (22.7) MUST ≥2: 356 (72.1) Median post DXT MUST score =2	<0.001	Median (Range) 1 (0-6)	Pre DXT 0.94 (0.80-1.10) Post DXT 1.60 (1.34-1.92)	0.412 <0.001
ECOG (0-1,2,3)	ECOG 0-1: 319 (64.6) ECOG 2: 128 (25.9) ECOG 3: 47 (9.5) Median pre DXT ECOG score =1	ECOG 0-1: 71 (14.6) ECOG 2: 323 (65.4) ECOG 3: 99 (20) Median post DXT ECOG score =2	<0.001	Median (Range) 1 (0-3)	Pre DXT 1.07 (0.90-1.27) Post DXT 1.31 (1.12-1.54)	0.452 <0.001

mGPS 0,1,2	mGPS 0: 130 (26.3) mGPS 1: 142 (28.7) mGPS 2: 222 (44.9) Median pre DXT mGPS score =1	mGPS 0: 30 (6.1) mGPS 1: 73 (14.9) mGPS 2: 388 (79) Median post DXT mGPS score =2	<0.001	Median (Range) 1 (0-2)	Pre DXT 1.21 (1.07-1.36) Post DXT 1.17 (0.97-1.42)	0.007 <0.001
NLR (<3,3-5,>5)	NLR <3 : 181 (36.6) NLR 3-5: 151 (30.6) NLR >5: 162 (32.8) Median pre DXT NLR score =1	NLR <3 : 33 (6.7) NLR 3-5: 72 (14.6) NLR >5: 387 (78.7) Median post DXT NLR score =2	<0.001	Median (Range) 1 (<3->5)	Pre DXT 1.07 (0.96-1.20) Post DXT 1.17 (0.97-1.42)	0.210 <0.001
Fat						
SFI	Median (Range) 92.41 (1.40-359.81)	Median (Range) 67.32 (-70.99-361.29)	<0.001	Median (Range) -13.66 (-80.45 to +188.95)	1.00 (1.00-1.01)	0.218
High SFI[6] Males>50.0 cm^2m^2 and Females>42.0 cm^2m^2	Normal: 96 (19.4%) High SFI: 398 (80.6%)	Normal: 164 (33.2%) High SFI: 330 (66.8%)	<0.001	High SFI: -13.8%	1.01 (0.79 – 1.30)	0.926
VFA	Median (Range) 223.14 (3.66-635.80)	Median (Range) 164.30 (2.82-654.71)	<0.001	Median (Range) -25.39 (-326.48 to +284.31)	1.00 (0.99 – 1.00)	0.789

High VFA **VFA in Males >160 cm^2 and Females >80 cm^2**	Normal: 103 (20.9%) High VFA: 391 (79.1%)	Normal: 181 (36.6%) High VFA: 313 (63.4%)	<0.001	High VFA: -15.7%	1.11 (0.88 – 1.40)	0.392
Muscle						
SMI	Median (Range) 46.11 (20.15-76.37)	Median (Range) 39.39 (18.79-69.29)	<0.001	Median (Range) -5.76 (-10.47 to +32.14)	1.00 (0.99-1.02)	0.923
High SMI (Martin Male/Female): SMI in Males>53 if BMI≥25 and >43 if BMI <25 **cm^2m^2 and Females>41 cm (about 1.35 ft)$^2m^2$**	High SMI: 298 (60.3%) Low SMI: 196 (39.7%)	High SMI: 150 (30.4%) Low SMI: 344 (69.6%)	<0.001	High SMI: -29.9%	0.96 (0.76-1.20)	0.696
SMD	Median (Range) 32.30 (1.23-78.89)	Median (Range) 28.43 (1.78-55.21)	<0.001	Median (Range) -3.28 (-36.69 to +54.60)	1.00 (0.99-1.01)	0.952
High SMD (Martin): SMD >41 HU if BMI <25 and SMD>HU 33 HU if BMI >25	High SMD: 158 (32.0%) Low SMD: 336 (68.0%)	High SMD: 95 (19.2%) Low SMD: 399 (80.8%)	<0.001	High SMD: -12.8%	0.94 (0.68-1.30)	0.712

These variables were presented as median and range and compared using paired Wilcoxon tests. Categorical variables were analysed using paired McNemar tests for 2 by 2 tables. Changes in clinicopathological characteristics and body composition were presented as median and ranges and compared using paired Kruskal-Wallis tests. Survival data were analysed using univariate categorical Cox regression survival analysis.

Table 5.3. Multiple linear regression analysis of changes in SMI against pre radiotherapy clinicopathological characteristics in patients with advanced lung cancer

Variable	Coefficient B	t	P-value	95% CI for B
Age (years)	-0.098	-2.104	0.036	-1.613 to -0.055
Sex	-0.014	-0.311	0.756	-1.384 to 1.006
ASA score	0.071	1.467	0.143	-0.281 to 1.937
MUST	-0.066	-1.427	0.154	-1.551 to 0.246
mFI	0.060	1.117	0.265	-0.359 to 1.306
TNM stage	-0.017	-0.370	0.712	-1.452 to 0.992
ECOG-PS	-0.034	-0.687	0.493	-1.319 to 0.636
mGPS	0.047	0.983	0.326	-0.381 to 1.144
NLR	0.007	0.142	0.887	-0.689 to 0.796

5.6 Figures and Legends:

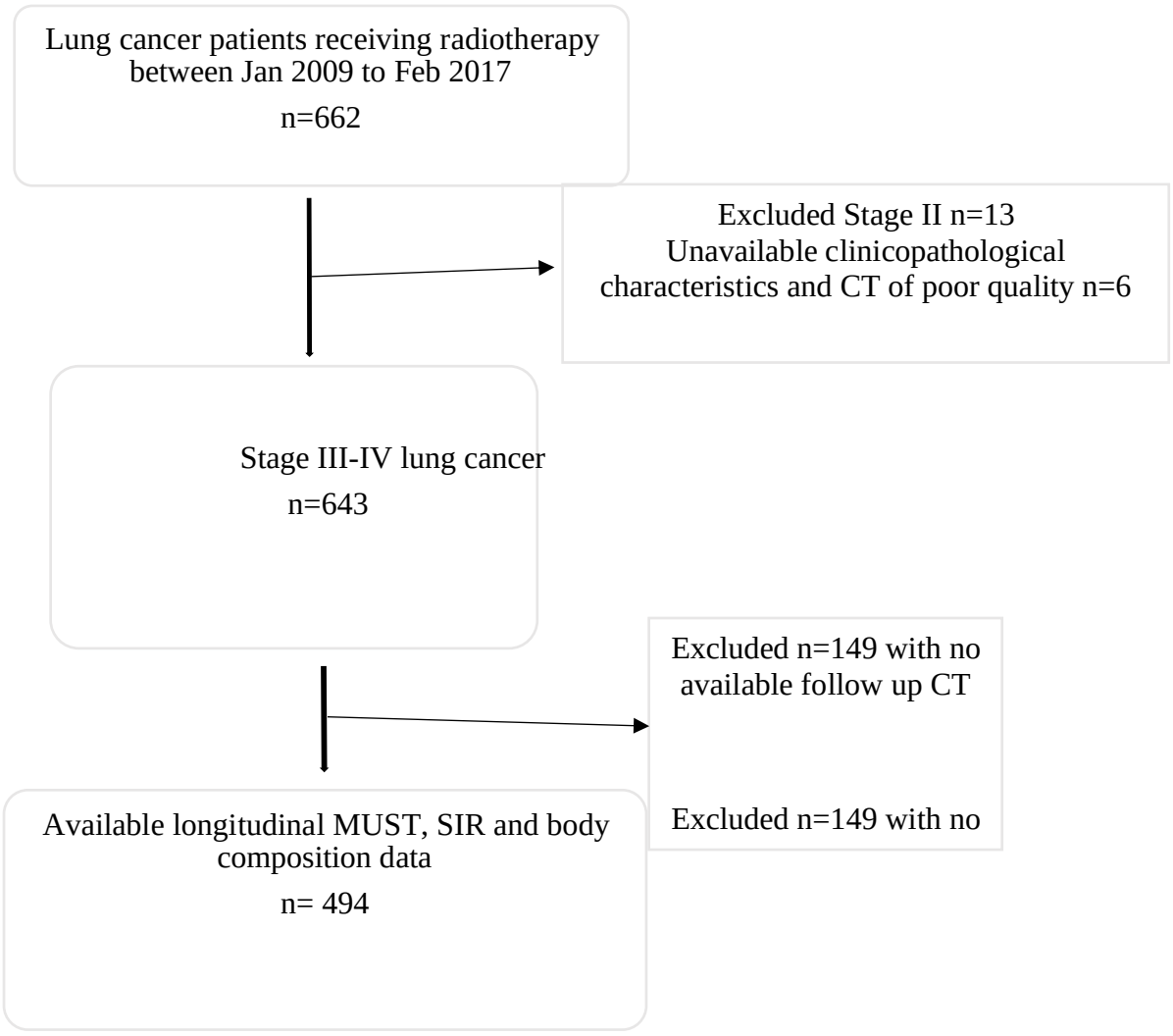


Figure 5.1. Flow diagram showing included patients in longitudinal lung cancer study

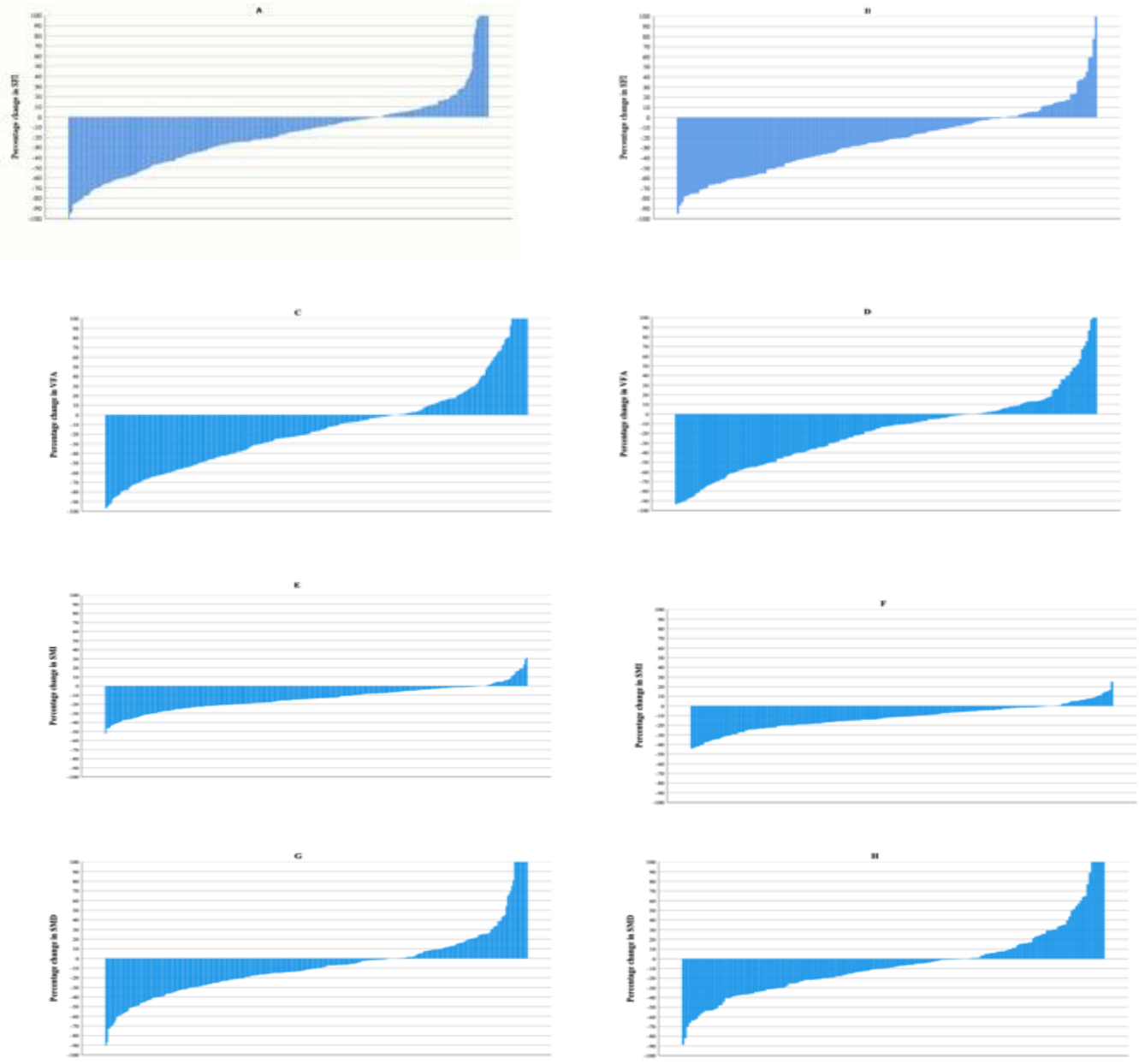


Figure 5.2 | (A) Percentage change in subcutaneous fat index (SFI) in patients <74 years of age (n = 307). (B) Comparison of percentage change in SFI in patients ≥74 years of age (n = 187) (p = 0.117). (C) Percentage change in visceral fat area (VFA) in patients <74 years of age (n = 307).(D) Comparison of percentage change in VFA in patients ≥74 years of age (n = 187) (p = 0.142). (E) Percentage change in skeletal muscle index (SMI) in patients <74 years of age (n = 307). (F) Comparison of percentage change in SMI in patients≥ 74 years of age (n = 187) (p = 0.134). (G) Percentage change in skeletal muscle density (SMD) in patients <74 years of age (n = 307). (H) Comparison of percentage change in SMD in patients ≥74 years of age (n = 187) (p = 0.440).

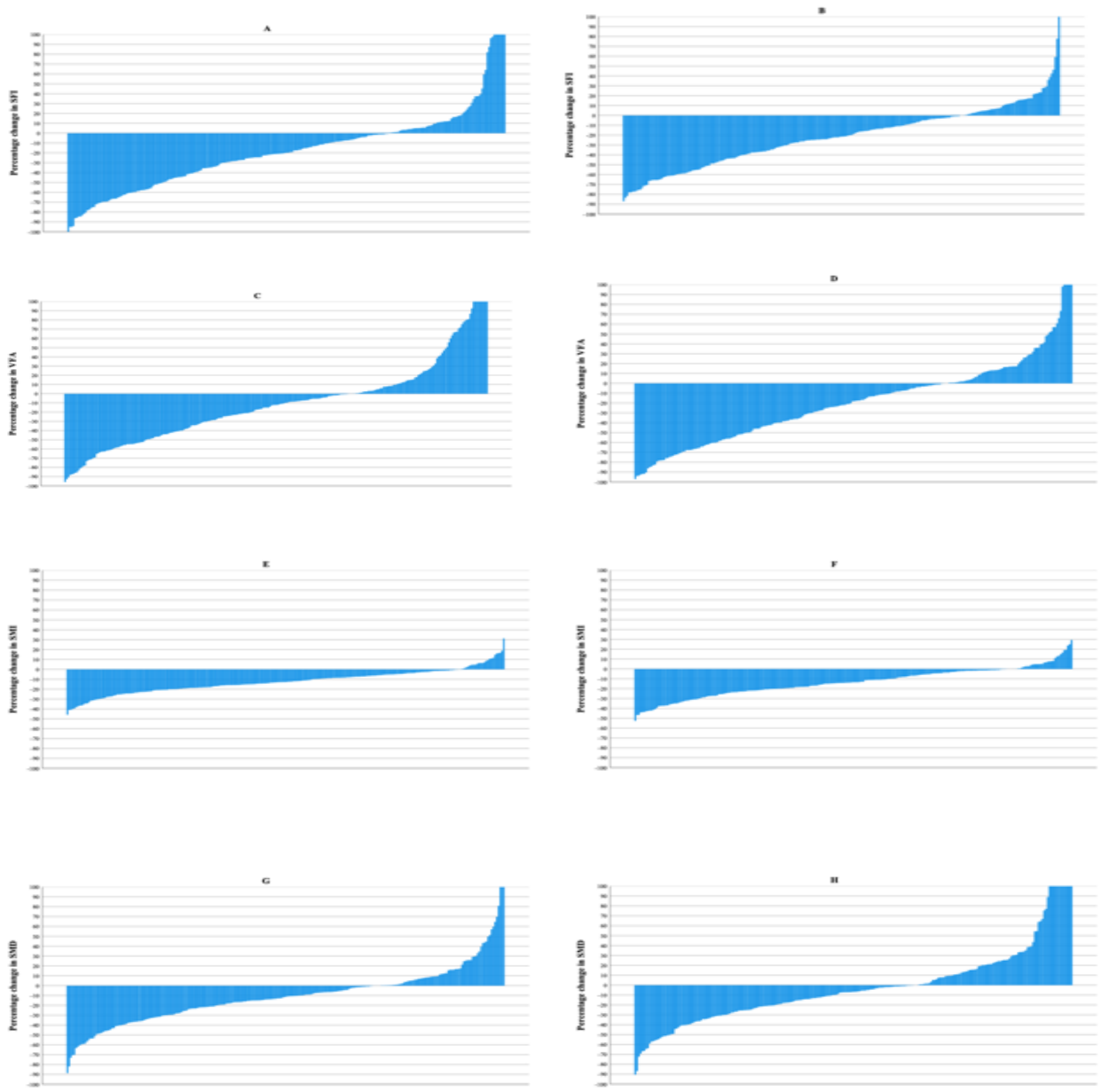


Figure 5.3 | (A) Percentage change in SFI in female patients (n = 240). (B) Percentage change in SFI in male patients (n = 254). Comparison of percentage change in SFI in female (n = 240) and male (n = 254) patients (p = 0.568). (C) Percentage change in VFA in female patients (n = 240). (D) Percentage change in VFA in male patients (n = 254). Comparison of percentage change in VFA in female (n = 240) and male (n = 254) patients (p = 0.057).(E) Percentage change in SMI in female patients (n = 240). (F) Percentage change in SMI in male patients (n = 254). Comparison of percentage change in SMI in female (n = 240) and male (n = 254) patients (p = 0.376). (G) Percentage change in SMD in female patients (n = 240). (H) Percentage change in SMD in male patients (n = 254). Comparison of percentage change in SMD in female (n = 240) and male (n = 254) patients (p = 0.004).

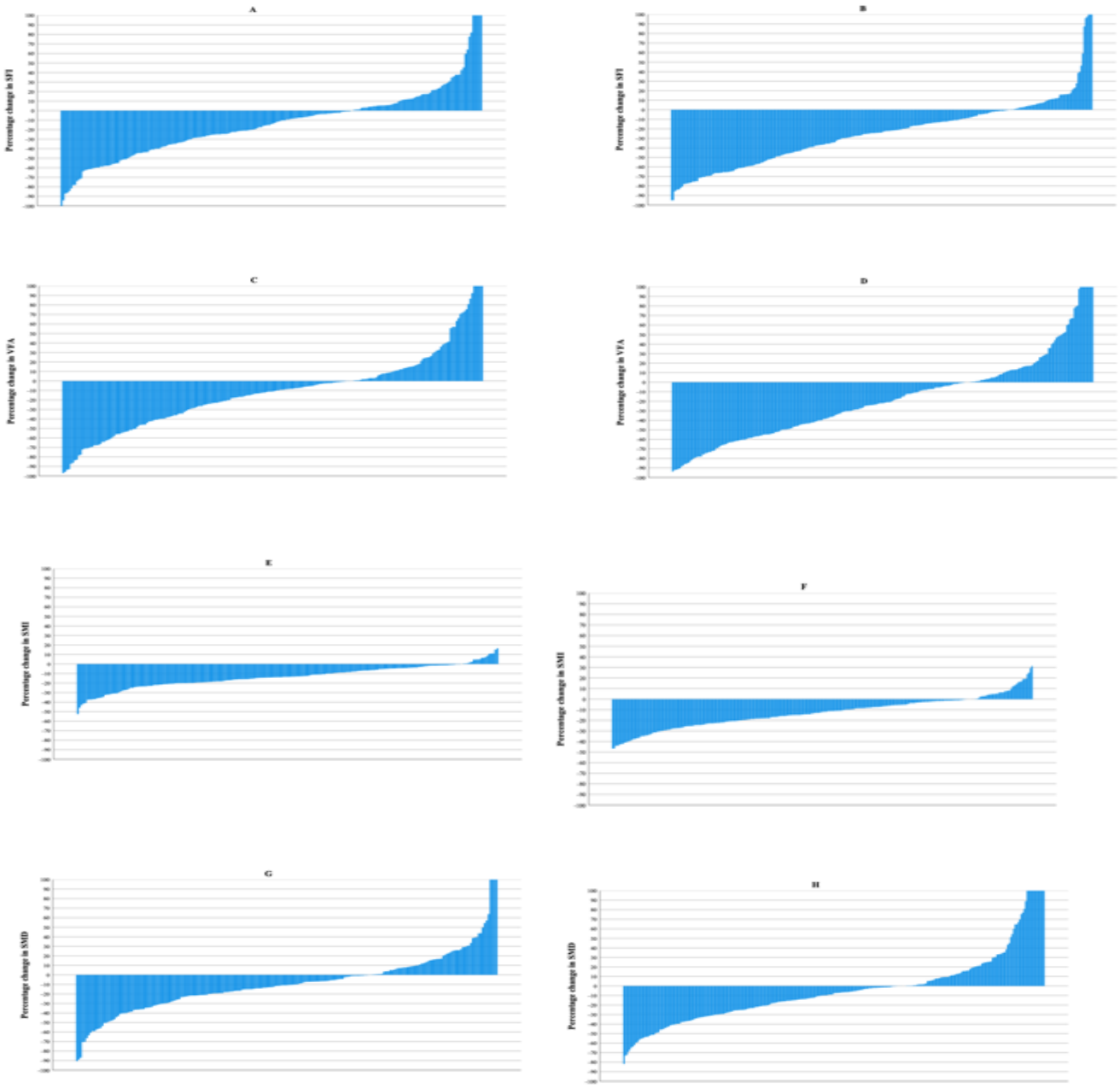


Figure 5.4| (A) Percentage change in SFI in patients with stage III (n = 215). (B) Percentage change in SFI in patients with stage IV (n = 279). Comparison of percentage change in SFI in stage III (n = 215) and stage IV (n =279) patients (p = 0.002). (C) Percentage change in VFA in patients with stage III (n = 215). (D) Percentage change in VFA in patients with stage IV (n =279). Comparison of percentage change in VFA in stage III (n = 215) and stage IV (n = 279) patients (p = 0.087).(E) Percentage change in SMI in patients with stage III (n=215). (F) Percentage change in SMI in patients with stage IV (n = 279). Comparison of percentage change in SMI in stage III (n = 215) and stage IV (n = 279) patients (p = 0.575). (G) Percentage change in SMD in patients with stage III (n=215). (H) Percentage change in SMD in patients with stage IV (n = 279). Comparison of percentage change in SMD in stage III (n = 215) and stage IV (n = 279) patients (p = 0.464).

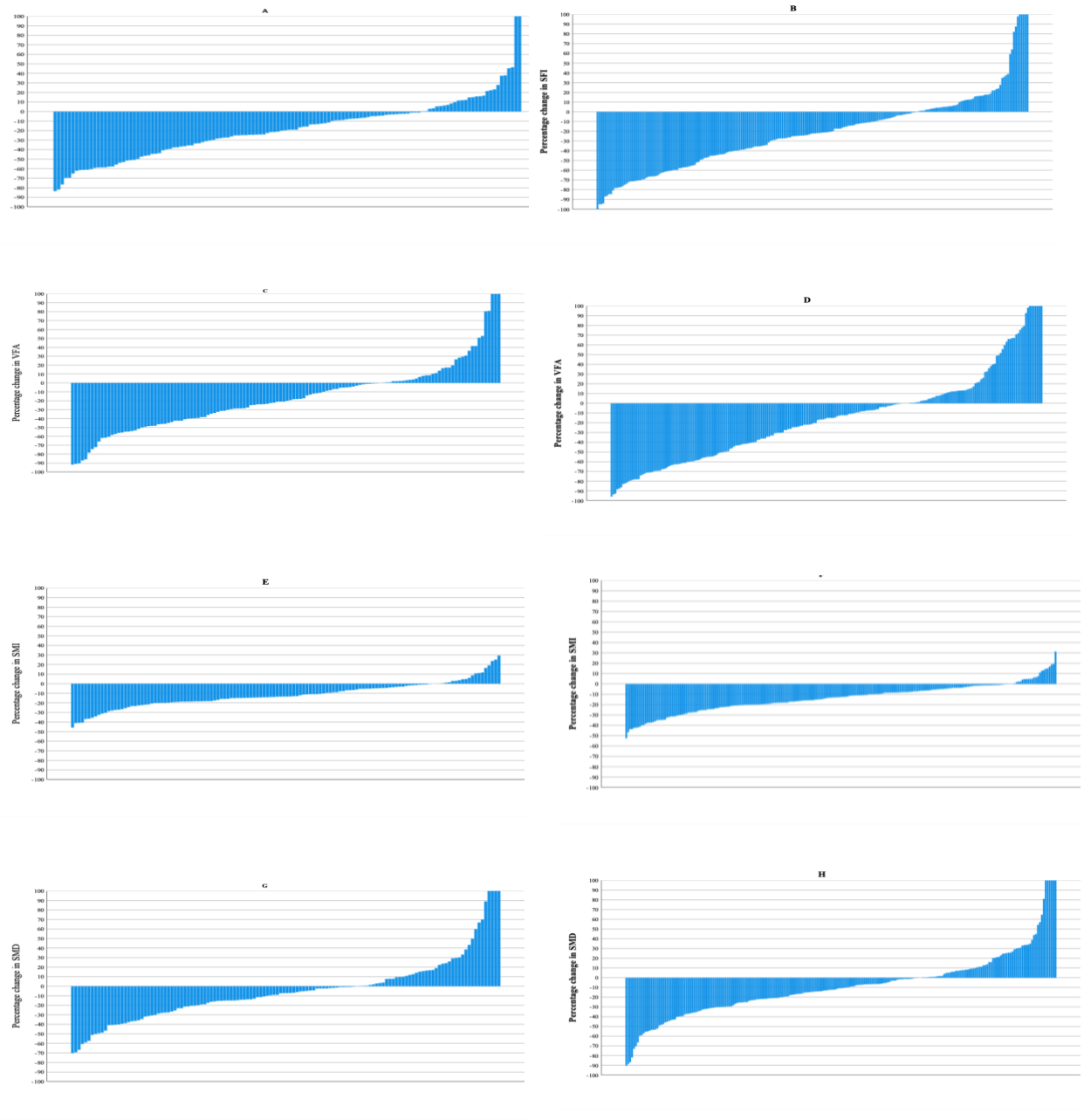


Figure 5.5 | (A) Percentage change in SFI in patients with a mGPS 0 (n = 130). (B) Percentage change in SFI in patients with a mGPS 2 (n =222). Comparison of percentage change in SFI in mGPS 0 (n = 130) and mGPS 2 (n = 222) patients (p = 0.639). (C) Percentage change in VFA in patients with a mGPS 0 (n = 130). (D) Percentage change in VFA in patients with a mGPS 2 (n =222). Comparison of percentage change in VFA in mGPS 0 (n = 130) and mGPS 2 (n = 222) patients (p = 0.799). (E) Percentage change in SMI in patients with a mGPS 0 (n = 130). (F) Percentage change in SMI in patients with a mGPS 2 (n = 222). Comparison of percentage change in SMI in mGPS 0 (n = 130) and mGPS 2 (n =222) patients (p = 0.197). (G) Percentage change in SMD in patients with a mGPS 0 (n = 130). (H) Percentage change in SMD in patients with a mGPS 2 (n = 222). Comparison of percentage change in SMD in mGPS 0 (n = 130) and mGPS 2 (n = 222) patients (p = 0.747).

6 CT DERIVED MEASUREMENTS OF BODY COMPOSITION: OBSERVATIONS FROM A COMPARATIVE ANALYSIS OF PATIENTS WITH PRIMARY OPERABLE COLORECTAL AND OF PATIENTS WITH ADVANCED LUNG CANCER

6.1 Introduction

The loss of weight and skeletal muscle has long been recognised to be associated with poor outcome in patients with advanced cancer (Simmons, McMillan et al. 2017, Baracos, Martin et al. 2018). More recently, body composition analysis has been carried out from CT images, collected as part of routine clinical care, and such cross sectional images offer an opportunity to better understand the alterations in body composition that occur across tumour types and stages of disease (Daly, Prado et al. 2018). Using this approach, a low skeletal muscle index (SMI) and low skeletal muscle density (SMD) have been extensively reported to have prognostic value (Shachar, Williams et al. 2016, Aleixo, Shachar et al. 2020).

There remains some debate over methodological aspects of CT-derived body compositional analysis (Abbass, Dolan et al. 2020, Abbass, Tsz Ho et al. 2020, Dolan, Tien et al. 2020) and the effects of potentially confounding factors such as comorbidity and the systemic inflammatory response (Abbass, Dolan et al. 2019, Dolan and McMillan 2020). However, taking account of tumour type, stage of disease, comorbidity, the systemic inflammatory response and the methodology of CT derived body composition has the potential to give unique insight into the relationship between CT derived body composition and survival. Also, such comparative studies may give insight into whether body composition features are constitutional or are secondary to the cancer itself. Nutritional decline is different across these two types of cancers. CRC involves gastrointestinal tract (GIT) and can cause nutritional decline by causing obstruction or

perforation whereas, in lung cancer, there is no involvement of GIT. To date, such comparative studies have rarely been carried out (Skipworth 2019). Dolan et al, published previous study with 650 patients with operable colorectal cancer (Dolan, Almasaudi et al. 2019) , however, the current analysis has been further expanded to include 1047 patients with colorectal cancer and 662 patients with lung cancer. The rationale for comparison of two types of cancers is to better understand the onset and changes in body composition which will help to target therapy to prevent patients going into refractory cachexia stage. Skipworth in his editorial proposed that "additional lessons that may be gleaned by comparing the epidemiology, methodology, and interpretation of these two studies (Dolan, Almasaudi et al. 2019, van Dijk, Krill et al. 2019) and other human body composition projects in cancer." More recently, further study has questioned the basis of the relationship between low SMI and SMD and survival in patients with cancer and whether the low SMI and SMD is a result of tumour progression per se (Dolan, Abbass et al. 2021, McGovern J, Dolan RD et al. 2021) or involves other factors too. To better understand the changes in body composition, inflammation, malnutrition and frailty in patients with cancer, further comparison across various types of cancers is required. This comparison can help to address the gaps in knowledge to improve our understanding of changes in body composition and plan interventions.

The aim of the present study was, in a comparative study using uniform methodology, to examine the relationship between clinicopathological characteristics, CT derived body composition and survival in patients with operable colorectal cancer (CRC) and advanced lung cancer (LC).

6.2 Patients and Methods:

Patients

Clinicopathological characteristics and clinical outcome data were collected from prospectively maintained database at Glasgow Royal Infirmary for CRC from March 2008 to March 2018. 1047 patients in CRC cohort with available pre-operative staging CT scans were analysed. Similar data were also collected for patients with lung cancer from a prospectively maintained database at The Beatson West of Scotland Cancer Institute from January 2009 to February 2017. 662 patients with advanced lung cancer with available pre radiotherapy CT scans were analysed. Together 1709 patients had available data for comparative analysis.

Clinical data including Malnutrition Universal Screening Tool score (MUST) (Elia 2003) and modified frailty index (mFI) were collected . mFI had been validated for assessment in patients with cancer (Ehlert, Najafian et al. 2016) (see Supplementary Table 1a &1b). Malnutrition using MUST score and frailty were important components of staging the host. Systemic inflammatory response and malnutrition have been recognised as important host characteristics affecting body composition. mGPS and NLR provide objective assessment of systemic inflammatory response. In order to study the relationship between clinicopathological characteristics and body composition measures in both types of cancers, these variables were included (see Tables 6.2 &6.4). The West of Scotland Research Ethics Committee provided approval for the collection and analysis of anonymised patient data.

Methods

CT has become gold standard for body composition analysis and single slice cross sectional analysis at L3 level has been shown to be valid tool for body composition

analysis (Shen, Punyanitya et al. 2004) .CT scans performed as part of staging before commencing treatment were used for analysis. L3 was located using fixed anatomical landmarks by counting downwards from thoracic 12 vertebra where 12th rib attaches or from sacrum upwards to L3 level. Body composition analysis was performed using NIH image software image J (https://imagej.nih.gov.ij/) by using established thresholds of

-29 to 150 HU for skeletal muscle and -190 to -30 HU for adipose tissue as previously described (Dolan, Almasaudi et al. 2018). Measurements were performed by two individuals (TA and RD) for 40 test scans and inter rater reliability was assessed using inter-class correlation coefficients (ICCs). ICC values for total fat area (TFA), visceral fat area (VFA), skeletal muscle area (SMA) and skeletal muscle density (SMD) were 0.999, 0.999, 0.996 and 0.993 respectively. Cross sectional areas were normalized for height squared to calculate fat and muscle indices.

Widely accepted thresholds which were studied in similar cancer patients were used for analysis. Subcutaneous adiposity was defined as increased subcutaneous fat index (SFI) of >50 cm^2/m^2 in males and >42 cm^2/m^2 in females (Ebadi, Martin et al. 2017). Visceral obesity was defined as VFA>160cm^2 in males and >80cm^2 in females (Doyle, Bennett et al. 2013). Martin and co-worker thresholds were used as has been studied in similar cohort i.e. patients with colorectal and lung cancer (n=1473) to calculate SMI and SMD in CRC and LC (Martin, Birdsell et al. 2013). SMI indicates the amount of skeletal muscle area normalised for height and SMD indicates the amount of fat infiltration in muscle also called myosteatosis. In males, low SMI was <43 cm^2/m^2 if BMI <25 and <53 if BMI≥25. In females, low SMI was <39 if BMI <25 and <41 if BMI ≥25 kg/m^2. In males/ females, low SMD was <41 if BMI <25 and <33 if BMI ≥25. As sex and BMI were used to define these thresholds, therefore, these variables were not used in binary regression analysis.

Binary logistic regression analysis was performed to assess the impact of a number of clinico-pathological factors on the measures of body composition. The analysis included eight independent variables (age, ASA, type of cancer, TNM stage, MUST, mFI, mGPS and NLR). The full model containing all variables was statistically significant, x^2 (8, N=1709) =87.88 p<0.001, indicating that the model was able to distinguish between patients with low and normal/high values of body composition. As TNM stage III was the most common tumour stage in this study cohort, further binary logistic regression analysis was carried out in TNM stage III (see Table 6.3).

Statistical Analysis

The categorical variables were analysed using Chi square test. Survival analysis was carried out using life tables and a p-value of <0.05 was considered significant. Patients were followed up until death or June 1, 2020 which was used as censor date. Median duration of follow up was 60 months for CRC and 18 months for lung cancer. Mortality rate was 27 % in operable CRC with median overall survival of 53 months and 98% in lung cancer with median overall survival of 11 months till censor date. Overall survival was defined as time in months from date of surgery or radiotherapy to time of death or time to end of study or loss to follow up. All of the statistical analysis was performed using SPSS version 25 (IBM Corporation, 2017, Armonk, NY).

6.3 Results

Comparison of the clinicopathological characteristics and CT derived body composition analysis of patients with CRC and LC was shown in Table 6.1a &6.1 b. Table 6.1a outlines the clinical characteristics of patients with CRC and LC as a total. Whereas, Table 6.1b outlines the clinical characteristics of patients with operable CRC and advanced lung cancer. The flow diagram of included patients is shown in Figure 6.1. Of the 1047 patients in the CRC group, the majority of patients were >65 years (65%), male (56%), had mild comorbidity (ASA Class I/II, 65%), were overweight (BMI>25, 64%), not at nutritional risk (MUST=0, 82%), were frail (mFI group 3/4, 54%), not systemically inflamed (mGPS=0, 72%, NLR<3, 51%), had subcutaneous adiposity (80%), visceral obesity (73%) , low SMI (51%) and a low SMD (67%) and survived 1 year (94%). Of the 662 patients in the LC group, the majority of patients were >65 years (70%), male (51%), had moderate/ severe comorbidity (ASA III/IV, 90%), were not over weight (BMI<25, 57%), at nutritional risk (MUST>0, 71%), were frail (mFI 3/4 , 76%), systemically inflamed (mGPS >0, 74%, NLR >3, 65%), had subcutaneous adiposity (78%), visceral obesity (76%), normal SMI (58%) and had low SMD (67%) and did not survive 1 year (46%) (Table 6.1). Compared with the CRC cohort, the LC cohort were of a similar age and sex, had higher ASA ($p<0.001$), lower BMI ($p<0.001$), higher MUST ($p<0.001$), higher mFI ($p<0.001$), higher mGPS ($p<0.001$), higher NLR ($p<0.001$), lower SMI ($p<0.001$) and had a poorer 1 year overall survival rate ($p<0.0001$).

Binary logistic regression analysis was performed in the whole cohort (CRC+LC) as well as in TNM stage III alone (CRC+LC). As shown in Table 6.2a, four variables had an independent statistically significant contribution in predicting subcutaneous adiposity. These included type of cancer (OR 1.47; 95% CI: 1.10-1.95; p=0.008), MUST (OR 0.47; 95% CI: 0.39-0.57; $p<0.001$), mFI (OR 1.23; 95% CI: 1.09-1.39; p=0.001) and NLR (OR 0.77; 95% CI: 0.66-0.90; $p<0.001$).

As shown in Table 6.2b, only three variables had an independent statistically significant contribution in predicting visceral obesity. These included type of cancer (OR 1.61; 95% CI: 1.23-2.10; p<0.001), MUST (OR 0.45; 95% CI: 0.38-0.54; p<0.001) and mFI (OR 1.38; 95% CI: 1.23-1.55; p<0.001).

As shown in Table 6.2c, only four variables had an independent statistically significant contribution in predicting low SMI. These included age (OR 1.46; 95% CI: 1.29-1.66; p<0.001), type of cancer (OR 0.45; 95% CI: 0.35-0.57; p<0.001), MUST (OR 1.34; 95% CI: 1.14-1.58; p<0.001) and mGPS (OR 1.40; 95% CI: 1.23-1.60; p<0.001).

As shown in Table 6.2d, only four variables had an independent statistically significant contribution in predicting low SMD. These included age (OR 1.97; 95% CI: 1.70-2.28; p<0.001), type of cancer (OR 0.71; 95% CI: 0.55-0.91; p=0.007), mFI (OR 1.31; 95% CI: 1.17-1.46; p<0.001) and mGPS (OR 1.21; 95% CI: 1.05-1.39; p=0.007).

As shown in Table 6.4a, only three variables had an independent statistically significant contribution in predicting subcutaneous adiposity in patients with TNM stage III CRC and LC. These included MUST (OR 0.53; 95% CI: 0.40-0.69; p<0.001), mFI (OR 1.24; 95% CI: 1.02-1.52; p=0.033) and NLR (OR 0.80; 95% CI: 0.62-1.03; p=0.080).

As shown in Table 6.4b, only three variables had an independent statistically significant contribution in predicting visceral obesity in patients with TNM stage III CRC and LC. These included type of cancer (OR 1.90; 95% CI: 1.20-2.99; p=0.006), MUST (OR 0.34; 95% CI: 0.25-0.46; p<0.001) and mFI (OR 1.53; 95% CI: 1.25-1.87; p<0.001).

As shown in Table 6.4c, only four variables had an independent statistically significant contribution in predicting low SMI in patients with TNM stage III CRC and LC. These included age (OR 1.40; 95% CI: 1.13-1.73; p=0.002), type of cancer (OR 0.49; 95% CI:

0.33-0.74; p<0.001), MUST (OR 1.33; 95% CI: 1.02-1.72; p=0.034) and mGPS (OR 1.31; 95% CI: 1.06-1.63; p=0.014).

As shown in Table 6.4d, only two variables had an independent statistically significant contribution in predicting low SMD in patients with TNM stage III CRC and LC. These included age (OR 1.75; 95% CI: 1.38-2.22; p<0.001) and mFI (OR 1.25; 95% CI: 1.05-1.49; p=0.013).

The relationship between measures of body composition in patients with operable CRC and advanced LC was shown in Appendix E.

6.4 Discussion

The results of the present study showed that, in CRC and LC cohorts, although there were marked difference in comorbidity, stage of disease, nutritional risk, systemic inflammation and survival, there was similar subcutaneous (80% and 78% respectively) and visceral obesity (73% and 76% respectively). Similar results were obtained for subcutaneous (80% and 75% respectively) and visceral obesity (74% and 77% respectively) when patients with TNM stage III disease were examined. Also, in CRC and LC cohorts, there were similar proportions of low SMI (51% and 42% respectively; TNM stage III 49% and 43% respectively) and low SMD (67% and 67% respectively; TNM stage III 63% and 67% respectively). Therefore, obesity and low skeletal muscle mass were common in both CRC and LC cohorts despite large differences comorbidity, nutritional risk, systemic inflammation and survival, even when normalised for TNM stage. These observations would support the hypothesis that, although prognostic, CT derived body composition analysis primarily reflects patient constitution rather than the effect of tumour stage in patients with cancer.

The present results, using a standard CT methodology across tumour type and stage of disease are consistent with a recent review which observed that, in particular, both a low SMI and a low SMD had a percentage prevalence between 35-50% and that this was similar irrespective of threshold used, tumour type and stage of disease. It was concluded that poor muscle quantity and quality are endemic in patients with cancer and that such poor muscle status is not materially affected by disease progression (McGovern J, Dolan RD et al. 2021). If this was indeed the case, this would indicate that other characteristics of the cancer link body composition (low SMI and SMD) to poor survival in patients with cancer. In the present study such potential characteristics may be comorbidity, nutritional risk, frailty and the systemic inflammatory response. Irrespective, the present results would suggest that body composition features may not be useful as clinical endpoints in the

treatment of the progressive nutritional and functional decline of patients with cancer. Further comparative longitudinal and intervention studies are required to confirm the present observations.

Of the factors that may confound the relationship between CT derived low SMI and SMD and survival, the systemic inflammatory response is plausible since it is consistently associated with a more aggressive tumour type (Dolan and McMillan 2020), comorbidity (Watt, Ramanathan et al. 2017), MUST (Almasaudi, McSorley et al. 2019), CT-derived body composition (Abbass, Dolan et al. 2019) and survival (Dolan, Lim et al. 2017, Dolan, McSorley et al. 2017). If the systemic inflammatory response (as evidenced by the mGPS) does indeed link low SMI and SMD to poor survival, it would confirm the systemic inflammatory response as an important therapeutic target (Diakos, Charles et al. 2014, Paul 2020, McGovern, Dolan et al. 2022) in patients with cancer. Therefore, it is of interest in a recent secondary analysis of the large EFFORT trial Merker and coworkers reported that, in 1950 patients receiving nutritional support, the presence of a systemic inflammatory response (as evidenced by C-reactive protein >100mg/l) was associated with no significant beneficial effect of nutritional support (Merker, Felder et al. 2020). Furthermore, Hacker and coworkers, in trial of >500 patients with gastro-oesophageal cancer, reported that systemic inflammation was correlated with low SMI and had superior prognostic value in patients undergoing first line treatment (Hacker, Hasenclever et al. 2022).

The limitations of the present study are similar to all retrospective cross-sectional studies. Namely, that they cannot prove causal relationships. However, a strength of the present study is that it is the first comparative study of CT derived body composition analysis, using a standard methodology, and included potentially confounding factors and survival in a large cohort of patients with cancer.

In summary, obesity and low skeletal muscle mass were common in both CRC and LC cohorts despite large differences comorbidity, nutritional risk, systemic inflammation and survival, even when normalised for TNM stage. These observations would support the hypothesis that, although prognostic, CT derived body composition analysis primarily reflects patient constitution rather than the effect of tumour stage in patients with cancer. Whilst TNM stage is important for planning treatment and has an association with body composition this may not be a direct or causal relationship. It is clear from the present study and by comparison the prevalence of low SMI across various types of cancers, that body composition is largely altered by the time of diagnosis of cancer whether at early stage or advanced stage. Therefore, the dogma that tumour itself is directly responsible for tissue wasting is challenged. Further similar large multicentre prospective studies in various cancers are warranted.

6.5 **Tables and Footnotes**

Table 6.1a: Comparison of clinical characteristics of patients with colorectal (CRC) and lung cancer (LC)

Characteristics	Total n=1709	CRC n=1047	LC n=662	P-value
Age, years				0.040
<65	561 (32.8)	364 (34.8)	197 (29.8)	
65-74	638 (37.3)	383 (36.6)	255 (38.5)	
>74	510 (29.8)	300 (28.7)	210 (31.7)	
Sex				0.051
Female	791 (46.3)	465 (44.4)	326 (49.2)	
Male	918 (53.7)	582 (55.6)	336 (50.8)	
ASA				<0.001
I	201 (11.8)	201 (19.2)		
II	547 (32)	482 (46.1)	65 (9.8)	
III	771 (45.1)	328 (31.3)	443 (66.9)	
IV	190 (11.1)	36 (3.4)	154 (23.3)	
TNM stage				<0.001
I	240 (14)	240 (22.9)	0	

II	423 (24.8)	404 (38.6)	19 (2.9)	
III	598 (35)	358 (34.2)	240 (36.3)	
IV	448 (26.2)	45 (4.3)	403 (60.9)	
MUST				<0.001
0	1044 (61.8)	845 (82.2)	199 (30.1)	
1	442 (26.2)	95 (9.2)	347 (52.4)	
≥2	204 (12.1)	88 (8.6)	116 (17.5)	
mFI				<0.001
Group 1	248 (14.5)	217 (20.7)	31 (4.7)	
Group 2	395 (23.1)	267 (25.5)	128 (19.3)	
Group 3	515 (30.1)	275 (26.3)	240 (36.3)	
Group 4	551 (32.2)	288 (27.5)	263 (39.7)	
mGPS				<0.001
0	929 (54.4)	754 (72)	175 (26.4)	
1	295 (17.3)	116 (11.1)	179 (27)	
2	485 (28.4)	177 (16.9)	308 (46.5)	
NLR				<0.001
<3	759 (45.3)	538 (51.4)	221 (35.1)	

3-5	508 (30.3)	322 (30.8)	186 (29.5)	
>5	410 (24.4)	187 (17.9)	223 (35.4)	
Subcutaneous fat area cm^2				0.009
Mean		231.898	251.145	
SD		122.025	138.396	
Subcutaneous adiposity (Ebadi threshold)				0.307
No	352 (20.8)	209 (20)	143 (22)	
Yes	1344 (79.2)	838 (80)	506 (78)	
Visceral Fat Area (cm^2)				0.044
Mean		202.151	214.976	
SD		117.470	124.414	
Visceral obesity (Doyle threshold)				0.255
No	439 (25.9)	281 (26.8)	158 (24.3)	
Yes	1257 (74.1)	766 (73.2)	491 (75.7)	
L3 total skeletal muscle index ($cm^{2/}m^2$)				0.790
Mean		46.065	45.810	

SD		10.171	9.618	
Low SMI (Martin threshold)				<0.001
No	898 (52.5)	517 (49.4)	381 (57.6)	
Yes	811 (47.5)	530 (50.6)	281 (42.4)	
Skeletal muscle density, HU				0.05
Mean		31.764	32.260	
SD		9.275	10.767	
Low SMD (Martin threshold)				0.922
No	560 (32.8)	344 (32.9)	216 (32.6)	
Yes	1149 (67.2)	703 (67.1)	446 (67.4)	
Survival				<0.0001
1 yr. overall survival % (SE)	75 (1)	94 (1)	46 (2)	

Table 6.1b: Patient clinical characteristics by, primary operable colorectal and advanced lung cancer

Characteristics	Total n=1645	Operable CRC n=1002	Advanced LC n=643	P-value
Age, years				0.126
<65	540 (32.8)	345 (34.4)	195 (30.3)	
65-74	616 (37.4)	367 (36.6)	249 (38.7)	
>74	489 (29.7)	290 (28.9)	199 (30.9)	
Sex				0.115
Female	761 (46.3)	448 (44.7)	313 (48.7)	
Male	884 (53.7)	554 (55.3)	330 (51.3)	
ASA				<0.0001
I	196 (11.9)	196 (19.6)		
II	516 (31.4)	456 (45.5)	60 (9.3)	
III	750 (45.6)	316 (31.5)	434 (67.5)	
IV	183 (11.1)	34 (3.4)	149 (23.2)	
BMI, kg/m^2				<0.0001
<20	171 (10.4)	64 (6.4)	107 (16.6)	

20-24.9	560 (34)	297 (29.6)	263 (40.9)	
25-29.9	503 (30.6)	336 (33.5)	167 (26)	
≥30	411 (25)	305 (30.4)	106 (16.5)	
MUST				<0.0001
0	999 (61.4)	810 (82.3)	189 (29.4)	
1	432 (26.6)	91 (9.2)	341 (53)	
≥2	196 (12)	83 (8.4)	113 (17.6)	
mFI				<0.0001
Group 1	245 (14.9)	214 (21.4)	31 (4.8)	
Group 2	381 (23.2)	259 (25.8)	122 (19)	
Group 3	495 (30.1)	258 (25.7)	237 (36.9)	
Group 4	524 (31.9)	271 (27)	253 (39.3)	
mGPS				<0.0001
0	900 (54.7)	731 (73)	169 (26.3)	
1	284 (17.3)	109 (10.9)	175 (27.2)	
2	461 (28)	162 (16.2)	299 (46.5)	
NLR				<0.0001
<3	737 (45.7)	523 (52.2)	214 (35)	

3-5	490 (30.4)	310 (30.9)	180 (29.4)	
>5	387 (24)	169 (16.9)	218 (35.6)	
Total Fat area, cm^2				0.008
Mean		433.872	463.965	
SD		199.315	236.779	
Subcutaneous fat area cm^2				0.009
Mean		232.011	249.656	
SD		122.292	138.020	
Subcutaneous obesity (Ebadi threshold)				0.273
No	340 (20.8)	200 (20)	140 (22.2)	
Yes	1292 (79.2)	802 (80)	490 (77.8)	
Visceral Fat Area (cm^2)				0.044
Mean		201.861	214.309	
SD		117.135	124.451	
Visceral obesity (Doyle threshold)				0.224
No	425 (26)	271 (27)	154 (24.4)	

Yes	1207 (74)	731 (73)	476 (75.6)	
L3 total skeletal muscle area (cm^2)				0.373
Mean		128.029	126.628	
SD		34.298	28.832	
L3 total skeletal muscle index ($cm^{2/}m^2$)				0.790
Mean		46.096	45.962	
SD		10.225	9.570	
Low SMI (Martin threshold)				0.001
No	869 (52.8)	495 (49.4)	374 (58.2)	
Yes	776 (42.7)	507 (50.6)	269 (41.8)	
Skeletal muscle density, HU				0.05
Mean		31.841	32.361	
SD		9.307	10.808	
Low SMD (Martin threshold)				0.931
No	547 (33.3)	334 (33.3)	213 (33.1)	

Yes	1098 (66.7)	668 (66.7)	430 (66.9)	
Survival				<0.0001
1 yr. overall survival % (SE)	76 (1)	95 (1)	45(2)	

Table 6.2: The relationship between clinicopathological characteristics and body composition measures in patients with CRC and LC

2a. Subcutaneous adiposity

Variable	Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Age (<65/65-74/>74)	1.01 (0.85-1.19)	0.913	-	-
ASA	0.86 (0.69-1.07)	0.187	-	-
Type of cancer	1.72 (1.15-2.58)	0.008	1.47 (1.10-1.95)	0.008
TNM stage	0.97 (0.81-1.15)	0.689	-	-
MUST	0.47 (0.39-0.57)	<0.001	0.47 (0.39-0.57)	<0.001
mFI	1.31 (1.12-1.55)	0.001	1.23 (1.09-1.39)	0.001
mGPS (0/1/2	0.99 (0.84-1.17)	0.909	-	-
NLR (<3/3-5/>5)	0.77 (0.66-0.91)	0.002	0.77 (0.66-0.90)	<0.001

2b. Visceral obesity

Variable	Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Age (<65/65-74/>74)	1.09 (0.94-1.28)	0.248	-	-
ASA	0.93 (0.76-1.15)	0.526	-	-
Type of cancer	1.87 (1.28-2.73)	0.001	1.61 (1.23-2.10)	<0.001
TNM stage	0.98 (0.84-1.14)	0.787	-	-
MUST	0.44 (0.37-0.53)	<0.001	0.45 (0.38-0.54)	<0.001
mFI	1.39 (1.19-1.61)	<0.001	1.38 (1.23-1.55)	<0.001
mGPS (0/1/2)	1.06 (0.91-1.24)	0.439	-	-
NLR (<3/3-5/>5)	0.88 (0.76-1.02)	0.092	-	-

2c. Low SMI

Variable	Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Age (<65/65-74/>74)	1.51 (1.32-1.73)	<0.001	1.46 (1.29-1.66)	<0.001
ASA	0.90 (0.75-1.08)	0.247	-	-
Type of cancer	0.46 (0.33-0.63)	<0.001	0.45 (0.35-0.57)	<0.001
TNM stage	1.02 (0.89-1.17)	0.770	-	-
MUST	1.33 (1.12-1.56)	<0.001	1.34 (1.14-1.58)	<0.001
mFI	1.02 (0.89-1.16)	0.785	-	-
mGPS (0/1/2)	1.39 (1.21-1.59)	<0.001	1.40 (1.23-1.60)	<0.001
NLR (<3/3-5/>5)	1.09 (0.96-1.25)	0.178	-	-

2d. Low SMD

Variable	Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Age (<65/65-74/>74)	1.98 (1.70-2.30)	<0.001	1.97 (1.70-2.28)	<0.001
ASA	1.06 (0.87-1.29)	0.575	-	-
Type of cancer	0.64 (0.44-0.92)	0.016	0.71 (0.55-0.91)	0.007
TNM stage	0.99 (0.85-1.14)	0.857	-	-
MUST	1.10 (0.91-1.32)	0.322	-	-
mFI	1.28 (1.11-1.47)	<0.001	1.31 (1.17-1.46)	<0.001
mGPS (0/1/2)	1.17 (1.00-1.36)	0.045	1.21 (1.05-1.39)	0.007
NLR (<3/3-5/>5)	1.07 (0.92-1.23)	0.374	-	-

Binary logistic regression, variables with p<0.1 on univariate analysis were entered into backward conditional multi variate analysis. P-value <0.05 was considered significant. ASA, American Society of Anaesthesiologists; MUST, Malnutrition Universal Screening Tool; mFI, modified frailty index, mGPS, modified Glasgow Prognostic Score; NLR, neutrophil lymphocyte ratio; SMD, skeletal muscle radio-density; SMI, skeletal muscle index.

Table 6.3: Comparison of clinical characteristics of patients with colorectal (CRC) and lung cancer (LC) in TNM stage III.

Characteristics	Total n=598	CRC n=358 (60)	LC n=240 (40)	P-value
Age, years				<0.001
<65	197 (32.9)	137 (38.3)	60 (25)	
65-74	221 (37)	130 (36.3)	91 (37.9)	
>74	180 (30.1)	91 (25.4)	89 (37.1)	
Sex				0.564
Female	268 (44.8)	157 (43.9)	111 (46.3)	
Male	330 (55.2)	201 (56.1)	129 (53.8)	
ASA				<0.001
I	69 (11.5)	69 (19.3)		
II	175 (29.3)	162 (45.3)	13 (5.4)	
III	277 (46.3)	118 (33)	159 (66.3)	
IV	77 (12.9)	9 (2.5)	68 (28.3)	
MUST				<0.001
0	350 (59.2)	286 (81.5)	64 (26.7)	
1	163 (27.6)	26 (7.4)	137 (57.1)	
≥2	78 (13.2)	39 (11.1)	39 (16.3)	

mFI				<0.001
Group 1	84 (14)	72 (20.1)	12 (5)	
Group 2	129 (21.6)	84 (23.5)	45 (18.8)	
Group 3	179 (29.9)	101 (28.2)	78 (32.5)	
Group 4	206 (34.4)	101 (28.2)	105 (43.8)	
mGPS				<0.001
0	333 (55.7)	262 (73.2)	71 (29.6)	
1	106 (17.7)	41 (11.5)	65 (27.1)	
2	159 (26.6)	55 (15.4)	104 (43.3)	
NLR				<0.001
<3	287 (48.5)	194 (54.2)	93 (39.7)	
3-5	171 (28.9)	100 (27.9)	71 (30.3)	
>5	134 (22.6)	64 (17.9)	70 (29.9)	
Subcutaneous fat area (cm^2)				0.830
Mean		229.653	251.145	
SD		122.478	123.222	
Subcutaneous adiposity (Ebadi threshold)				0.206
No	132 (22.1)	73 (20.4)	59 (24.8)	
Yes	464 (77.9)	285 (79.6)	179 (75.2)	

Visceral Fat Area (cm^2)				0.446
Mean		206.912	214.976	
SD		119.019	123.222	
Visceral obesity (Doyle threshold)				0.428
No	148 (24.8)	93 (26)	55 (23.1)	
Yes	448 (75.2)	265 (74)	183 (76.9)	
L3 total skeletal muscle area (cm^2)				0.065
Mean		130.213	126.182	
SD		36.020	27.170	
L3 total skeletal muscle index ($cm^{2/}m^2$)				0.256
Mean		46.740	45.763	
SD		10.886	9.390	
Low SMI (Martin threshold)				0.117
No	318 (53.2)	181 (50.6)	137 (57.1)	
Yes	280 (46.8)	177 (49.4)	103 (42.9)	
Skeletal muscle density, HU				0.403
Mean		31.915	32.594	

SD		9.425	10.140	
Low SMD (Martin threshold)				0.414
No	211 (35.3)	131 (36.6)	80 (33.3)	
Yes	387 (64.7)	227 (63.4)	160 (66.7)	
Survival				<0.0001
1 yr. overall survival % (SE)	79 (2)	91 (1)	59 (3)	

Table 6.4: The relationship between clinicopathological characteristics and body composition measures in patients with TNM stage III CRC and LC

6.4a. Subcutaneous adiposity

Variable	Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Age (<65/65-74/>74)	1.01 (0.76-1.32)	0.968	-	-
ASA	0.79 (0.55-1.13)	0.199	-	-
Type of cancer	1.47 (0.83-2.62)	0.188	-	-
MUST	0.51 (0.38-0.68)	<0.001	0.53 (0.40-0.69)	<0.001
mFI	1.36 (1.04-1.77)	0.022	1.24 (1.02-1.52)	0.033
mGPS (0/1/2)	0.96 (0.74-1.25)	0.761	-	-
NLR (<3/3-5/>5)	0.80 (0.62-1.04)	0.099	0.80 (0.62-1.03)	0.080

6.4b. Visceral obesity

Variable	Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Age (<65/65-74/>74)	1.04 (0.79-1.37)	0.780	-	-
ASA	1.00 (0.70-1.44)	0.987	-	-
Type of cancer	1.74 (0.96-3.15)	0.069	1.90 (1.20-2.99)	0.006
MUST	0.32 (0.23-0.44)	<0.001	0.34 (0.25-0.46)	<0.001
mFI	1.52 (1.17-1.97)	0.002	1.53 (1.25-1.87)	<0.001
mGPS (0/1/2)	1.23 (0.93-1.61)	0.150	-	-
NLR (<3/3-5/>5)	0.92 (0.71-1.20)	0.554	-	-

6.4c. Low SMI

Variable	Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Age (<65/65-74/>74)	1.39 (1.11-1.75)	0.005	1.40 (1.13-1.73)	0.002
ASA	0.92 (0.68-1.25)	0.594	-	-
Type of cancer	0.50 (0.31-0.81)	0.005	0.49 (0.33-0.74)	<0.001
MUST	1.32 (1.01-1.73)	0.039	1.33 (1.02-1.72)	0.034
mFI	1.07 (0.86-1.32)	0.569	-	-
mGPS (0/1/2)	1.28 (1.02-1.60)	0.036	1.31 (1.06-1.63)	0.014
NLR (<3/3-5/>5)	1.10 (0.89-1.38)	0.369	-	-

6.4d. Low SMD

Variable	Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Age (<65/65-74/>74)	1.77 (1.38-2.26)	<0.001	1.75 (1.38-2.22)	<0.001
ASA	1.10 (0.80-1.52)	0.544	-	-
Type of cancer	0.73 (0.43-1.22)	0.231	-	-
MUST	1.02 (0.77-1.36)	0.881	-	-
mFI	1.21 (0.97-1.52)	0.097	1.25 (1.05-1.49)	0.013
mGPS (0/1/2)	1.06 (0.83-1.35)	0.662	-	-
NLR (<3/3-5/>5)	1.15 (0.91-1.45)	0.248	-	-

Binary logistic regression, variables with p<0.1 on univariate analysis were entered into backward conditional multi variate analysis. P-value <0.05 was considered significant. ASA, American Society of Anaesthesiologists; MUST, Malnutrition Universal Screening Tool; mFI, modified frailty index, mGPS, modified Glasgow Prognostic Score; NLR, neutrophil lymphocyte ratio; SMD, skeletal muscle radio-density; SMI, skeletal muscle index; TNM, tumor, node, metastasis.

Table 6.5: Patient clinical characteristics by, primary operable colorectal and advanced lung cancer with mGPS=0 (n= 900)

Characteristics	Total n=900	Operable CRC n=731 (73%)	Advanced lung cancer n=169 (27%)	P-value
Age, years				0.329
<65	314 (34.9)	259 (35.4)	55 (32.5)	
65-74	336 (37.3)	274 (37.5)	62 (36.7)	
>74	250 (27.8)	198 (27.1)	52 (30.8)	
Sex				0.104
Female	418 (46.4)	330 (45.1)	88 (52.1)	
Male	482 (53.6)	401 (54.9)	81 (47.9)	
ASA				<0.0001
I	158 (17.6)	158 (21.6)	0	
II	354 (39.3)	340 (46.5)	14 (8.3)	
III	333 (37)	215 (29.4)	118 (69.8)	
IV	55 (6.1)	18 (2.5)	37 (21.9)	
BMI, kg/m^2				<0.0001
<20	67 (7.4)	41 (5.6)	26 (15.4)	
20-24.9	279 (31)	208 (28.5)	71 (42)	

25-29.9	296 (32.9)	247 (33.8)	49 (29)	
≥30	258 (28.7)	235 (32.1)	23 (13.6)	
MUST				<0.0001
0	705 (79.1)	623 (86.3)	82 (48.5)	
1	121 (13.6)	56 (7.8)	65 (38.5)	
≥2	65 (7.3)	43 (6)	22 (13)	
mFI				<0.0001
Group 1	185 (20.6)	171 (23.4)	14 (8.3)	
Group 2	237 (26.3)	197 (26.9)	40 (23.7)	
Group 3	238 (26.4)	182 (24.9)	56 (33.1)	
Group 4	240 (26.7)	181 (24.8)	59 (34.9)	
NLR				0.012
<3	509 (57.3)	427 (58.4)	82 (52.2)	
3-5	253 (28.5)	213 (29.1)	40 (25.5)	
>5	126 (14.2)	91 (12.4)	35 (22.3)	
Subcutaneous obesity (Ebadi threshold)				0.663
No	171 (19.1)	138 (18.9)	33 (20.4)	
Yes	722 (80.9)	593 (81.1)	129 (79.6)	

Visceral obesity (Doyle threshold)				0.760
No	234 (26.2)	190 (26)	44 (27.2)	
Yes	659 (73.8)	541 (74)	118 (72.8)	
Low SMI (Martin threshold)				0.052
No	499 (55.4)	394 (53.9)	105 (62.1)	
Yes	401 (44.6)	337 (46.1)	64 (37.9)	
Low SMI (Dolan threshold)				0.149
No	493 (54.8)	392 (53.6)	101 (59.8)	
Yes	407 (45.2)	339 (46.4)	68 (40.2)	
Low SMD (Martin threshold)				0.838
No	331 (36.8)	270 (36.9)	61 (36.1)	
Yes	569 (63.2)	461 (63.1)	108 (63.9)	
Low SMD (Dolan threshold)				0.018
No	406 (45.1)	316 (43.2)	90 (53.3)	
Yes	494 (54.9)	415 (56.8)	79 (46.7)	
Survival				<0.001
1 yr overall survival % (SE)	89 (1)	96 (1)	59 (4)	

6.6 Figures

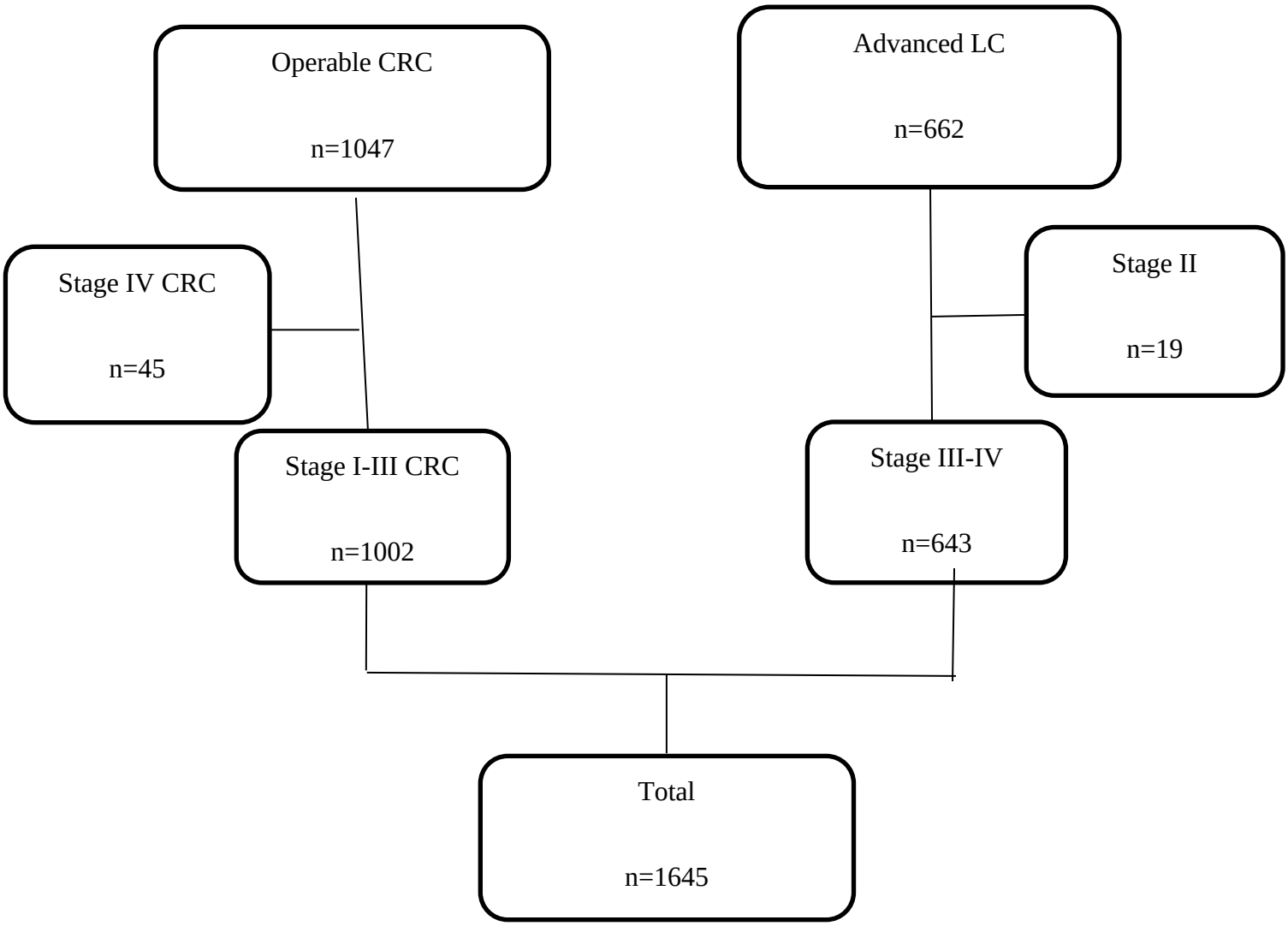


Figure 6.1: PRISMA Flow diagram of included patients with primary operable colorectal and advanced lung cancer

7 THE USE OF CT AND PET CT IMAGING TO MEASURE BODY COMPOSITION AND TUMOUR ACTIVITY IN PATIENTS WITH ADVANCED LUNG CANCER TRAETED WITH RADIOTHERAPY

7.1 Introduction

Globally lung cancer is the most common cancer (2.09 million reported cases in 2018) with 1.76 million deaths (https://www.who.int/news-room/fact-sheets/detail/cancer). PET CT is performed where suspected Unequivocal nodal/ metastatic disease (benign, granuloma vs malignant nodule), persistent mass where neoplastic or inflammatory aetiology suspected, recurrence post resection or new primary suspected or to assess uptake in liver, brain and adrenal and to properly stage the patient in case of borderline fitness. SUV uptake on PET is related to tumour biological activity (Pankowska, Malkowski et al. 2019). The FDG uptake is related to systemic inflammatory response (McSorley, Khor et al. 2018, Dolan, McLees et al. 2019). However, 18 F-FDG-PETCT tumour activity relationship to malnutrition, performance status and body composition has not been studied.

Anthropometric measures (BMI/ weight loss grade), hand grip strength, time up and go (TUG), 2-minute walk test (2 MWT) provide valuable information in prospective studies. Retrospective studies lack information on these clinical parameters most of the time. We hypothesized that malnutrition universal screening tool (MUST) devised by British Association of Parenteral Nutrition (BAPEN) and 11 point modified frailty index (mFI) (Velanovich, Antoine et al. 2013) will provide valuable information and its relationship to PET activity will have prognostic value.

Assessment of patient with advanced cancers is complex. Clinical, inflammatory and body composition assessment is likely to provide best treatment decision algorithm and help in informed discussion with patients and their families.

Informed decision-making process should take into consideration host status (nutritional, performance, inflammatory) and tumour status (TNM stage) to guide ongoing treatment. Patients with lung cancer undergo clinical, laboratory and radiological investigations and study of this relationship these studies discussed in MDT for collective decision making and treatment planning. The aim of the study was to examine the relationship between malnutrition, systemic inflammation, body composition overall survival and tumour metabolic activity in patients with advanced lung cancer

7.2 Patients and Methods

Patients with advanced lung cancer who had PET-CT carried out from August 2008 to April 2016 at Beatson West of Scotland PET CT Centre prior to radiotherapy were included in analysis (n=335) based on The European Association of Nuclear Medicine guidelines (Boellaard, Delgado-Bolton et al. 2015). 13 patients with TNM stage II were excluded. 322 patients with stage III-IV were included in final analysis as shown in Figure 7.1. Overall study end point was overall survival. Patients were injected with 368 mb of 18F- FDG. Low dose CT in addition to PET CT was carried out for attenuation correction and anatomical localisation.

SUV Max and tumour size was reported and obtained from radiology reporting. Patients were classified depending upon PET FDG avidity as shown in Table 7.2. We defined patients into three groups SUVmax <5 as "low", 5-10 as "moderate" >10 gram/ml as "intense" (Hofman and Hicks 2016).

MUST score (see Figure 1.1) was obtained from pre-treatment oncology assessment prior to commencing radiotherapy. Modified frailty index (mFI) is 11 items co-morbidity score (see Table 1.1) and classified into four groups as shown in Table 1.2. Inflammatory markers modified Glasgow prognostic score (mGPS) and neutrophil lymphocyte ratio (NLR) were obtained from pre-treatment bloods. Longitudinal analysis was carried out 3/12 following completion of radiotherapy.

L3 DICOM image was selected from staging CT scans performed within 3 months of starting radiotherapy. The DICOM image was analysed using image J (NIH version 1.47, http://rsbweb.nih.gov/ij/) for measurement of total fat area (TFA), subcutaneous fat area (SFA), visceral fat area (VFA), skeletal muscle area (SMA) and skeletal muscle density (SMD) using thresholds of -190 to -30 for fat and -29 to +150 for skeletal muscles .TFA, SFA, VFA and SMA were normalised for height in squared meters ^{2} to obtain total fat

index (TFI), subcutaneous fat index (SFI), visceral fat index (VFI) and skeletal muscle index (SMI). These patients were further classified using widely accepted thresholds studied in similar patient populations as shown in Table 1.3.2. Ebadi et al. threshold for subcutaneous adiposity (Ebadi, Martin et al. 2017), Doyle et al. threshold for visceral obesity (Doyle, Bennett et al. 2013) and Martin et al. threshold for SMI and SMD (Martin, Birdsell et al. 2013). 40 test scans were analysed by two investigators (TA, RD) with inter class correlation coefficients (ICCC) 0.999 for TFA and VFA; 0.996 for SMA and 0.993 for SMD respectively.

The relationship between clinicopathological characteristics including MUST, mFI, ECOG-PS, systemic inflammation body composition and 12 months survival was examined as stratified by SUV Max is shown in Table 7.1.

Longitudinal data were collected in this population 3 months post radiotherapy. The longitudinal data were available for MUST, ECOG-PS, NLR, mGPS and body composition analysis carried out using same thresholds on follow up CT scans post treatment. The relationship between post treatment MUST, ECOG-PS, NLR, mGPS and body composition was examined (see Table 7.2).

Statistical Analysis

Chi square test was used for analysis of categorical variables. Cox proportional hazards model was used to calculate HR and 95% CI for overall survival. Kaplan Meier curve was used for survival analysis. Overall survival was calculated in months from the date of diagnosis using CT until death or censored if alive at follow up date of 1st June 2020. Significant variables ($P<0.1$) were entered multivariate analysis in backward conditional manner. P- value <0.05 was considered significant. The statistical analysis was performed using SPSS software version 25 (IBM Corporation, 2017, Armonk, NY).

Median duration of follow up was 10 months. By the censor date, 8 patients (2.5%) were alive and 314 (97.5%) were dead. The median overall survival was 14 months.

34 patients also had longitudinal PET available. SUV max increased in patients with available longitudinal scan in advanced cancer (Median 14.9 with range 2.9 – 25.5).

7.3 Results

The majority of patients were male (53%), over 65 (73%), medium malnutrition risk (53%), ASA III (65%), frail (75% group III-IV), NSCLC (93%), ECOG-PS 0-1 (65%), NLR >3 (60%) and mGPS 1/2 (71%). Median tumour size was 4.5 cm (range 0.7 – 14.5).

FDG SUV max uptake as shown in Table 7.1 was significantly associated with modified frailty index (p=0.007) and mGPS (p=0.001) and not associated to pre-treatment age (p=0.575), sex (p=0.698), BMI (p=0.879), MUST (p=0.158), ASA (0.756), ECOG-PS (0.471), NLR (p=0.629), low SMI (0.857). It was significantly associated with 12 months overall survival (p<0.001). Frailty (p=0.007), SIR score i.e. mGPS were associated with increased tumour metabolic activity.

The relationship between available post radiotherapy variables and FDG SUVmax uptake was shown in Table 7.2. This was significantly associated with post treatment MUST (p=0.049). However, was not significant for post treatment ECOG (p=0.132), NLR (0.143), mGPS (p=0.128), SMI (p=0.747) and SMD (0.649).

Inflammation was shown to play an important role in muscle loss and frailty. PET activity was related to systemic inflammation. Tumour metabolic activity was strongly associated with overall survival. As tumour metabolic activity increases, this was associated with increase in proportion of patients with low SMI (71% of patients with low SMI in post treatment group as compared to 40% in pre-treatment group in intense uptake). 66% of patients had low SMD in pre-treatment group as compared to 81% of patients in post treatment group. As tumour metabolic activity increases, SMI and SMD decrease.

The relationship between clinicopathological , malnutrition, systemic inflammation, overall survival in patients with advanced lung cancer using Cox-proportional hazard model was shown in Table 7.3. On univariate analysis, MUST (p=0.007), mFI, TNM

stage, SUV Max uptake (p <0.0001 each), ECOG-PS (p=0.001), mGPS (<0.0001) were associated with overall survival. On multivariate analysis, MUST (HR 1.25; 95% CI , 1.05-1.47, p=0.010), mFI (HR 1.26; 95% CI 1.10-1.45, p<0.0001), TNM stage (HR 1.61; 95% CI 1.27-2.03, p<0.0001), SUV max uptake (HR 1.65; 95% CI 1.32-2.07, p<0.0001) and mGPS (HR 1.26; 95% CI 1.10-1.45, p=0.001) were independently associated with overall survival.

Cox regression analysis for effect of available post treatment variables and overall survival was shown in Table 7.4. On univariate analysis, post treatment MUST, ECOG-PS and mGPS were significantly associated with overall survival (p<0.0001). On multivariate analysis, post treatment MUST (HR 1.60; 95% CI 1.35-1.90, p<0.0001), ECOG-PS (HR 1.31; 95% CI 1.13-1.52, p<0.0001) and mGPS HR, 1.26 95% C.I. 1.07 – 1.50, p=0.007) were independently associated with overall survival. The longitudinal nutritional, performance status and inflammatory status evaluation had independent prognostic value.

Multivariate analysis for significant factors was shown in Table 7.5. As compared to group 1 mFI, group II, group III and group IV had progressive increase in mortality with OR of 1.40, 2.067 and 2.42 respectively. As compared to non-inflamed patients with mGPS=0, OR of patients with mGPS=1 and mGPS=2 were 1.23 and 1.78 respectively. There is increased mortality risk as frailty and inflammation increases.

Kaplan Meier survival analysis curve was shown in Fig. 7.3. In this analysis, there were 10 patients in low FDG uptake cohort and none of them died over 12-month period. In contrast, in intense FDG uptake cohort 113 patients died over this study period.

7.4 **Discussion**

This study demonstrates that tumour metabolic activity measured by SUV max is associated with frailty, mGPS and overall survival. Malnutrition, frailty, TNM stage, mGPS, SUV uptake were independently associated with overall survival. Patients who are malnourished, frail, poor ECOG-PS, advanced stage, inflamed and sarcopenic constitute the worst phenotype. These patients should have realistic discussions and considered for palliation with end of life care discussion and DNACPR in place. Indeed, these patients have very poor prognosis and will benefit from hospice care.

Longitudinal assessment of nutritional status using MUST score, objective ECOG and inflammatory assessment can help in decision making and source utilization. With advanced lung cancer, these commonly bed side evaluations hold independent prognostic value. While CT does provide objective body composition evaluation, it does not hold independent prognostic value when compared to other clinical measures in this cohort. mFI data were easily obtained from electronic clinical portal and can indirectly be used for frailty assessment.

This study had few limitations. Firstly, this is retrospective study and comes with limitations associated with this study design. Secondly, is small sample size. Thirdly, PET activity was assessed using radiologist reporting and other measures of PET activity like TMV (tumor metabolic volume) and TLG (total lesion glycolysis) were not available. However, this study provides important prognostic information about interaction between tumour and host characteristics. This study also combines comprehensive tumour and host characteristics to aid in treatment decision algorithm in patients with advanced lung cancer.

Conclusion:

In patients with advanced lung cancer, there is progressive increase in inflammatory response, worsening malnutrition, frailty, loss of visceral adipose tissue, low SMI and low SMD. Tumour metabolic activity is related to systemic inflammation and frailty. The elevated host systemic inflammatory response and increased tumour metabolic activity were associated with poor prognosis in patients with advanced lung cancer treated with radiotherapy.

Key Results:

Tumour metabolic activity was associated with increased systemic inflammatory response. Potential treatment strategies should aim at measures to improve the host and tumour factors. Palliative measures should be considered in patients with non-modifiable factors.

7.5 Tables and Footnotes

Table 7.1: The relationship between pre-treatment MUST, clinicopathological characteristics, systemic inflammation, CT derived body composition and overall survival in patients with advanced lung cancer (n=322), by FDG uptake

Characteristics	Total n=322	Low FDG uptake 11 (3.4 %)	Medium FDG uptake 59 (18.3%)	High FDG uptake 252 (78.3%)	p-value
Age, y					0.575
<65	87 (27)	4 (36.4)	13 (22)	70 (27.8)	
65-74	116 (36)	6 (54.5)	23 (39)	87 (34.5)	
>74	119 (37)	1 (9.1)	23 (39)	95 (37.7)	
Sex					0.698
Male	170 (52.8)	6 (54.5)	29 (49.2)	135 (53.6)	
Female	152 (47.2)	5 (45.5)	30 (50.8)	117 (46.4)	
BMI					0.879
<20	49 (15.2)	1 (9.1)	9 (15.3)	39 (15.5)	
20-25	135 (41.9)	4 (36.4)	25 (42.4)	106 (42.1)	
25-30	89 (27.6)	4 (36.4)	19 (32.2)	66 (26.2)	
>30	49 (15.2)	2 (18.2)	6 (10.2)	41 (16.3)	
Pre Rx MUST					0.158

Low risk	99 (30.7)	5 (45.5)	18 (30.5)	76 (30.2)	
Medium risk	169 (52.5)	6 (54.5)	33 (55.9)	130 (51.6)	
High risk	54 (16.8)	0	8 (13.6)	46 (18.3)	
ASA					0.756
II	27 (8.4)	2 (18.2)	4 (6.8)	21 (8.3)	
III	210 (65.2)	7 (63.6)	38 (64.4)	165 (65.5)	
IV	85 (26.4)	2 (18.2)	17 (28.8)	66 (26.2)	
Modified Frailty Index					.007
Group I	12 (3.7)	1 (9.1)	4 (6.8)	7 (2.8)	
Group II	67 (20.8)	6 (54.5)	14 (23.7)	47 (18.7)	
Group III	116 (36)	4 (36.4)	15 (25.4)	97 (38.5)	
Group IV	127 (39.4)	0	26 (44.1)	101 (40.1)	
Cancer Type					0.738
NSCLC	298 (92.5)	10 (90.9)	56 (94.9)	232 (92.1)	
SCLC	24 (7.5)	1 (9.1)	3 (5.1)	20 (7.9)	
TNM					0.476
3	178 (55.3)	8 (72.7)	32 954.2)	138 (54.8)	
4	144 (44.7)	3 (27.3)	27 (45.8)	114 (45.2)	
ECOG					0.471

0-1	209 (64.9)	10 (90.9)	35 (59.3)	164 (65.1)	
2	86 (26.7)	1 (9.1)	19 (32.2)	66 (26.2)	
3	27 (8.4)	0	5 (8.5)	22 (8.7)	
NLR (Pre-Rx)					0.629
<3	128 (39.8)	4 (36.4)	26 (44.1)	98 (38.9)	
3-5	91 (28.3)	5 (45.5)	13 (22)	73 (29)	
>5	103 (32)	2 (18.2)	20 (33.9)	81 (32.1)	
mGPS					0.001
0	95 (29.5)	6 (54.5)	26 (44.1)	63 (25)	
1	87 (27)	4 (36.4)	11 (18.6)	72 (28.6)	
2	140 (43.5)	1 (9.1)	22 (37.3)	117 (46.4)	
Body composition					
Subcutaneous adiposity (Ebadi threshold)					0.817
No	67 (20.8)	2 (18.2)	12 (20.3)	53 (21)	
Yes	255 (79.2)	9 (81.8)	47 (79.7)	199 (79)	
Visceral obesity (Doyle threshold)					0.535
No	73 (22.7)	1 (9.1)	14 (23.7)	58 (23)	

Yes	249 (77.3)	10 (90.9)	45 (76.3)	194 (77)	
Low SMI (Martin threshold)					0.857
No	194 (60.2)	8 (72.7)	32 (54.2)	154 (61.1)	
Yes	128 (39.8)	3 (27.3)	27 (45.8)	98 (38.9)	
Low SMD (Martin threshold)					0.328
No	104 (32.3)	4 (36.4)	14 (23.7)	86 (34.1)	
Yes	218 (67.7)	7 (63.6)	45 (76.3)	166 (65.9)	
Adjuvant Chemotherapy					0.122
Yes	147 (45.7)	9 (81.8)	26 (44.1)	112 (44.4)	
No	175 (54.3)	2 (18.2)	33 (55.9)	140 (55.6)	
Radiotherapy Intent					0.160
Radical	111 (34.5)	5 (45.5)	24 (40.7)	82 (35.8)	
Palliative	211 (65.5)	6 (54.5)	35 (59.3)	170 (67.5)	
Survival					<0.001
12 months survival % (SE)		1 (0)	79 (5)	54 (3)	

Table 7.2: The relationship between post treatment MUST, clinicopathological characteristics, systemic inflammation, CT derived body composition and overall survival in patients with advanced lung cancer (n=322).

Characteristics	Total n=322	Low FDG uptake 11 (3.4 %)	Medium FDG uptake 59 (18.3%)	High FDG uptake 252 (78.3%)	p-value
Post Treatment MUST					0.049
Low risk	22 (6.9)	4 (36.4)	6 (10.2)	12 (4.8)	
Medium risk	79 (24.6)	1 (9.1)	12 (20.3)	66 (26.3)	
High risk	220 (68.5)	6 (54.5)	41 (69.5)	173 (68.9)	
Modified Frailty Index					.007
Group I	12 (3.7)	1 (9.1)	4 (6.8)	7 (2.8)	
Group II	67 (20.8)	6 (54.5)	14 (23.7)	47 (18.7)	
Group III	116 (36)	4 (36.4)	15 (25.4)	97 (38.5)	
Group IV	127 (39.4)	0	26 (44.1)	101 (40.1)	
Post treatment ECOG					0.132
0-1	53 (16.5)	5 (45.5)	10 (16.9)	38 (15.1)	
2	212 (65.8)	5 (45.5)	38 (64.4)	169 (67.1)	
3	57 (17.7)	1 (9.1)	11 (18.6)	45 (17.9)	

NLR (Post-Rx)					0.143
<3	21 (6.6)	1 (9.1)	6 (10.2)	14 (5.6)	
3-5	42 (13.2)	3 (27.3)	7 (11.9)	32 (12.9)	
>5	255 (80.2)	7 (63.6)	46 (78)	202 (81.5)	
mGPS					0.128
0	19 (5.9)	1 (9.1)	5 (8.5)	13 (5.2)	
1	46 (14.4)	4 (36.4)	7 (11.9)	35 (14)	
2	255 (79.7)	6 (54.5)	47 (79.7)	202 (80.8)	
Post Rx Body composition					0.143
Post Rx Subcutaneous adiposity (Ebadi threshold)					
No	108 (34.2)	5 (45.5)	24 (40.7)	79 (32.1)	
Yes	208 (65.8)	6 (54.5)	35 (59.3)	167 (67.9)	
Visceral obesity (Doyle threshold)					0.361
No	117 (37)	4 (36.4)	26 (44.1)	87 (35.4)	
Yes	199 (63)	7 (63.6)	33 (55.9)	159 (64.6)	
Post Rx Low SMI (Martin threshold)					0.747
No	91 (28.8)	2 (18.2)	18 (30.5)	71 (28.9)	

Yes	225 (71.2)	9 (81.8)	41 (69.5)	175 (71.1)	
Low SMD **(Martin threshold)**					0.649
No	60 (19)	4 (36.4)	9 (15.3)	47 (19.1)	
Yes	256 (81)	7 (63.6)	50 (84.7)	199 (80.9)	

Table 7.3: The relationship between clinicopathological characteristics and overall survival in patients with advanced lung cancer: Univariate and multivariate analysis (n=332).

	Univariate analysis		Multivariate analysis	
Variables	HR (95%CI)	p-value	HR (95%CI)	p-value
Clinico-pathological				
Age (<65/65-74/>74)	0.99 (0.85 – 1.14)	0.852		
Sex (Male/Female)	1.04 (0.83 – 1.30)	0.747		
ASA (II-IV)	0.84 (0.68 – 1.04)	0.112		
mFI (I/II/III/IV)	1.38 (1.21-1.57)	<0.0001	1.26 (1.10- 1.45)	<0.0001
TNM stage (III-IV)	1.53 (1.22- 1.93)	<0.0001	1.61 (1.27 – 2.03)	<0.0001
FDG uptake (low/mod/high)	1.68 (1.35-2.09)	<0.0001	1.65 (1.32 – 2.07)	<0.0001
MUST (0/1/≥2)	1.25 (1.06-1.48)	0.007	1.25 (1.05 – 1.47)	0.010
ECOG-PS (0-1/2/3)	1.34 (1.12- 1.60)	0.001		0.591
NLR (<3,3-5,>5)	1.13 (0.99-1.29)	0.075		0.857
mGPS (0/1/2)	1.34 (1.17-1.53)	<0.0001	1.26 (1.10 – 1.45)	0.001
Body Composition				
Subcutaneous adiposity (Ebadi threshold)	1.05 (0.80-1.38)	0.714		
Visceral adiposity	1.02 (0.78 – 1.33)	0.889		

(Doyle threshold)				
Low SMI (Martin threshold)	1.14 (0.91 – 1.43)	0.254		
Low SMD (Martin threshold)	1.16 (0.92 – 1.48)	0.216		

Cox regression analysis, variables with $p<0.1$ on univariate analysis were entered into backward conditional multi variate analysis. P-value <0.05 was considered significant. ASA, American Society of Anaesthesiologists score; mFI, modified Frailty Index; TNM, tumor, node, metastasis.; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil lymphocyte ratio; SMI, skeletal muscle index; SMD, skeletal muscle radiodensity

Table 7.4: The relationship between post radiotherapy clinicopathological characteristics, overall survival in patients with advanced lung cancer: Univariate and multivariate analysis (n=332).

	Univariate analysis		Multivariate analysis	
Variables	HR (95%CI)	p-value	HR (95%CI)	p-value
Clinico-pathological				
Post Rx MUST (0/1/≥2)	1.79 (1.46-2.19)	<0.0001	1.60 (1.35 – 1.90)	<0.0001
Post Rx ECOG-PS (0/1/2/3)	1.56 (1.30 - 1.87)	<0.0001	1.31 (1.13 – 1.52)	<0.0001
Post Rx NLR (<3,3-5,>5)	1.29 (1.05-1.58)	0.016		0.124
Post Rx mGPS (0/1/2)	1.69 (1.36-2.11)	<0.0001	1.26 (1.07 – 1.50)	0.007
Body Composition				
Post Rx Subcutaneous adiposity (Ebadi threshold)	0.99 (0.78-1.25)	0.940		
Post Rx Visceral adiposity (Doyle threshold)	1.07 (0.85 – 1.34)	0.583		
Post Rx Low SMI (Martin threshold)	1.04 (0.81 – 1.33)	0.788		
Post Rx Low SMD (Martin threshold)	1.07 (0.80 – 1.43)	0.661		

Cox regression analysis, variables with p<0.1 on univariate analysis were entered into backward conditional multi variate analysis. P-value <0.05 was considered significant. ASA, American Society of Anaesthesiologists score; mFI, modified Frailty Index; TNM, tumor, node, metastasis.; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil lymphocyte ratio; SMI, skeletal muscle index; SMD, skeletal muscle radio density

Table 7.5. Classification of patients according to modified Frailty Index, MUST and mGPS with mortality. Multivariate analysis

Characteristics	Group I	Group II OR, 95% CI	Group III OR, 95% CI	Group IV OR, 95% CI	p-value
mFI	1	1.40 (0.91-2.16)	2.07 (1.36-3.13)	2.42 (1.59-3.67)	<0.001
MUST 0/1/≥2	1				0.117
mGPS 0/1/2	1	1.23 (.91 – 1.65)	1.78 (1.36 – 2.33)		<0.001

7.6 Figures

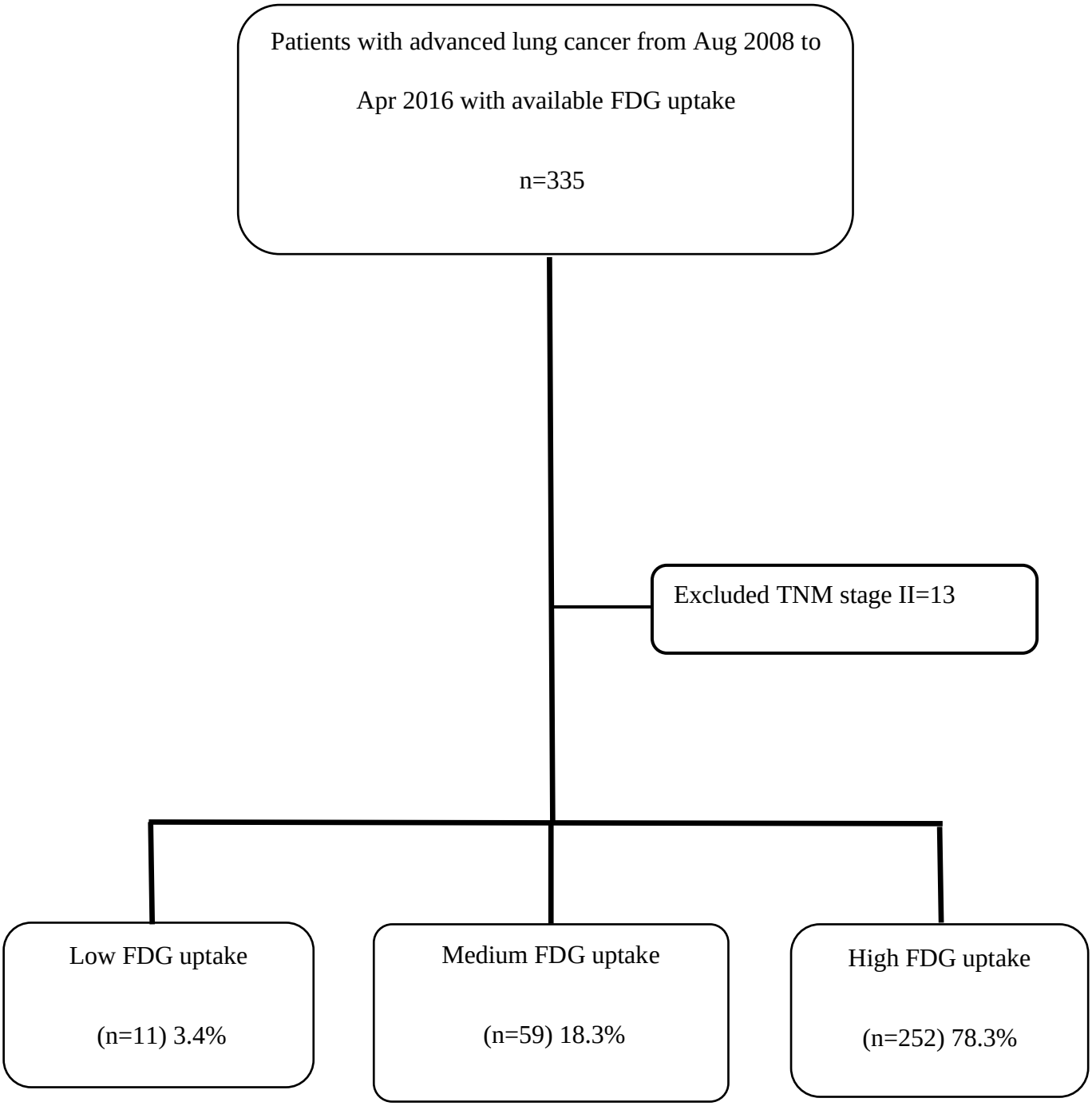


Figure 7.1: A PRISMA Flowchart demonstrating study selection process

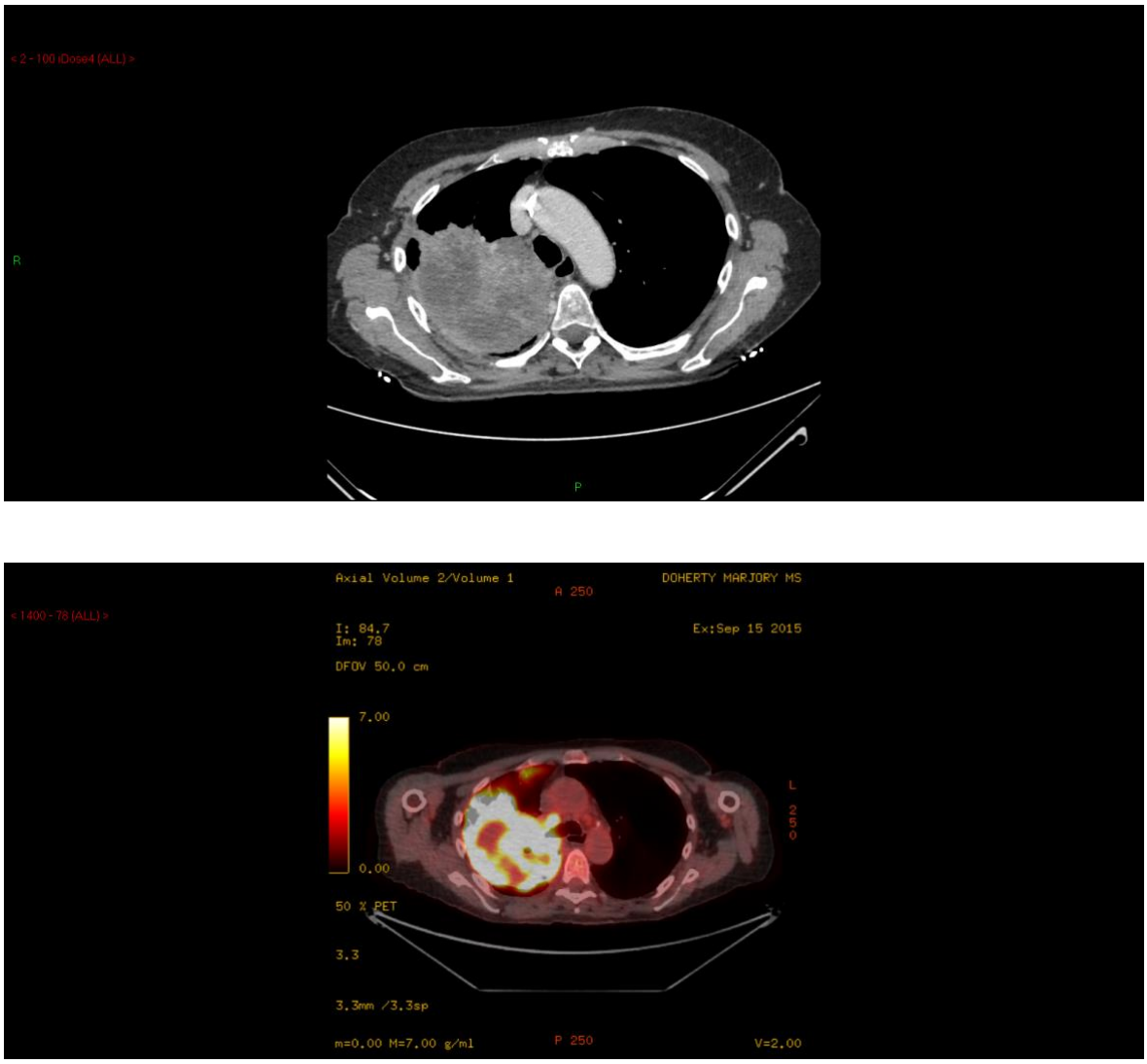
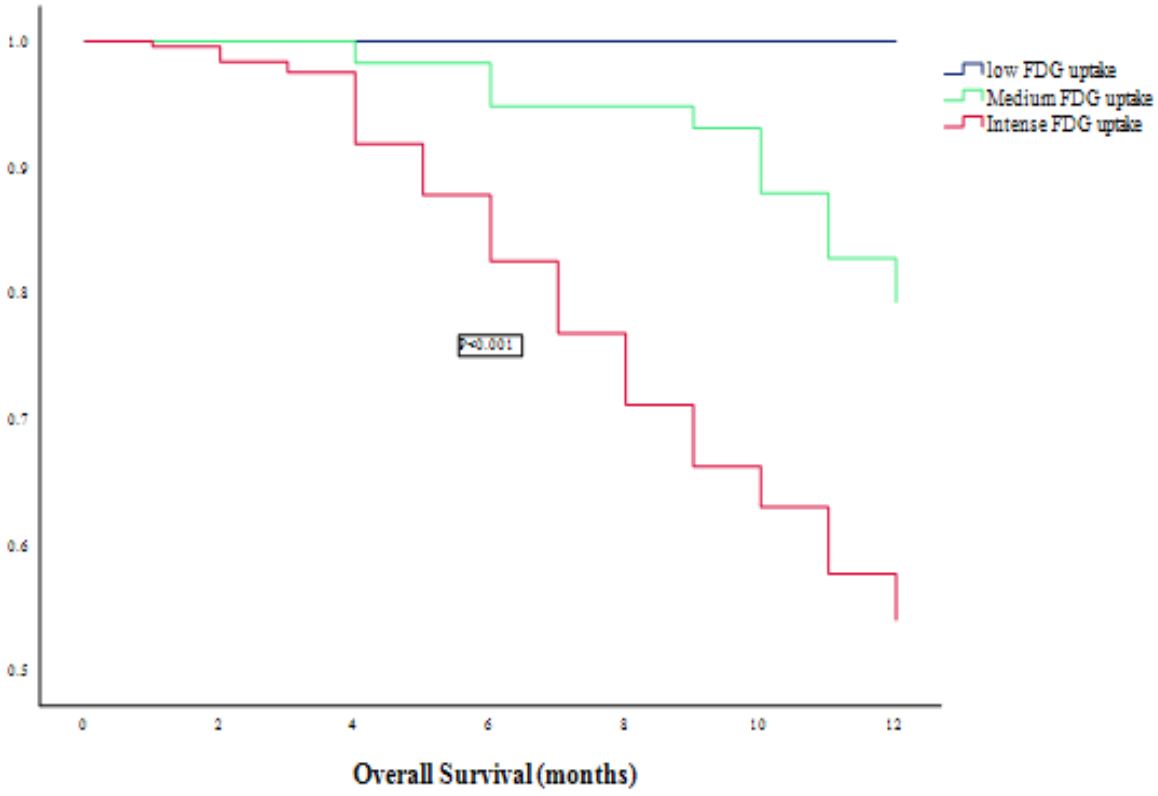


Figure 7.2 FDG avid right lung cancer



Low FDG uptake	10	10	10	10	10	10	10
Medium FDG uptake	58	58	57	55	55	51	46
High FDG uptake	246	242	226	203	175	155	133

Fig 7.3. Overall survival as per FDG tumour uptake

8 CONCLUSIONS/ Discussion

8.1 Overview of thesis

In treatment of patients with cancer, currently staging the tumour is foremost with staging of the host currently a less important formalised process in the treatment decision making process. In this thesis, where both primary operable and advanced inoperable common solid tumours were examined, the patient/ host was staged by using combination of various clinical, pathological, laboratory and radiological parameters. In particular, host nutritional risk was staged using MUST, body composition was staged using CT-scan and systemic inflammation was staged using the mGPS and NLR. Using a common clinical end point of overall survival, the prognostic value of tumour and host staging was compared and this work emphasises the relative importance of host staging and in particular the host systemic inflammatory response. The relative importance of host systemic inflammatory response suggests that it may be an important therapeutic target in the future treatment of host response in patients with cancer.

The results of chapter 1.2 showed the clinical utility of body composition derived from tumour staging CT. In particular, CT is the gold standard investigation for body composition analysis superior to other modalities. Moreover, longitudinal examination of body composition can be readily integrated into routine treatment plans. However, various anatomical landmarks and various muscles have been used in measurements. The anatomical landmark most commonly used is L3.

Among the measures of body composition, SFI, VFI and SMI have clear anatomical, physiological and prognostic value, however, the clinical value of VFD and SMD is less clear. VFD and SMD are affected by the phase of CT. The potential limitations in routine CT reporting of body composition analysis include lack of standardisation in terminology,

methodology and interpretation. Given the increasing number of groups active in body composition along with development of semi-automated and automated softwares, it is hoped that reference ranges according to age, sex, ethnicity and BMI will be standardised and this will indirectly help in routine reporting of body composition results when reporting CT results. Patients with low SMI will be flagged up to treating clinicians and targeted measures will be commenced to improve the host status. The use of artificial intelligence to create a large data base globally will help to identify the reference ranges for patients with cancer. In body composition, use of automated segmentation by use of artificial intelligence is getting increasing popularity and this is likely to replace manual segmentation in future (Dijk, Volmer et al. 2023). While use of machine learning in diagnosis, operative video analysis and image interpretation is being considered to improve patient outcomes (Hashimoto, Rosman et al. 2018). One limitation of artificial intelligence (AI) in the field of body composition is that this relies heavily on available data that may be biased. For body composition to gain widespread application in clinical practice, standardised practice using accepted terminology, software, muscle group selection and prognostic thresholds are required.

The results of chapter 1.3 report that in a systematic review of approximately 10,000 patients with cancer, there was consistent association between CT-derived SMI and SMD and systemic inflammatory response. There were 23 included studies which were mostly retrospective cross sectional studies from single centre. Because of the limitations of study design in these studies, it was not possible to determine the cause or effect relationship whether low SMI was the cause of increased systemic inflammatory response or whether increased systemic inflammatory response led to low SMI. Since there is little evidence that increasing muscle mass is associated with reduction in cancer associated inflammation, a possible explanation is that host experiences a pro inflammatory state

which leads to low SMI. This relationship between SIR and SMI has significant impact on definition and treatment of cancer cachexia. Large prospective multicentric studies including cancers with good and poor prognosis are required to better understand the relationship and apply these findings into routine clinical practice.

Chapter 2, compared the psoas and whole skeletal muscles at L3 level in 1002 patients with primary operable CRC. The studies involving whole L3 skeletal muscles outnumber the psoas muscle selection for body composition analysis. Although, psoas muscle measurements are less time consuming and moderately correlated with L3 SMI, only L3 SMI had independent prognostic value. Because low SMI is related to elevated systemic inflammatory response (Abbass, Dolan et al. 2019), furthermore, nutrition is an important component of treatment of patients with cancer, these were studied together in chapter 3 and 4. Moreover, the cancers where L3 area is not imaged routinely, alternative reliable landmarks providing reliable body composition analysis are required. Further longitudinal studies, involving operable and advanced cancers with semi-automated and automated soft wares are required.

In Chapter 3, in approximately 1000 patients with operable CRC, the relationship between MUST, SIR and CT derived body composition were examined. Both in patients with low to medium/ high nutrition risk, elevated mGPS was associated with low SMI, greater length of hospital stay and poorer 3 year overall survival. The combined assessment of MUST and mGPS has complementary value and cachexia may be defined as disease related inflammation with malnutrition. In patients with operable CRC, mGPS was an important measure of nutritional assessment. However, these findings are from retrospective cross sectional study from single institution and confirmatory multicentre longitudinal studies will be required. Nutritional supplements containing arginine,

glutamine and β-hydroxy-β-methylybutyrate are proposed to counteract low SMI in patients with cancer, further large longitudinal studies are required to clarify the use of nutritional supplements in patients with cancer (Berk, James et al. 2008). Since, SIR was associated with SMI and SMD, addressing the inflammation will help to target measures at reducing muscle wasting.

In chapter 4, the relationship between MUST, ECOG-PS, SIR and CT derived body composition were examined in 643 patients with advanced lung cancer. 71% of these patients were at moderate/high malnutrition risk. The results of chapter 4 report that in patients with advanced lung cancer, higher MUST score was associated with poor performance status, raised host inflammatory response and low SMI. Higher MUST, poor performance status and raised inflammatory response were associated with poor overall survival and had independent prognostic value. MUST had independent prognostic value, whereas body composition measures did not. Therefore, nutritional assessment by experienced nutritionist along with performance status and SIR assessment were important components in treatment decision making process. These studies are limited by retrospective design from single institution. In operable CRC (chapter 3) and advanced LC (chapter 4), SIR has prognostic value. This MUST, ECOG and mGPS combined framework provides comprehensive value to identify patients amenable to targeted treatment. In EXPAND II trial with 761 patients with upper gastrointestinal cancers, mGPS was related to skeletal muscle index and density and had superior prognostic value when compared to body composition parameters (Hacker, Hasenclever et al. 2022). Large prospective longitudinal studies are required to better understand the cause effect relationship.

Chapter 5 examined the longitudinal relationship between MUST, SIR and CT derived body composition in 494 patients with available post treatment CT. Over 3/12 period, there was

worsened malnutrition, performance status, mGPS, fat and muscle mass. This change was greater than seen in patients with CRC. There was increase in percentage of patients being inflamed (74% in LC vs 35% in CRC). The loss of muscle was associated with SIR. Loss of muscle mass was not associated with overall survival, whereas changes in MUST, ECOG and SIR were associated with overall survival. This was also supported by a multicentre study involving 307 advanced cancer patients, where prognostic value of mGPS dominated the CT derived body composition (McGovern, Dolan et al. 2023). Therefore, loss of muscle mass should be considered in the context of malnutrition risk, performance status and systemic inflammation. Further, multicentre large scale longitudinal studies are required to verify these observations.

The results of chapter 6 report comparison between operable and inoperable cancers. Since there were salient differences in prognosis between two cancers, CRC and LC were combined to study the differences and identify therapeutic end points. This included 643 patients with advanced lung cancer and 1002 patients with operable colorectal cancer. The hypothesis tumour causes muscle wasting was challenged. The percentage of patients with low SMI were similar between two cancers when normalised for TNM stage. There was large differences in comorbidity, nutrition risk, systemic inflammation and overall survival. Compared to patients with operable CRC, patients with advanced lung cancer had elevated inflammatory response with elevated mGPS and NLR. These observations would support the hypothesis that although prognostic, CT derived body composition analysis primarily reflects patient constitution rather than the effect of tumour stage. The present observations would suggest that body composition features may not be useful clinical end points in the treatment of the progressive nutritional and functional decline of patients with cancer. Further directions should include comparative large scale longitudinal and intervention studies to confirm these observations.

Chapter 7 examined the relationship between MUST, ECOG-PS, frailty and its relationship to SIR and CT derived body composition in 322 patients with advanced lung cancer with available PET-CT scans. This chapter further clarified that patients who were malnourished, frail, inflamed, low SMI and elevated tumour metabolic activity had poorer clinical outcome. These findings, if confirmed in subsequent studies will improve stratification of patients such that patients benefit from treatment e.g. early referral for palliative care. CT derived body composition did not have independent prognostic value in this cohort. In this cohort, elevated tumour metabolic activity and SIR were significantly associated and predicted overall survival. Further, large scale longitudinal and interventional studies are required to confirm these findings.

It is now clear that different cancer types present with varying magnitude of SIR and the presence of SIR occurs early in cancer path and increases during the course of cancer progression. This was the case in the present thesis (e.g. primary operable CRC vs lung cancer). The importance of such findings are supported with recent evidence that where nutritional support in patients with high CRP >100 was not associated with nutritional and survival benefit (Bargetzi, Bargetzi et al. 2021). It is likely that as our understanding of cancer and host factors increase, individualised approach by taking into consideration the tumour and host characteristics will form the basis of personalised treatment. For example, immunotherapy by modulating the host immune response to tumour is increasingly being used in patients with cancer e.g., use of nivolumab, pembrolizumab and ipilimumab in patients with lung cancer. However, the patients with elevated mGPS are unlikely to benefit from this therapy (Huai, Luo et al. 2023, Tanimura, Takeda et al. 2023). The mGPS can also, be used to stratify patients likely to have cancer progression when measured longitudinally in oncological treatment before surveillance cross sectional imaging (Saal, Bald et al. 2023). It has been shown that pre-habilitation programme focussed at addressing malnutrition,

frailty, inflammation and body composition are associated with improved post-operative outcomes (Trépanier, Minnella et al. 2019). Pre op malnutrition, elevated mGPS, cachexia and frailty were associated with negative postoperative outcomes in patients undergoing CRC resection. Similar effects were also seen in patients with advanced lung cancer. By taking into consideration the studies included in this thesis, cancer cachexia may be defined as part of disease related inflammation with malnutrition and this concept may be useful in stratifying patients with cancer.

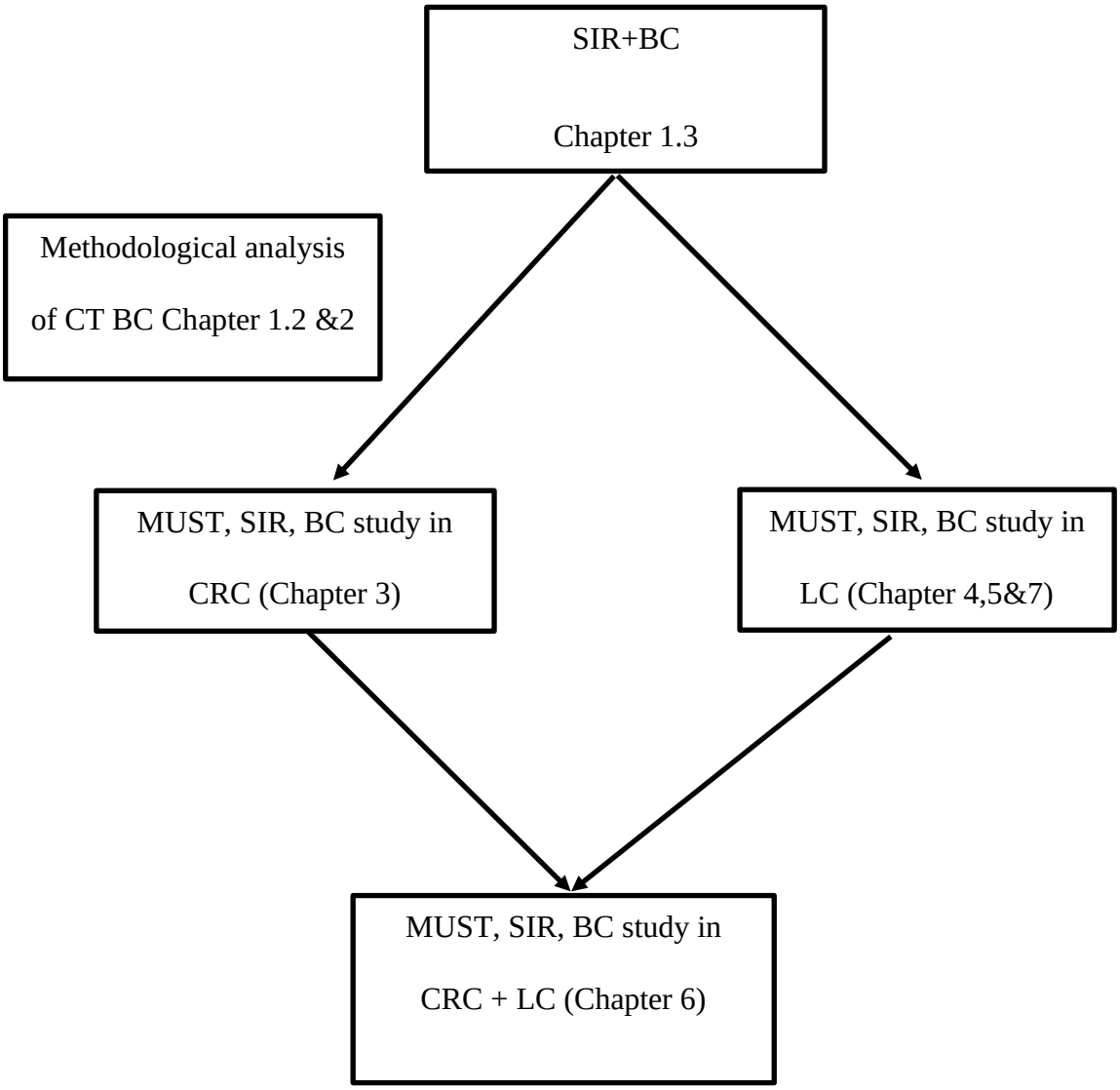


Figure 8.1: Schematic representation of relationships investigated in this thesis and chapters relating to each

8.2 Future work

It is increasingly recognised that, as part of staging the host, malnutrition, frailty, inflammatory status and sarcopenia should be assessed at diagnosis and be included in MDT discussions. These observations will form the basis of multimodal care for the host concurrent with tumour based treatment. It would be proposed that maintaining muscle mass would reduce the toxicity of cancer treatment and improve overall clinical outcomes, including survival. However, it remains to be determined which aspect of such multimodal care is most important. In this respect there a number of important clinical trials to be reported. In particular, the results of the MENAC trial is eagerly awaited (Solheim, Laird et al. 2018). Also, the results of anamorelin trials will inform on the best approach to maintain muscle mass (Taniguchi, Mikura et al. 2023). From the work in the present thesis it is likely that systemic inflammation will be an important component in improving the efficacy of treatment of patients with cancer.

Limitations

This thesis had various limitations. Muscle strength was not included and variables such as walking speed, grip strength and walk up and go which are synonymous with low skeletal muscle index were not included. The studies included retrospective study analysis and come with limitations associated with such study design. The included studies were retrospective from single centre based in the West of Scotland. In longitudinal LC study, follow up CT was analysed at 3/12 interval as most of these patients has short overall survival and meaningful changes in SIR and BC were present for analysis.

Final Thoughts

MUST, SIR and BC are important components of host assessment. Nutritional assessment combined with SIR provides an important component for assessment of cachexia. While staging the tumour is very important part of cancer treatment, staging the host by combining clinical, laboratory and CT body composition assessment are very important factors to consider for providing best outcome in care of patients with cancer.

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Appendices

Appendix A: Sample study selection proforma for systematic review

Study name and reference =

Checklist for inclusion

Is the study included relevant with regards to topic selected (body composition using CT, Systemic inflammation and is in cancer patients?	
If yes- what is conclusion?	
If yes examine below by using relevant checklist, printed and filled as correctly as possible	

Authors Year (Reference)	Type of study	N (F/M)	Age and duration of studied population	country	Single/ Multicentre	Systemic inflammation measured using which parameters	Body composition measured using CT	Any other measure of body composition used	Which cancer studied	Stage Metastatic/ advanced/ non- metastatic	Rx offered	FU (months)	Comments Cut-off male/ female/ %low SMI	Outcome (survival) OS, CSS, DFS

Appendix B: Sample STROBE checklist for reporting observational studies

	Item No.	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		

Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Appendix C: Sample Preferred Reporting Items for Systematic Reviews and Meta-analyses

Section/topic	#	Checklist item	Reported on page #	Comments
TITLE				
Title	1	Identify the report as a systematic review, meta-analysis, or both.		
ABSTRACT				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.		
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of what is already known.		
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).		
METHODS				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.		
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.		
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.		
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.		

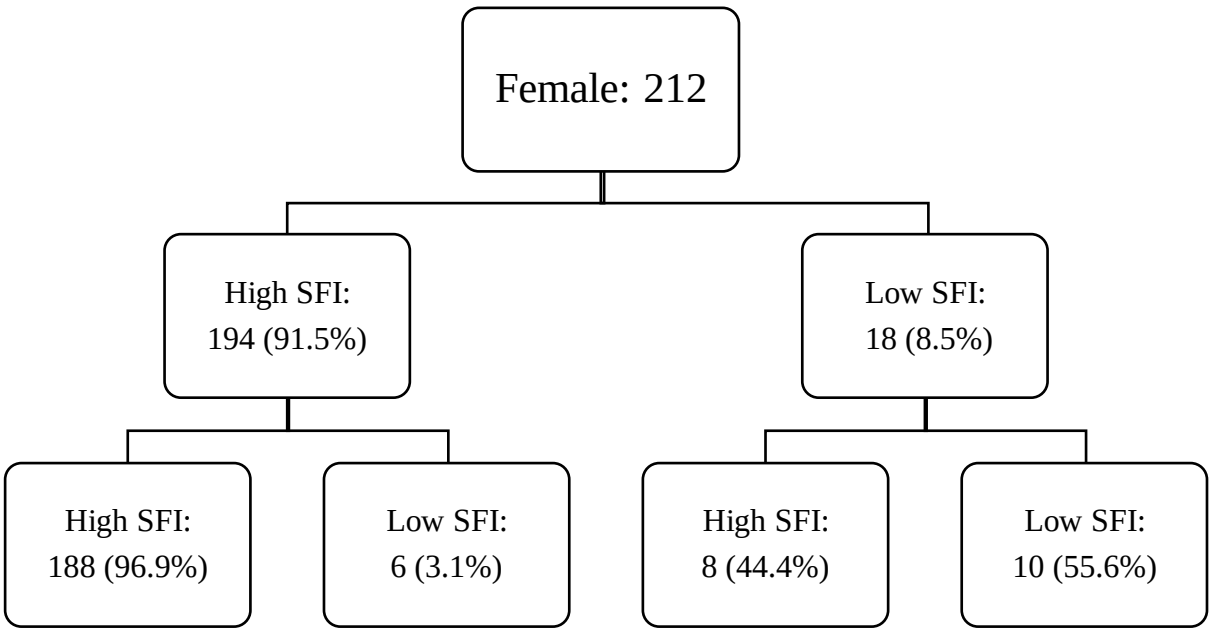
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).		
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.		
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.		
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.		
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).		
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.		

Section/topic	#	Checklist item	Reported on page #	Comments
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).		
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.		
RESULTS				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.		
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.		
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).		
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.		
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.		
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).		
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).		
DISCUSSION				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).		

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).		
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.		
FUNDING				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.		

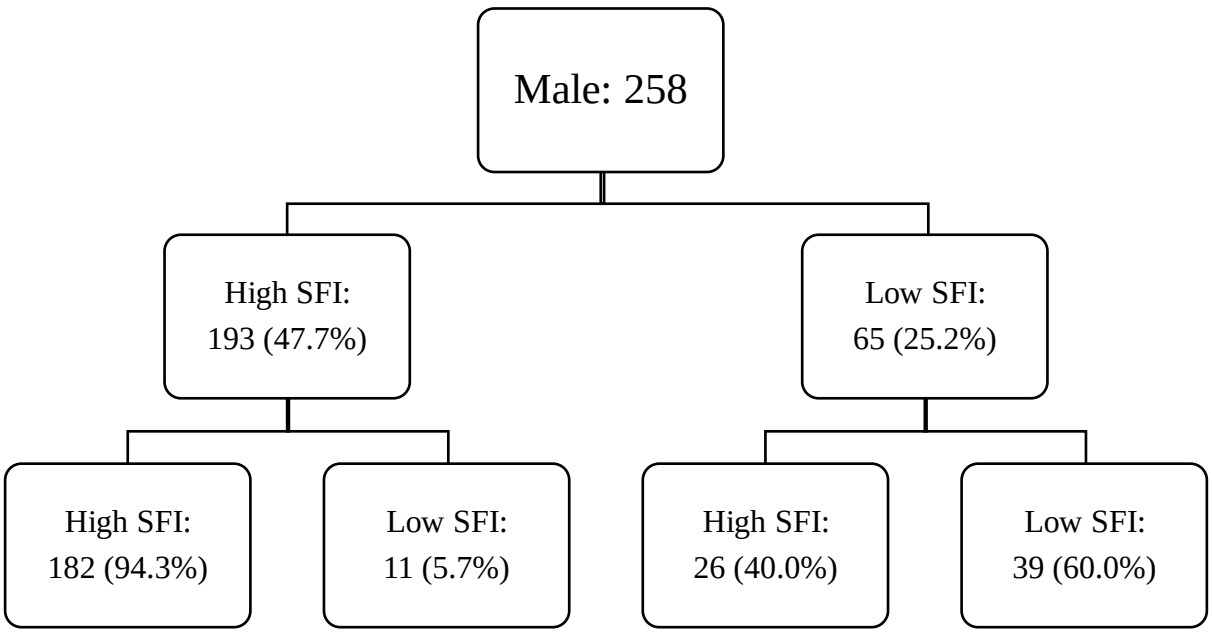
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Appendix D: Longitudinal changes in body composition in patients with lung cancer according to sex



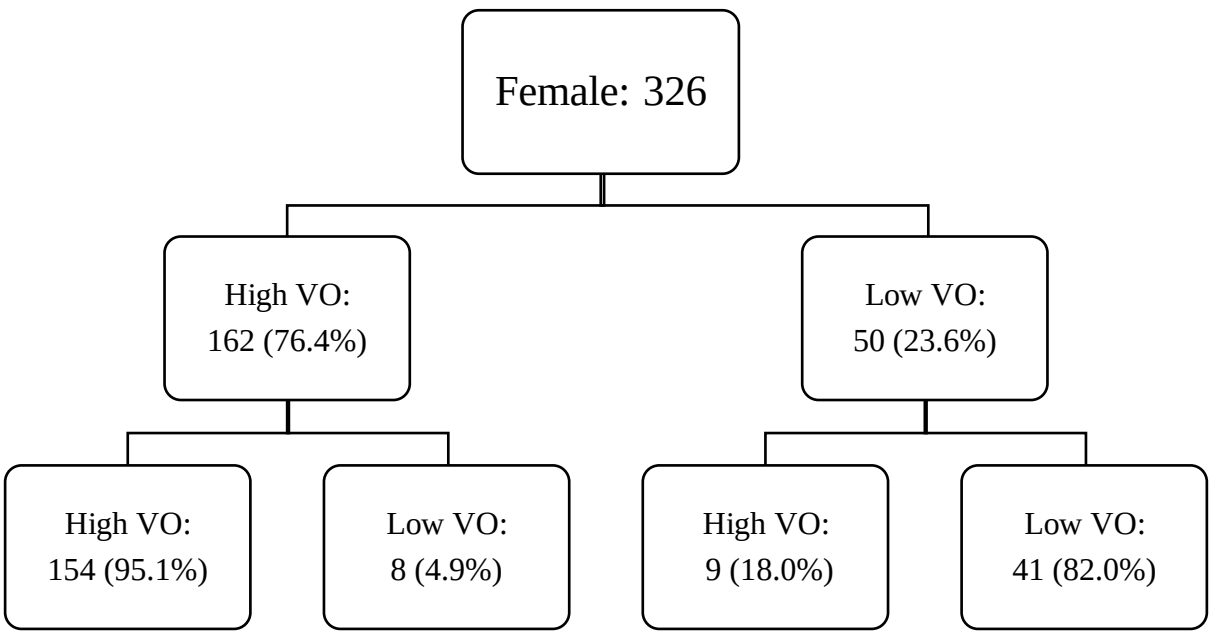
mGPS	**High SFI: 188 (96.9%)**	**Low SFI: 6 (3.1%)**	**High SFI: 8 (44.4%)**	**Low SFI: 10 (55.6%)**
0	147 (78.2)	6 (100)	7 (87.5)	6 (60.0)
1	15 (8.0)	0 (0)	0 (0)	1 (10.0)
2	26 (13.8)	0 (0)	1 (12.5)	3 (30.0)
NLR				
<3	106 (56.4)	4 (66.7)	4 (50.0)	6 (60.0)
3-5	60 (31.9)	2 (33.3)	4 (50.0)	3 (30.0)
>5	22 (11.7)	0 (0)	0 (0)	1 (10.0)

Figure D.1: Prisma diagram of changes SFI between initial staging and follow up CT scans in female patients undergoing surgery for colorectal cancer (n=212) with changes in inflammatory markers in pre and post treatment period



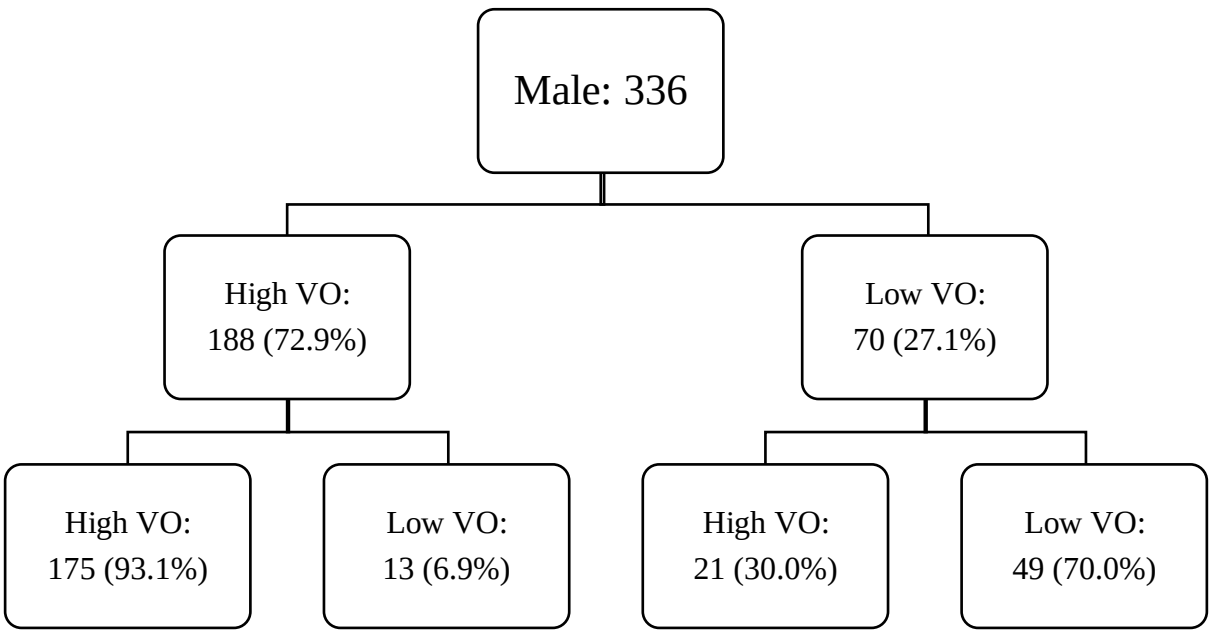
mGPS	**High SFI: 182 (94.3%)**	**Low SFI: 11 (5.7%)**	**High SFI: 26 (40.0%)**	**Low SFI: 39 (60.0%)**
0	141 (77.5)	7 (63.6)	17 (65.4)	33 (84.6)
1	20 (11.0)	2 (18.2)	4 (15.4)	4 (10.3)
2	21 (11.5)	2 (18.2)	5 (19.2)	2 (5.1)
NLR				
<3	105 (57.7)	7 (63.6)	7 (26.9)	15 (38.5)
3-5	50 (27.5)	4 (36.4)	11 (42.3)	17 (43.6)
>5	27 (14.8)	0 (0)	8 (30.8)	7 (17.9)

Figure D.2: Prisma diagram of changes SFI between initial staging and follow up CT scans in male patients undergoing surgery for colorectal cancer (n=258) with changes in inflammatory markers in pre and post treatment period



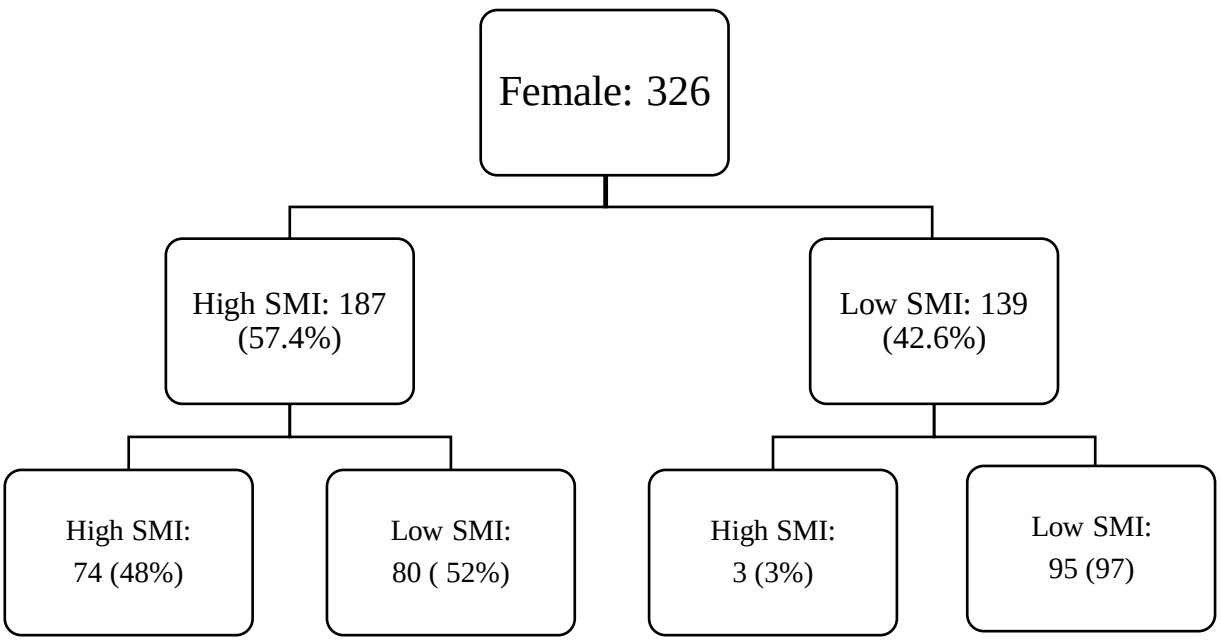
mGPS	**High VO: 154 (95.1%)**	**Low VO: 8 (4.9%)**	**High VO: 9 (18.0%)**	**Low VO: 41 (82.0%)**
0	117 (76.0)	7 (87.5)	8 (88.9)	34 (82.9)
1	14 (9.1)	0 (0)	0 (0)	2 (4.9)
2	23 (14.9)	1 (12.5)	1 (11.1)	5 (12.2)
NLR				
<3	82 (53.2)	5 (62.5)	6 (66.7)	27 (65.9)
3-5	53 (34.4)	2 (25.0)	3 (33.3)	11 (26.8)
>5	19 (12.3)	1 (12.5)	0 (0)	3 (7.3)

Figure D.3: Prisma diagram of changes VO between initial staging and follow up CT scans in female patients with advanced lung cancer (n=326) with changes in inflammatory markers in pre and post treatment period.



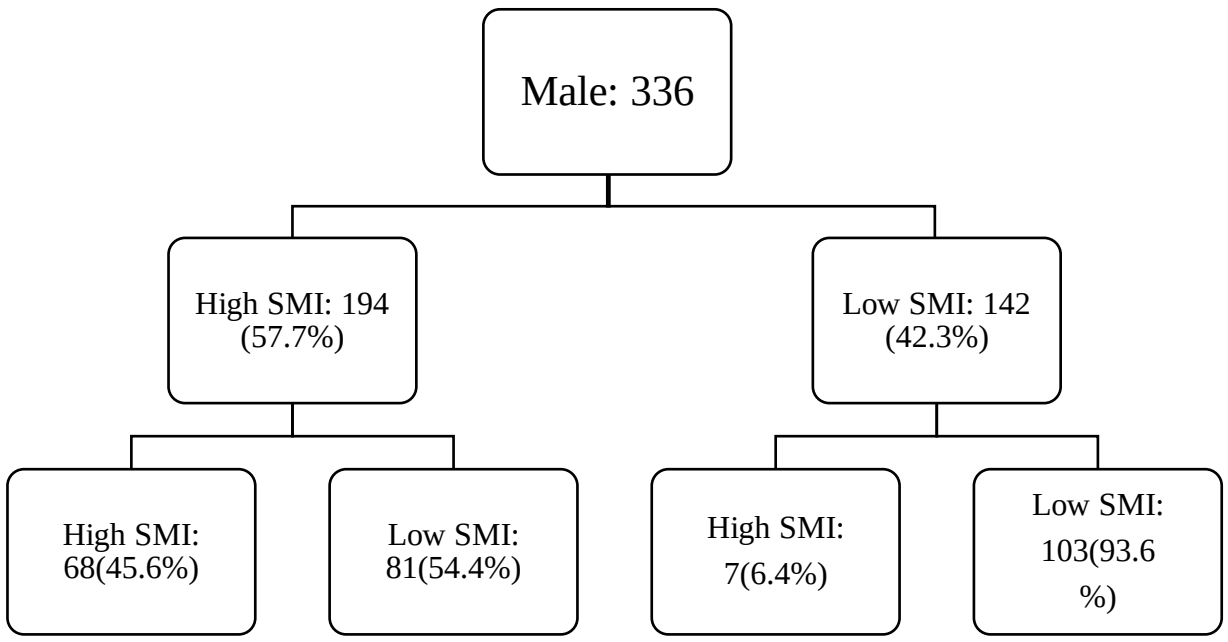
mGPS	**High VO: 175 (93.1%)**	**Low VO: 13 (6.9%)**	**High VO: 21 (30.0%)**	**Low VO: 49 (70.0%)**
0	136 (77.7)	11 (84.6)	12 (57.1)	39 (79.6)
1	21 (12.0)	2 (15.4)	2 (9.5)	5 (10.2)
2	18 (10.3)	0 (0)	7 (33.3)	5 (10.2)
NLR				
<3	98 (56.0)	9 (69.2)	6 (28.6)	21 (42.9)
3-5	54 (30.9)	3 (23.1)	11 (52.4)	14 (28.6)
>5	23 (13.1)	1 (7.7)	4 (19.0)	14 (28.6)

Figure D.4: Prisma diagram of changes VO between initial staging and follow up CT scans in male patients with advanced lung cancer (n=336) with changes in inflammatory markers in pre and post treatment period.



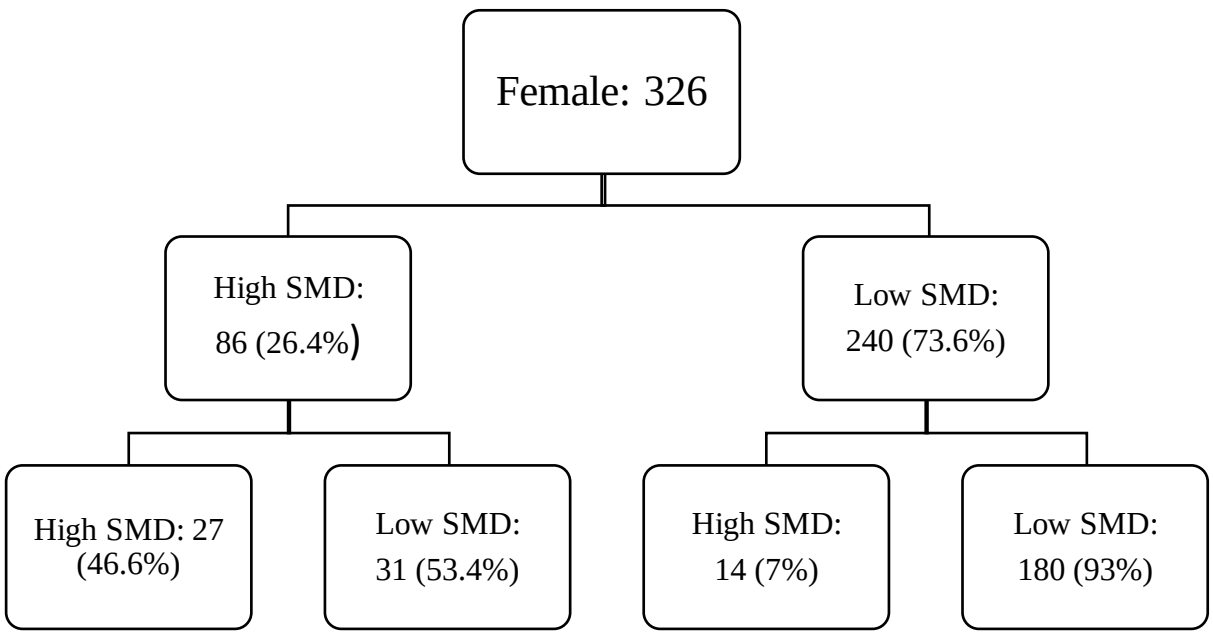
mGPS	**High SMI: 74 (48%)**	**Low SMI: 80 (52%)**	**High SMI: 3 (3%)**	**Low SMI: 95 (97%)**
0	20 (27) ➔5 (6.8)	25 (31.3)➔7 (8.8)	1 (33.3)➔0	24 (25.3)➔2 (2)
1	31 (42) ➔14 (19.2)	28 (35)➔17 (21.3)	0 ➔0	23 (24.2)➔18 (19)
2	23 (31) ➔54 (74)	27 (33.8)➔56 (70)	2 (66.7)➔3 (100)	48 (50.5)➔75 (79)
NLR				
<3	28 (37.8)➔3 (4.1)	35 (43.8)➔6 (7.6)	1 (33.3)➔0	32 (33.7)➔9 (9.5)
3-5	23 (31.1)➔14 (19.2)	30 (37.5)➔11 (13.9)	1 (33.3)➔0	24 (25.3)➔14 (14.7)
>5	23 (31.1)➔ 56 (76.7)	15 (18.8)➔62 (78.5)	1 (33.3)➔ 3 (100)	39 (41.1)➔72 (75.8)

Figure D.5: Prisma diagram of changes SMI (Martin) between initial staging and follow up CT scans in female patients with advanced lung cancer (n=336) with changes in inflammatory markers in pre and post treatment period



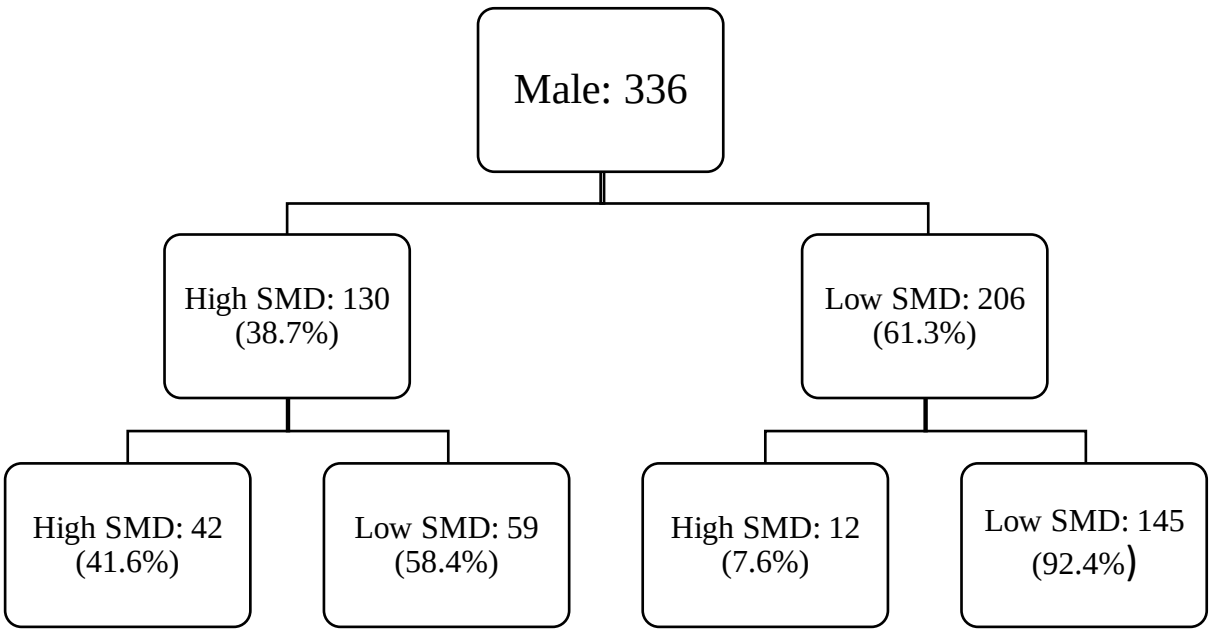
mGPS	**High SMI: 68 (45.6%)** **Pre & post DXT**	**Low SMI: 81 (54.4%)** **Pre & post DXT**	**High SMI: 7 (6.4%)** **Pre & post DXT**	**Low SMI: 103 (93.6%) Pre & post DXT**
0	22 (32.4)➔5(7.5)	19 (23.5) ➔5 (6.3)	3 (42.9)➔1 (14.3)	22 (21.4)➔7 (6.8)
1	14 (20.6)➔8 (11.9)	27 (33.3) ➔14 (17.5)	2 (28.6)➔0	20 (19.4)➔7 (6.8)
2	32 (47.1)➔54(80.6)	35 (43.2) ➔ 61 (76.3)	2 (28.6)➔6 (85.7)	61 (59.2)➔89 (86.4)
NLR				
<3	28 (41.2)➔5 (7.5)	26 (32.1)➔5 (6.2)	2 (28.6)➔1 (14.3)	35 (34)➔5 (4.69)
3-5	23 (33.8)➔9 (13.4)	22 (27.2)➔11 (13.6)	3 (42.9)➔1 (14.3)	31 (30)➔16 (15.5)
>5	17 (25)➔53 (79.1)	33 (40.7)➔65 (80.2)	2 (28.6)➔5 (71.4)	37 (36)➔82 (79.6)

Figure D.6: Prisma diagram of changes SMI (Martin) between initial staging and follow up CT scans in male patients with advanced lung cancer (n=336) with changes in inflammatory markers in pre and post treatment period



mGPS	**High SMD: 27 (46.6%)**	**Low SMD: 31 (53.4%)**	**High SMD: 14 (7%)**	**Low SMD: 180 (93%)**
0	11 (40.7)➔2 (7.4)	7 (22.6) ➔1 (3.2)	8 (57.1) ➔2 (14.3)	44 (24.4) ➔9 (5)
1	8 (29.6)➔4 (14.8)	13 (41.9) ➔11 (35.5)	3 (21.4) ➔4 (28.6)	58 (32.2) ➔30 (17)
2	8 (29.6)➔21 (77.8)	11 (35.5) ➔19 (61.3)	3 (21.4) ➔8 (57.1)	78 (43.3) ➔140 (78)
NLR				
<3	11 (40.7) ➔2 (7.4)	13 (41.9) ➔5 (16.7)	11 (78.6) ➔2 (15.4)	61 (34) ➔9 (5)
3-5	9 (33.3) ➔3 (11.1)	10 (32.3) ➔3 (10)	2 (14.3) ➔3 (23.1)	57 (32) ➔30 (16.7)
>5	7 (25.9) ➔22 (81.5)	8 (25.8) ➔22 (73.3)	1 (7.1) ➔8 (61.5)	62 (34) ➔141 (78.3)

Figure D.7: Prisma diagram of changes SMD (Martin) between initial staging and follow up CT scans in female patients in advanced lung cancer (n=326) with changes in inflammatory markers in pre and post treatment period



mGPS	**High SMD: 42 (41.6%)**	**Low SMD: 59 (58.4%)**	**High SMD: 12 (7.6%)**	**Low SMD: 145 (92.4%)**
0	11 (26.2)➔3 (7.3)	14 (23.7)➔8 (13.6)	4 (33.3)➔1 (8.3)	37 (25.5)➔6 (4.2)
1	9 (21.4)➔3 (7.3)	8 (13.6)➔7 (11.9)	4 (33.3)➔ 3 (25)	42 (29)➔16 (11.1)
2	22 (52.4)➔35 (85.4)	37 (62.7)➔44 (74.6)	4 (33.3)➔8 (66.7)	66 (45.5)➔122 (84.7)
NLR				
<3	17 (40.5)➔3 (7.1)	21 (35.6)➔1 (1.7)	6 (50)➔2 (16.7)	47 (32.4)➔10 (6.9)
3-5	11 (26.2)➔5 (11.9)	17 (28.8)➔5 (8.5)	2 (16.7)➔1 (8.3)	49 (33.8)➔26 (18.1)
>5	14 (33.3)➔34 (81)	21 (35.6)➔53 (89.8)	4 (33.3)➔9 (75)	49 (33.8)➔108 (75)

Figure D.8: Prisma diagram of changes SMD (Martin) between initial staging and follow up CT scans in male patients undergoing radiotherapy for advanced lung cancer (n=336) with changes in inflammatory markers in pre and post treatment period

Appendix E: The relationship between measures of body composition in patients with operable colorectal and advanced lung cancer

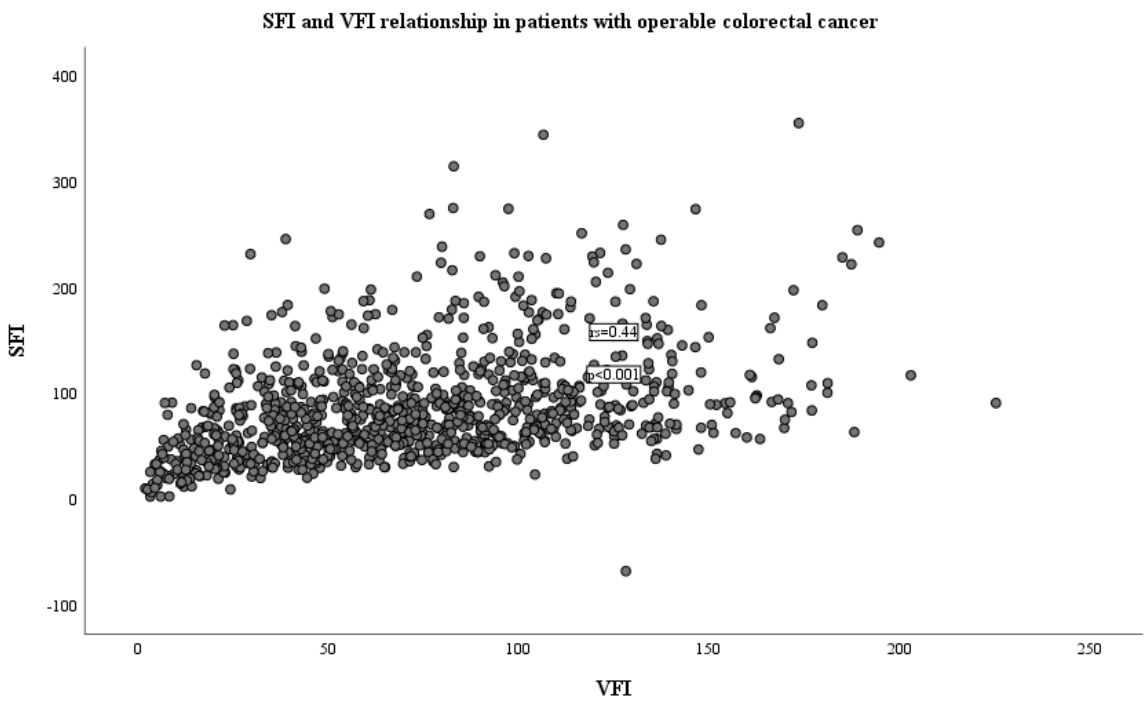


Figure E.1a: Scatter plot of the relationship between subcutaneous fat index and visceral fat index at L3 (n=1002, r_s=0.44, p<0.001)

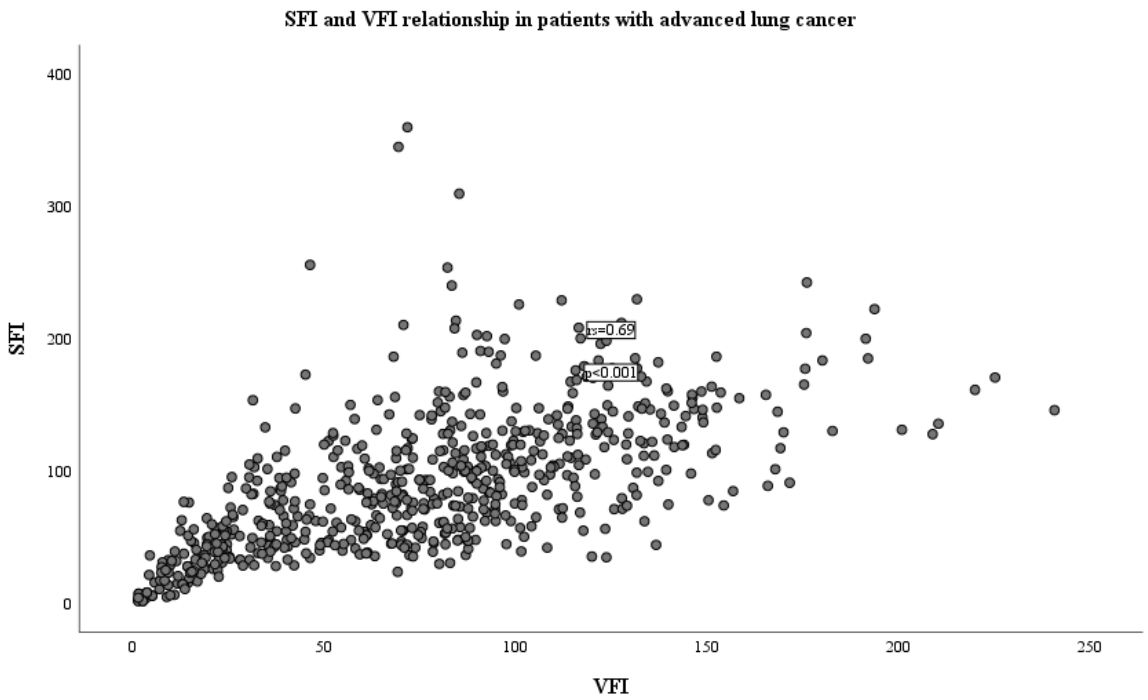


Figure E.1b: Scatter plot of the relationship between subcutaneous fat index and visceral fat index at L3 (n=643, r_s=0.69, p<0.001)

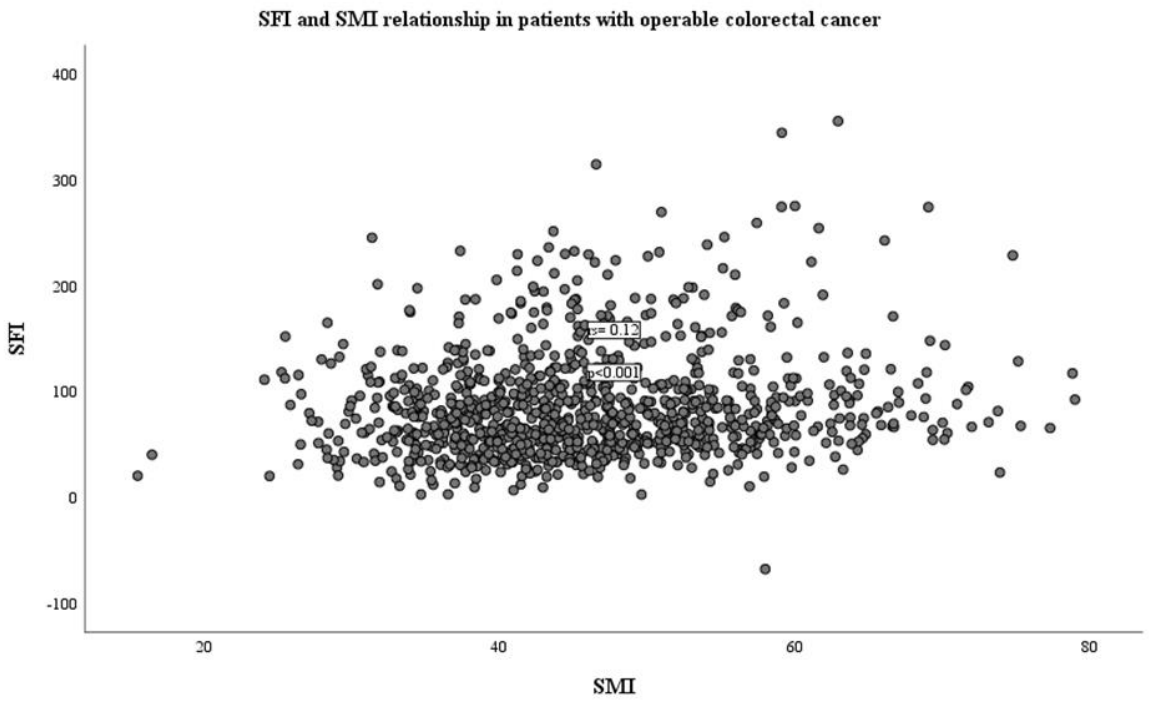


Figure E.2a: Scatter plot of the relationship between subcutaneous fat index and skeletal muscle index at L3 (n=1002, r_s=0.12, p<0.001)

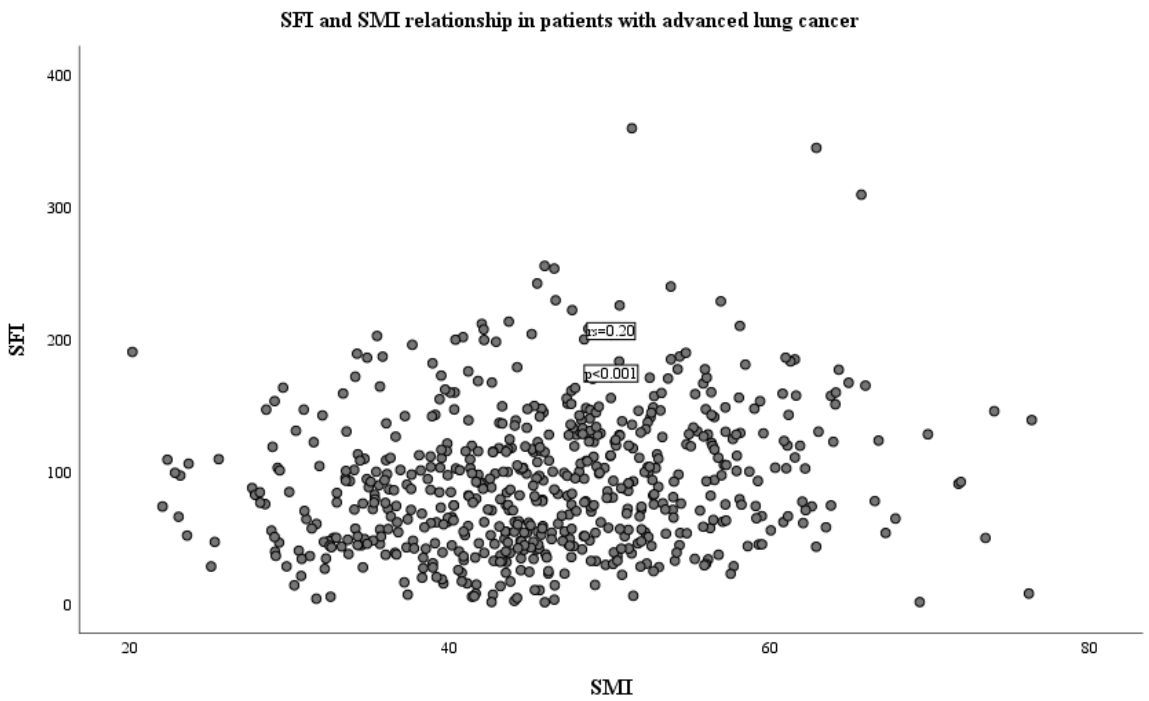


Figure E.2b: Scatter plot of the relationship between subcutaneous fat index and skeletal muscle index (n=630, r_s=0.20, p<0.001)

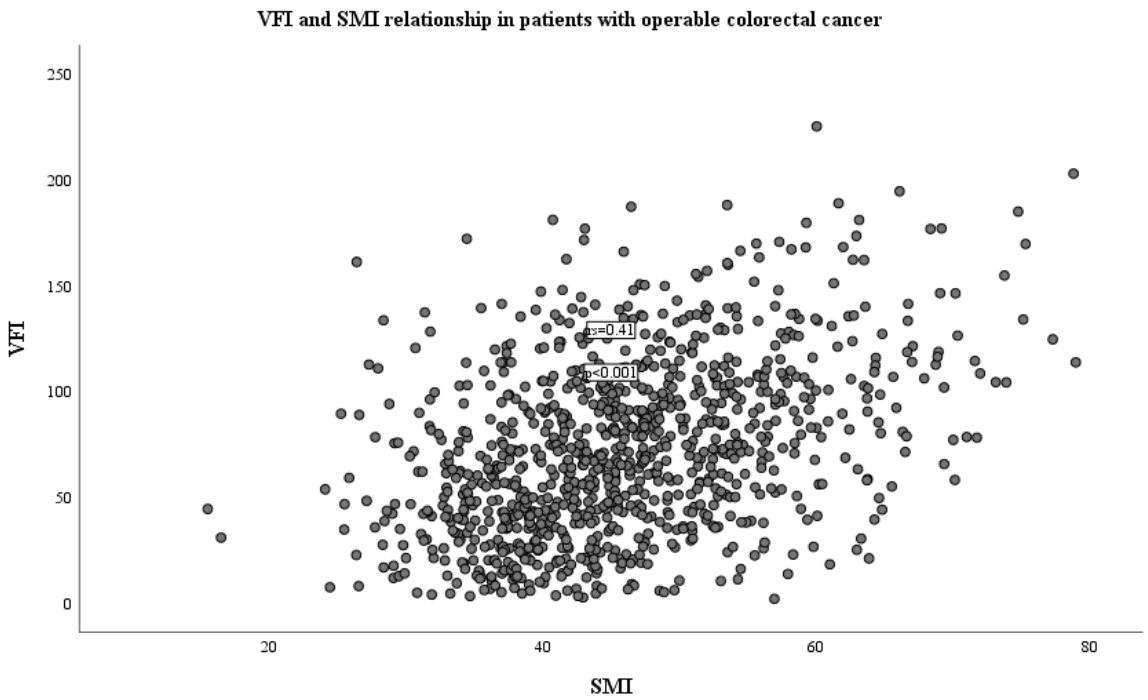


Figure E.3a: Scatter plot of the relationship between visceral fat index and skeletal muscle index at L3 (n=1002, r_s=0.41, p<0.001)

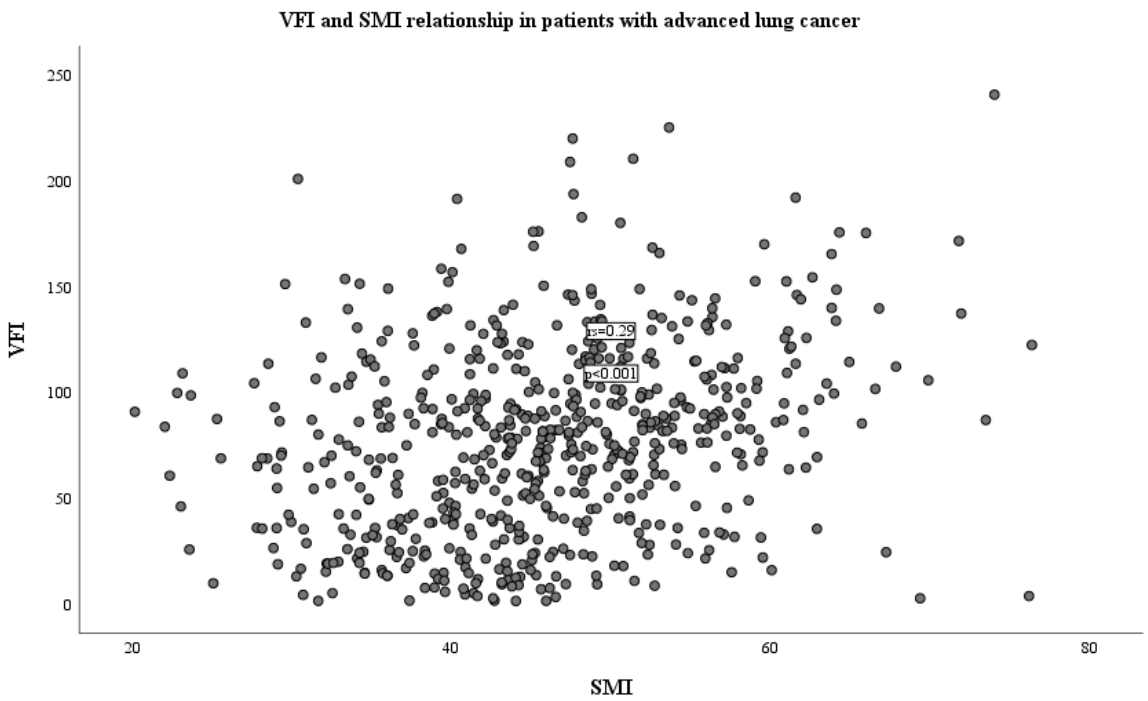


Figure E.3b: Scatter plot of the relationship between visceral fat index and skeletal muscle index (n=630, r_s=0.29, p<0.001)

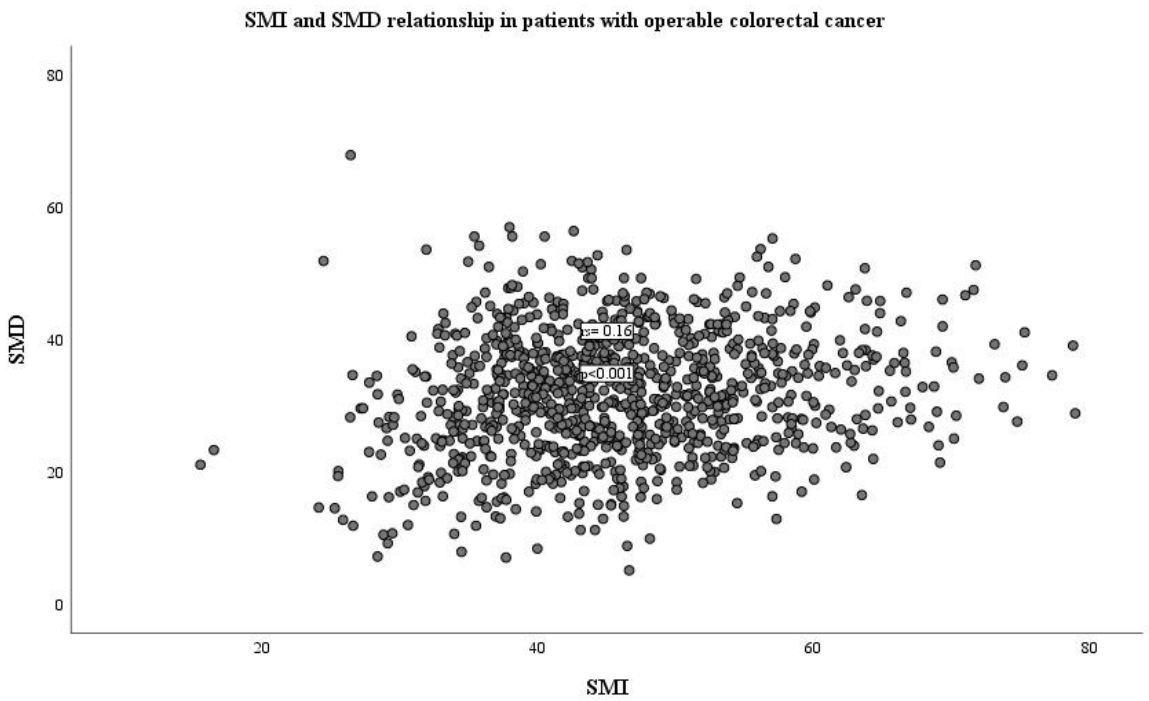


Figure E.4a: Scatter plot of the relationship between skeletal muscle index and skeletal muscle density at L3 (n=1002, r_s=0.16, p<0.001)

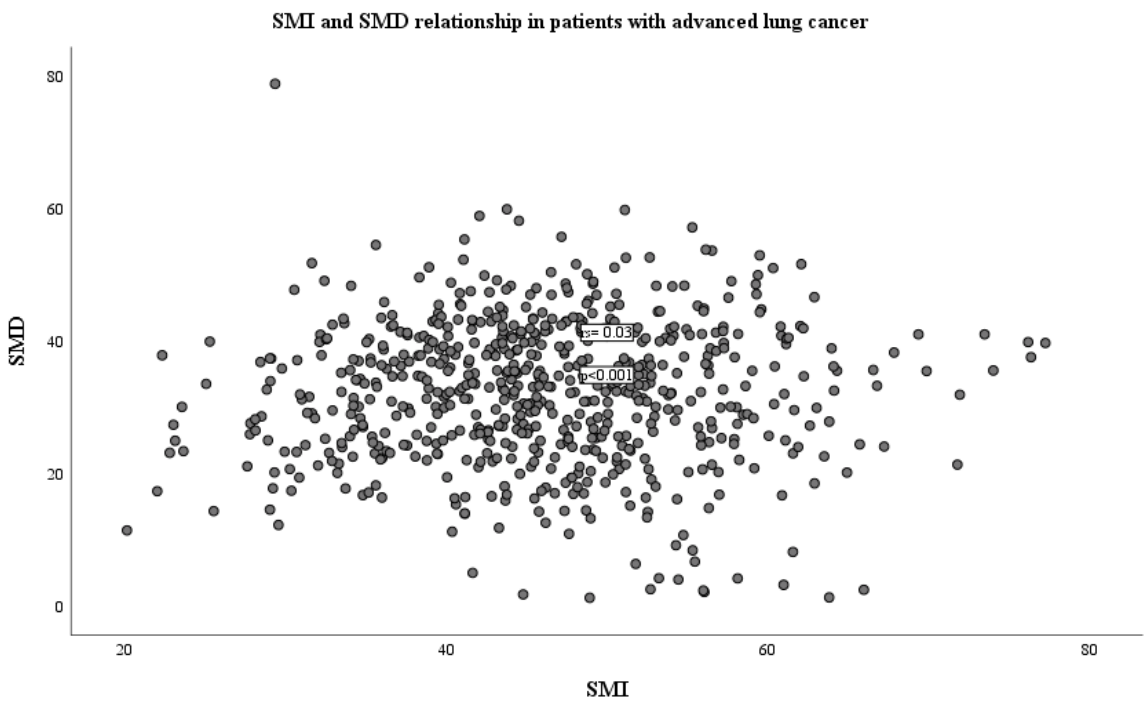


Figure E.4b: Scatter plot of the relationship between skeletal muscle index and density at L3 (n=643, r_s=0.03, p<0.001)

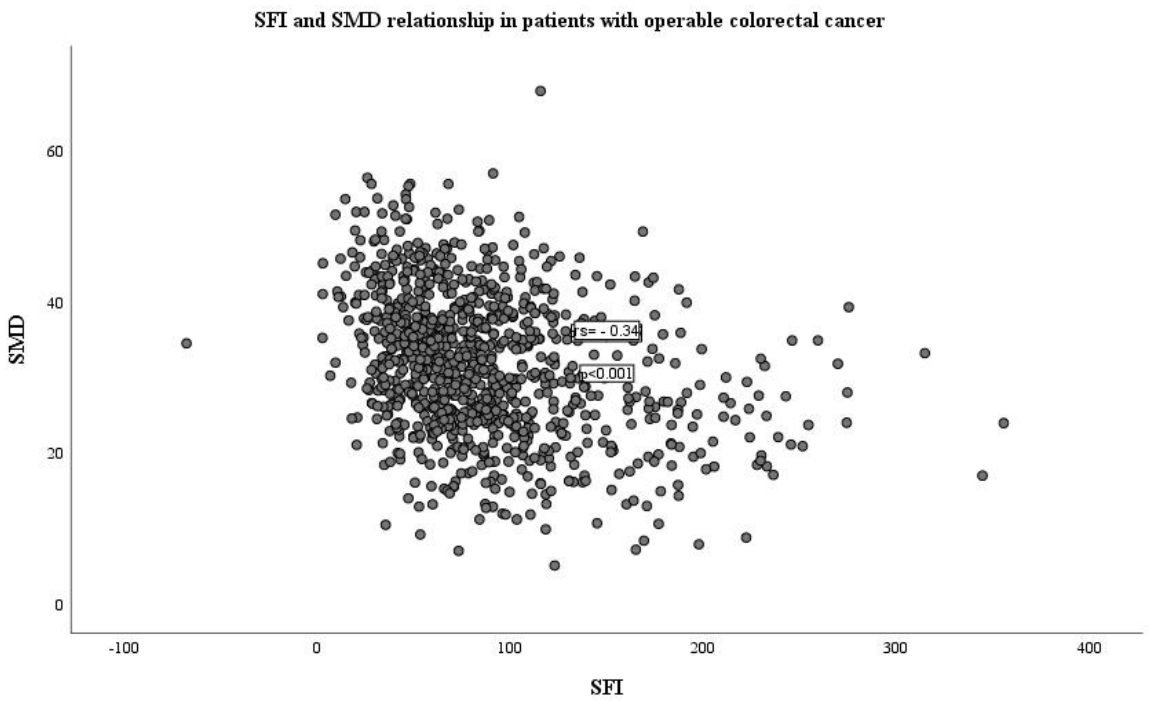


Figure E.5a: Scatter plot of the relationship between subcutaneous fat index and skeletal muscle density at L3 ($n=1002$, $r_s= - 0.34$, $p<0.001$)

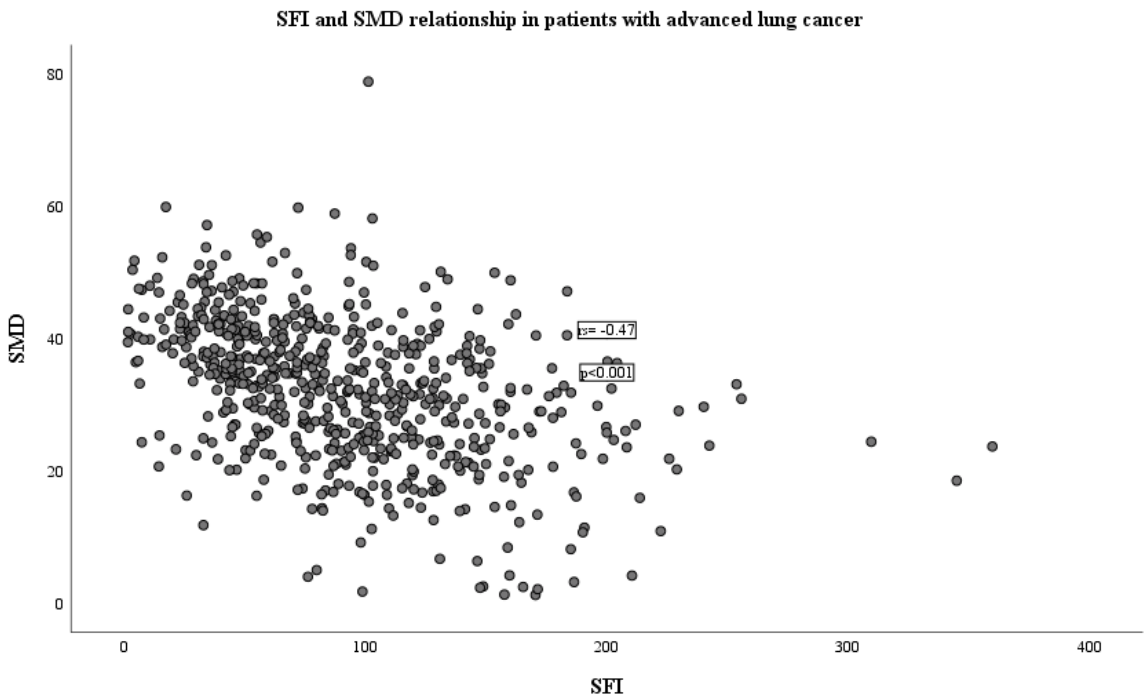


Figure E.5b: Scatter plot of the relationship between subcutaneous fat index and skeletal muscle density at L3 (n=643, r_s = - 0.47, p<0.001)

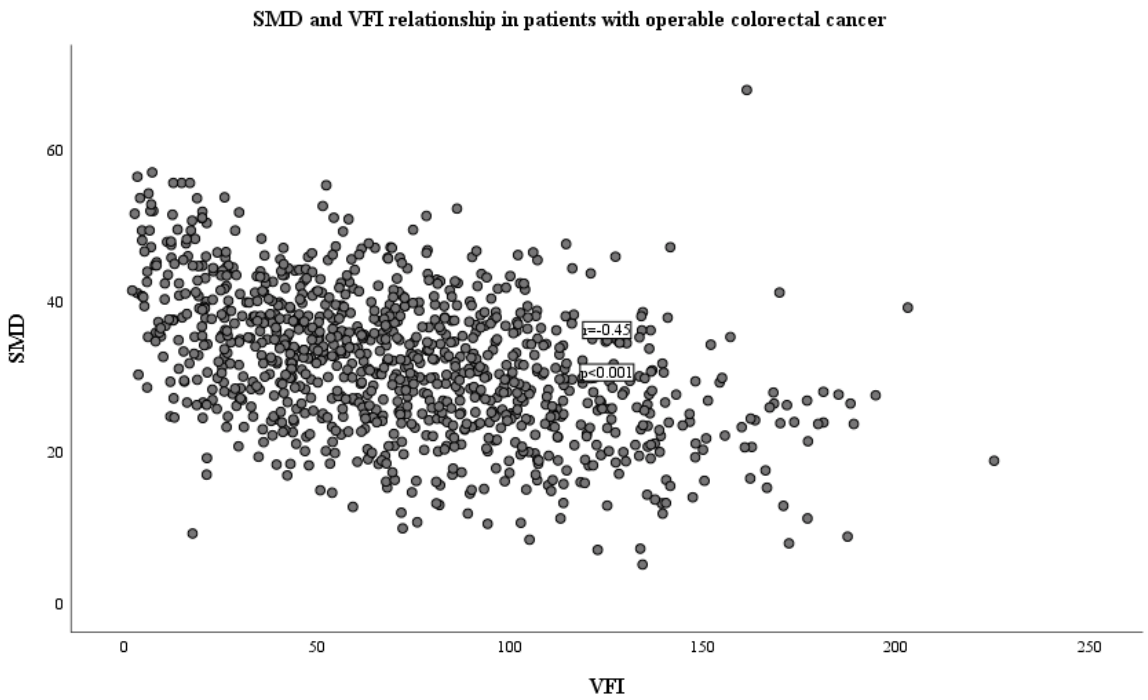


Figure E.6a: Scatter plot of the relationship between skeletal muscle density and visceral fat index at L3 (n=1002, r_s= - 0.45, p<0.001)

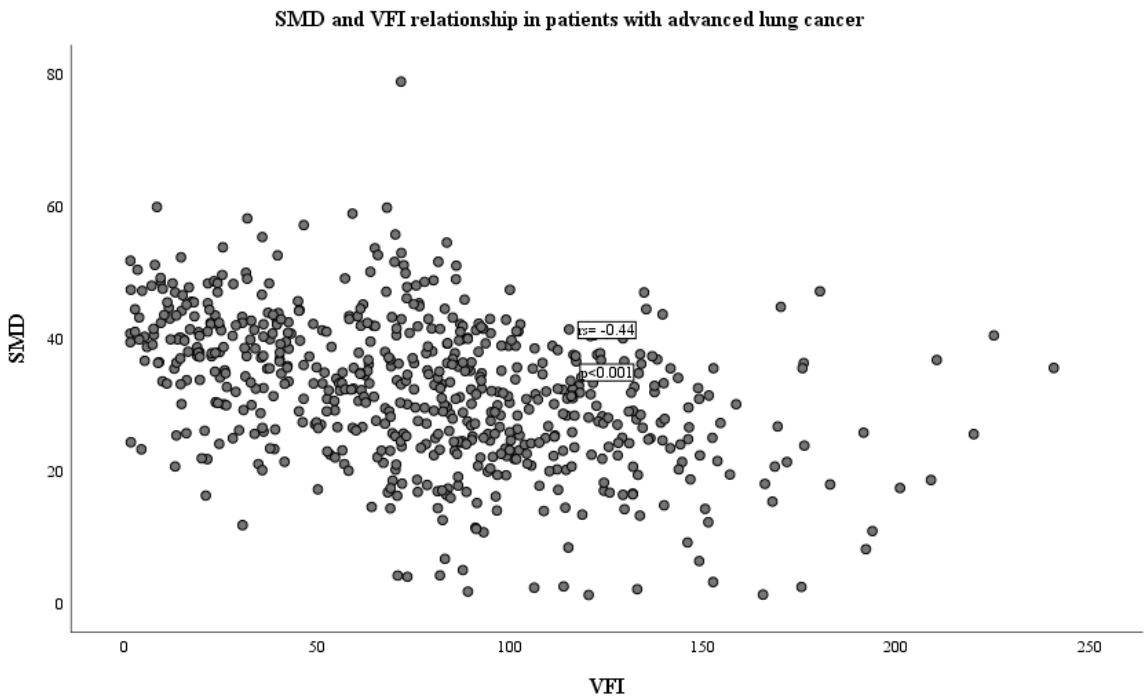


Figure E.6b: Scatter plot of the relationship between skeletal muscle density and visceral fat index at L3 n=643, r_s= -0.44, p<0.001)