An investigation of computed tomography-derived skeletal muscle measurements in clinical cancer care

By

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Abstract

Cancer is a leading cause of death globally, responsible for nearly 10 million deaths annually. In the UK, it is responsible for one in four deaths. Despite the significant mortality rates, cancer survival continues to improve. Such advances are considered multifactorial and attributable to the evolution of new anti-cancer therapies and the identification of novel biomarkers for the optimization of anti-cancer therapy.

Determining which patients will derive benefit from anti-cancer therapy, and when in their cancer journey, remains an area of interest in oncology. At present, such decisions are informed by tumour and host factors. With reference to the tumour, cancer stage and grade are commonly utilised by clinicians for the determination of treatment intent and modality. With reference to the host, age and performance status are routinely considered when determining the appropriateness of anti-cancer therapy. Whilst performance status has historically been considered a robust determinant of likely outcome to anti-cancer therapy, a lack of granularity in the measures of performance status has meant that there is continued interest in the identification of tools that can objectively determine functional status in cancer patients.

Computed tomography (CT)- derived skeletal muscle measurements, skeletal muscle index (SMI) and density (SMD), are considered surrogate markers of muscle quantity and quality, respectively. Readily quantified from the analysis of CT images obtained during routine clinical cancer care, SMI and SMD have been reported to be associated with functional status in patients with cancer. Moreover, are considered to provide a global assessment of the cancer patient, that also inform of nutritional and frailty status. The work presented in this thesis examines how CT-derived measurements of skeletal muscle may be utilised in clinical cancer care.

The prevalence and determinants of CT-derived skeletal muscle measurements, SMI and SMD, are examined in Chapter 4. The results of Chapter 4 reported that a low SMI and SMD had a percentage prevalence of between 30-60% in a substantial cohort of patients with cancer and that this was similar irrespective of threshold

values used to define a low SMI/SMD. Moreover, reported that a low SMI and SMD are endemic across a range of cancer subtypes and disease stages, suggesting the poor muscle status is largely constitutional and not the result of the cancer per se.

Given their respective associations with skeletal muscle mass and function, the combination of SMI and SMD, may provide an objective measure by which sarcopenia can be characterized. Chapters 5 and 6 examined the relationships between the CT-derived sarcopenia score (CT-SS), a score that combines SMI and SMD, and physical function, malnutrition, systemic inflammation and survival in patients with potentially curative disease. Chapter 5 reported that the CT-SS was significantly associated with malnutrition, systemic inflammation and poorer survival in 1,002 patients with primary operable colorectal cancer. Chapter 6 reported that CT-SS was associated with cardio-pulmonary exercise testing (CPET) performance, an assessment of cardiopulmonary fitness likely to inform on the patient's baseline functional status, systemic inflammation and survival in 232 oesophagogastric cancer patients with good performance status who underwent neoadjuvant chemotherapy with a view to potentially curative surgical resection. However, that the prognostic value of CT-SS to survival was not maintained when adjusted for systemic inflammation.

The relationship between CT-derived skeletal muscle measurements, systemic inflammation and survival in patients with cancer remains unclear. This relationship was further examined in Chapter 7, that reported systemic inflammation, but not the CT-SS, was significantly associated with survival in 307 good performance status patients with advanced cancer. Taken collectively, the results of Chapter 6 and 7 support the hypothesis that systemic inflammation dominates the prognostic value of CT-derived skeletal muscle measurements in patients with cancer. Therefore, further examination of the relationship between CT-derived skeletal muscle measurements, systemic inflammation and survival in patients with cancer is required to determine if CT-derived skeletal muscle measurements have independent prognostic value to clinical outcomes and are a useful adjunct for the prediction of likely outcome in patients with cancer.

Sarcopenia is considered a cause of frailty in older adults with cancer. However, the relationship between the CT-SS, frailty and clinical outcomes in patients with cancer is unclear. Specifically, if CT-derived skeletal muscle measurements capture the prognostic value of frailty in patients with cancer. Chapter 8 examined the prevalence and prognostic value of frailty screening tools in patients with colorectal cancer, reporting that frailty was prevalent and had prognostic value to both short- and long-term clinical outcomes. Chapter 9 examined the relationship between frailty and malnutrition, CT-derived skeletal muscle measurements, systemic inflammation and short-term clinical outcomes in 1,002 patients undergoing potentially curative surgery for colorectal cancer. The results reported that frailty was associated with CT-derived skeletal muscle measurements. However, remained independently associated with short-term clinical outcomes (post-operative complications) when adjusted for CT-derived skeletal muscle measurements. The results suggest that whilst sarcopenia and frailty are closely associated in patients with cancer, CT-derived muscle measurements do not completely capture the prognostic significance of frailty. Nevertheless, the results suggest that the CT-SS may be a useful adjunct to frailty screening tools/measures in patients with cancer.

Cancer cachexia is a complex metabolic syndrome that is associated with dysregulated glucose metabolism. However, there is currently a paucity of studies examining the relationship between an elevated serum lactate dehydrogenase (LDH), an early biomarker of dysregulated glucose metabolism, and a low skeletal muscle mass, considered the defining feature of cachexia. Chapter 10 reported that an elevated LDH was significantly associated with performance status, systemic inflammation and survival in 436 patients with advanced cancer. However, also reported that there was no significant association between an elevated LDH and a low SMI. Whilst the results of Chapter 10 do not suggest that the loss of skeletal muscle mass is directly related to dysregulated glucose metabolism in patients with cancer, further study is required.

Whilst skeletal muscle mass is considered to reduce with cancer progression, liver mass is thought to be preserved. CT is considered a reliable modality for the quantification of both skeletal muscle and liver mass. However, the quantification of liver mass is significantly more time-consuming and laborious compared with

that of skeletal muscle. The current gold-standard methodology requires the measurement of the total liver volume, calculated by manual segmentation of sequential axial CT images. As such, there is a paucity of studies examining the relationship between skeletal muscle and liver mass, quantified using CT, in patients with cancer. We hypothesized that the maximal cross-sectional liver area on an axial CT slice, determined using manual segmentation, may be an easily quantified surrogate measure of liver mass, analogous to how skeletal muscle mass is quantified using CT. Chapter 11 reported that the maximal cross-sectional liver area was strongly correlated with the total liver volume in patients undergoing potentially curative surgery for colonic cancer, suggesting that it was a reliable surrogate marker. Chapter 12 reported that CT-derived liver mass, quantified using the novel proposed methodology, was significantly associated with SMI in 385 patients undergoing potentially curative surgery for colonic cancer, suggesting that a higher skeletal muscle mass is associated with a higher liver mass in patients with early-stage disease. The results are informative and provide a foundation for future work examining the relationship between skeletal muscle and liver mass in patients with cancer.

In summary, a low SMI and SMD appear to be constitutional and not the result of cancer per se. The combination of SMI and SMD would appear to objectively characterize sarcopenia and is closely associated with malnutrition, physical function, frailty and systemic inflammation in patients with cancer. However, it remains unclear if CT-derived skeletal muscle measurements have independent prognostic value to clinical outcomes and therefore questions their utility as prognostic tools in patients with cancer. Whilst a low skeletal muscle mass was not found to be significantly associated with biomarkers of dysregulated metabolism, it was significantly associated with CT-derived liver mass. The present work reports a reliable methodology for future examination of this relationship in patients with cancer.

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Author's Declaration

The work presented in this thesis was undertaken during a period of research between 2020 and 2023 in the University of Glasgow Academic Unit of Surgery, at Glasgow Royal Infirmary. The work was completed whilst working as a Specialty Registrar in General Surgery in the West of Scotland Deanery between 2023 and 2024.

I declare that the work presented in this thesis was undertaken by myself, except where indicated below:

- Assistance with data collection and scan analysis was provided by Dr Douglas Black, Dr Stephen McSorley and Dr Ross Dolan (Chapter 5)

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The work presented in this thesis has resulted in the following published papers:

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McGovern J, Dolan RD, Horgan PG, Laird BJ, McMillan DC. The prevalence and prognostic value of frailty screening measures in patients undergoing surgery for colorectal cancer: observations from a systematic review. BMC Geriatr. 2022; 22(1): 260

McGovern J, Golder A, Dolan RD, Roxburgh CS, Horgan PG, McMillan DC. The combination of computed tomography-derived muscle mass and muscle density and relationship with clinicopathological characteristics and survival in patients undergoing potentially curative surgery for colorectal cancer. JCSM Clinical Reports 2022; 7: 65–76

McGovern J, Delaney J, Forshaw MJ, McCabe G, Crumley AB, McIntosh D, Laird BJ, Horgan PG, McMillan DC, McSorley ST, Dolan RD. The relationship between computed tomography-derived sarcopenia, cardiopulmonary exercise testing performance, systemic inflammation, and survival in good performance status patients with oesophagogastric cancer undergoing neoadjuvant treatment. JCSM Clinical Reports 2022; 8: 3–11

McGovern J, Dolan RD, Simmons CPL, Daly LE, Ryan AM, Power DG, Maguire D, Fallon MT, Laird BJ, McMillan DC. Lactate dehydrogenase: relationship with the diagnostic GLIM criterion for cachexia in patients with advanced cancer. Br J Cancer. 2023; 128(5): 760-765

McGovern J, Grayston A, Coates D, Leadbitter S, Hounat A, Horgan PG, Dolan RD, McMillan DC. The relationship between the modified frailty index score (mFI-5), malnutrition, body composition, systemic inflammation and short-term clinical

outcomes in patients undergoing surgery for colorectal cancer. BMC Geriatr. 2023; 23(1): 9

McGovern J, Dolan RD, Simmons C, Daly LE, Ryan AM, Power DG, Fallon MT, Laird BJ, McMillan DC. Are CT-Derived Muscle Measurements Prognostic, Independent of Systemic Inflammation, in Good Performance Status Patients with Advanced Cancer? Cancers (Basel). 2023; 15(13): 349

McGovern J, Mackay C, Freireich R, Golder AM, Dolan RD, Horgan PG, Holroyd D, Jamieson NB, McMillan DC. The Relationship between Liver Volume, Clinicopathological Characteristics and Survival in Patients Undergoing Resection with Curative Intent for Non-Metastatic Colonic Cancer. Tomography 2024; 28;10(3): 349-359

Presentations

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

CT-defined low skeletal muscle index and density in cancer patients- Observations from a systematic review
Cancer Cachexia Society 6th Annual meeting, Florida, USA 2021 (poster)

The relationship between CT-derived sarcopenia, measures of pre-treatment fitness and systemic inflammation in patients with oesophagogastric cancer
15th International Conference on Cachexia, Sarcopenia & Muscle Wasting, Lisbon, Portugal 2022 (poster)

The relationship between frailty and malnutrition, body composition, systemic inflammation and short-term clinical outcomes in patients undergoing surgery for colorectal cancer
European Society of Coloproctology 17Th Scientific & Annual Meeting, Dublin, Ireland 2022 (poster)

The relationship between CT-derived sarcopenia and systemic inflammation, physical function and survival in patients with advanced cancer
ASCO Gastrointestinal Cancers Symposium, San Francisco, USA 2023 (poster)

Definitions/Abbreviations

AJCC American Joint Committee on Cancer

ASA American Society of Anaesthesiologists physical status classification system

AT Anaerobic Threshold

BIA Bioimpedance Analysis

BMI Body Mass Index

CD Clavien Dindo Grade

CGA Comprehensive Geriatric Assessment

COPD Chronic Obstructive Pulmonary Disease

CPET Cardio-Pulmonary Exercise Testing

CRP C-reactive protein

CRUK Cancer Research United Kingdom

CSHA-CFS Canadian Study of Health and Aging-Clinical Frailty Scale

CT Computed Tomography

CT-SS CT-Derived Sarcopenia Score

DEXA Dual Energy X-ray Absorptiometry

ECOG-PS Eastern Co-operative Oncology Group's Performance Status

EWGSOP European Working Group on Sarcopenia in Older People

EWGSOP2 Second European Working Group on Sarcopenia in Older People

GI Gastrointestinal

GLIM Global Leadership in Malnutrition

HGS Hand-grip Strength

HR Hazard Ratio

HU Hounsfield Units

ICCC Intra-class Correlation Coefficients

IQR Interquartile Range

L3 3rd Lumbar Vertebra

LDH Lactate Dehydrogenase

LMI Liver Mass Index

mFI-5 Five-Item Modified Frailty Index

mFI-11 Eleven-Item Modified Frailty Index

mGPS Modified Glasgow Prognostic Score

MRI Magnetic Resonance Imaging

MUST Malnutrition Universal Screening Tool

MV Multivariate

NAC Neoadjuvant Chemotherapy

NLR Neutrophil: Lymphocyte Ratio

NOS Newcastle-Ottawa Scale

OR Odds Ratio

PMI Psoas Muscle Index

PRISMA-P Preferred Reporting Items for Systematic Review and Meta-analysis protocols

RCS Retrospective Cohort Study

RCT Randomized Controlled Study

ROBINS-I Risk of Bias in Non-randomized Studies of Interventions

SCC Squamous Cell Carcinoma

SFA Subcutaneous Fat Area

SFI Subcutaneous Fat Index

SMD Skeletal Muscle Density

SMG Skeletal Muscle Gauge

SMI Skeletal Muscle Index

STROBE Strengthening the Reporting of Observational studies in Epidemiology

UK United Kingdom

VFA Visceral Fat Area

1 Introduction

1.1 The right treatment, for the right patient, at the right time

Cancer is a leading cause of death globally, responsible for 10 million deaths worldwide in 2020 (1). In the United Kingdom (UK), it is considered responsible for one in four deaths annually (2). Despite the significant mortality rates, cancer survival continues to improve with contemporary evidence suggesting that it has doubled in the UK over the last 50 years (3). Such advances are considered to be multifactorial and attributable to the evolution of new anti-cancer therapies and the identification of novel biomarkers for the optimization of anti-cancer therapy (4).

The primary aim of anti-cancer treatment remains to cure the disease using a combination of local and systemic treatment modalities (5). However, a curative option is not available for all patients, such as those with locally advanced or metastatic disease. In this setting, the aims of treatment shift to the prolongation of survival, improvement of quality of life and control of symptom burden (6). Whilst cytotoxic therapies remain a mainstay of disease palliation, novel anti-cancer treatments including immunotherapy and targeted therapies have now made their way into clinical practice (7). Determining which patients will derive benefit from anti-cancer therapy and when in their cancer journey remains an area of interest in oncology (8).

In the age of precision medicine, it is imperative that the right treatment be given to the right patient, at the right time. Decisions regarding who is the right patient for a certain treatment are often complex and consideration should be given to both the tumour and the host (9). With reference to the tumour, cancer stage and grade have historically been utilised by clinicians to predict the clinical behaviour of malignancies and establish appropriate therapy (10). More recently, there has been increased recognition of the importance that the cellular and acellular components of the tumour microenvironment have on the response to anti-cancer therapy (11). Identification of novel biomarkers that inform on the tumour biology remains a focus of clinical cancer research with studies utilizing genomics,

transcriptomics and proteomics to identify tumour characteristics that may further optimize anti-cancer therapy (4).

With reference to the host, age (12) and performance status (13) are routinely considered when determining the eligibility of a patient for anti-cancer treatment. Advanced age and poor performance status have long been considered adversely associated with tolerance to anti-cancer treatment, treatment response (13-15) and survival outcomes (15-17). Recently, the importance of chronological age has been questioned in a meta-analysis of 102 randomized control trials by Arciero and co-workers, who reported similar relative survival benefits from novel anti-cancer therapies in both younger and older patients (18). Whilst the observations of Arciero and co-workers questions the prognostic significance that age has to anti-cancer treatment, the results may be confounded by the inclusion of only patients who fulfilled clinical trial eligibility, with good performance status often a pre-requisite (19, 20). Therefore, a comprehensive and multifactorial assessment, that includes an assessment of performance status, has been recommended in older adults with cancer (12, 21).

To date, performance status remains a mainstay in oncology for prognostication (16, 22) and determination of treatment intent and modality (14, 23, 24). Widely utilised in clinical practice are the World Health Organization's Zubrod Performance Status scale, the Karnofsky Performance Status scale and the Eastern Co-operative Oncology Group's (ECOG) Performance Status scale (13, 25). The relative simplicity of such tools has made them readily applicable to standard clinical practice. However, their subjective nature means that they are subject to limitations including bias and reliability of observations (25). Moreover, such assessments lack granularity and do not differentiate between the various causes of impaired performance status (musculoskeletal, cardiopulmonary co-morbidity etc), meaning there is significant heterogeneity amongst patients categorised as having borderline performance status (26). As such, it is plausible that poor performance status patients receiving anti-cancer therapy may have markedly different outcomes (27, 28). Indeed, it has been reported that novel anti-cancer therapies may be safe and of clinical benefit in advanced cancer patients with borderline performance status (20, 29). Therefore, tools that can objectively determine functional status in cancer patients remain of interest (25).

1.2 The loss of skeletal muscle mass in patients with cancer

The loss of skeletal muscle mass is thought to begin in middle age, with up to 50 % of skeletal muscle mass lost by the 8th decade of life (30). Such losses are associated with reduced muscle strength and physical performance (31). Therefore, the assessment of skeletal muscle mass may provide an objective measure of functional status, that could be used to in conjunction with performance status.

Age-related losses of skeletal muscle mass may be compounded by diseases such as cancer (32). Cancer-associated skeletal muscle loss is distinct from age-related loss in that it cannot be completely reversed by conventional nutritional therapy (33). This is considered attributable to the different pathophysiological mechanisms underlying the loss of skeletal muscle, with cancer-associated skeletal muscle wasting considered the result of a complex interaction between the tumour and host (34).

The aetiology of skeletal muscle loss in patients with cancer is considered multifactorial, with several tumour-derived mediators including pro-inflammatory cytokines, parathyroid hormone-related protein and micro ribonucleic acids considered to play a role (35, 36). These tumour-derived mediators are considered to induce the loss of skeletal muscle mass through several pathological mechanisms including systemic inflammation, activation of the hypothalamic-pituitary-adrenal axis, disordered glucose metabolism resulting in a pro-catabolic state and the derangement of the renin–angiotensin–aldosterone system (37, 38). Moreover, may be contributed to further by physical inactivity, impaired nutritional intake and by the treatment of the cancer itself, with chemotherapy and other anti-cancer therapies also implicated (39). Such changes result in the increase in muscle protein degradation, the inhibition of myogenesis, enhanced autophagy, the promotion of intramuscular catabolism and alterations in mitochondrial biogenesis (40, 41).

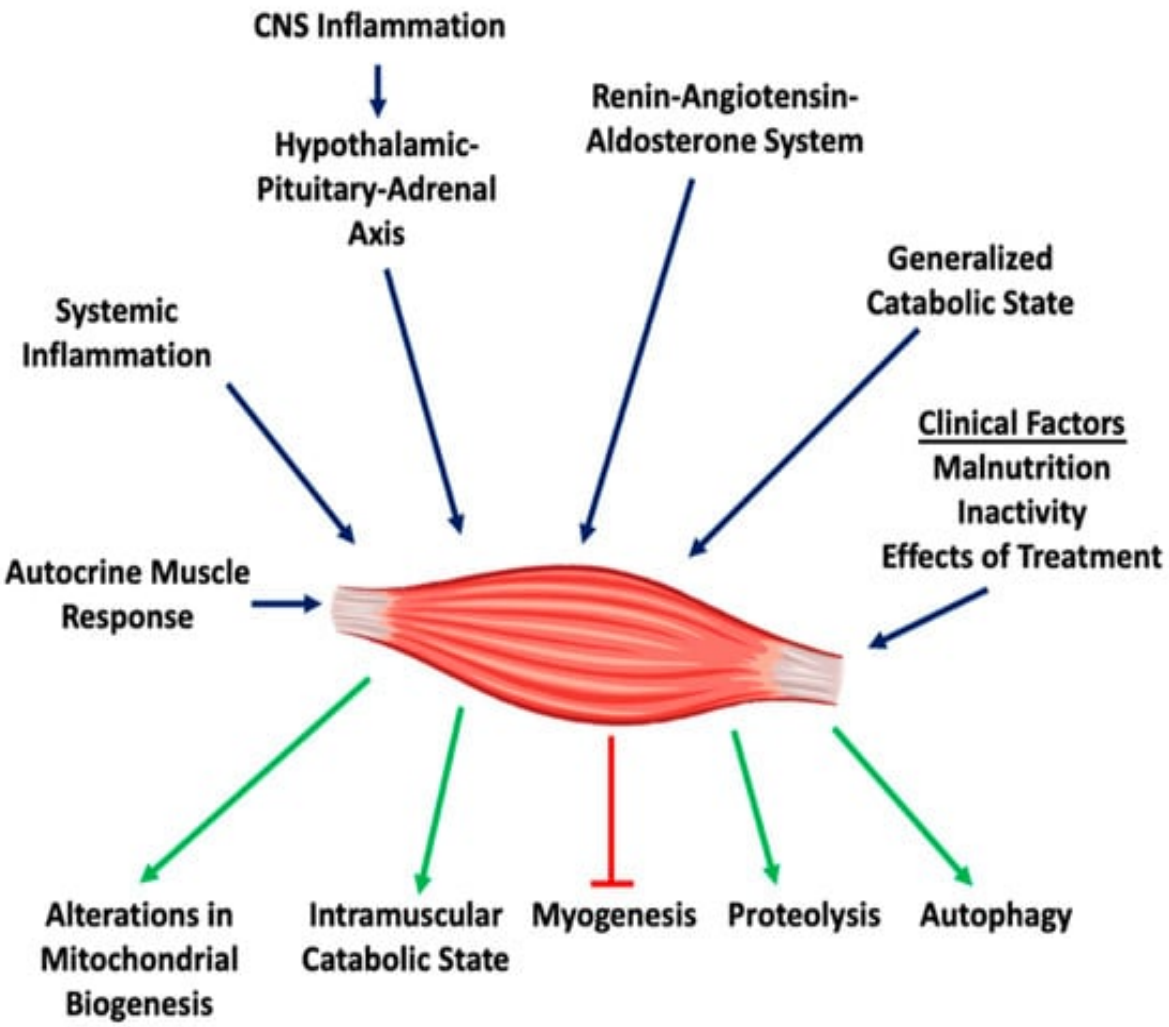


Figure 1-1: The pathological mechanisms of skeletal muscle wasting. Adapted from Armstrong and co-workers (36)

1.3 The measurement of skeletal muscle mass in patients with cancer

A range of non-invasive techniques have been proposed for the measurement of skeletal muscle mass including anthropometry, dual energy x-ray absorptiometry (DEXA), bioimpedance analysis (BIA), total or partial body potassium per fat-free soft tissue, magnetic resonance imaging (MRI) and computed tomography (CT, (31, 42). Variation exists between the modalities with regards to cost, availability and ease of use. As such, DEXA, BIA and anthropometry have all been considered for the measurement of skeletal muscle mass in routine clinical practice (43).

Variable	Research	Clinical practice
Muscle mass	Computed tomography (CT)	BIA
	Magnetic resonance imaging (MRI)	DXA
	Dual energy X-ray absorptiometry (DXA)	Anthropometry
	Bioimpedance analysis (BIA)	
	Total or partial body potassium per fat-free soft tissue	

Figure 1-2: Modalities for the quantification of skeletal muscle mass. Adapted from Cruz-Jentoft and co-workers (43)

Anthropometry is generally considered the most simplistic of all modalities for the quantification of skeletal muscle mass (44). Anthropometric measures provide an inexpensive and routinely available surrogate measure of skeletal muscle mass in clinical practice (45). The most utilised measures are body mass index (BMI), skinfold thickness, calf circumference and mid-arm muscle circumference (44, 46). However, such measures are considered crude and not reliable for the quantification of skeletal muscle mass in older adults or obese individuals given the age-related changes in skin elasticity and fat deposition, respectively (43, 44). Given both advanced age and obesity are closely associated with the incidence of cancer (47), anthropometric measures would not appear a reliable method for the quantification of skeletal muscle mass in patients with cancer.

DEXA is one of the most widely studied methodologies and is generally considered quick, safe and inexpensive (46). DEXA utilises two X-rays beams with different energies to measure lean soft tissue mass (48). Measurements are routinely obtained from the upper or lower extremities and reported as the appendicular skeletal muscle mass (ASMM, (49). Studies have reported that the ASMM measurements obtained using DEXA are highly correlated with those of other modalities (48). However, questions remain around the reliability of DEXA to quantify skeletal muscle mass with variation in measurements reported between different scanners and software packages (31). Furthermore, the observations obtained using DEXA may be compounded by several patient factors including co-morbidity and obesity (48).

The use of BIA for quantification of skeletal muscle mass has also been widely studied (31). BIA utilises an electrical current that is passed between two components, often placed at the wrist and ankle, with the patient in a supine position (50). Measurements obtained are then placed into an equation to estimate the skeletal muscle mass (48). BIA is generally considered a safe, inexpensive and easy to use modality for the quantification of skeletal muscle mass (45). However, like DEXA, is subject to limitations and measurements may be confounded by a number of factors including the patient's hydration status, recent physical activity and time spent being horizontal (48). Furthermore, measurements obtained using BIA have been reported to have low correlation with other modalities generally considered more reliable (51, 52).

CT and MRI are widely considered the gold-standard modalities for the quantification of skeletal muscle mass in patients with cancer, with measurements reported to be accurate and reliable (42, 44). In comparison to other modalities, CT/MRI have significant financial implications including the cost of the scanners, logistical issues including the storage of such equipment and the need for qualified medical professionals to operate them (46). However, the routine use of such imaging modalities for the diagnosis/ staging of cancer as part of standard clinical care has provided a readily available substrate for clinical research (53). Indeed, CT is now the most widely studied modality for the quantification of skeletal muscle mass in the present literature (53, 54).

1.4 The use of CT to measure skeletal muscle mass

CT is the most utilised modality for the quantification of skeletal muscle mass in studies of patients with cancer (55). This methodology uses computer software programs that reconstruct cross-sectional CT images into a two-dimensional map of pixels. Each pixel is assigned a numerical value in Hounsfield units (HU) based on their relative radio attenuation of the tissue (56). Skeletal muscle and fat have specific HU ranges (-29 to +150 and −190 to −30 HU, respectively), meaning tissues can be differentiated and quantified (57). The tissue area is derived by multiplying the number of pixels for a given tissue by the surface area of said tissue, with values reported in centimetres squared (cm^2, (56).

A range of software programs have been utilised for the quantification of skeletal muscle mass within the present literature. These include ImageJ (National Institutes of Health), SliceOmatic (Tomovision) and OsiriX (Pizmeo). Whilst some programs use manual segmentation to obtain measurements, other programs can perform semi-automated measurement, making the process more time-efficient (55). Contemporary studies have reported excellent agreement between the measurements of the various software programs (58, 59), meaning that it is unlikely to be a confounding factor to observations or introduce error if such measurements were to be applied to clinical cancer care.

Skeletal muscle mass is routinely determined from a single axial CT image, obtained at a fixed anatomical landmark (54). Within the present literature, studies have utilised axial images obtained at the level of the twelfth thoracic (60), third lumbar (61) and fourth lumbar vertebrae (62) for quantification of skeletal muscle mass. By far the most utilised level is the third lumbar vertebrae (L3), with two distinct methods proposed (55). The first involves measurement of the cross-sectional area of the two psoas muscles only to determine the skeletal muscle mass (63). Measurements are normally divided by the patient's height in meters squared (m^2) to form the psoas muscle index (PMI, cm^2/m^2). This method is largely considered flawed (64), with studies reporting that the total psoas muscle area is not representative of the total body muscle mass (65).

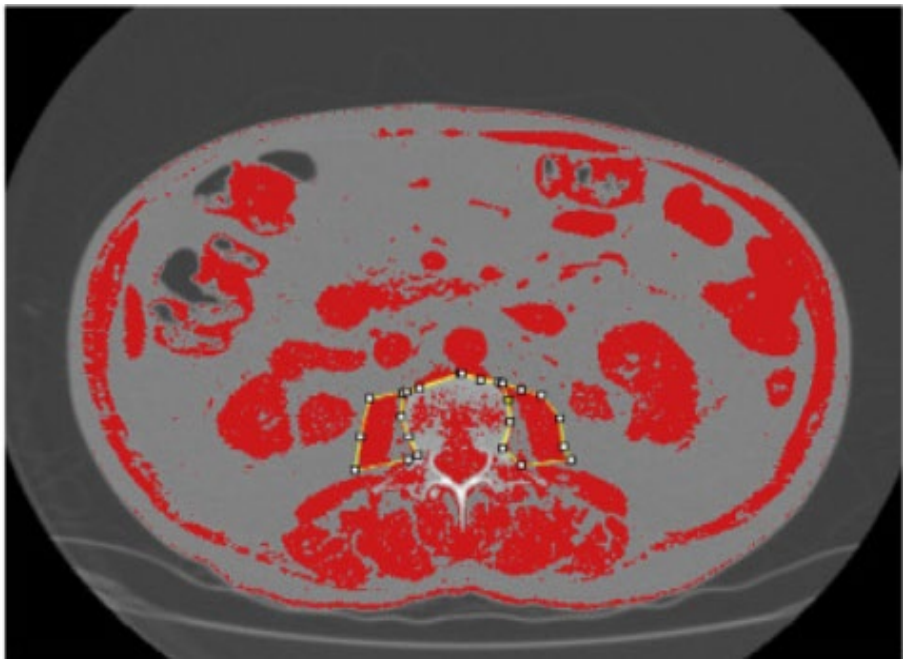


Figure 1-3: Measurement of the cross-sectional area of the left and right psoas muscles on an axial CT slice at the level of L3, using ImageJ. Adapted from Abbass and co-workers (66)

The second and more prevalent method measures the total cross-sectional area of the abdominal musculature at L3, with the rectus abdominus, abdominal, psoas and paraspinal muscles included (61). This method is generally considered superior (67), with studies reporting that total abdominal skeletal muscle area correlated well with total body muscle mass in healthy adult patients (68, 69) and in patients with cancer (70). Cumulative skeletal muscle cross-sectional area measurements are routinely normalised by division of the patient's height in meters squared (m^2) and reported as the skeletal muscle index (SMI, cm^2/m^2, (55).

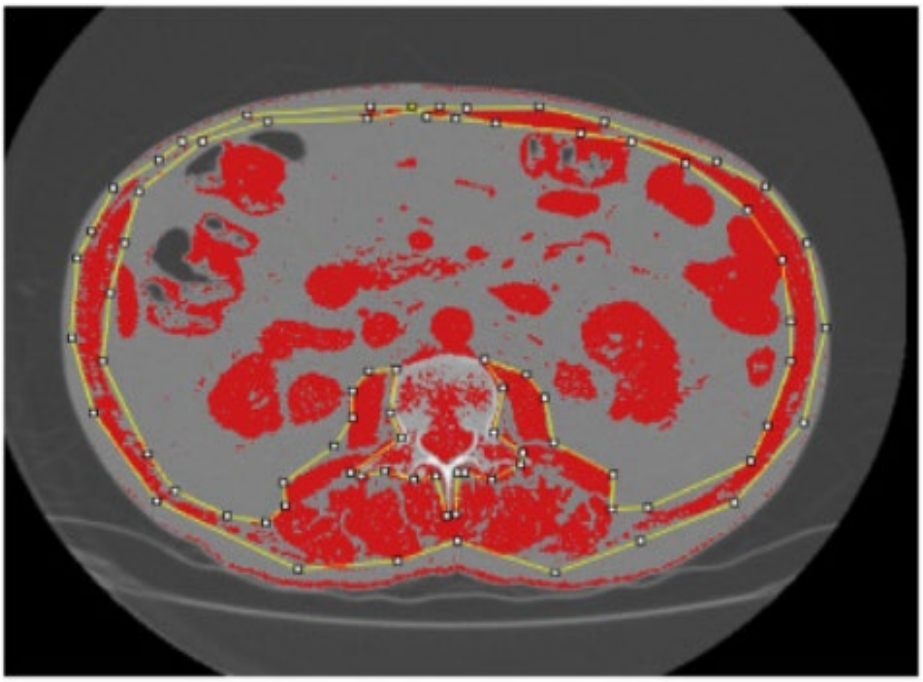


Figure 1.4: Measurement of the cross-sectional area of the rectus abdominus, abdominal, psoas, and paraspinal muscles on an axial CT slice at the level of L3, using ImageJ. Adapted from Abbass and co-workers (66)

Several seminal population-based studies have used optimal stratification to derive threshold values to define a low SMI in patients with cancer. The first were those of Prado and co-workers, who in a cohort of 2,115 patients with solid tumours or the respiratory and gastrointestinal tract, proposed threshold values of <52·4 cm^2/m^2 for men and <38·5 cm^2/m^2 for women (71). This was followed with a study by Martin and coworkers, who in a cohort of 1,473 patients with lung and gastrointestinal cancer, proposed threshold values adjusted for BMI (<43 cm^2/m^2 if BMI ≤24·9 kg/m^2 and <53 cm^2/m^2 if BMI ≥25 kg/m^2 for men; <41 cm^2/m^2 for women, irrespective of BMI), consider more appropriate for non-obese cohorts (61). More recently, Caan and co-workers proposed cancer-specific threshold values in a study of 3,262 patients with non-metastatic cancer (<52·3 cm^2/m^2 if BMI <30 kg/m^2 and <54·3 cm^2/m^2 if BMI ≥30 kg/m^2 for men; <38·6 cm^2/m^2 if BMI <30 kg/m^2 and <46·6 cm^2/m^2 if BMI ≥30 kg/m^2 for women (72).

Whilst such threshold values have been adjusted for sex and BMI, skeletal muscle mass is thought to be influenced by a number of factors including age, co-morbidity, physical activity and ethnicity (73). The importance of ethnicity was highlighted by Fujiwara and co-workers, who in a study of 1,257 patients with hepatocellular carcinoma (74), reported optimal thresholds values for SMI that were significantly lower than those proposed by studies of Caucasian populations (<36·2 cm^2/m^2 for men and <29·0 cm^2/m^2 for women). The observations highlight the difficulty in identifying universally applicable threshold values for a low SMI, with a one-size-fits-all approach likely to introduce selection bias.

Variation exists in the prevalence of low SMI reported by studies of different cancer subtypes and disease stages in the present literature (55). This observation may be the result of heterogeneity in the methodology between studies, with a breadth of threshold values used to define low SMI, ranging from 36 to 55·8 cm^2/m^2 for men and 29 to 46·6 cm^2/m^2 for women (55). Moreover, in the method used to derive threshold values for a low SMI, with studies using optimal stratification (61, 71, 72), pre-determined percentiles (75, 76) and the median (77, 78). To date, there is a paucity of studies examining the importance of threshold value to the prevalence of low SMI in patients with cancer. Similarly, examining the importance of cancer subtype and disease stage to the prevalence of low SMI, controlling for threshold value used.

1.5 The use of CT to measure skeletal muscle quality

In addition to facilitating the quantification of skeletal muscle mass, CT-imaging also provides information regarding its composition (73). The infiltration of intramuscular adipose tissue is thought to decrease the number of pixels depicted within the skeletal muscle tissue, resulting in a lower mean muscle radiation attenuation (45). Such changes are generally considered to be reflective of poor muscle quality (79), and have been reported to be negatively correlated with strength, mobility and insulin resistance (80) . Moreover, it has been hypothesized that the infiltration of adipose tissue may lead to the loss of skeletal muscle mass (81, 82). As such, skeletal muscle radiation attenuation remains an area of interest in patients with cancer.

Similar to skeletal muscle mass, heterogeneity exists with regard to terminology used when reporting skeletal muscle radiation attenuation (79). The mean muscle radiation attenuation is commonly reported as the skeletal muscle density (SMD), with a low SMD often termed myosteatosis (83). Other terms reported within the literature include muscle attenuation, skeletal muscle attenuation and low-quality skeletal muscle (84). Heterogeneity also exits in the present literature with regard to the methodology used for measuring SMD. Firstly, whilst a HU range of -29 to +150 has conventionally been used for skeletal muscle, other studies have opted for different lower and upper limits of HU (79, 84). Secondly, heterogeneity exists with regard to the vertebral level and muscle group at which the mean muscle radiation attenuation was measured (84). Moreover, whether this was determined by measuring an isolated region of interest within the muscle or across of the whole muscle area (79). Lastly, technical factors such as the slice thickness of CT images and phase of imaging used to determine the SMD, as well as the use of contrast media (83, 85).

As is the case with SMI, there is currently no universal thresholds values to define a low SMD in patients with cancer. Indeed, a range of threshold values, ranging between <28 to 44·1 HU for men and <23·8 to 40·5 HU for women, have been proposed in the present literature (55). Whilst the prevalence of a low SMD has been reported to vary greatly between studies (55), the importance of threshold

value is presently unclear. Similarly, the importance of cancer subtype and disease stage to the prevalence of a low SMD is also unclear.

1.6 The utility of CT-derived skeletal muscle measurements as prognostic biomarkers in patients with cancer

There is now a significant volume of literature examining the prognostic value of a low SMI in patients with cancer, with studies consistently reporting a negative association with tolerance to anti-cancer therapy (86) and survival (87, 88). Similarly, a low SMD is generally considered an important prognostic factor in patients with cancer (89), with studies within reporting that SMD had superior prognostic value compared with SMI alone (90-92). Given both a low SMI and SMD have been widely reported to have independent prognostic value to clinical outcomes in patients with cancer, it is plausible that if used in combination, such measurements may provide a global assessment of skeletal muscle (mass and quality) that has superior prognostic value.

Previous studies have proposed a combination of these measurements in the form of the skeletal muscle gauge (SMG, (93), the product of SMI x SMD. Despite being reported to have prognostic value to clinical outcomes in patients with cancer (93-95), the studies used arbitrary threshold values derived using optimal stratification to define a low SMG, thereby introducing further heterogeneity into the literature. A score that combines CT-derived skeletal muscle measurements, with SMI and SMD considered as dichotomous variables and categorised using validated threshold values, may provide a simpler and more reliable method. However, no such score has been proposed within the present literature.

1.7 The utility of CT-derived skeletal muscle measurements for the diagnosis of sarcopenia in patients with cancer

The term sarcopenia was coined by Irwin Rosenberg over three decades ago to describe the loss of skeletal muscle mass and subsequent functional impairment observed with advancing age (96). At present, the consensus definition from the European Working Group on Sarcopenia in Older People (EWGSOP) is that sarcopenia is a "syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength, with a risk of adverse outcomes such as physical disability, poor quality of life and death" (97).

In line with this definition, the EWGSOP proposed that a diagnosis of sarcopenia required both the presence of a low skeletal muscle mass and either low muscle strength or physical performance (31). Following their first meeting in 2010, the EWGSOP produced a diagnostic framework to aid in the diagnosis of sarcopenia. For the quantification of skeletal muscle mass, EWGSOP recommended the use of BIA, DEXA or anthropometry. Moreover, gait speed and hand-grip strength (HGS) were recommended for the determination of low physical performance and muscle strength, respectively.

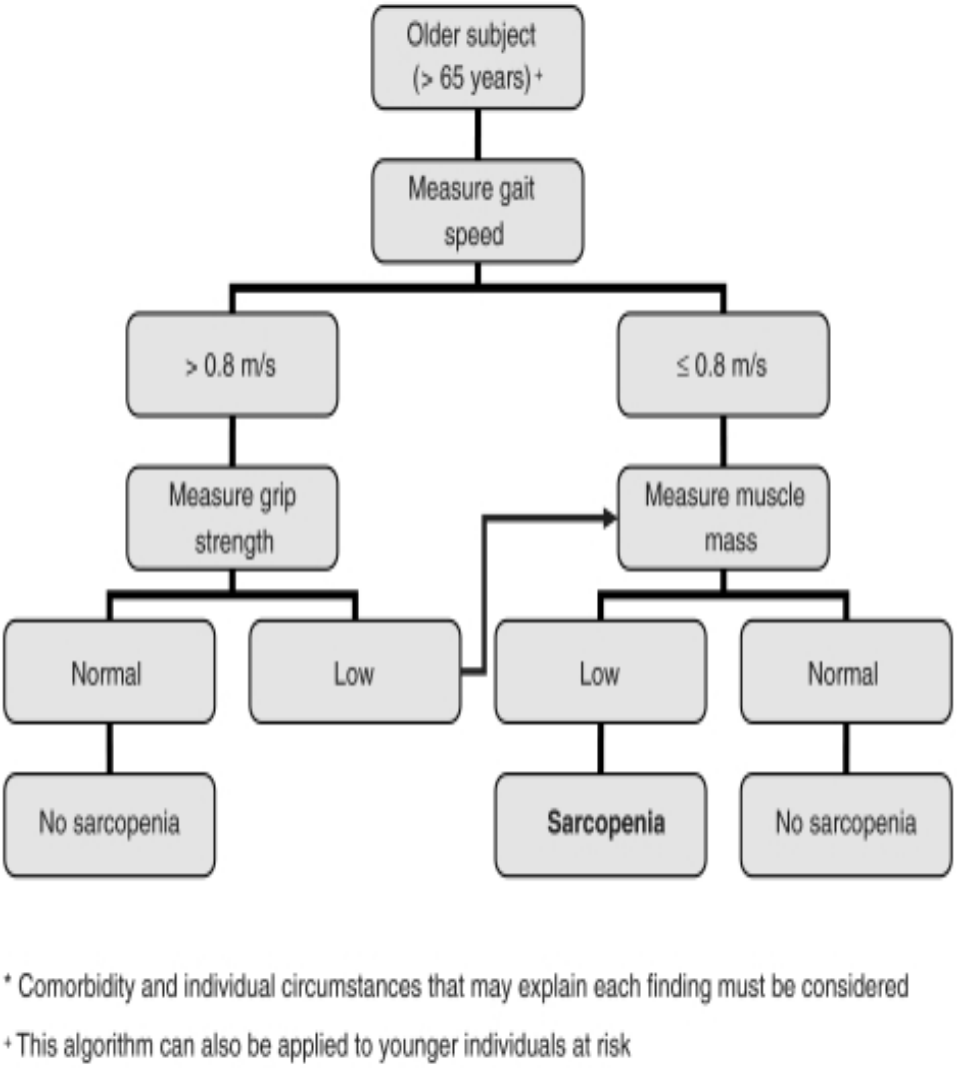


Figure 1-5: EWGSOP framework for the diagnosis of sarcopenia. Adapted from Cruz-Jentoft and co-workers (43)

Nearly a decade later, the EWGSOP met again in 2018 to review their definition and provide further guidance for diagnosing sarcopenia (31). Considering new scientific findings and clinical evidence, the consensus of the second EWGSOP meeting (EWGSOP2) was that sarcopenia should be considered "a muscle disease or failure". Moreover, they proposed that muscle strength should be the principal determinant of sarcopenia, with recent evidence suggesting that muscle strength had greater prognostic value for predicting adverse outcome compared with muscle mass. For assessment of muscle strength, the EWGSOP2 recommended the use of either the chair-stand test or HGS for the assessment of muscle strength, with the latter utilised in recent clinical trials examining the prognostic value of low muscle strength to clinical outcomes (98, 99).

Based on their new operational definition, the EWGSOP2 produced an updated framework for the diagnosing and stratifying the severity of sarcopenia. Firstly, screening for the condition using measures of strength such as HGS. Secondly, confirming the diagnosis of sarcopenia with the presence of low muscle mass or quality. The latter being a new diagnostic criterion, not previously considered at the time of the first EWGSOP meeting. Finally, the EWGSOP2 proposed that the presence of low physical performance, in addition to the first two criteria, constitutes severe sarcopenia (31).

Table 1. 2018 operational definition of sarcopenia

Probable sarcopenia is identified by Criterion 1.
Diagnosis is confirmed by additional documentation of Criterion 2.
If Criteria 1, 2 and 3 are all met, sarcopenia is considered severe.
1. Low muscle strength
2. Low muscle quantity or quality
3. Low physical performance

Figure 1-6: EWGSOP2 framework for the diagnosis of sarcopenia. Adapted from Cruz-Jentoft and co-workers (31)

Whilst only considered suitable for research purposes at the time of the first EWGSOP meeting, EWGSOP2 advocated the use of CT for the determination of skeletal muscle mass (31). Similarly, for assessing muscle quality by determining its radiation attenuation (31). Given a low SMD has consistently been associated with muscle strength and physical function in studies of patients with cancer (100-102), the combination of SMI and SMD may provide an objective method by which sarcopenia can be routinely characterised and its clinical impact studied using readily available methodology.

1.8 The utility of CT-derived of skeletal muscle measurements for the diagnosis of frailty in patients with cancer

Frailty is a complex multifactorial syndrome, characterised by increase in vulnerability and worsened health outcomes (103). Considered to be prevalent in older adults with cancer, a recent systematic review by Handforth and co-workers reported that nearly half (42%) of the 2,916 older adults with cancer studied were considered frail (104). Moreover, that frailty was also associated with tolerance to anti-cancer treatment, the incidence of post-operative complications and survival (104).

Frailty is thought to provide a global assessment of the cancer patients and has been reported to be closely associated with co-morbidity, nutritional status and physical function (105). It has also been reported to be associated with a low skeletal muscle mass in patients with cancer (106), with the loss of skeletal muscle and subsequent functional impairment considered a major cause of frailty (107). Indeed, low muscle strength and physical activity have been included as diagnostic criterion in frailty screening tools such as the Fried frailty phenotype (108).

To date, studies examining the relationship between CT-derived skeletal muscle measurements and frailty in patients with cancer have reported conflicting observations. Zwart and co-workers reported a close association between SMI and frailty in a study of 112 patients with locally advanced and metastatic head and neck cancer (109). In contrast, Williams and co-workers reported that SMD, but not SMI, was significantly associated with frailty in a study of 162 older adults with cancer (110). Therefore, the relationship between CT-derived muscle measurements and frailty in patients with cancer is currently unclear. Specifically, whether CT-derived muscle measurements could be used to objectively diagnose frailty. Moreover, it remains unclear if SMI/SMD capture the prognostic value frailty has to clinical outcomes in patients with cancer.

1.9 The utility of CT-derived skeletal muscle measurements for examination pathophysiology of cancer cachexia

Cancer cachexia is a complex syndrome defined by the loss of skeletal muscle mass (67). The degradation of skeletal muscle is thought to be the result of disruption of the hormonal network that maintain skeletal muscle mass (111), with a reduction in circulating anabolic hormones such as insulin-like growth factor-1 and the development of insulin resistance has been reported in patients with cancer cachexia (112, 113). Moreover, the production of pro-catabolic factors including angiotensin II, interleukin-6 and tumour necrosis factor alpha (114). At a cellular level, the ubiquitin-mediated proteasome system, autophagy-lysosome system and calcium-activated protease calpains have reported to be implication in the loss of skeletal muscle mass (115-118).

The degradation of skeletal muscle protein results in an efflux of amino acids into the circulation, which are utilised by the tumour and the host. Glutamine derived from skeletal muscle degradation is used by the tumour for synthesis of protein and Deoxyribonucleic acid (38). Moreover, nitrogen delivered to the liver, predominantly in the form of alanine, is utilised for gluconeogenesis and the synthesis of acute-phase proteins (114). Despite CT being considered a reliable modality for the quantification of both skeletal muscle and liver mass, there is presently a paucity of studies examining the relationship between CT-derived skeletal muscle and liver mass in patients with cancer.

Cancer cachexia is also associated with significant metabolic alterations (38). Specifically, dysregulated glucose metabolism and decreased insulin sensitivity/resistance (119). The liver is considered to be central to such changes and is actively co-opted to perform gluconeogenesis (114), utilizing lactate produced from the enhanced glycolysis of tumour cells (38). However, this pathway is inefficient and has higher energy demands, increasing the resting energy expenditure and resulting in the loss of lean mass in patients with cancer cachexia (120). Whilst dysregulated glucose metabolism and the loss of skeletal mass are thought to be closely related (119), there remains a paucity of studies examining the relationship between skeletal muscle mass and biomarkers of dysregulated glucose metabolism in patients with cancer.

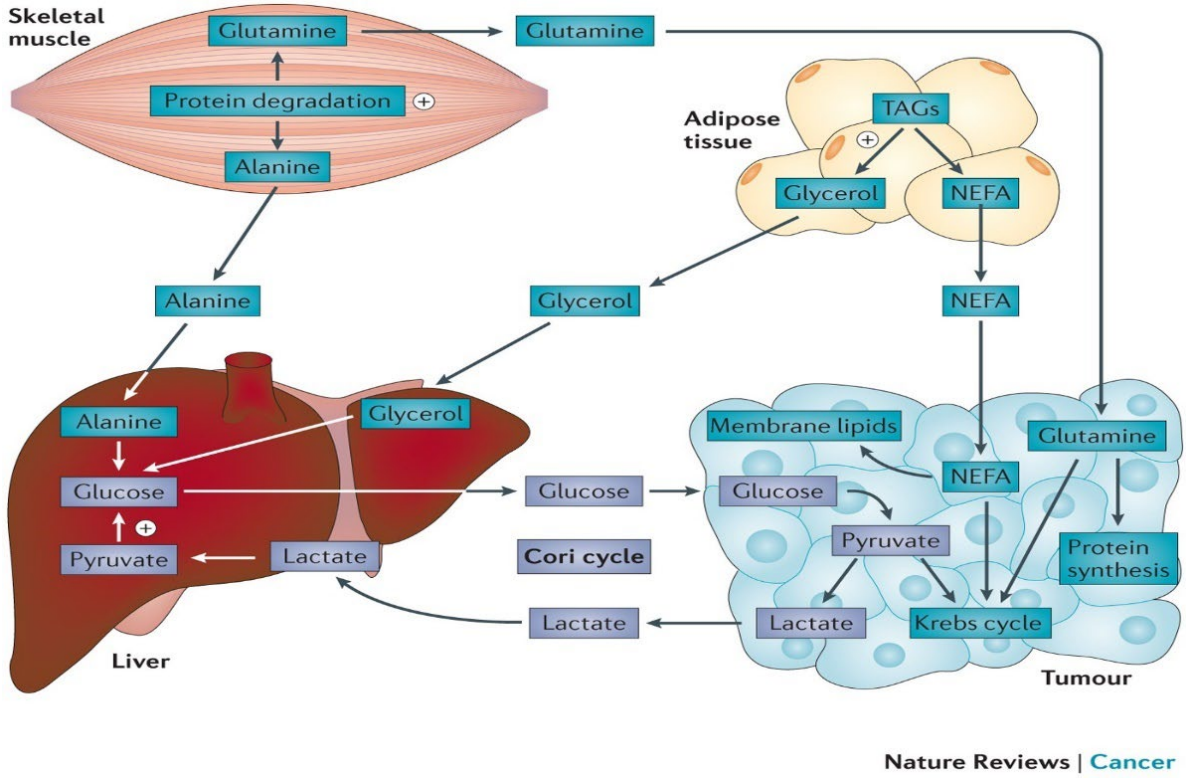


Figure 1-7: Alterations in metabolism in patients with cancer. Adapted from Argilés and co-workers (38)

2 Summary and Aims

The pathological loss of skeletal muscle mass in patients with cancer remains an area of interest, with studies consistently reporting an association with treatment and survival outcomes. Historically, such losses were considered a phenomenon exclusive to certain cancer subtypes and advanced disease stage. However, this observation has been challenged with studies reporting that a low skeletal muscle mass is prevalent in patients with potentially curative, early-stage disease, across a range of histological subtypes of cancer.

Whilst several methodologies have been proposed for the quantification of skeletal muscle mass in patients with cancer, measurement of the cross-sectional area of the total abdominal skeletal muscle on CT images obtained at L3 is considered the gold standard. In addition to the quantification of skeletal muscle mass (SMI), CT is considered to inform on the quality of skeletal muscle (SMD). At present, the prevalence of a low SMI and SMD in patients with cancer remains unclear. Specifically, the importance of tumour subtype and disease stage. Moreover, it remains unclear whether the prevalence of low SMI and SMD is subject to which threshold values are used.

A low SMI and SMD have consistently been reported to be negatively associated with clinical outcomes in studies of patients with cancer. Similarly, have been reported to be associated with other prognostic host factors including physical function, frailty, malnutrition and systemic inflammation. Therefore, at present, the basis of the relationship between CT-derived skeletal muscle measurements and clinical outcomes remains unclear. Specifically, if such measurements have independent prognostic value to clinical/survival outcomes in patients with cancer? Alternatively, if SMI and SMD are simply reflective of the functional, frailty and nutritional status of the patient.

Cancer cachexia is a complex metabolic syndrome that is associated with dysregulated glucose metabolism. However, there is currently a paucity of studies examining the relationship between a serum lactate dehydrogenase (LDH) concentration, an early biomarker of dysregulated glucose metabolism, and a low

skeletal muscle mass, the defining feature of cancer cachexia. Moreover, whilst the products of skeletal muscle degradation are thought to be captured and utilised by the liver in patients with cancer cachexia, the relationship between skeletal muscle mass and liver mass is unclear.

The present thesis aims to further examine how CT-derived measurements of skeletal muscle may be utilised in clinical cancer care. Specifically, to:

1. Examine the prevalence and determinants of CT-derived SMI and SMD in patients with cancer.

2. Determine whether the combination of CT-derived muscle measurements is associated with physical function, frailty, malnutrition, systemic inflammation and survival in patients with cancer.

3. Examine the relationship between CT-derived skeletal muscle mass and biomarkers of dysregulated glucose metabolism, specifically LDH, in patients with cancer.

4. Quantify liver mass in patients with cancer using CT and examine the relationship with CT-derived skeletal muscle mass in patients with cancer.

3 Methods

3.1 Cancer Staging

Tumours were staged using the Tumour, Node, Metastasis (TNM) staging system developed by the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC). Cancer stage was determined from radiological imaging (clinical stage) or from resected specimens in those who underwent surgery (pathological stage). Once the T, N and M were determined, patients were categorised into stage groups (I-IV) according to the relevant edition of the AJCC Cancer Staging Manual.

3.2 Co-morbidity

Patient comorbidity was classified using the American Society of Anaesthesiologists (ASA) physical status classification system: ASA 1, a normal healthy patient; ASA 2, a patient with mild systemic disease; ASA 3, a patient with severe systemic disease that is not incapacitating; and ASA 4, a patient with incapacitating severe systemic disease that is a constant threat to life (121).

3.3 Malnutrition

The Malnutrition Universal Screening Tool (MUST) was used to determine the overall risk of malnutrition. MUST is a 3-component score consisting of the patient's current weight status using BMI, unintentional weight loss, and the acute disease effect. Assessment was made by clinical nursing staff, using a dedicated proforma, within 24 hours of admission. Patients were categorised as into low risk (MUST score=0), medium risk (MUST score=1) and high risk (MUST score ≥2) of malnutrition. The MUST score is described below.

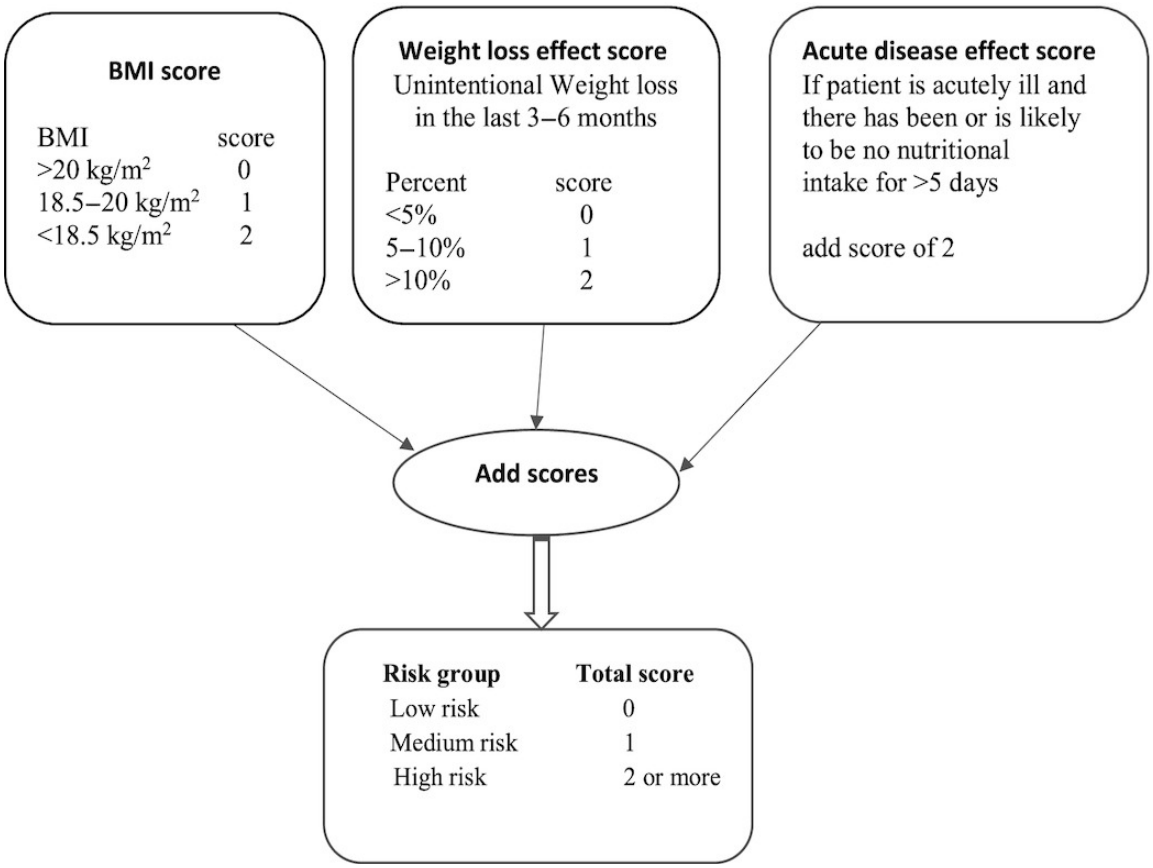


Figure 3-1: The MUST for determining malnutrition risk. Adapted from Almasaudi and co-workers (122)

3.4 BMI

BMI was calculated by division of the patient's weight in kilograms (kg) by their height in meters squared (m^2). Values were reported as (kg/m^2).

3.5 CT-derived Body Composition

All CT images used for body composition analysis were obtained at the level of L3, during the portal-venous phase of the scan, as previously described (123). Scans with significant movement artefact or missing region of interest were considered unsuitable and excluded. All images were analysed using the free-ware program (NIH Image J, version 1.47, http://rsbweb.nih.gov/ij/). CT-derived body composition measurements included the total fat area (TFA), visceral fat area

(VFA), skeletal muscle area (SMA). Attenuation thresholds were -190 to +30 HU for fat and -29 to +150 HU for muscle.

The TFA was quantified by depicting the outer contours of the abdominal wall as shown below (Figure 3-1). The VFA was quantified by depicting the inner contour of the psoas and abdominal wall muscles as shown below (Figure 3-1). The subcutaneous fat area (SFA) was calculated by subtraction of the VFA from TFA. SFA measurements were then normalized by division of the patient's height in meter squared to generate subcutaneous fat index (SFI, cm^2/m^2).

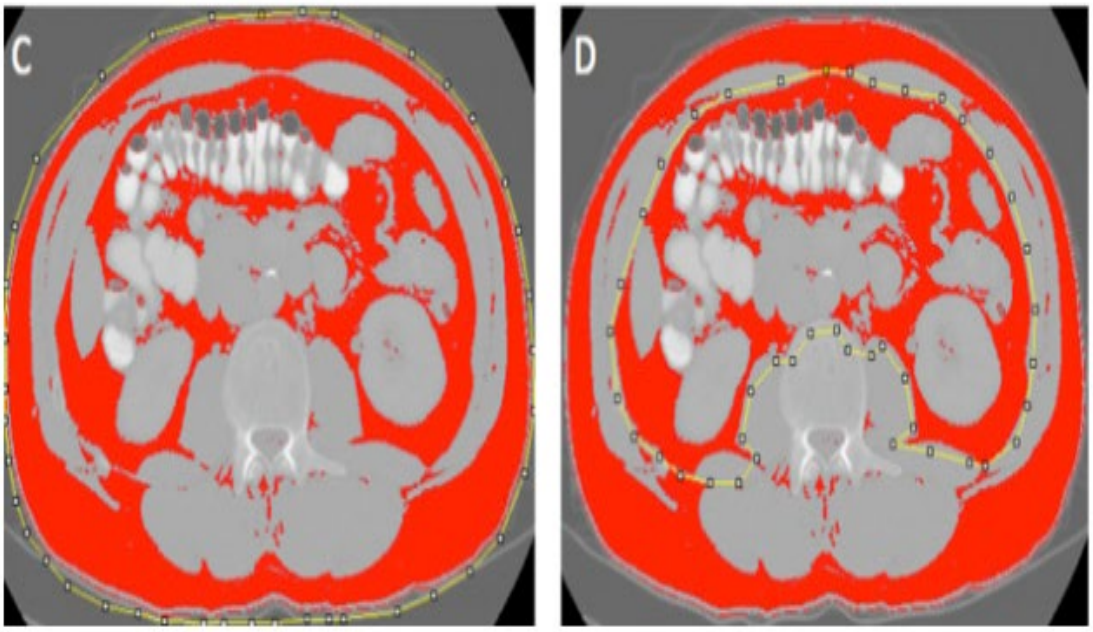


Figure 3-2: Measurement of the cross-sectional area of the TFA and VFA on an axial CT slice at the level of L3, using ImageJ. Adapted from McSorley and co-workers (123)

The SMA was quantified by manually delineating the cross-sectional area of the abdominal skeletal musculature including the quadratus lumborum, psoas, rectus abdominus, erector spinae, transversus abdominus and internal and external oblique muscle groups (Figure 3-2). Like SFA, SMA measurements were then normalized by division of the patient's height in meter squared to generate the SMI (cm^2/m^2). The SMD was calculated from the skeletal muscle area used to

calculate SMI. CT-derived body composition measurements were categorised using threshold values described in Table 3-1.

CT-derived body composition measurements were made by clinical researchers who had undergone appropriate training and had satisfactory inter-rater reliability. This was assessed in a sample of 30 scans using intra-class correlation coefficients (ICCC). The minimum required ICCC for each measurement was >0.99.

Table 3-1: Threshold values of CT-derived body composition measurements

High SFI
Ebadi and co-workers (124): SFI >50.0 cm^2/m^2 for male patients and SFI >42.0 cm^2/m^2 for female patients
High VFA
Doyle and co-workers (125): VFA >160 cm^2 for male patients and VFA >80 cm^2 for female patients
Low SMI
Caan and co-workers (72): SMI <52.3 cm^2/m^2 if BMI <30 kg/m^2 and SMI <54.3 cm^2/m^2 if BMI ≥30 kg/m^2 for male patients and SMI <38.6 cm^2/m^2 if BMI <30 kg/m^2 and SMI <46.6 cm^2/m^2 if BMI ≥30 kg/m^2 for female patients **Martin and co-workers (61):** SMI <43 cm^2/m^2 if BMI <25kg/m^2 and SMI <53 cm^2/m^2 if BMI ≥25kg/m^2 for male patients and SMI <41 cm^2/m^2 if BMI <25kg/m^2 or SMI <41 cm^2/m^2 if BMI ≥25kg/m^2 for female patients **Prado et al. (71):** SMI <52.4 cm^2/m^2 for male patients and <38.5 cm^2/m^2 for female patients
Low SMD
Martin and co-workers (61): SMD <41 HU if BMI <25 kg/m^2 and SMD <33 HU if BMI ≥25 kg/m^2 **Xiao and co-workers (11):** SMD <34.1 HU for male patients and BMI <25kg/m^2 and SMD <34.4 HU for female patients

3.6 CT-derived Sarcopenia Score

CT-derived SMI and SMD were combined to form the CT- Sarcopenia score (CT-SS). Patients were categorized as normal/high SMI (irrespective of SMD) =0, low SMI and normal/high SMD =1 and low SMI and low SMD =2.

3.7 Performance Status

Performance status was determined using the ECOG Performance Status Scale (ECOG-PS). Patients were categorized as 0-5. The ECOG-PS is described below.

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Figure 3-3: The ECOG Performance Status Scale. Adapted from Oken and co-workers (14)

3.8 Cardiopulmonary Exercise Testing

Cardiopulmonary Exercise Testing (CPET) was performed using a ZAN 600 (nSpire Health, Hertford, UK) and Ergoselect bicycle ergometer (Ergoline, Bitz, Germany). Testing was performed in the presence of a doctor and with resuscitation equipment available. Physiological parameters including electrocardiography, blood pressure, oxygen uptake and carbon dioxide output from analysis of inspiratory and expiratory gases were monitored during testing. All patients were exposed to an incremental physical exercise protocol until their maximally tolerated level was reached. This was determined by patient exhaustion, symptomatic breathlessness or pain. The measured parameters, along with the exercise protocol, allowed VO2 at anaerobic threshold (AT) and Peak exercise to be quantified.

3.9 Systemic Inflammation

Systemic inflammatory status was determined using the neutrophil/lymphocyte ratio (NLR), modified Glasgow Prognostic Score (mGPS) and systemic inflammatory grade (SIG). All measures were calculated from venous blood samples.

The NLR was calculated by division of the neutrophil count by the lymphocyte count, obtained from the full blood count (FBC). Values were categorised as follows, <3 (considered normal), 3–5 (considered moderately raised), and >5 (considered significantly raised).

The mGPS is a score that combines serum C-reactive protein (CRP, mg/L) and albumin (g/L) concentrations. The concentration of CRP and albumin were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK). The mGPS was calculated as follows; CRP ≤10 mg/L=0, CRP >10 mg/L & albumin ≥35 g/L=1, CRP >10 mg/L and albumin <35 g/L=2. An mGPS ≥1 was considered evidence of a systemic inflammatory response.

The NLR and mGPS were combined to form the SIG. Patients were categorised as grade 0-4. The calculation of the SIG is described below.

Systemic Inflammatory Grade (SIG)	
SIG 0	mGPS 0 and NLR < 3
SIG 1	mGPS 0 and NLR 3–5 or mGPS 1 and NLR < 3
SIG 2	mGPS 0 and NLR > 5 or mGPS 2 and NLR < 3 or mGPS 1 and NLR 3–5
SIG 3	mGPS 1 and NLR > 5 or mGPS 2 and NLR 3–5
SIG 4	mGPS 2 and NLR > 5

Figure 3-4: Calculation of the SIG. Adapted from Golder and co-workers (126)

3.10 Frailty

Frailty risk was determined using the five-item modified frailty index (mFI-5), developed from the American College of Surgeons National Surgical Quality Improvement Program (127). The mFI-5 screening tool combines the assessment of co-morbidity and functional status to calculate a score from 0-5. Patients were allocated 1 point for each of the following criterion present- congestive heart failure, chronic obstructive pulmonary disease (COPD) or recent pneumonia, hypertension requiring medication, diabetes mellitus and non-independent functional status. The presence of co-morbid disease and functional status for all patients was retrospectively identified from pre-operative anaesthetic assessments and electronic medical records.

3.11 Global Leadership Initiative on Malnutrition framework

The Global Leadership Initiative on Malnutrition (GLIM) framework for the diagnosis of cancer-related malnutrition involves a two-step approach. Firstly, screening to identify those at risk of malnutrition using validated tools such as the MUST. Secondly, diagnosing and grading the severity of malnutrition using agreed diagnostic criterion (128). These include three phenotypic (low body mass index, non-volitional weight loss and reduced muscle mass) and two aetiologic criterion (reduced food intake/assimilation and disease burden/inflammation), with a diagnosis of cachexia requiring the presence of one criterion from each group (128). The GLIM diagnostic framework is shown below.

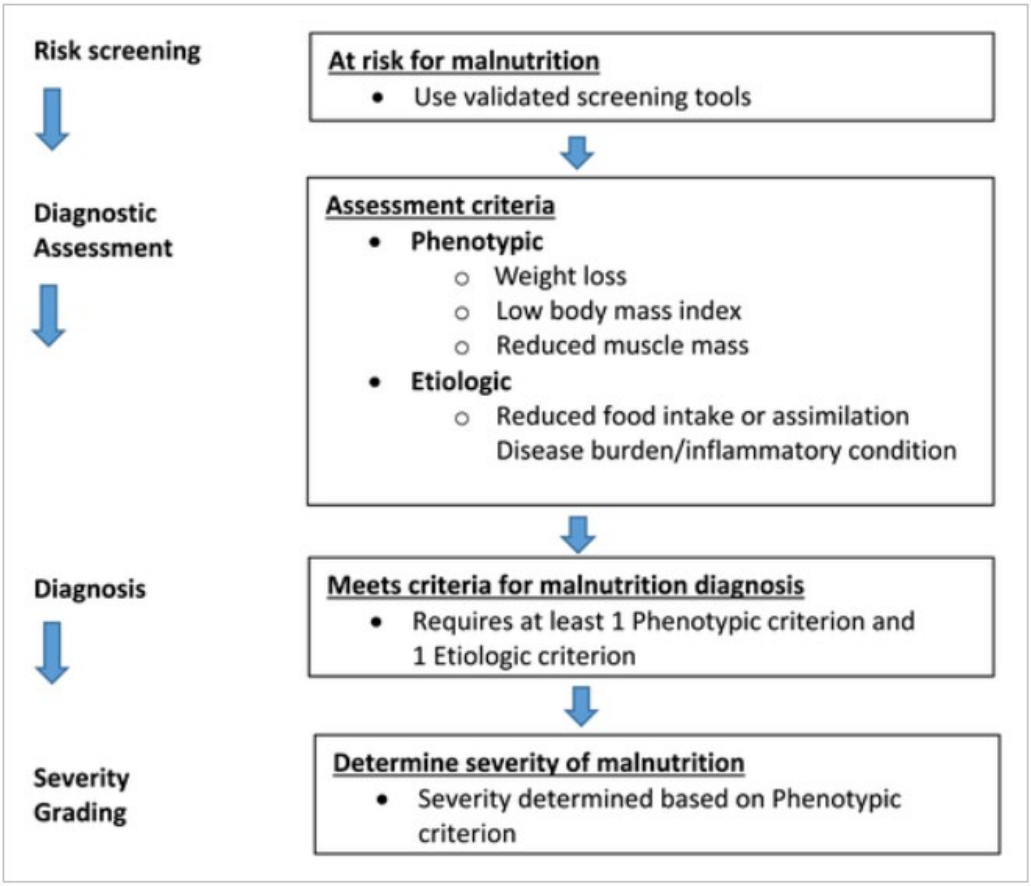


Figure 3-5: The GLIM framework for diagnosing cancer cachexia. Adapted from Cederholm and co-workers (128)

3.12 CT-derived Liver Mass

CT-derived liver measurements included the maximal cross-sectional liver area on axial CT slice (cm^2) and total liver volume (cm^3). The cross-sectional area of liver (cm^2) was manually delineated on portal-venous CT scans using the freehand measurement tool available within the Carestream Vue Picture Archive and Communications System (PACS, Graphics>measurement>freehand). The gallbladder and the inferior cava were excluded from the region of interest, however intrahepatic biliary and vascular structures were included, as previously described in the literature (129). Where possible, benign liver lesions were also excluded from the region of interest.

The maximal cross-sectional liver area was calculated by manual delineation of sequential images, approximated to be the largest area by the naked eye, from the slice at which the liver first appeared cranially. The maximal cross-sectional liver area on an axial CT slice was then normalized for height in meters squared to create the liver mass index (LMI). The cross-sectional area of liver on sequential axial CT images was then manually delineated on all slices as described above, at 5 mm intervals, from the slice at which the liver first appeared caudally. A slice interval of 5 mm was selected as this has been shown to be both time-efficient and provide good correlation with total liver volume in previous studies (129, 130). The sum of all liver cross-sectional area measurements was multiplied by the slice interval to give the total liver volume (cm^3).

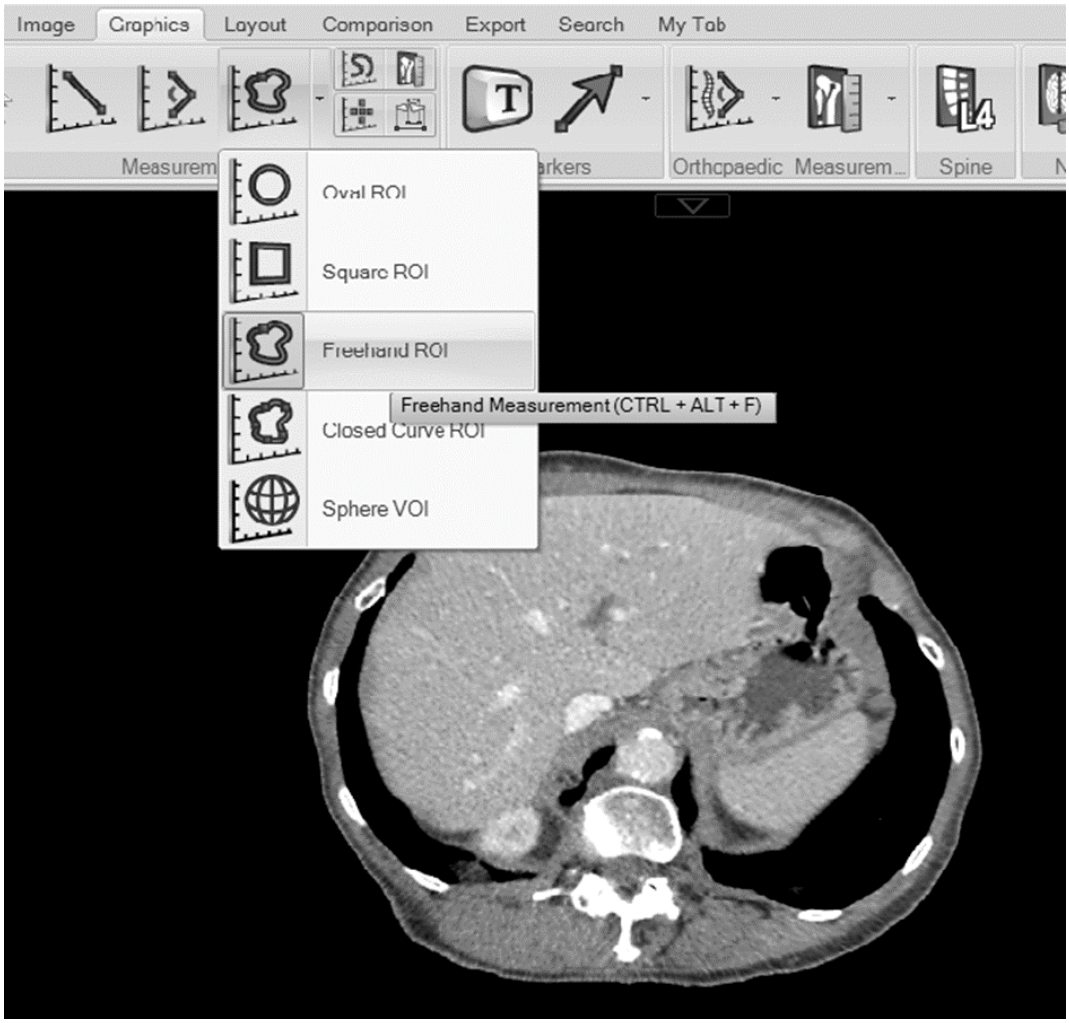


Figure 3-6: Freehand measurement tool available within the Carestream Vue PACS

4 CT-defined low skeletal muscle index and density in cancer patients- observations from a systematic review

4.1 Introduction

One in two people born in the UK after 1960 will be diagnosed with cancer during their lifetime (131). In the age of precision medicine, factors that aid the prediction of likely outcome in patients with cancer are vital in determining the modality and extent of treatment.

Body composition analysis using CT has garnered considerable interest with regards to its utility in predicting likely outcome. Within the last decade, there has been a substantial volume of research exploring the relationship between SMI (88) and SMD (89), and outcomes in patients with operable and advanced cancers, across a breadth of histological subtypes and treatment modalities. The expansion in the number of studies of examining the relationship between CT-derived body composition and outcomes is attributable to the routine use of CT in the staging of tumours and advances in the computer software to carry out such analysis (132).

Whilst a low SMI and SMD have consistently been reported to be associated with poorer outcomes in patients with cancer (88, 89), a range of thresholds values have been used to define a low SMI (61, 71, 72) and SMD (11, 61). At present, the importance of threshold value to the prevalence of a low SMI/SMD is unknown. Similarly, the importance of histological subtype and disease stage. In this chapter, the prevalence of low SMI and SMD, taking into account the threshold value used for these CT-derived skeletal muscle measurements and tumour stage, across a range of common solid tumours was investigated.

4.2 Patients and Methods

The protocol for this systematic review was developed using the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) guidelines (133). A systematic search of PubMed was carried out to identify studies reporting CT-derived SMI and SMD in patients with cancer. The search terms used were related to the following key words: “body composition”, “computed tomography”, “CT”, “cancer”, “skeletal muscle”, “skeletal muscle index”, “SMI”, “skeletal muscle density”, “SMD”, “sarcopenia”, “myosteatosis” and “cachexia”. The search was conducted from the start of the relevant database to the 30th of August 2020. Reference lists from studies of relevance were then hand-searched for any other eligible studies. All relevant studies assessing the relationship between CT-derived SMI/SMD and clinical outcomes, in the chosen cancer groups, were included. Conference abstracts, non-English language studies, as well as meta-analyses and systematic reviews were excluded. Studies were then individually screened for relevance based on title alone, prior to review of abstracts, and later, full texts.

The primary outcome of interest was the prevalence of low SMI or SMD. The type of cancer, whether curative or non-curative disease, the measure studied, and the threshold value used to define low SMI/SMD were recorded. The prevalence of low SMI/SMD was reported as median (Interquartile range, IQR). Studies included in the curative cohort were those with patients who had TNM stage I-III disease treated with curative intent. Studies involving patients with unresectable disease, TNM stage IV disease or those that examined at metastases were included in the non-curative cohort. Any issues relating to the interpretation of significance, or discrepancies in validity of results within the individual studies, were addressed by re-examination with a senior colleague. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist, a validated methodological quality assessment tool, was then used to assess all eligible studies for quality (134).

4.3 Results

A total of 1,225 studies were identified on initial search of the PubMed database. Following the exclusion of duplicates by the screening of titles, 1,163 abstracts were reviewed. 321 full papers were then deemed suitable for review, with 160 meeting inclusion criteria for qualitative analysis (Figure 4-1). A total of 161 records identified did not meet the eligibility criteria and were therefore excluded. Studies were excluded from qualitative analysis for the following reasons: their being systematic reviews and meta-analyses, using total psoas muscle area for calculation of SMI, using CT analysis of vertebral level other than L3 for calculation of total muscle area, those that did not report a SMI (cm^2/m^2) or SMD (HU), as well as studies that did not publish threshold values used to define a low SMI or SMD.

4.3.1 Skeletal Muscle Index

Of the 156 studies assessing SMI in cancer patients, 56% (n=87) involved patients with curative disease and 44% (n=69) involved patients with non-curative disease (Appendix A). 24% (n=38) of studies used thresholds described by Martin (61), 30% (n=47) used those described by Prado (71) and 46% (n=71) of studies reported low SMI using other threshold values (Table 4-1). In studies not using threshold values described by Martin or Prado, threshold values for low SMI ranged from ≤25.7 cm^2/m^2 (135) to ≤55.4 cm^2/m^2 (136-138) for males and ≤21.7 cm^2/m^2 (135) to ≤46.4 cm^2/m^2 (139) for females. Across the entire cohort, the median percentage of patients with low SMI was 45% (30–58). In studies of patients with curative cancer, the median low SMI was 40% (27–50) compared with 51% (35–64) in studies of patients with non-curative disease (Table 4-2). With regards to the prevalence of low SMI across the entire cohort, using specific threshold values, median values were similar in studies using thresholds described by either Martin or Prado, 49% (33–59) and 50% (39–60), respectively. However, a low SMI was less prevalent in studies using other threshold values at 36% (21–50, Table 4-2).

4.3.2 Skeletal Muscle Density

Of the 35 studies assessing SMD in patients with cancer, 60% (n=21) involved patients with curative disease and 40% (n=14) involved patients with non-curative disease (Appendix B). 49% (n=17) of studies assessing SMD used threshold values described by Martin (61). In the remaining 18 studies assessing SMD, threshold values used ranged from ≤22.0 HU (140) to ≤44.4 HU (74, 141, 142) in males and ≤23.5 HU (140) to ≤39.3 HU (141) in females (Table 4-3). Across the whole cohort, the prevalence of low SMD was 50% (32–60). The median percentage of patients with low SMD was higher in the non-curative cohort than in the curative cohort, 57% (33–65) and 48% (33–53), respectively (Table 4-4). When comparing studies using the thresholds for low SMD described by Martin with studies using other threshold values, the prevalence of a low SMD was similar, 53% (35-60) and 48% (30-54), respectively (Table 4-4).

4.3.3 Cancer Specific Analysis

4.3.3.1 Colorectal

The largest volume of studies assessing SMI involved patients with colorectal cancer (n=39 studies, Table 4-1). 23 studies (n=12,188) were of patients with curative disease and 16 studies (n=2,135) involved patients with non-curative disease. 15 studies used threshold values described by Martin, 13 studies used those described by Prado, and the remaining 11 studies used other threshold values (Table 4-1). When assessing the curative cohort, the median percentage of patients with low SMI was 41% (29-55) compared with 49% (43–61) in the non-curative cohort (Table 4-5). With reference to patients with low SMI across specific thresholds, the prevalence was 50% (43-60) in those using threshold values described by Martin, 48% (40–60) in those using threshold values described by Prado, and 28% (25–41) in studies using other threshold values (Table 4-7). When comparing curative and non-curative studies, the prevalence of low SMI was 50% (32-59) compared to 54% (48–59) in studies using threshold values described by Martin, 54% (43–60) compared to 44% (39–59) in studies using threshold values described by Prado and 27% (25–35) compared to 47% (33-55) in studies using other threshold values (Table 4-7).

A total of 13 studies composed of 7,997 patients with colorectal cancer assessed SMD using CT (Appendix B). Of these studies, 70% (n=9) were of patients with curative disease and 30% (n=4) of non-curative disease. Eight studies used the threshold values described by Martin and the remaining five studies used other threshold values (Table 4-3). Across the whole cohort of patients with colorectal cancer, the median percentage of those with a low SMD was 52% (30-64). When assessing the curative cohort, the median percentage of patients with low SMD was 52% (31-54) compared with 45% (23-66) in the non-curative cohort (Table 4-8). When examining specific thresholds, the median percentage of patients with low SMD using thresholds described by Martin was 58% (37-66), and 30% (27–53) in the studies using other threshold values (Table 4-8).

4.3.3.2 Oesophageal

Twenty-six studies, comprised of 4,205 patients, reported CT analysis of SMI in patients with oesophageal cancer (Table 4-1). 69% (n=18) of studies included patients with curative disease with the remaining 31% (n=8) comprising of patients with non-curative cancer. 12 studies (46%) assessed SMI using threshold values described by Prado (71), with only 12% (n=3) using threshold values described by Martin (61). The remaining 42% (n=11) of studies used other threshold values to define low SMI. Across the entire cohort, the prevalence of low SMI was 50% (39–62). With regards to curative and non-curative cohorts, prevalence of low SMI was similar, 48% (35–61) and 53% (49–62), respectively (Table 4-5).

Two studies reported SMD using threshold values described by Martin to define low SMD, one with curative cancer patients and the other non-curative. Across the whole cohort, the prevalence of low SMD was 54% (52-56, (Table 4-6).

4.3.4.3 Gastric

Twenty-one studies, comprised of 4,774 patients, reported CT analysis of SMI in patients with gastric cancer (Table 4-1). 67% (n=14) of studies included patients with curative disease with the remaining 33% (n=7) comprising of patients with non-curative cancer. Seven studies (33%) assessed SMI using threshold values

described by Martin, with 19% (n=4) using threshold values described by Prado. The remaining 48% (n=10) of studies used other threshold values to define low SMI. Across the entire cohort, the prevalence of low SMI was 30% (23–43). With regards to curative and non-curative cohorts, prevalence of low SMI was 30% (16–36) and 48% (37–64), respectively (Table 4-5).

Two studies reported SMD in patients with gastric cancer, one with curative cancer patients and the other non-curative. Across the whole cohort, the prevalence of low SMD was 71% (65-78, (Table 4-6).

4.3.3.4 Hepatobiliary

Twenty-six studies, comprised of 5,109 patients, reported CT analysis of SMI in patients with hepatobiliary cancer (Table 4-1). 35% (n=9) of studies included patients with curative disease and 65% (n=17) comprising of patients with non-curative cancer. Two studies (8%) assessed SMI using threshold values described by Martin, 15% (n=4) using threshold values described by Prado, and 77% (n=20) of studies used other threshold values to define low SMI. Across the entire cohort, the prevalence of low SMI was 42% (30-59). With regards to curative and non-curative cohorts, prevalence of low SMI was 47% (41-58) and 35% (15-59), respectively (Table 4-5).

Four studies reported SMD in patients with hepatobiliary cancer, using other threshold values to define a low SMD. Across the whole cohort, the prevalence of low SMD was 57% (49-70, (Table 4-6).

4.3.3.5 Pancreatic

Twenty-three studies, comprised of 4,689 patients, reported CT analysis of SMI in patients with pancreatic cancer (Table 4-1). 52% (n=12) of studies included patients with curative disease and 48% (n=11) comprising of patients with non-curative cancer. Six studies (26%) assessed SMI using threshold values described by Martin, 30% (n=7) using threshold values described by Prado, and 43% (n=10) of studies used other threshold values to define low SMI. Across the entire cohort, the prevalence of low SMI was 50% (25-62). With regards to curative and non-

curative cohorts, prevalence of low SMI was 33% (25-48) and 63% (58-65), respectively (Table 4-5).

Seven studies reported SMD in patients with pancreatic cancer (6 curative, 1 non-curative Across the whole cohort, the prevalence of low SMD was 33% (30-50), Table 4-6).

4.3.3.6 Breast

Twelve studies, comprised of 4,889 patients, reported CT analysis of SMI in patients with breast cancer (Table 4-1). 67% (n=8) of studies included patients with curative disease and 33% (n=4) comprising of patients with non-curative cancer. Three studies (25%) assessed SMI using threshold values described by Martin, 42% (n=5) using threshold values described by Prado, and 33% (n=4) of studies used other threshold values to define low SMI. Across the entire cohort, the prevalence of low SMI was 34% (16-42). With regards to curative and non-curative cohorts, prevalence of low SMI was 26% (14-35) and 49% (37-60), respectively (Table 4-5).

Five studies reported SMD in patients with breast cancer (3 curative, 2 non-curative). Three studies used the threshold values described by Martin to define a low SMD, with the remaining two studies using other threshold values. Across the whole cohort, the overall prevalence of low SMD was 53% (37-60), Table 4-6).

4.3.3.7 Lung

Nine studies, comprised of 1,451 patients, reported CT analysis of SMI in patients with lung cancer (Table 4-1). 33% (n=3) of studies included patients with curative disease and 67% (n=6) comprising of patients with non-curative cancer. Two studies (22%) assessed SMI using threshold values described by Martin, 22% (n=2) using threshold values described by Prado, and 56% (n=5) of studies used other threshold values to define low SMI. Across the entire cohort, the prevalence of low SMI was 50% (42-61). With regards to curative and non-curative cohorts, prevalence of low SMI was 42% (38-56) and 50% (48-58), respectively (Table 4-5).

Two studies reported SMD in patients with non-curative lung cancer. One study used the threshold values described by Martin to define a low SMD, with the study using other threshold values. The prevalence of low SMD was 19% (15-24), Table 4-6).

4.4 Discussion

The present systematic review included 160 studies that used CT to determine SMI and SMD in patients with cancer. In this substantial cohort it was of interest that both a low SMI and a low SMD had a percentage prevalence between 30-60% and that this was similar irrespective of threshold used, tumour type and stage of disease. Therefore, it would appear a low SMI and SMD are endemic in patients with cancer and that such poor muscle status occurs prior to diagnosis.

There is now a substantial literature that shows the detrimental impact that low SMI and SMD have on survival outcomes of patients with cancer (88, 89). However, in the present review, a low SMI and SMD had similar prevalence across cancer types. Given that there is wide variation in survival across cancer types this would suggest that body composition is not the main determinant of survival. It may be that the prognostic value of SMI reflects its measure of the nutritional and functional reserve of the cancer patient and that this reserve is eroded by the magnitude of the immune/ inflammatory challenge posed by the tumour to the host. Indeed, previous studies have shown that systemic inflammatory response is associated with a more aggressive tumour type (143), CT-derived low SMI and SMD (144) and survival (145, 146). It is therefore imperative that CT-derived muscle measurements be used in conjunction with other factors, such as systemic inflammation, to stage the host, as well as the tumour (147).

Patients with cancer often experience anorexia, loss of weight and skeletal muscle mass as the cancer progresses and systemic inflammation (148). This is termed cancer cachexia and has been shown to be associated with poorer outcomes (67). Despite the impact cancer cachexia has on outcomes for patients with cancer, the pathogenesis for the changes in body composition is not clearly understood (149). Patients with certain cancers, such as lung and gastrointestinal, are often thought of as having higher losses of weight/skeletal muscle mass. However, the results of this systematic review clearly show that a low SMI and SMD are endemic across all cancer types, present in both curative and non-curative cohorts (Table 4-5 and 4-6). This is made evident in comparison of prevalence of low SMI in curative colorectal cancer studies using Prado's thresholds, 50% (43-60), with those in studies of patients with curative oesophageal cancer 47% (30-60) and non-curative

pancreatic cancer 64% (60-65) using the same thresholds (Appendix A). The results of this systemic review challenge the perceived phenotype hypothesised for individuals with specific cancers. This in turn suggests that muscle status may only be one of number of factors determining the outcome of those with cancer.

There are several limitations of this systematic review. Firstly, the studies included were mainly retrospective with implications for the introduction of sample bias. However, the effect of this is likely to be minimised due to the volume of studies included. Secondly, most of the studies were from single institutions. To truly determine the utility of body composition parameters in determining outcomes of those with cancer, larger multi-centre, prospective studies will be required. Thirdly, CT-derived low SMI has been reported using different threshold values and methodological approaches (54). However, over half of the included studies reporting SMI, used thresholds defined by Martin (61) or Prado (71). When comparing just these threshold values, the median overall prevalence of low SMI was 49% and 50%, respectively. Furthermore, when these studies were stratified by curative and non-curative disease, there was little variation in the prevalence of low SMI (44% vs 57%) and (46% vs 56%), respectively (Table 4-2). However, universal thresholds will be required to reliably determine the prevalence of low SMI and SMD in patients with cancer and allow for future investigation of the effect of body composition parameters on outcomes. Fourthly, over half of studies assessing SMD failed to report important technical considerations such as the administration of contrast media prior to CT imaging. This has the potential to introduce further confounding variables into the methodology and supports the argument for standardized protocols. Finally, age-related sarcopenia (age at cancer diagnosis) is a potential confounding variable in the present analysis. Since Martin and co-workers provided thresholds for both SMI and SMD, age was compared in the Martin studies (n=38), across the curative (n=21) and non-curative cohorts (n=17). This analysis showed that age was similar in the curative and non-curative cohorts (mean 64+/-8 and 62+/-5 years, respectively) and therefore unlikely to be a major confounding factor in the present analysis. Nevertheless, it will be important to carry out analysis in multiple tumour types and stages of disease using the same methodology to eliminate the aforementioned potential confounding factors and to confirm the present observations.

In conclusion, a low SMI and SMD are endemic across a range of cancer types and disease stage. To date there has been a belief that skeletal muscle parameters differ between cancers which are curable versus more advanced stages. The present observations herein challenge this belief with similar levels of prevalence observed. However, further multicentre studies are required to produce international disease-specific thresholds for clinically relevant CT-derived body composition.

4.5 Tables and Footnotes

Table 4-1: The number of studies and the threshold values used to define low SMI in patients with cancer

Cancer subtype	Martin (n=)	Prado (n=)	Other (n=)	Total (n=)
Colorectal	15	13	11	39
Oesophageal	3	12	11	26
Gastric	7	4	10	21
Hepatobiliary	2	4	20	26
Pancreatic	6	7	10	23
Breast	3	5	4	12
Lung	2	2	5	9
Total (n)	38	47	71	156

Table 4-2: The percentage prevalence of low SMI by threshold value used

Cohort	Overall	Martin	Prado	Other
All	45% (30-58)	49% (33-59)	50% (39–60)	36% (21–50)
Curative	40% (27-50)	44% (32-50)	46% (35-60%)	33% (25-43)
Non-curative	51% (35-64%)	57% (47-61)	56% (44-65)	48% (23-61)

Each cell percentage prevalence (IQR)

Table 4-3: The number of studies and the threshold values used to define low SMD in patients with cancer

Cancer subtype	Martin (n=)	Other (n=)	Total (n=)
Colorectal	8	5	13
Oesophageal	2	0	2
Gastric	1	1	2
Hepatobiliary	0	4	4
Pancreatic	3	4	7
Breast	3	2	5
Lung	1	1	2
Total (n)	17	18	35

Table 4-4: The percentage prevalence of low SMD by threshold value used

Cohort	Overall	Martin	Other
All	50% (32-60)	53% (35-60)	48% (30-54)
Curative	48% (33-53)	52% (35-58)	37% (32-51)
Non-curative	57% (33-65)	57% (45-61)	57% (31-80)

Each cell percentage prevalence (IQR)

Table 4-5: The percentage prevalence of low SMI by cancer type

Cancer subtype	Overall cohort	Curative	Non-curative
Colorectal	46% (33–60)	41% (29-55)	49% (43-61)
Oesophageal	50% (39–62)	48% (35–61)	53% (49–62)
Gastric	30% (23–43)	30% (16–36)	48% (37–64)
Hepatobiliary	42% (30-59)	47% (41–58)	35% (15–59)
Pancreatic	50% (25–62)	33% (25–48)	63% (58–65)
Breast	34% (16–42)	26% (14–35)	49% (37–60)
Lung	50% (42–61)	42% (38–56)	50% (48–58)
All	44% (30–58)	40% (26–50)	51% (35–64)

Each cell percentage prevalence (IQR)

Table 4-6: The percentage prevalence of low SMD by cancer type

Cancer subtype	Overall cohort	Curative	Non-curative
Colorectal	52% (30-64)	52% (31-54)	45% (24-66)
Oesophageal	54% (52-56)	59%*	50%*
Gastric	71% (65-78)	84%*	59%*
Hepatobiliary	57% (49-70)	49%*	65% (57-75)
Pancreatic	33% (30-50)	33% (28-44)	55%*
Breast	53% (37-60)	37% (36-45)	73% (67-80)
Lung	NR	NR	19% (15-24)
All	50% (32-60)	48% (33-53)	57% (33-65)

Each cell percentage prevalence (IQR)

** Denotes cohorts with a solitary study. No studies reported SMD in patients with curative lung cancer*

Table 4-7: The percentage prevalence of low SMI by threshold value used in studies of colorectal cancer patients

Cohort	Overall	Martin	Prado	Other
All	46% (33–60)	50% (43-60)	48% (40-60)	28% (25-41)
Curative	41% (29-55)	50% (32-59)	54% (43-60)	27% (25-35)
Non-curative	49% (43-61)	54% (48-59)	44% (39-59)	47% (33-55)

Each cell percentage prevalence (IQR)

Table 4-8: The percentage prevalence of low SMD by threshold value used in studies of colorectal cancer patients

Cohort	Overall	Martin	Other
All	52% (30-64)	58% (37-66)	30% (27-53)
Curative	52% (31-54)	52% (39-64)	42% (30-53)
Non-curative	45% (24-66)	64% (42-68)	25%*

Each cell percentage prevalence (IQR)

** Denotes cohorts with a solitary study*

4.6 Figures and Legends

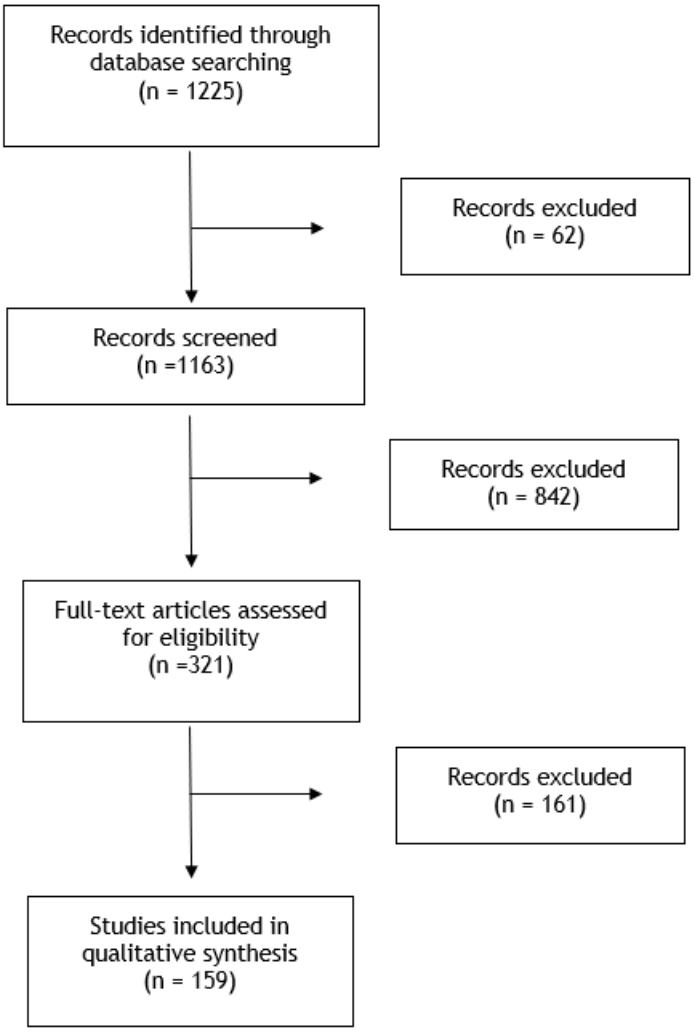


Figure 4-1: Flow diagram of literature search and included/excluded studies

5 The combination of CT- derived muscle mass and muscle radiodensity and relationship with clinicopathological characteristics and survival in patients undergoing potentially curative surgery for colorectal cancer

5.1 Introduction

The EWGSOP2 revised operational definition of sarcopenia highlighted the importance of assessing muscle strength, in addition to muscle mass, for diagnosing sarcopenia (31). A variety of approaches have been used to determine muscle strength in patients with cancer including subjective assessments such as performance status and objective assessments such as HGS (150). However, to date, there is no widely accepted objective assessment to supplement performance status. Therefore, there is continued interest in identifying objective assessments of muscle strength to characterize sarcopenia and determine its impact on clinical outcomes.

In patients with cancer, CT-derived body composition analysis has facilitated quantification of SMI and SMD as part of routine clinical investigations (61, 71). CT-derived SMI has been reported to be a reliable method for the quantification of skeletal muscle mass, with measurements reported to be consistent with other modalities (151). Moreover, whilst subject to confounding factors (54), there is now consistent evidence that SMD is associated with physical function in patients with cancer, across a range of cancer subtypes and disease stages (80, 101, 152). Therefore, taken together, SMI and SMD, may provide a routine clinical methodology by which sarcopenia can be characterised.

In isolation, a low SMI and SMD have been negatively associated with clinical outcomes in patients with colorectal cancer (153-155). Furthermore, have been reported to be associated with prognostic host factors including malnutrition (156) and systemic inflammation (144). However, the relationship between CT-derived sarcopenia, malnutrition, systemic inflammation and clinical outcomes in colorectal cancer has yet to be examined. Specifically, whether these measurements together, if carried out using standardised methodology (54), may

have complementary prognostic value. This chapter examined the relationship between CT-derived sarcopenia and clinicopathological characteristics and survival in patients undergoing potentially curative surgery for colorectal cancer.

5.2 Patients and Methods

5.2.1 Patients

Consecutive patients who underwent potentially curative surgery for colorectal cancer within NHS Greater Glasgow and Clyde, between April 2008 and April 2018, were identified from a prospectively maintained database. Those patients with a pre-operative CT scan, recorded height and weight, pre-operative assessment of the systemic inflammatory response and had TNM stage I-III disease were assessed for inclusion. Exclusion criteria were as follows; patients without satisfactory pre-operative CT imaging, without a recorded height and weight, had no pre-operative assessment of the systemic inflammatory response or had TNM stage IV disease.

Patients were operated on at Glasgow Royal Infirmary, a single tertiary referral teaching hospital. Prophylactic antibiotics were administered at the induction of anaesthesia. As per unit policy, subcutaneous low molecular weight heparin and pneumatic compression stockings were given to patients as venous thromboprophylaxis.

The primary end point was overall survival. Patients were followed up for a minimum of 3 years following surgery. The date of death was confirmed using hospital electronic case records. Date of last recorded follow-up or last review of electronic case records (1st October 2021), which served as the censor date. Ethical approval was granted by the West of Scotland Research Ethics Committee, Glasgow.

5.2.2 Methods

Routine demographic details included age, sex and BMI. Age categories were grouped into <64, 65-74 and >74 years. BMI was categorized as <20, 20-24.9, 25-29.9 and ≥30 kg/m^2. Tumour site was identified from pre-operative CT imaging, endoscopic and pathology reports. Tumours were staged using the fifth edition of the TNM classification, consistent with practice in the UK during the study period (157), as described in Chapter 3. Patient comorbidity was classified using ASA grading system as described in Chapter 3. The MUST was used to determine the

overall risk of malnutrition, with scores calculated as described in Chapter 3. Systemic inflammation was determined using the NLR and mGPS, calculated from pre-treatment venous blood samples, as described in Chapter 3. NLR values were grouped as <3/3-5/>5 and mGPS values as 0/1/2.

CT-derived body composition analysis was carried out as described in Chapter 3. A high SFI and VFA were defined using the threshold values of Ebadi and co-workers and Doyle and co-workers, respectively (124, 125). A low SMI was defined using the threshold values of Martin and co-workers (61) and Caan and co-workers (72). A low SMD was defined using the threshold values of Martin and co-workers (61) and Xiao and co-workers (11). The CT-SS was determined as described in Chapter 3.

5.2.3 Statistical Analysis

Clinicopathological variables, ASA, MUST, BMI, SFI, VFA, CT-SS, NLR, mGPS and overall survival were presented as categorical variables. The Pearson Chi square test was used to examine the associations between categorical variables and the Chi square test for linear trend was used for ordered variables with multiple categories.

Survival data were analysed using univariate and multivariate Cox's proportional hazards model. Those variables associated with a degree of $p < 0.1$ were entered into a backward conditional multivariate model. Overall survival was defined as the time between the date of surgery and the date of death of any cause. Patients who died within 30-days of surgery were excluded from subsequent survival analysis.

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 27.0 (SPSS Inc., Chicago, IL, USA).

5.3 Results

The clinicopathological characteristics of the included patients are shown in Table 5-1 (n=1,002). 55% (n=554) of patients were male and 66% (n=657) were aged 65 years or older. 24% (n=240) of patients had TNM stage I disease, 40% (n=404) stage II and 36% (n=358) stage III disease. 35% (n=350) of patients were ASA grade ≥3. 18% (n=174) of patients with a pre-operative MUST were at risk of malnutrition. The median BMI of the cohort was 27 kg/m^2 and 65% (n=652) of patients had a BMI≥ 25 kg/m^2. A high VFA was present in 73% (n=731) of patients and 80% (n=803) had a high SFI. A low SMI and SMD were present in 51% (n=507) and 67% (n=668), respectively. 48% (n=479) of patients had an NLR ≥3 and 27% (n=271) had an mGPS ≥1. 83% (n=834) of patients who underwent surgical resection for non-metastatic colorectal cancer with curative intent were alive at 3-years. When stratified by site of tumour, 82% (n=491) of patients with colonic tumours were alive at 3-years post-operatively and 86% (n=343) of those with rectal tumours.

The relationship between SMI, SMD and overall survival in patients who underwent potentially curative surgery for colorectal cancer, using thresholds of Martin and co-workers, is shown in Table 5-2a. In patients with a low SMI, a low SMD was significantly associated with overall survival ($p<0.01$). The relationship between SMI, SMD and overall survival in patients who underwent potentially curative surgery for colorectal cancer, using thresholds of Caan/Xiao and co-workers, is shown in Table 5-2b. In patients with a low SMI, a low SMD was significantly associated with overall survival ($p<0.001$).

The prevalence of CT-derived sarcopenia scores in patients who underwent potentially curative surgery for colorectal cancer, using thresholds of Martin and co-workers and Caan/Xiao is shown in Table 5-3. A similar prevalence was observed irrespective of threshold combination used (49%/12%/39% vs. 43%/19%/38%, respectively).

The relationship between the CT-SS and clinicopathological characteristics, CT-derived body composition measurements, systemic inflammation and overall survival in patients who underwent potentially curative surgery for colorectal cancer, is shown in Table 5-4a and 5-4b. On univariate analysis, the CT-SS

(Martin/Martin) was significantly associated with age ($p<0.001$), tumour site ($p<0.05$), ASA ($p<0.05$), MUST ($p<0.001$), BMI ($p<0.001$), NLR ($p<0.001$), mGPS ($p<0.001$) and overall survival ($p<0.001$, Table 5-4a). On univariate analysis, the CT-SS (Caan/Xaio) was significantly associated with age ($p<0.001$), sex ($p<0.001$), tumour site ($p<0.05$), TNM stage ($p<0.05$), ASA ($p<0.001$), BMI ($p<0.001$), high SFI ($p<0.05$), NLR ($p<0.001$), mGPS ($p<0.001$) and overall survival ($p<0.001$, Table 5-4b).

The relationship between clinicopathological characteristics, CT-derived body composition measurements, CT-SS (Martin), systemic inflammation and overall survival in patients who underwent potentially curative surgery for colorectal cancer is shown in Table 5-5a. On univariate analysis, age ($p<0.001$), TNM stage ($p<0.001$), ASA ($p<0.001$), MUST ($p<0.001$), CT-SS (Martin, $p<0.001$), NLR ($p<0.001$) and mGPS ($p<0.001$) were significantly associated with overall survival. On multivariate analysis, TNM stage ($p<0.001$), ASA ($p<0.001$), MUST ($p<0.001$), NLR ($p<0.05$) and mGPS ($p<0.05$) remained significantly associated with overall survival (Table 5-5a).

The relationship between clinicopathological characteristics, CT-derived body composition measurements, CT-SS (Caan/Xiao), systemic inflammation and overall survival in patients who underwent potentially curative surgery for colorectal cancer is shown in Table 5-5b. On univariate analysis, CT-SS (Caan/Xiao) was significantly associated with overall survival ($p<0.001$). On multivariate analysis, TNM stage ($p<0.001$), ASA ($p<0.05$), MUST ($p<0.001$), NLR ($p<0.05$) and mGPS ($p<0.05$) remained significantly associated with overall survival (Table 5-5b).

5.4 Discussion

The results of the present study showed that in a large cohort of patients with primary operable colorectal cancer, the combination of low CT-derived skeletal muscle mass and density (CT-sarcopenia score, CT-SS) was significantly associated with older age, greater comorbidity and nutritional risk, systemic inflammation and poorer survival, irrespective of threshold value used to define a low SMI or SMD. Therefore, this simple objective score has clinical utility to inform on likely outcome and may be useful in the investigation of the underlying mechanisms of sarcopenia in patients with cancer.

Whilst CT-derived skeletal muscle mass and density measurements have been reported to have independent prognostic value in patients with cancer (88, 89), the present results show that patients with both a low SMI and SMD had significantly reduced overall survival compared to patients with a norFmal SMI and SMD. These results suggests that the prognostic value of CT-derived skeletal muscle measurements is likely to be greatest when used in combination, such as the proposed CT-SS. Combining CT-derived muscle measurements has previously been proposed in the literature in the form of the unvalidated SMG (SMI x SMD). However, the methodology used did not account for the relative importance and accuracy of the individual components. In contrast, the proposed CT-SS is based on the measurement of SMI using standardized threshold values and methodology validated against other techniques (151). Furthermore, the CT-SS utilises standardized threshold values for SMD and accounts for potential confounding factors in the methodology, such as the phase of CT scan in which images were obtained and the use of contrast media (54, 158). Therefore, the CT-SS reflects an incremental approach to defining sarcopenia and examining its impact on clinical outcomes.

CT-derived skeletal muscle measures (SMI and SMD) have consistently been reported to be closely associated with systemic inflammation (144). In contrast, the relationship between a low SMI/SMD and disease stage is unclear. In the present study, the association between CT-derived sarcopenia and TNM stage was inconsistent and threshold dependent, suggesting that disease stage is not a major determinant of muscle status (Table 5-4 and 5-4b). The present observations are

in keeping with those of Chapter 4, that reported a similar prevalence of low SMI and SMD in patients with primary operable and advanced cancer, across a range of cancer subtypes. Taken together, the results suggest that sarcopenia (a low SMI and low SMD) is endemic and are consistent with the hypothesis that poor muscle status is largely constitutional and not the result of the cancer per se

In the present study, a low SMI and SMD were found to be prevalent, on a background of CT-derived obesity (high SFI and VFA). These observations are consistent with recent work of Martin and co-workers, who reported that a low skeletal muscle mass and density were endemic in a study of 1,157 overweight/obese patients with cancer (159). However, in contrast to other studies within the literature that have reported an association with CT-derived fat measurements and survival in patients with primary operable colorectal cancer (72, 124), neither a high SFI or VFA had prognostic value to survival in the present study. The studies are difficult to compare with heterogeneity in the prevalence of high SFI and VFA, threshold values used to define a high SFI/VFA and the survival outcomes examined. Therefore, further examination is required to determine whether CT-derived muscle and fat measures have complimentary prognostic value to survival outcomes in patients with cancer.

There are a number of limitations to the present study. Firstly, this is a retrospective study and may be subject to bias and missing data. Indeed, eighteen of the included patients did not have a pre-operative MUST score to assess the risk of malnutrition. However, given pre-operative MUST score was available in 98% (n=984) of patients, this was not considered to be a confounding factor to the present observations. Secondly, CT analysis of SMD has been shown to be dependent on methodology, such as contrast media enhancement (160). However, only patients who underwent a portal-venous CT with the administration of contrast media were included in the present study. Thirdly, patients included in the present study underwent potentially curative surgery for colorectal cancer over a decade long time frame. Whilst nuances may have occurred in the treatment of patients across the study period, there was no significant association between the year of surgery and overall survival (HR 0.99, 95% CI 0.94-1.04, p=0.589). Therefore, this was also not considered to be a confounding factor. Lastly, given the use of BMI in the MUST scoring framework and for the

stratification of CT-derived muscle measurements, there was a potential for collinearity in the Cox's proportional hazard models.

In conclusion, the objective CT-SS was significantly associated with older age, comorbidity, nutritional risk and systemic inflammation in patients with primary operable colorectal cancer. Moreover, when used in combination, CT-derived skeletal muscle measurements (SMI and SMD) have additional prognostic value to survival.

5.5 Tables and Footnotes

Table 5-1: Clinicopathological characteristics of included patients (n=1,002)

Clinicopathological Characteristic	n=
Age (<65/65-74/>74)	345/367/290
Sex (Female/Male)	448/554
Tumour Site (Colon/Rectum)	602/400
TNM Stage (I/II/III)	240/404/358
ASA (1/2/≥3)	196/456/350
MUST risk (Low/Medium/High)	810/91/83
BMI (<20/20-24.9/25-29.9/≥30 kg/m^2)	58/292/337/315
High SFI (No/Yes)	199/803
High VFA (No/Yes)	271/731
Low SMI (No/ Yes)	495/507
Low SMD (No/ Yes)	334/668
NLR (<3/3-5/>5)	523/310/169
mGPS (0/1/2)	731/109/162
Overall Survival (Yes/No)	834/168

Table 5-2a: The relationship between SMI, SMD and overall survival in patients who underwent potentially curative surgery for colorectal cancer, using threshold values of Martin and co-workers (n=1,002)

	Normal SMI (n=495)	**Low SMI** (n=507)	**Total** (n=1,002)	**p value**
Normal SMD (n=334)	190 (88%)	106 (89%)	296 (89%)	0.864
Low SMD (n=668)	238 (85%)	300 (77%)	538 (81%)	0.013
Total (n=1,002)	428 (87%)	406 (80%)	834 (83%)	0.007
p value	0.277	0.005	0.001	

Table 5-2b: The relationship between SMI, SMD and overall survival in patients who underwent potentially curative surgery for colorectal cancer, using threshold values of Caan/Xiao and co-workers (n=1,002)

	Normal SMI (n=432)	**Low SMI** (n=570)	**Total** (n=1,002)	**p value**
Normal SMD (n=418)	202 (87%)	165 (89%)	367 (88%)	0.439
Low SMD (n=584)	171 (86%)	296 (77%)	467 (80%)	0.010
Total (n=1,002)	373 (86%)	461 (81%)	834 (83%)	0.022
p value	0.817	<0.001	0.001	

Table 5-3: The prevalence of CT-derived sarcopenia scores in patients who underwent potentially curative surgery for colorectal cancer, using threshold values of Martin and co-workers and Caan/Xiao and co-workers (n=1,002)

	CT-SS 0 (n=%)	**CT-SS 1** (n=%)	**CT-SS 2** (n=%)
Martin et al	495 (49%)	119 (12%)	388 (39%)
Caan/Xiao et al	432 (43%)	185 (19%)	296 (38%)

Table 5-4a: The relationship between the CT-derived sarcopenia score (CT-SS, Martin) and clinicopathological characteristics, systemic inflammation, CT-derived body composition measurements and overall survival in patients who underwent potentially curative surgery for colorectal cancer (n=1,002)

	CT-SS 0 (n=495)	**CT-SS 1** (n=119)	**CT-SS 2** (n=388)	**p value**
Age (<65/65-74/>74)	217/174/104	46/55/19	82/138/168	<0.001
Sex (Female/Male)	222/273	59/60	167/221	0.626
Tumour Site (Colon/Rectum)	281/214	69/50	252/136	0.015
TNM Stage (I/II/III)	143/171/181	26/40/53	71/193/124	0.221
ASA (1/2/≥3)	103/227/165	35/55/29	58/174/156	0.014
MUST risk (Low/Medium/High)	433/29/29	91/11/10	286/51/44	<0.001
BMI (<20/20-24.9/25-29.9/≥30 kg/m^2)	17/128/129/221	7/26/69/17	34/138/139/77	<0.001
High SFI (No/Yes)	87/408	33/86	79/309	0.261
High VFA (No/Yes)	124/371	42/77	105/283	0.449
NLR (<3/3-5/>5)	277/147/71	74/32/13	172/131/85	<0.001
mGPS (0/1/2)	394/56/45	89/17/13	248/36/104	<0.001
Overall Survival (Yes/No)	428/67	106/13	300/88	<0.001

Table 5-4b: The relationship between the CT-derived sarcopenia score (CT-SS, Caan/Xiao) and clinicopathological characteristics, systemic inflammation, CT-derived body composition measurements and overall survival in patients who underwent potentially curative surgery for colorectal cancer (n=1,002)

	CT-SS 0 (n=432)	**CT-SS 1** (n=185)	**CT-SS 2** (n=385)	**p value**
Age (<65/65-74/>74)	203/152/77	69/77/39	73/138/174	<0.001
Sex (Female/Male)	237/195	83/102	128/257	<0.001
Tumour Site (Colon/Rectum)	242/190	101/84	259/126	0.001
TNM Stage (I/II/III)	126/152/154	42/80/63	72/172/141	0.033
ASA (1/2/≥3)	96/203/133	47/86/52	53/167/165	<0.001
MUST risk (Low/Medium/High)	372/29/26	130/24/26	308/38/31	0.060
BMI (<20/20-24.9/25-29.9/≥30 kg/m^2)	17/84/151/180	20/95/47/34	21/113/139/112	<0.001
High SFI (No/Yes)	52/380	74/111	73/312	0.008
High VFA (No/Yes)	98/334	95/90	78/307	0.566
NLR (<3/3-5/>5)	254/128/50	89/64/32	180/118/87	<0.001
mGPS (0/1/2)	345/46/41	134/25/26	252/38/95	<0.001
Overall Survival (Yes/No)	373/59	165/20	296/89	<0.001

Table 5-5a: The relationship between clinicopathological characteristics, CT-derived body composition measurements, CT-SS (Martin), systemic inflammation and overall survival in patients who underwent potentially curative surgery for colorectal cancer (n=1,002)

	Univariate HR (95% CI)	**p value**	**Multivariate HR (95% CI)**	**p value**
Age (<65/65-74/>74)	1.46 (1.19-1.77)	<0.001	-	0.194
Sex (Female/Male)	1.21 (0.89-1.64)	0.232	-	-
Tumour Site (Colon/ Rectum)	0.75 (0.55-1.04)	0.080	-	0.498
TNM Stage (I/II/III)	1.65 (1.33-2.04)	<0.001	1.54 (1.23-1.93)	<0.001
ASA (1/2/≥3)	1.59 (1.27-1.98)	<0.001	1.48 (1.17-1.86)	<0.001
MUST risk (Low/Medium /High)	2.07 (1.72-2.48)	<0.001	1.79 (1.48-2.17)	<0.001
High SFI (No/Yes)	0.77 (0.54-1.10)	0.148	-	-
High VFA (No/Yes)	0.85 (0.61-1.19)	0.346	-	-
CT-SS (0/1/2)	1.36 (1.15-1.60)	<0.001	-	0.227
NLR (<3/3-5/>5)	1.46 (1.21-1.77)	<0.001	1.25 (1.03-1.53)	0.027
mGPS (0/1/2)	1.55 (1.30-1.84)	<0.001	1.26 (1.05-1.52)	0.014

HR- Hazard ratio, CI- Confidence interval

Table 5-5b: The relationship between clinicopathological characteristics, CT-derived body composition measurements, CT-SS (Caan/Xiao), systemic inflammation and overall survival in patients who underwent potentially curative surgery for colorectal cancer (n=1,002)

	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
Age (<65/65-74/>74)	1.46 (1.19-1.77)	<0.001	-	0.253
Sex (Female/Male)	1.21 (0.89-1.64)	0.232	-	-
Tumour Site (Colon/ Rectum)	0.75 (0.55-1.04)	0.080	-	0.490
TNM Stage (I/II/III)	1.65 (1.33-2.04)	<0.001	1.52 (1.21-1.91)	<0.001
ASA (1/2/≥3)	1.59 (1.27-1.98)	<0.001	1.43 (1.14-1.81)	0.002
MUST risk (Low/Medium /High)	2.07 (1.72-2.48)	<0.001	1.80 (1.49-2.17)	<0.001
High SFI (No/Yes)	0.77 (0.54-1.10)	0.148	-	-
High VFA (No/Yes)	0.85 (0.61-1.19)	0.346	-	-
CT-SS (0/1/2)	1.39 (1.17-1.64)	<0.001	-	0.077
NLR (<3/3-5/>5)	1.46 (1.21-1.77)	<0.001	1.23 (1.01-1.50)	0.041
mGPS (0/1/2)	1.55 (1.30-1.84)	<0.001	1.22 (1.01-1.48)	0.040

HR- Hazard ratio, CI- Confidence interval

5.6 Figures and Legends

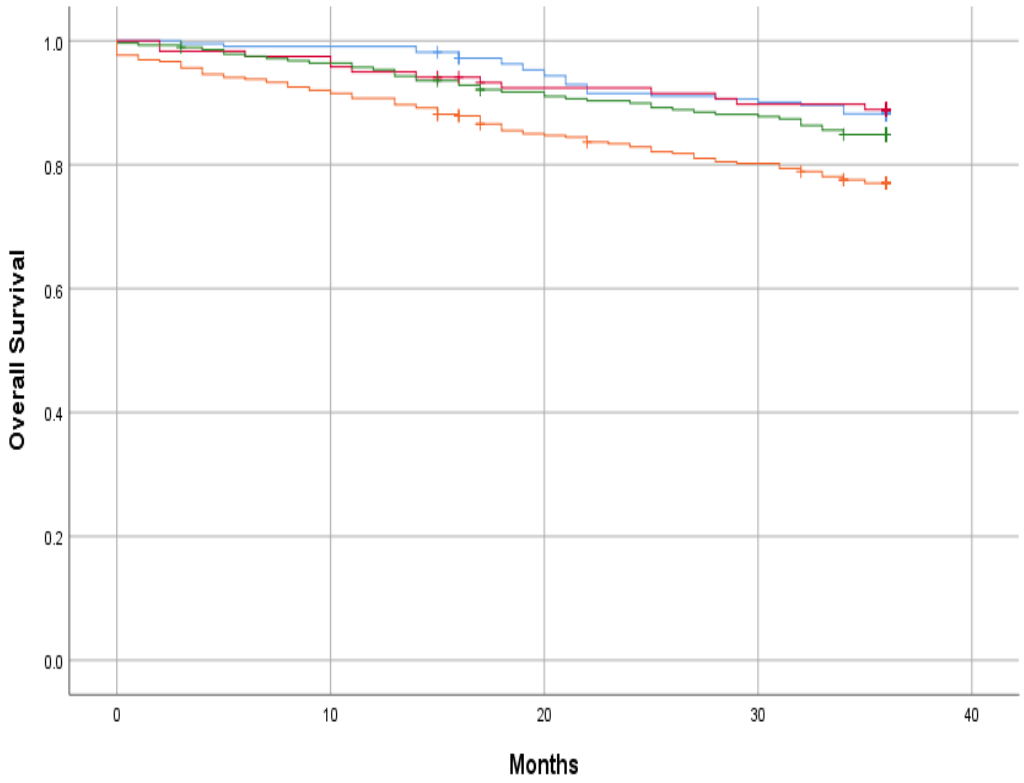


Figure 5-1: The relationship between SMI, SMD and overall survival in patients who underwent potentially curative surgery for colorectal cancer (n=1,002). The blue line denotes normal/high SMI and normal/high SMD, the red line denotes low SMI and normal/high SMD, the green line denotes normal/high SMI and low SMD and the orange line low SMI and low SMD (Log rank p<0.001)

6 The relationship between CT-derived sarcopenia and CPET performance, systemic inflammation and survival in good performance status patients with oesophagogastric cancer who underwent neoadjuvant treatment with a view to potentially curative surgical resection

6.1 Introduction

Despite a fall in incidence rates, survival of patients with oesophagogastric cancer in the UK remains poor (161, 162). Neo-adjuvant chemotherapy (NAC), in combination with surgical resection is the gold-standard radical treatment for oesophagogastric cancer (163). However, studies have demonstrated the adverse effects of chemotherapy on quality of life (164), as well as the negative impact that post-operative complications have on long-term oncological outcomes (165). Therefore, in the age of precision medicine, it is imperative that the right treatment be given to the right patient, at the right time.

ECOG-PS is a cornerstone of assessment of patient fitness and is routinely considered by clinicians when making decisions on the appropriateness of anti-cancer treatment (26). Whilst ECOG-PS is widely reported to be a robust predictive and prognostic tool (26), it is a subjective assessment that may be prone to bias or inter-observer variability (25). Therefore, there is continued interest in identifying objective pre-treatment host assessments that can further stratify the prognostic value of ECOG-PS to clinical outcomes in patients with cancer. One such example is systemic inflammation, with the ECOG/mGPS framework reported to stratify survival in patients with cancer (16, 166).

The CT-SS, a combination of SMI and SMD, is considered to capture the functional and nutritional reserve of the cancer patient (Chapter 5). Whilst CT-derived muscle measurements have been shown to have prognostic value in oesophagogastric cancer (167, 168), whether the CT-SS score can stratify survival in patients with oesophagogastric is unknown. Specifically, in good performance status (ECOG-PS 0/1) patients. Furthermore, it has yet to be examined whether

the CT-SS has complimentary prognostic value to CPET or systemic inflammation, also reported to be prognostic factors in patients with oesophagogastric cancer (169-171). This chapter examined whether the CT-SS could stratify survival in good performance status patients with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection. Moreover, examined whether CT-SS had complimentary prognostic value to CPET performance or systemic inflammation.

6.2 Methods

6.2.1 Patients

Consecutive patients with confirmed oesophagogastric cancer, who received NAC with a view to potentially curative surgical resection, between 1st January 2010 and 31st of December 2015, within NHS Greater Glasgow and Clyde and NHS Forth Valley, were identified from a prospectively maintained database. Patients with a documented pre-NAC ECOG-PS 0/1, recorded height and weight, suitable CT-imaging for body composition analysis and who underwent pre-NAC CPET were assessed for inclusion. Exclusion criteria were as follows; patients who did not have satisfactory pre-operative CT imaging for body composition analysis, did not have recorded height and weight prior to NAC, did not undergo pre-NAC CPET, did not have a recorded ECOG-PS or were ECOG-PS >1, received radical chemoradiation without plans for surgery, had metastatic disease at diagnosis and those who received palliative treatment only.

NAC regimens included a combination of epirubicin, cisplatin and either fluorouracil or capecitabine. Selected patients had a combination of cisplatin and fluorouracil alone. A median period of eight weeks was left between the end of treatment and commencing surgery, during which time re-staging occurred. Patients who proceeded to surgery were operated on at Glasgow Royal Infirmary, a single tertiary referral teaching hospital. Patients with oesophageal cancer underwent either transhiatal, Ivor-Lewis, left thoraco-abdominal or three-stage oesophagectomy depending on tumour site and surgeon preference. Patients with gastric cancer underwent either sub-total or total gastrectomy. Prophylactic antibiotics were administered at the induction of anaesthesia. As per unit policy, subcutaneous low molecular weight heparin and pneumatic compression stockings were given to each patient as venous thromboprophylaxis.

The primary endpoints were progression to surgery and survival at 3-years post-NAC. The cause and date of death were confirmed with the Registrar General (Scotland). Death records were complete until 1st March 2019 that served as the censor date. Informed consent was obtained from patients prior to surgery. This

study was approved with the need for individual patient consent waived by the Oxford B Research Ethics Committee due to the nature of the study *(19/SC/0653)*.

6.2.2 Methods

Routine demographic details included age, sex and BMI. Age categories were grouped into <64, 65-74 and >74 years. BMI was categorized as <20, 20-24.9, 25-29.9 and ≥30 kg/m^2. Tumour site and histological subtype were identified from pre-operative endoscopy and pathology reports. Tumour site was categorized as oesophageal, junctional and gastric. Histological subtype was categorised as adenocarcinoma and squamous cell carcinoma (SCC). All tumours were retrospectively staged using the eighth edition of the TNM classification and categorized into clinical AJCC stage groupings (172).

Performance status was determined using the ECOG-PS and assessed by a clinician prior to commencement of NAC, as described in Chapter 3. Systemic inflammation was determined using the NLR and mGPS, calculated in patients whom pre-NAC venous blood samples were available, as described in Chapter 3. NLR values were grouped as <3/3-5/>5 and mGPS values as 0/1/2.

CT-derived body composition analysis was carried out as described in Chapter 3. A high SFI and VFA were defined using the threshold values of Ebadi and co-workers and Doyle and co-workers, respectively (124, 125). A low SMI and SMD were defined using the threshold values of Martin and co- workers (61). The CT-SS was determined as described in Chapter 3.

CPET was performed as described in the Chapter 3. Threshold values for V02 AT were ≤11 and >11 ml/kg/min, and ≤19 and >19 ml/kg/min for V02 Peak, as used in previous studies (173).

6.2.3 Statistical Analysis

Kaplan–Meier curves for overall survival were constructed over a 36-month period. The log-rank test was used to compare survival between groups of patients. Clinicopathological variables, VO2 AT and Peak, CT-derived fat measurements, CT-SS, NLR, mGPS, progression to surgery, 3-year survival were presented as categorical variables. Categorical variables were analysed using Chi square test for linear-by-linear association. Binary logistic regression of variables associated with 3-year survival was performed. Variables that had a p value <0.1 at univariate analysis were included in multivariate binary logistic regression using a backward conditional model.

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 27.0 (SPSS Inc., Chicago, IL, USA).

6.3 Results

Of the 335 patients with oesophagogastric cancer, who were ECOG-PS 0/1 and underwent NAC with a view to potentially curative surgical resection, during the study timeframe, 103 did not meet the inclusion criteria. Of the 232 patients, who were ECOG-PS 0/1, underwent pre-NAC CPET and had CT-imaging suitable for body composition analysis, 9% (n=20) did not proceed to surgery (15 had disease progression whilst undergoing NAC and 5 patients had significantly impaired performance status post-NAC, Figure 6-1).

The clinicopathological characteristics of the included patients are shown in Table 6-1. 75% (n=174) were male, 54% (n=126) were 65 years of age or older and 60% (n=139) were overweight/obese (BMI ≥25kg/m^2). 33% (n=77) of patients had an oesophageal tumour, 58% (n=135) had junctional tumours and 9% (n=20) had gastric. 93% (n=215) of patients had an adenocarcinoma and 7% (n=17) had an SCC. 9% (n=21) of patients had TNM stage I disease, 26% (n=61) had stage II, 60% (n=137) had stage III and 5% (n=11) had stage IV disease. The median V02 AT value on CPET was 11.6 ml/kg/min (10.0-13.1) and 39% (n=91) of patients had an V02 AT ≤11 ml/kg/min. The median V02 Peak value on CPET was 19.2 ml/kg/min (16.9-22.4) and 52% (n=120) of patients had an V02 Peak ≤19 ml/kg/min. 67% (n=155) of patients were CT-SS of 0, 9% (n=21) were CT-SS 1 and 24% (n=56) were CT-SS 2. 67% (n=156) of patients had a high SFI and 66% (n=152) had a high VFA. Of the 204 patients who had pre-NAC bloods facilitating calculation of NLR, 40% (n=81) had an NLR ≥3. Of the 200 patients that had pre-NAC bloods facilitating calculation of the mGPS, 28% (n=55) were mGPS ≥1. 53% (n=122) of patients were alive at 3-years post-NAC.

The relationship between the CT-SS and clinicopathological characteristic, CPET performance, CT-derived body composition measurements, systemic inflammation and clinical outcomes in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection is shown in Table 6-1. On univariate analysis, CT-SS was significantly associated with sex ($p<0.05$), histological subtype ($p<0.05$), low VO2 AT (<0.05), low V02 Peak ($p<0.05$), BMI ($p<0.05$), NLR ($p<0.05$), mGPS ($p<0.05$) and 3-year survival ($p<0.05$, Table 6-1).

The Kaplan–Meier curve in Figure 6-2 shows the relationship between the CT-SS and 3-year survival in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection (Log rank $p<0.05$).

The relationship between clinicopathological characteristic, CPET performance, CT-SS, systemic inflammation and 3-year survival in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a with a view to potentially curative surgical resection is shown in Table 6-2. On univariate analysis, clinical TNM stage ($p<0.05$) and CT-SS ($p<0.05$) were significantly associated with 3-year survival. On multivariate analysis, clinical TNM stage ($p<0.05$) and CT-SS ($p<0.05$) remained significantly associated with 3-year survival (Table 6-2).

The relationship between CT-SS, VO2 AT and 3-year survival in good performance status patients (ECOG-PS 0/1) with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection is shown in Table 6-3. On univariate analysis, CT-SS was not significantly associated with 3-year survival in patients who did not have a low VO2 AT ($p=0.066$). A low VO2 AT was not significantly associated with 3-year survival in patients who were CT-SS 0 ($p=0.922$, Table 6-3).

The relationship between CT-SS, VO2 Peak and 3-year survival in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection is shown in Table 6-4. On univariate analysis, CT-SS was not significantly associated with 3-year survival in patients who did not have a low VO2 Peak ($p=0.065$). A low VO2 Peak was not significantly associated with 3-year survival in patients who were CT-SS 0 ($p=0.297$, Table 6-4).

The relationship between CT-SS, NLR and 3-year survival in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a view to curative resection is shown in Table 6-5. On univariate analysis, CT-SS was not significantly associated with 3-year survival in patients who were

NLR<3 (p=0.242). NLR was not significantly associated with 3-year survival in patients who were CT-SS 0 (p=0.359, Table 6-5).

The relationship between CT-SS, mGPS and 3-year survival in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection is shown in Table 6-6. On univariate analysis, CT-SS was significantly associated with 3-year survival in patients who were mGPS 0 (p<0.05). mGPS was not significantly associated with 3-year survival in patients who were CT-SS 0 (p=0.732, Table 6-6).

6.4 Discussion

The results of the present study show that the CT-SS was associated with CPET performance, systemic inflammation and survival in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection. Whilst the CT-SS did not add to the prognostic value of CPET performance or systemic inflammation, it was found to be an important determinant of survival. Therefore, the CT-SS would appear to not only capture the nutritional and functional reserve of patients undergoing potentially curative treatment for oesophagogastric cancer, but also provides a useful objective measure for stratifying long-term survival.

In the present study, the CT-SS was significantly associated with a low VO2 AT and Peak (Table 6-1). These observations are consistent with those of West and co-workers, who reported that CT-derived skeletal muscle measurements were associated with CPET performance in patients with OG (174) and hepatopancreatobiliary cancer (101). Taken collectively, the observations suggest that the CT-SS is an objective measure that reflects, in part, the patients cardiopulmonary fitness and may be utilised in patients where CPET is contraindicated (175). Moreover, given the reported prognostic value to survival, confirms the importance of an assessment of sarcopenia in these patients. Further research is therefore merited into the utility of the CT- SS as an objective assessment of pre-treatment fitness in patients with cancer.

The results of the present study show that the CT-SS was significantly associated with systemic inflammation and survival in good performance status patients (ECOG-PS 0/1) with oesophagogastric cancer. However, also show that when adjusted for systemic inflammation (mGPS), the CT-SS did not retain prognostic value to survival (Table 6-6). The present results are in keeping with those Hacker and co-workers that reported CT-derived skeletal muscle measurements (SMD) did not retain their prognostic value to survival when adjusted for mGPS in a cohort of 509 patients with advanced gastric and esophago-gastric junctional cancers (171). Therefore, whilst it is clear that there is an close relationship between CT-derived skeletal muscle measures and the systemic inflammatory response in patients with cancer (144), it remains to be determined if CT-derived skeletal

muscle measures have independent prognostic value when adjusted for systemic inflammation.

There are several limitations to the present study. Firstly, this is a single-centre, retrospective cohort study with a relatively small sample size and has limitations associated with this study design. However, despite patients being good performance status (ECOG-PS 0/1), a low VO2 AT and Peak were prevalent in the present cohort and so mitigated the relatively small sample size. Moreover, highlights the need for population specific thresholds for CPET, specifically in malnourished, inflamed and de-conditioned patients with cancer (128). Lastly, although the CT-SS has been shown to be prognostic in the present study and in other cancer subtypes cancer (Chapter 5), the use of CT-derived body composition is currently limited to research purposes. This in in part due to the training requirements and time-consuming nature of scan analysis. The emergence of fully-automated, artificial intelligence-based software for CT-derived body composition analysis may readily facilitate the use of measures such as the CT-SS in routine clinical practice (176).

In conclusion, the CT-SS would appear to capture the nutritional and functional reserve of patients with oesophagogastric cancer undergoing potentially curative treatment. Furthermore, the CT-SS may stratify survival in good performance status patients who are not inflamed.

6.5 Tables and Footnotes

Table 6-1: The relationship between the CT-SS and clinicopathological characteristic, CPET performance, CT-derived body composition measurements, systemic inflammation and clinical outcomes in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection (n=232)

	CT-SS 0 (n=155)	CT-SS 1 (n=21)	CT-SS 2 (n=56)	p value
Age (<65/65-74/>74)	70/60/25	16/4/1	20/22/14	0.261
Sex (Female/Male)	32/123	6/15	20/36	0.024
Tumour Site (Oesophageal /Junctional/Gastric)	47/94/14	10/10/1	20/31/5	0.417
Histological Subtype (Adenocarcinoma/SCC)	149/6	17/4	49/7	0.015
Clinical TNM stage (I/II/III/IV)	15/39/90/9	2/6/13/0	4/16/34/2	0.932
Low VO2 AT (No/Yes)	104/51	14/7	23/33	0.001
Low VO2 Peak (No/Yes)	85/70	10/11	17/39	0.002
BMI (<20/20-24.9/25-29.9/≥30 kg/m^2)	4/56/56/39	5/3/12/1	6/19/23/8	0.034
High SFI (No/Yes)	55/100	9/12	12/44	0.084
High VFA (No/Yes)	49/106	12/9	19/37	0.504
NLR (<3/3-5/>5)[1]	92/37/12	13/4/2	18/18/8	0.006
mGPS (0/1/2)[2]	103/23/9	14/1/4	28/8/10	0.008
Proceeded to surgery (Yes/No)	144/11	18/3	50/6	0.333
3-year urvival (Yes/No)	89/66	13/6	20/36	0.009

[1] *21 patients did not have pre-NAC bloods for calculation of NLR*

[2] *32 patients did not have pre-NAC bloods for calculation of mGPS*

Table 6-2: The relationship between clinicopathological characteristic, CPET performance, CT-SS, systemic inflammation and 3-year survival in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection (n=232)

	Univariate OR (95% CI)	**p value**	**Multivariate OR (95% CI)**	**p value**
Age (<65/65-74/>74)	1.18 (0.83-1.68)	0.348	-	-
Sex (Male/Female)	1.38 (0.76-2.53)	0.289	-	-
Tumour Site (Oesophageal/ Junctional/Gastric)	0.91 (0.59-1.40)	0.664	-	-
Histological subtype (Adenocarcinoma/SSC)	0.76 (0.28-2.07)	0.594	-	-
Clinical TNM stage (I/II/III/IV)	1.46 (1.01-2.12)	0.046	1.73 (1.14-2.64)	0.011
Low VO2 AT (No/Yes)	1.32 (0.78-2.24)	0.300	-	-
Low VO2 Peak (No/Yes)	1.43 (0.85-2.39)	0.180	-	-
BMI (<20/20-24.9/25-29.9/≥30 kg/m^2)	0.78 (0.57-1.06)	0.107	-	-
CT-SS (0/1/2)	1.50 (1.10-2.05)	0.010	1.42 (1.01-2.00)	0.047
NLR (<3/3-5/>5)	1.50 (1.00-2.26)	0.052	-	0.128
mGPS (0/1/2)	1.12 (0.75-1.68)	0.590	-	-

OR- Odds ratio, CI- Confidence interval

Table 6-3: The relationship between CT-SS, VO2 AT and 3-year survival in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection (n=232)

	VO2 AT >11 ml/kg/min (n=91)	**VO2 AT ≤11 ml/kg/min (n=141)**	**p value**
CT-SS 0 (n=155)	60 (66 %)	29 (21 %)	0.922
CT-SS 1 (n=21)	10 (11 %)	3	0.204
CT-SS 2 (n=56)	8 (9 %)	12 (9 %)	0.903
p value	0.066	0.108	

Table 6-4: The relationship between CT-SS, VO2 Peak and 3-year survival in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection (n=232)

	VO2 Peak >19 ml/kg/min (n=91)	**VO2 Peak ≤19 ml/kg/min (n=141)**	**p value**
CT-SS 0 (n=155)	52 (57 %)	37 (26 %)	0.297
CT-SS 1 (n=21)	6	7 (5 %)	0.864
CT-SS 2 (n=56)	14 (15 %)	6	0.965
p value	0.065	0.112	

Table 6-5: The relationship between CT-SS, NLR and 3-year survival in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection (n=204)

	NLR <3 (n=123)	**NLR 3-5 (n=59)**	**NLR >5 (n=22)**	**p value**
CT-SS 0 (n=135)	56 (61%)	20 (54%)	6	0.359
CT-SS 1 (n=19)	8 (62%)	2	1	0.672
CT-SS 2 (n=46)	8 (44 %)	8 (44 %)	1	0.478
p value	0.242	0.507	0.101	

Table 6-6: The relationship between CT-SS, mGPS and 3-year survival in good performance status patients (ECOG-PS 0/1) with oesophagogastric cancer who underwent NAC with a view to potentially curative surgical resection (n=200)

	mGPS 0 (n=145)	**mGPS 1 (n=32)**	**mGPS 2 (n=23)**	**p value**
CT-SS 0 (n=135)	57 (39 %)	11 (34 %)	5	0.732
CT-SS 1 (n=19)	9 (6 %)	0	2	0.504
CT-SS 2 (n=46)	8 (6 %)	3	4	0.478
p value	0.026	0.560	0.506	

6.6 Figures and Legends

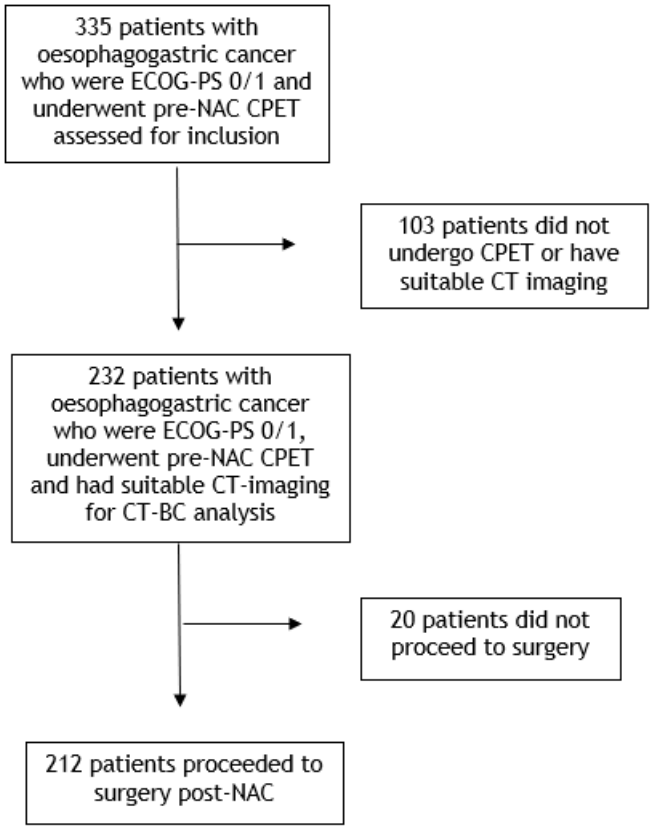
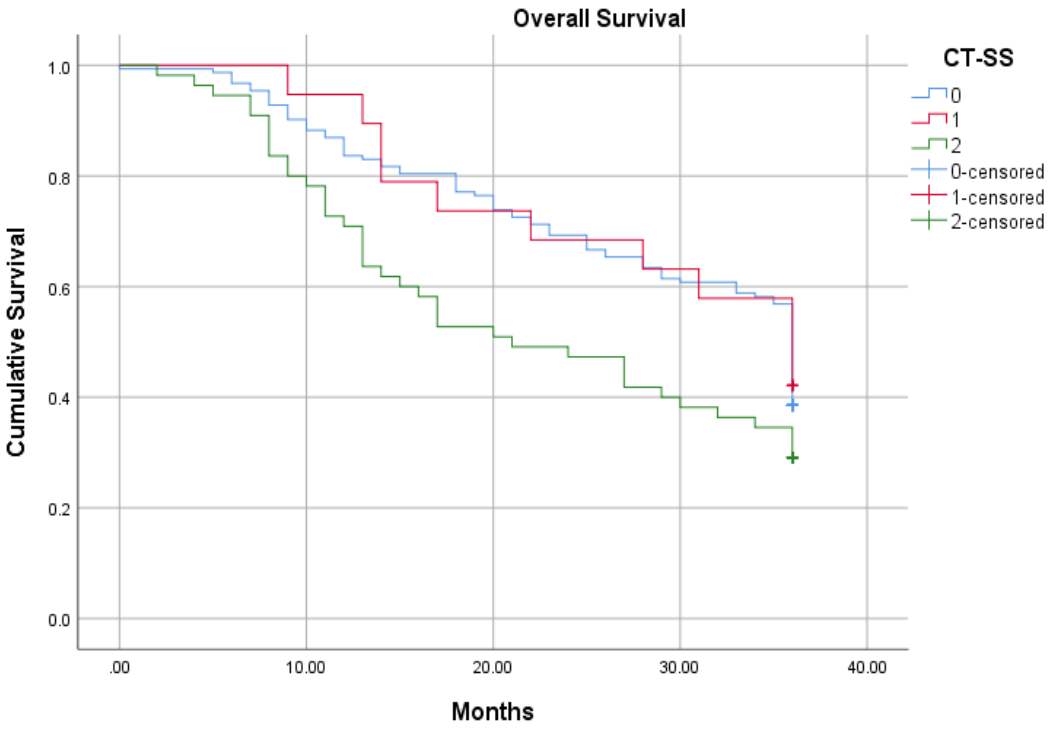


Figure 6-1: Flowchart of patients included in the study



(Log rank p= 0.036)

Figure 6-2: Kaplan Meier curve of the relationship between CT-SS and 3-year survival in in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer who underwent NAC with a view to curative resection (n=232)

7 The relationship between CT-derived sarcopenia, systemic inflammation and survival in patients with advanced cancer

7.1 Introduction

Contemporary evidence suggests that there is around 167,000 cancer deaths in the UK every year (2). Furthermore, that nearly half of all newly diagnosed cancer cases involve locally advanced or metastatic disease, where treatment options are limited (177). Given that most patients with advanced disease will likely die from their malignancy, there is continued interest in identifying prognostic factors that can stratify tolerance to anti-cancer therapy and survival in patients with advanced cancer (178).

Whilst CT-derived skeletal muscle measures have consistently been reported to have prognostic value in patients with cancer (88, 89), a low SMI and SMD were found to have a similar prevalence across cancer types and disease stages (Chapter 4). Given the variation in survival outcomes in patients with primary operable and advanced disease, it was hypothesized that body composition alone may not be the main determinant of survival. Moreover, highlighted that CT-derived skeletal muscle measures should be used in conjunction with other factors, such as performance status and systemic inflammation, to stage the host (147).

This issue was highlighted in a recent study by Hacker and co-workers, who reported that although associated with ECOG-PS and systemic inflammation (mGPS), CT-derived muscle measurements were not independently associated with survival, in a study of 509 advanced oesophagogastric cancer patients with good performance status (171). This led the authors to conclude that cancer-related systemic inflammation, rather that sarcopenia, represented the main causal association with poorer survival (171).

If the observations of Hacker and co-workers were confirmed in future studies, then it would have implications to the utility of CT-derived muscle measurements as biomarkers in clinical practice. Specifically, whether such measures add

prognostic information to the recognised framework of ECOG-PS and mGPS in patients with advanced cancer (16). The present chapter examined the relationships between CT-derived muscle measurements, systemic inflammation and survival in good performance status (ECOG-PS 0/1) patients with advanced lung and gastrointestinal (GI) cancer.

7.2 Patients and Methods

7.2.1 Patients

An international database of patients with advanced cancer was retrospectively analysed. Data were prospectively collected data across nine sites in the UK and Ireland, between 2011–2016 (102, 166, 179). Eligible adult patients with advanced lung or GI cancer (defined as locally advanced or with histological, cytological or radiological evidence of metastasis), who were good performance status (ECOG-PS 0/1) and had suitable pre-treatment CT-imaging for body composition analysis were considered for inclusion.

The primary endpoint was overall survival from entry to study. The date of death was confirmed using hospital electronic records, until the 18th of June 2018, which served as the censor date. The study had ethical approval in both the UK and Ireland (West of Scotland Ethics Committee UK: 18/WS/0001 (18/01/2018) and Cork Research Ethics Committee Ireland: ECM 4 (g) (03/03/2015)) and was conducted in accordance with the Declaration of Helsinki.

7.2.2 Methods

General demographic data and clinicopathological characteristics were recorded for each patient. Primary cancer type was broadly classified as lung or GI. The presence of metastatic disease was identified from staging CT-imaging obtained prior to study entry. BMI was categorised as <25/≥25 kg/m^2. Performance status was determined using the ECOG-PS and assessed by a clinician or clinical researcher at the institute the patient was receiving treatment, at entry to the study, as described in Chapter 3. ECOG-PS was categorised as 0 or 1. In patients whom venous blood samples were obtained at entry to study, the mGPS was calculated as described in Chapter 3. mGPS values were grouped as 0/1/2.

CT-derived body composition analysis was carried out as described in Chapter 3. A low SMI and SMD were defined using the threshold values of Martin and co-workers (61). The CT-SS was determined as described in Chapter 3.

7.2.3 Statistical Analysis

Clinicopathological variables, SMI, SMD, CT-SS, ECOG-PS, mGPS and overall survival were presented as categorical variables. Categorical variables were analysed using Chi square test for linear-by-linear association.

Univariate and multivariate survival data were analysed using Cox's proportional-hazards model. Variables associated with overall survival at a significance level of $p<0.1$ on univariate analysis were included in multivariate modelling using backward conditional regression where a two-sided p value <0.05 was considered statistically significant. Overall survival was defined as the time (months) from the entry to study to the date of death due to any cause.

Missing data were excluded from analysis on a variable-by-variable basis. Statistical analysis was performed using SPSS software version 27.0 (SPSS Inc., Chicago, IL, USA).

7.3 Results

A total of 307 patients met the inclusion criteria (Figure 7-1). The clinicopathological characteristics of the included patients are shown in Table 7-1. 62% (n=190) of patients were male and 47% (n=144) were ≥65 years of age. 32% (n=99) of patients had primary lung tumours and 68% (n=208) had GI tumours. 87% (n=268) of patients had metastatic disease on staging CT-imaging. 92% (n=283) of patients received chemotherapy prior to study entry and 6% (n=19) received radiotherapy. 50% (n=155) of patients were overweight (BMI ≥25 kg/m^2). 38% (n=118) patient had a low SMI and 46% (n=142) a low SMD. 62% (n=189) of patients were CT-SS 0, 16% (n=48) CT-SS 1 and 23% (n=70) were CT-SS 2. 48% (n=146) of patients were ECOG-PS 0 and 52% (n=161) were ECOG-PS 1. Of the 240 patients with bloods facilitating calculation of mGPS, 47% (n=112) of patients were inflamed (mGPS≥1). The median survival from entry to the study was 11.1 months (1-68.1).

The relationship between the CT-SS and clinicopathological characteristic, CT-derived skeletal muscle measurements, ECOG-PS, systemic inflammation and overall survival in good performance status (ECOG-PS 0/1) patients with advanced lung and GI cancer is shown in Table 7-1. On univariate analysis, the CT-SS was significantly associated with age ($p<0.05$), sex ($p<0.001$), BMI ($p<0.05$), low SMI ($p<0.001$) and low SMD ($p<0.001$, Table 7-1).

The relationship between clinicopathological characteristic, CT-derived skeletal muscle measurements, ECOG-PS, systemic inflammation and overall survival in good performance status (ECOG-PS 0/1) patients with advanced lung and GI cancer is shown in Table 7-2. On univariate analysis, cancer type ($p<0.05$) and mGPS ($p<0.001$) were significantly associated with overall survival. On multivariate analysis, only mGPS ($p<0.001$) remained significantly associated with overall survival (Table 7-2).

The relationship between ECOG-PS, mGPS and CT-SS in good performance status (ECOG-PS 0/1) patients with advanced lung and GI cancer is shown in Table 7-3. In patients who were ECOG-PS 0, mGPS was significantly associated with CT-SS

($p<0.05$). In patients who were mGPS 0, ECOG-PS was not significantly associated with CT-SS ($p=0.286$, Table 7-3).

7.4 Discussion

The results of the present study show that mGPS was independently associated with survival in good performance status (ECOG-PS 0/1) patients with advanced lung and GI cancer. However, although significantly associated with ECOG-PS and mGPS, the CT-SS was not associated with survival. The present observations are in keeping with those of Hacker and co-workers (171), and taken collectively, further question the importance that sarcopenia has to survival in patients with advanced cancer (19). Moreover, they support the concept that systemic inflammation (mGPS) dominates the prognostic value of CT-derived sarcopenia in good performance status patients with advanced cancer.

Whilst differences exist between the present study and that of Hacker and co-workers, specifically tumour subtype and sample size, the distribution of performance status (ECOG-PS 0=48% vs. 57%) and inflammatory status (mGPS ≥1= 47% vs. 49%) amongst included patients was similar. However, there were significant differences in the median SMI and SMD between studies (median SMI 47.0 cm^2/m^2 vs. 61.6 cm^2/m^2 and median SMD 38 HU vs 46.2 HU, respectively). Given age, gender and BMI are all likely to be confounding factors to CT-derived skeletal muscle measures, the contrasting observations may be explained by an increased prevalence of female patients (38% vs 24%), older patients (47% ≥65 years or age vs. 26%) and obese patients (51% BMI≥ 25 kg/m^2 vs. 33%) in the present study. Furthermore, significant differences in muscle status have been observed when comparing studies reporting CT-derived skeletal muscle measurements from different European countries; highlighting that lifestyle and diet may also be confounding factors (147). Therefore, whilst the present observations support those of Hacker and co-workers, further examination is warranted to determine whether mGPS dominates the prognostic value of CT-derived sarcopenia in good performance status patients with advanced cancer.

The assessment of CT-images acquired as part of standard cancer care has demonstrated that cancer cachexia is associated with a loss of skeletal muscle mass (low SMI) and reduced muscle radiation attenuation (low SMD, (53). Despite being considered objective surrogate markers of nutritional status, Arulananda and Segelov recently questioned the clinical utility of CT-derived muscle

measurements given their inferior prognostic value (180). If the present observations were confirmed in future studies, then it may have implications to both the diagnosis and management of cancer cachexia. Specifically, to the currently proposed GLIM diagnostic framework that includes both reduced muscle mass and inflammation as independent diagnostic criterion (128). Indeed, if inflammation is found to dominate the prognostic value of CT-derived skeletal muscle mass (181), then consideration should be given to whether it becomes the dominant criterion for identifying cachexia in patients with cancer.

ECOG-PS remains an important determinant of eligibility for anti-cancer treatment (16), with almost all good performance status patients conventionally considered candidates for optimal treatment. Furthermore, ECOG-PS is universally utilized as a tool for stratifying eligibility for randomized clinical trials, with only good performance status (ECOG-PS 0/1) patients generally considered suitable (182). However, the subjective nature of performance status has implications for the external validity of clinical trials in real-world clinical practice (183). Indeed, contemporary evidence is challenging the exclusion of ECOG-PS 2 patients from randomized clinical trials of immunotherapy, with recent studies by Yang and co-workers and Singh and co-workers reporting that the inclusion of ECOG-PS 2 patients did not adversely affect trial outcomes (182, 184). Furthermore, there is thought to be significant heterogeneity in ECOG-PS 2 patients, with continued interest in identifying additional predictive biomarkers that can further stratify likely outcome in such patients (185). Examples include biomarkers of the nutritional status of the patient, such as CT-derived skeletal muscle measurements and systemic inflammation. Whilst both factors have prognostic value to clinical outcomes in patients with advanced cancer, their close association questions the causality of these relationships and the order of dominance. The present observations, together with those in recent clinical trials (171), favour a framework where the systemic inflammatory response is the dominant factor in patients with good performance status and should be used to predict the likely outcome.

There are several limitations to the present study. Principally, the analysis is retrospective on a prospective dataset and may be subject to sample bias. Secondly, in contrast to contemporary literature, CT-derived skeletal muscle

measurements were not independently associated with survival in the present study. This may be explained by the sample size or the inclusion of good performance status patients only. Nevertheless, these measurements are routinely available in clinical practice and the present observations should be readily tested. Lastly, the observations of this modest-sized study of good performance status patients with advanced lung and GI cancer suggest that mGPS dominates the prognostic value of CT-derived muscle measurements, in keeping with contemporary literature (171). However, further large cohort studies across a range of tumour subtypes are still required to determine the order of dominance in good-performance status patients with advanced cancer.

In conclusion, the present results suggest that mGPS dominates the prognostic value of CT-derived sarcopenia in good performance status patients with advanced lung and GI cancer. These results may have implications to the use of CT-derived skeletal muscle measurements for prognostication in patients with advanced cancer.

7.5 Tables and Footnotes

Table 7-1: The relationship between the CT-SS and clinicopathological characteristic, ECOG-PS, systemic inflammation and overall survival in good performance status (ECOG-PS 0/1) patients with advanced lung and GI cancer (n=307)

	CT-SS 0 (n=189)	CT-SS 1 (n=48)	CT-SS 2 (n=70)	p value
Age (<65/65-74/>74)	105/56/28	32/9/7	26/29/15	0.042
Sex (Female/Male)	55/134	23/25	39/31	<0.001
Cancer Type (Lung/GI)	60/129	12/36	27/43	0.431
Metastatic disease (No/Yes)	29/160	3/45	7/63	0.157
Chemotherapy (Yes/No)	174/15	44/4	65/5	0.859
Radiotherapy (Yes/No)	10/179	3/45	6/64	0.339
BMI (<25/≥25 kg/m^2)	86/103	21/27	45/25	0.014
Low SMI (No/Yes)	189/0	0/48	0/70	<0.001
Low SMD (No/Yes)	117/72	48/0	0/70	<0.001
ECOG-PS (0/1)	93/96	26/22	27/43	0.197
mGPS (0/1/2)[1]	78/23/41	24/3/12	26/5/28	0.058
Overall survival (Yes/No)	43/146	12/36	13/57	0.548

[1] 67 patients did not have bloods facilitating calculation of mGPS

Table 7-2: The relationship between clinicopathological characteristic, CT-derived skeletal muscle measurements, ECOG-PS, systemic inflammation and overall survival in good performance status (ECOG-PS 0/1) patients with advanced lung and GI cancer (n=307)

	Univariate HR (95% CI)	**p value**	**Multivariate HR (95% CI)**	**p value**
Age (<65/65-74/>74)	0.88 (0.74-1.05)	0.146	-	-
Sex (Female/Male)	0.95 (0.73-1.23)	0.691	-	-
Cancer type (Lung/GI/other)	0.66 (0.50-0.87)	0.003	-	0.119
Metastatic Disease (No/Yes)	1.00 (0.69-1.46)	0.995	-	-
Chemotherapy (No/Yes)	0.87 (0.50-1.49)	0.606	-	-
Radiotherapy (No/Yes)	1.79 (0.87-3.68)	0.112	-	-
BMI (<25/≥25, kg/m^2)	0.97 (0.75-1.25)	0.805	-	-
CT-SS (0/1/2)	1.06 (0.92-1.24)	0.421	-	-
ECOG-PS (0/1)	1.21 (0.94-1.56)	0.142	-	-
mGPS (0/1/2)	1.33 (1.13-1.55)	<0.001	1.33 (1.13-1.55)	0.001

HR- Hazard ratio, CI- Confidence interval

Table 7-3: The relationship between ECOG-PS, mGPS and CT-SS in good performance status (ECOG-PS 0/1) patients with advanced lung and GI cancer (n=240)

	mGPS 0 (n=128)	**mGPS 1 (n=31)**	**mGPS 2 (n=81)**	**p value**
ECOG-PS 0 (n=146)	CT-SS 0 37 (65%) CT-SS 1 11 (19%) CT-SS 2 9 (16%)	CT-SS 0 11 (73%) CT-SS 1 1 (7%) CT-SS 2 3 (20%)	CT-SS 0 11 (39%) CT-SS 1 6 (21%) CT-SS 2 11 (39%)	0.016
ECOG-PS 1 (n=161)	CT-SS 0 41 (57%) CT-SS 1 13 (18%) CT-SS 2 17 (24%)	CT-SS 0 12 (76%) CT-SS 1 2 (12%) CT-SS 2 2 (12%)	CT-SS 0 30 (57%) CT-SS 1 6 (11%) CT-SS 2 17 (32%)	0.602
p value	0.286	0.739	0.251	

7.6 Figures and Legends

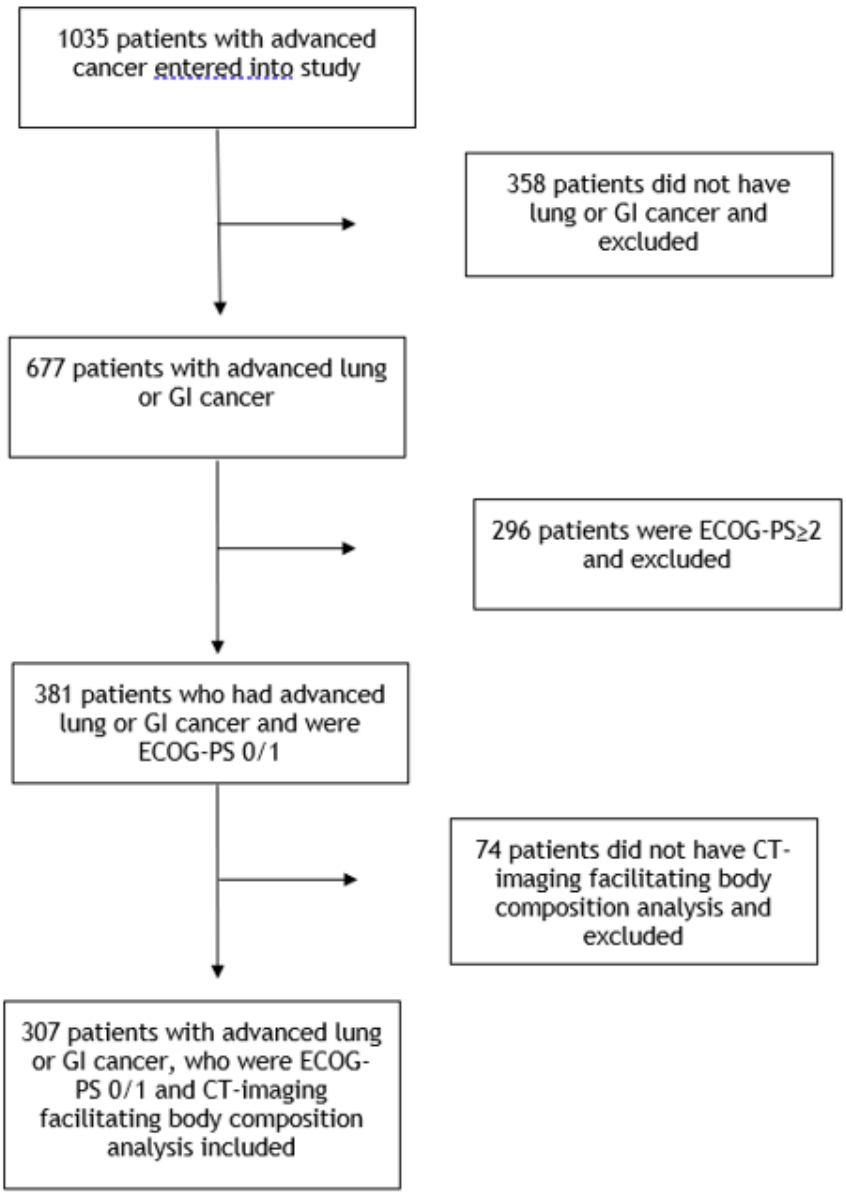


Figure 7-1: Flowchart of patients included in the study

8 The prevalence and prognostic value of frailty screening measures in patients undergoing surgery for colorectal cancer: observations from a systematic review

8.1 Introduction

Colorectal cancer accounts for approximately 12% of new cancer cases diagnosed within the UK each year (186). Nearly half of all colorectal cancer cases are in patients aged 75 years or older, with the highest rates observed in the 85 to 89 age group (186). Given advanced age is associated with recognised prognostic factors including co-morbidity (187), sarcopenia (43) and frailty (103), deciding whether to embark on potentially curative treatment is often difficult in older adults with colorectal cancer.

Frailty is a complex multifactorial syndrome, characterised by a clinically significant increase in vulnerability and worsened health outcomes (103). The multi-domain character of frailty (physical and psychological factors) means that it can be difficult for non-experienced clinicians to diagnose. At present, Comprehensive Geriatric Assessment (CGA) is regarded as the gold standard framework for diagnosing frailty (188). The use of CGA is recommended in older adults with cancer by the International Society of Geriatric Oncology (189), with recent studies reporting that frailty, determined by CGA, was adversely associated with clinical outcomes in patients with colorectal cancer (190, 191). However, CGA is time consuming and may not be readily applied to clinical practice (192).

In recent years, a number of screening measures/tools have been developed to aid physicians in diagnosing frailty (193). These range from the image-based Canadian Study of Health and Aging-Clinical Frailty Scale (CSHA-CFS, (194), to the American College of Surgeons National Surgical Quality Improvement Programs five- and eleven-item modified frailty indices (mFI-5 and mFI-11), that combine functional status and co-morbidity (195, 196), to multi-modal screening measures that include assessments of physical function, nutritional status, co-morbidity and subjective, patient-reported elements; examples include the

Edmonton Frail Scale (197), Groningen Frailty Indicator (198), Geriatric G8 questionnaire (199) and Fried frailty phenotype (108).

Despite the range of frailty screening measures available, there is a paucity of research examining the prevalence and prognostic value of frailty in patients with colorectal cancer. In this chapter, the prevalence and prognostic value of frailty in patients undergoing surgery for colorectal cancer, across commonly employed clinical frailty measures, was investigated.

8.2 Patients and Methods

The protocol for this systematic review was developed using the PRISMA-P guidelines, including flowchart (133). The primary outcome of interest was the prevalence of frailty, as defined by frailty screening measures, in patients with colorectal cancer undergoing surgery. The secondary outcome of interest of this systematic review was the association between frailty and clinical outcomes in patients undergoing surgery for colorectal cancer. Clinical outcomes recorded were the incidence of post-operative complication (using both Clavien Dindo, CD, classification, or descriptive definitions), thirty-day mortality and overall survival. Patient demographic details, TNM stage, frailty measure used and the prevalence of frailty within the population were also recorded.

A literature search was made of the US National Library of Medicine (MEDLINE) and PubMed, from the start of the relevant database to the 3rd of May 2021. The search terms used were related to the following key words: “frailty”, “colon”, “rectal”. “colorectal”, “cancer”, “elderly”, “surgery”, “resection”, “frailty index”, “frailty score”, “Canadian Study of Health and Aging-Clinical Frailty Scale”, “CSHA-CSF”, “Fried frailty phenotype”, “Onco-geriatric screening tool”, “G8 questionnaire”, “Modified frailty index-5” and “MFI-5”, “Modified frailty index-11”, “MFI-11”, “Edmonton Frail Scale”, and “Groningen Frailty Indicator”. The search terms were chosen following multiple pilot searches using more inclusive terms that returned large numbers of abstracts which on initial assessment were irrelevant to the present review topic.

The title and abstracts of all studies returned by the search were examined for relevance. The full text of each study deemed potentially relevant was obtained and analysed. Review articles, non-English papers, duplicate data sets and abstract only results were excluded. To be included a study had to examine the prevalence of frailty, using any of the common frailty scoring measures previously described, in patients undergoing surgery for colorectal cancer. Furthermore, the relationship with frailty and post-operative complications, with severity defined by CD classification or descriptive definitions, thirty-day mortality or overall survival. Reference lists of included papers, and excluded systematic reviews and

meta-analyses, were then hand searched for additional relevant studies. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies.

Assessment of the risk of bias was carried out using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool (200). Meta-analysis was not performed because of significant heterogeneity in study methodology, populations and outcomes measured. Ethical approval was not required for the present study as this was a systematic review of published data.

8.3 Results

A total of 467 studies were identified on initial search of the Medline and PubMed databases. Following the exclusion of duplicates by the screening of titles, 208 abstracts were reviewed. 49 full papers were then deemed suitable for review, with 15 meeting inclusion criteria for qualitative analysis. Of 34 studies deemed not to meet the eligibility criteria and therefore excluded, reasons include: post-operative outcome measured other than those listed above (n=13), duplicate publication of the same population (n=4), inclusion of another cancer subtype in the cohort examining the relationship with frailty and post-operative outcomes (n=1), cohort included patients with non-cancerous pathology such as inflammatory bowel disease (n=5), studies in which patients did not undergo surgery or received anti-cancer treatment only (n=9) and lastly, studies that failed to report the prevalence of frailty or threshold used to define frailty in the population (n=2, Figure 8-1).

8.3.1 Qualitive Analysis

15 studies (6 prospective and 9 retrospective, 97,898 patients) were included in the qualitative analysis (Table 8-1). The breakdown of the quality of these studies, determined using the Newcastle-Ottawa Scale (NOS), is shown in Figure 8-2. To define frailty, three studies used the CSHA-CFS, three used the G8 questionnaire, two used Fried frailty phenotype and four used the mFI-5 score. The mFI-11, Groningen frailty indicator and Edmonton frail scale were each used in one study. Of these studies, twelve reported the incidence of post-operative complications (201-212), four studies reported the incidence of thirty-day mortality (205, 207, 209, 213) and three studies reported long-term survival outcomes (213-215).

In all but two studies reporting median/mean age (202, 216), the majority included patients aged 70 years or older. Over 80% (n=81,803) of patients included were from a single study by Lo and co-workers (204), who reported approximately 20% of patients were frail (mFI-5 ≥2*)*. Tamura and co-workers reported the highest prevalence of frailty at 56% (n=278), in a study of 500 patients that used the G8 questionnaire (211). Chen and co-workers reported the lowest prevalence at 12% in a study of 1928 patients, that used the mFI-5 (202).

8.3.2 Studies reporting the relationship between frailty and the incidence of post-operative complications

Studies reporting the relationship between frailty and the incidence of post-operative complications are shown in Table 8-2a. Twelve studies including 96,329 patients reported the incidence of post-operative complications in frail patients undergoing surgery for colorectal cancer (201-212). Post-operative complications included in the studies ranged from CD grade ≥1 in three studies, CD grade ≥2 in four studies and CD grade ≥3 in five studies. In one of the three studies reporting the incidence of CD grade ≥1 complications, frailty was reported to be significantly associated with the development of post-operative complications on univariate analysis ($p<0.05$, (201). Three out of the four studies reporting the incidence of CD grade ≥2 complications, reported that frailty was associated with the incidence of post-operative complications (205, 210, 212). Furthermore, this association remained significant on multivariate binary logistics regression analysis in two studies (205, 212). Lastly, in studies reporting the incidence of serious complications i.e., CD grade ≥3, three reported that frailty was significantly associated with post-operative complications on multivariate binary logistics regression analysis (202, 204, 206). Of the studies showing an association with frailty and the incidence of post-operative complications on multivariate analysis (See Table 8-2a) , the strength of this association was found to be moderate in two studies (202, 204) and strong in the other three (205, 206, 212).

8.3.3 Studies reporting the relationship between frailty and thirty-day mortality

Studies reporting the relationship between frailty and thirty-day mortality are shown in Table 8-2b. Four studies including 9,850 patients reported the incidence of thirty-day mortality in frail patients undergoing surgery for colorectal cancer (205, 207, 209, 213). Two studies, one using the CSHA-CFS (213) and the other using the mFI-5 (205), reported that frailty was significantly associated with thirty-day mortality. In the latter, this association remained significant on multivariate binary logistics regression analysis ($p<0.001$, (205). The strength of the association was strong (OR 20.8, 95% CI 6.2-70.0, $p<0.001$, See Table 8-2b). In

the remaining two studies, the association between frailty and thirty-day mortality was not significant on univariate analysis (207, 209).

8.3.4 Studies reporting the relationship between frailty and overall survival

Studies reporting the relationship between frailty and overall survival are shown in Table 8-2c. Three studies including 1,569 patients reported the association between frailty and overall survival (213, 214, 216). Artiles-Armas and co-workers reported follow-up at 5 years (213). Mima and co-workers reported a median follow-up of 3.5 years (interquartile range: 2.5-5.1 years, (214). Feliciano and co-workers reported a median follow-up of 5.8 years (interquartile range: 1 month-19.9 years, (216). Frailty, defined by the CSHA-CFS and fried frailty phenotype, was reported to be significantly associated with overall survival in two studies (both, $p<0.001$ (214, 216). In both studies this association was moderate strength (HR 2.40, 95% CI 1.40-2.99, $p<0.001$ and HR 1.94, 95% CI 1.39-2.69, $p<0.001$, Table 8-2c).

8.3.5 Assessment of Bias

The ROBINS-I tool was used to assess the risk of bias in included studies. All fifteen of the included studies were deemed at moderate or severe risk of bias (Figure 8-2). Bias due to confounding factors, selection bias and reporting of results was prevalent.

8.4 Discussion

To our knowledge, the present systematic review examining the relationship between frailty and post-operative outcomes in older adults undergoing surgery for colorectal cancer is the most comprehensive to date, including 15 studies totalling 97,898 patients. The results suggest that frailty is prevalent in older adults undergoing surgery for colorectal cancer, and is negatively associated with clinical outcomes, across a range of screening measures. However, due to the limited literature, it is not clear which frailty screening measures have clinical utility in the treatment of colorectal cancer. Moreover, the basis of the relationship between frailty and post-operative outcomes is also currently unclear.

Frailty is a spectrum that reflects the systemic burden of chronological aging and the erosion of the patients homeostatic reserve (217). As such one would expect that frailty would be adversely associated with short- and long-term clinical outcomes. However, in the present study, frailty was only adversely associated with clinical outcomes in 9 of the 15 studies included. As such, the results cast doubt on the reliability of observations in some of the included studies and question the clinical utility of certain frailty measures. Moreover, highlight the need for frailty screening measures that assess a broad range of domains, yet are simple and time-efficient enough to be readily employed in clinical practice. Potential examples are the mFI-5, shown to have prognostic value in older adults undergoing surgery for colorectal cancer (218, 219), and the CSHA-CFS, which is quick to perform, requires limited training of staff and has been shown to have good inter-observer reliability (220, 221).

Frailty is an area of growing interest and importance across different subspecialities of medicine. It is thought to encompass not only age, but a number of recognised domains including physical function, malnutrition, co-morbidity, cognition, socio-economic and psychological factors (12, 222). Indeed, recent work by Miller and co-workers reported that frailty, but not age, had an independent prognostic value in patients with colorectal cancer (205). Moreover, of the seven frailty screening measures included in the present review, only the G8 questionnaire includes an assessment of age (223). The results suggest that simply screening older adults is insufficient and that those who are functionally

restricted or cachexic are likely to also be frail, with frailty reported to be associated with malnutrition and sarcopenia (224, 225). Given these factors are independently associated with adverse clinical outcomes in patients undergoing surgery for colorectal cancer, it remains unclear if frailty per se has independent prognostic value or is simply reflective of the functional and nutritional reserve of the patient. Further study is therefore warranted to determine the basis of the relationship between frailty and clinical outcomes in older adults undergoing surgery for colorectal cancer.

Whilst the pathophysiological changes underlying and preceding frailty are not clearly understood, it is plausible that an exaggerated systemic inflammatory response is responsible (226). Indeed, a recent systematic review by Soysal and co-workers reported that frailty was associated with elevated systemic inflammatory biomarkers including CRP and IL-6 (226). Moreover, systemic inflammation has been reported to be associated with other recognised domains of frailty including malnutrition (128) and sarcopenia (227). Therefore, the success of therapeutic interventions to arrest or reverse frailty may require modulation of the systemic inflammatory response, in addition to nutritional supplementation and physical exercise (228), as proposed for the prehabilitation of patients with advanced cancer (229).

There are several limitations of the present systematic review. Firstly, the studies included were mainly retrospective and are therefore subject to confounding factors and selection bias. An example being that patients who were deemed to be frail at diagnosis are more likely to undergo minimally invasive laparoscopic surgery, associated with better outcomes in colorectal cancer (230). Furthermore, those who were deemed to be very frail at diagnosis are unlikely to be considered for surgery. Secondly, the absence of a meta-analysis or a pooled prevalence. Neither were considered to be appropriate because of significant heterogeneity of the studies and the large number of observations confined to a few individual studies. Lastly, the majority of studies included in the review are of patients who underwent surgery for colorectal cancer with curative intent. Therefore, future studies will be required to assess the prevalence and prognostic value of frailty in those with advanced, inoperable disease.

In conclusion, frailty was prevalent in older adults undergoing surgery for colorectal cancer, across a range of frailty screening measures. Which of these has the greatest utility in clinical practice is unclear and requires further study. Furthermore, whilst frailty would appear to be adversely associated with post-operative outcomes, the basis of this relationship is also unclear. Specifically, if frailty per se has an independent prognostic value or is simply reflective of the nutritional and functional reserve of the patient.

8.5 Tables and Footnotes

Table 8-1: Characteristics of included studies

Study	Design	Patient (n=)	Frailty screening tool	Prevalence of frailty (%)
Artiles-Armas et al (2021, (213)	Prospective	149	CSHA-CFS	42 (CSHA-CFS ≥4)
Bessems et al (2021, (201)	Retrospective	132	Geriatric 8 questionnaire	40 (G8 ≤14)
Chen et al (2018, (202)	Retrospective	1,928	mFI-5	12 (mFI ≥2)
Feliciano et al (2020, (216)	Prospective	691	Fried frailty phenotype	18 (Fried criteria ≥3/5)
Gearhart et al (2020, (203)	Retrospective	1,676	mFI-5	25 (mFI ≥2)
Lo et al (2020, (204)	Retrospective	81,803	mFI-5	20 (mFI ≥2)
Miller et al (2020, (205)	Retrospective	9,252	mFI-5	15 (mFI ≥2)
Mima et al (2020, (214)	Retrospective	729	CSHA-CFS	35 (CSHA-CFS ≥4)
Okabe et al (2019, (206)	Prospective	269	CSHA-CFS	29 (CSHA-CF S≥4)
Reisinger et al (2015, (207)	Retrospective	310	Groningen frailty indicator	25 (GFI ≥5)
Richards et al (2021, (208)	Prospective	86	Edmonton frail scale	14 (EFS ≥8)
Souwer et al (2018, (209)	Retrospective	139	Geriatric 8 questionnaire	50 (G8 ≤14)
Suzuki et al (2021, (210)	Retrospective	151	mFI-11	35 (mFI ≥3)
Tamura et al (2021, (211)	Prospective	500	Geriatric 8 questionnaire	56 (G8 ≤14)
Tan et al (2012, (212)	Prospective	83	Fried frailty phenotype	28 (Fried criteria ≥3/5)

Table 8-2a: Studies reporting the relationship between frailty and post-operative complications in patients undergoing surgery for colorectal cancer

Study	Observations
Bessems et al (2021, (201)	Frailty associated with complication incidence on UV analysis (p=0.038)
Chen et al (2018, (202)	Frailty associated with complication incidence on MV binary log regression (OR 2.12, 95% CI 1.47-3.04, p<0.001)
Gearhart et al (2020, (203)	Frailty not associated with complication incidence on MV binary log regression (p=0.19)
Lo et al (2020, (204)	Frailty associated with complication incidence on MV binary log regression (OR 1.56, 95% CI 1.07-2.25, p=0.018)
Miller et al (2020, (205)	Frailty associated with complication incidence on MV binary log regression (OR 6.7, 95% CI 4.5-10.0, p<0.001)
Okabe et al (2019, (206)	Frailty associated with complication incidence on MV binary log regression (OR 3.42, 95% CI 1.62-7.29. p=0.001)
Reisinger et al (2015, (207)	Frailty not associated with complication incidence on UV binary log regression (p=0.19)
Richards et al (2021, (208)	Frailty not associated with complication incidence on MV binary log regression (p=0.62)
Souwer et al (2018, (209)	Frailty not associated with complication incidence on UV analysis (p=0.70)
Suzuki et al (2021, (210)	Frailty associated with complication incidence on UV analysis (p=0.02)
Tamura et al (2021, (211)	Frailty not associated with complication incidence on UV binary log regression (p=0.355)
Tan et al (2012, (212)	Frailty associated with complication incidence on MV binary log regression (OR 4.08, 95% CI, 1.43-11.6, p=0.006)

UV- Univariate, MV-Multivariate, OR-Odds ratio, CI- Confidence interval

Table 8-2b: Studies reporting the relationship between frailty and thirty-day mortality in patients undergoing surgery for colorectal cancer

Study	Observations
Artiles-Armas et al (2021, (213)	Frailty associated with increased mortality on UV analysis (p=0.009)
Miller et al (2020, (205)	Frailty associated with increased mortality on MV binary log regression (OR 20.8, 95% CI 6.2-70.0, p<0.001)
Reisinger et al (2015, (207)	Frailty not associated with increased mortality on UV binary log regression (p=0.72)
Souwer et al (2018, (209)	Frailty not associated with increased mortality on UV binary log regression (p=1.00)

UV-Univariate. MV-Multivariate, OR- Odds ratio, CI- Confidence interval

Table 8-2c: Studies reporting the relationship between frailty and overall survival in patients undergoing surgery for colorectal cancer

Study	Comments
Artiles-Armas et al (2021, (213)	Frailty not associated with reduced survival on UV binary log regression (p=0.249)
Feliciano et al (2020, (216)	Frailty associated with OS on MV binary log regression (HR 1.94, 95% CI 1.39-2.69, p<0.001)
Mima et al (2020, (214)	Frailty associated with OS on MV binary log regression (HR 2.40, 95% CI 1.40-2.99, p<0.001)

UV-Univariate, MV- Multivariate, HR- Hazard ratio, CI- Confidence interval

8.6 Figures and Legends

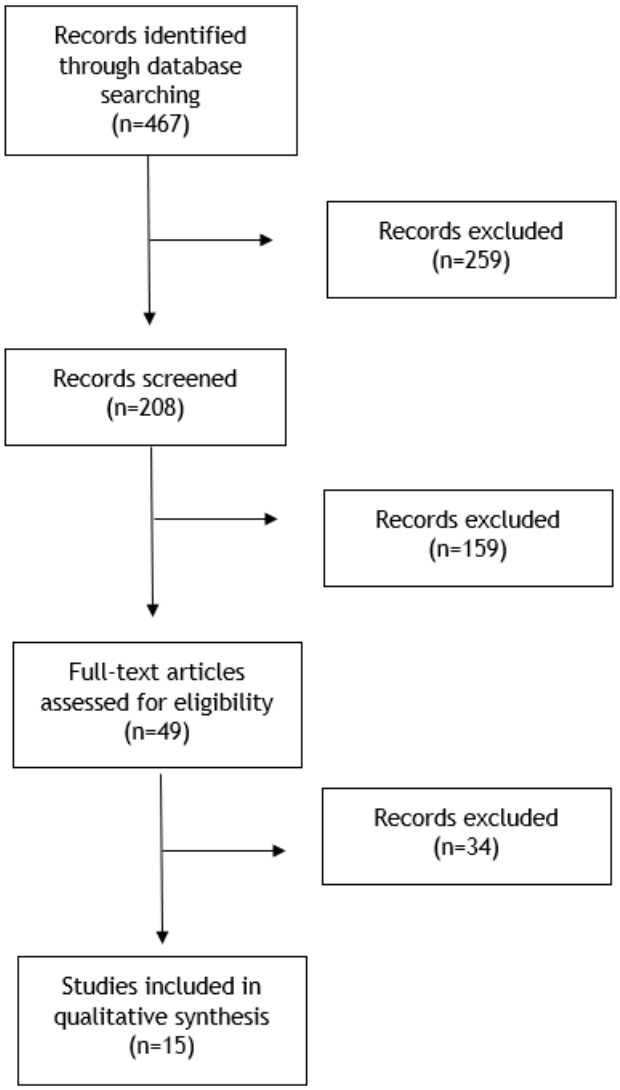


Figure 8-1: Flow diagram of literature search and included/excluded studies

	Selection				Comparability	Outcome		
	1	2	3	4	1	1	2	3
Artiles-Armas et al (2021)		*	*		**	*	*	*
Bessems et al (2020)		*	*	*		*	*	*
Chen et al (2017)	*	*	*	*	**	*	*	*
Feliciano et al (2020)		*	*	*	**	*	*	*
Gearhart et al (2020)			*	*	*	*	*	*
Lo et al (2020)	*	*	*	*	**	*	*	*
Miller et al (2020)	*	*	*	*	*	*	*	*
Mima et al (2020)	*	*	*	*	**	*	*	*
Okabe et al (2019)			*	*	**	*	*	*
Reisinger et al (2015)	*	*	*	*	**	*	*	*
Richards et al (2021)			*	*	*	*	*	*
Souwer et al (2018)			*	*		*	*	*
Suzuki et al (2021)			*	*		*	*	*
Tamura et al (2021)			*	*	*			
Tan et al (2012)			*	*	*	*	*	*

Figure 8-2: Quality assessment of included studies using the NOS

9 The relationship between the five-item modified frailty index (mFI-5) score and malnutrition, CT-derived body composition, systemic inflammation and short-term clinical outcomes in patients undergoing potentially curative surgery for colorectal cancer

9.1 Introduction

Frailty is a complex multifactorial syndrome, characterised by a clinically significant increase in vulnerability and worsened health outcomes (103). Considered to represent the systemic burden of chronological aging and the erosion of the patients homeostatic reserve (217), frailty remains a growing area of interest in many subspecialities of medicine. Particularly, in surgery, with frailty reported to have clinical utility in determining likely outcome in older adults undergoing surgery (231-233).

In the UK, over a third of newly diagnosed colorectal cancers involve patients aged 75 years and older (186). As such, the prognostic value of frailty to clinical outcomes in patients undergoing surgery for colorectal cancer has been widely examined, across a range of screening measures (234-236). One such example is the American College of Surgeons National Surgical Quality Improvement Programs five-item modified frailty index (mFI-5 (196). Scores are calculated on the presence of co-morbid disease and non-independent functional status, with increased mFI-5 score associated with the incidence of post-operative complications and thirty-day mortality in older adults undergoing surgery for colorectal cancer (Chapter 8).

Whilst the current literature suggests an association between frailty and clinical outcomes in patients undergoing surgery for colorectal cancer (236), the basis of relationship is unclear. Indeed, frailty has been associated with prognostic, pre-operative host factors including malnutrition, sarcopenia and systemic inflammation (226, 237, 238). Therefore, it remains unclear if frailty has independent prognostic value to clinical outcomes in patients undergoing surgery

for colorectal cancer. In this chapter, the relationship between frailty, screened for using the mFI-5, and malnutrition, CT-derived body composition, systemic inflammation and short-term clinical outcomes in patients undergoing potentially curative surgery for colorectal cancer was examined.

9.2 Patients and Methods

9.2.1 Patients

Retrospective analysis of prospectively collected data from consecutive patients who underwent potentially curative surgery for colorectal cancer, at Glasgow Royal Infirmary, between April 2008 and April 2018 was carried out. Patients who had electronic medical records facilitating the calculation of the mFI-5 score, pre-operative CT imaging suitable for body composition analysis, recorded height and weight, pre-operative assessment of systemic inflammatory status and had TNM stage I-III disease were assessed for inclusion. Exclusion criteria were as follows; patients whose medical records did not facilitate calculation of mFI-5 score, patients without satisfactory pre-operative CT imaging, patients without a recorded height and weight, patients who had no pre-operative assessment of the systemic inflammatory response or had TNM Stage IV disease.

Patients were operated on at Glasgow Royal Infirmary, a single tertiary referral teaching hospital. A proportion of patients, primarily those with rectal tumours, received neo-adjuvant chemotherapy. Prophylactic antibiotics were administered at the induction of anaesthesia. As per unit policy, subcutaneous low molecular weight heparin and pneumatic compression stockings were given to patients as venous thromboprophylaxis. Postoperatively, all patients underwent daily clinical assessment by a member of the surgical team. Additional investigations and management were instigated at the discretion of the surgical team based on the relevant clinical findings. The incidence of post-operative complications was prospectively recorded using the CD classification (239). Patients were categorised as complication/no complication. The incidence of thirty-day mortality was also prospectively recorded.

The primary outcomes of interest were the incidence of post-operative complications and thirty-day mortality. Ethical approval from the West of Scotland Ethics Committee, Glasgow was granted to collect such routine clinicopathological data. Written informed consent for each patient was obtained prior to surgery for the collection of routine clinicopathological details. There are no patient

identifiable details included requiring consent. The study was conducted in accordance with the Declaration of Helsinki and conformed to the STROBE guidelines for cohort studies.

9.2.2 Methods

Routine demographic details included age, sex and BMI. Age categories were grouped into <64, 65-74 and >74 years. Tumour site was identified from pre-operative CT imaging, endoscopic and pathology reports. Tumours were staged using the fifth edition of the TNM classification, consistent with practice in the UK during the study period (157).

Frailty was determined using the five-item modified frailty index (mFI-5), as described in Chapter 3. Patients scores were grouped as 0/1/≥2. MUST was used to determine the overall risk of malnutrition, as described in Chapter 3. BMI was categorised as <20, 20-24.9, 25-29.9 and ≥30 kg/m^2. Systemic inflammation was determined using the NLR, mGPS and SIG. The NLR and mGPS were calculated from pre-operative venous blood samples and combined to form the SIG, as described in Chapter 3. NLR values were grouped as <3/3-5/>5 and mGPS values as 0/1/2. SIG values were grouped as 0/1/2/≥3.

CT-derived body composition analysis was carried out as described in Chapter 3. A high SFI and VFA were defined using the threshold values of Ebadi and co-workers and Doyle and co-workers, respectively (124, 125). A low SMI and SMD were defined using the threshold values of Martin and co- workers (61). The CT-SS was determined as described in Chapter 3.

9.2.3 Statistical Analysis

Clinicopathological variables, mFI-5 score, MUST risk, BMI, CT-derived body composition measurements, NLR, mGPS, SIG, incidence of post-operative complication and thirty-day mortality were presented as categorical variables. The Pearson Chi square test was used to examine the associations between categorical variables and the Chi square test for linear trend was used for ordered variables with multiple categories.

Binary logistic regression of variables associated with the incidence of post-operative complications was performed. Variables that had a p value <0.1 at univariate analysis were included in multivariate binary logistic regression using a backward conditional model.

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 27.0 (SPSS Inc., Chicago, IL, USA).

9.3 Results

In total, 1,002 patients met the inclusion criteria. 55% (n=554) of patients were male and 66% (n=657) were aged 65 years or older. 60% (n=602) of patients had colonic tumours and 40% (n=400) had rectal. 24% (n=240) of patients had TNM stage I disease, 40% (n=404) stage II and 36% (n=368) had stage III disease. 14% (n=138) of patients received neo-adjuvant chemotherapy. 18% (n=174) of those with a pre-operative MUST were at risk of malnutrition (MUST≥1). The median BMI of the cohort was 27 kg/m2 and 65% (n=652) of patients had a BMI ≥25 kg/m2. A high VFA was present in 73% (n=731) of patients and 80% (n=803) had a high SFI. A low SMI and SMD were present in 51% (n=507) and 67% (n=668), respectively. 51% (n=507) were CT-SS ≥1. 48% (n=479) of patients had an NLR ≥3 and 27% (n=271) had an mGPS ≥1. 43% (n=427) of patients were SIG 0, 26% (260) SIG 1 and 31% (n=315) were SIG ≥2. 39% (n=388) had a post-operative complication (CD I-IV). 1% (n=11) of patients died within thirty days of surgery.

The prevalence of mFI-5 frailty screening items of included patients is shown in Table 9-1. 2% (n=21) of patients had congestive heart failure, 7% (n=66) had COPD or recent pneumonia, 45% (n=451) had hypertension requiring medication, 15% (n=151) had diabetes mellitus and 18% (n=184) had non-independent functional status. The prevalence of mFI-5 frailty scores of included patients is shown in Table 9-2. 40 % (n=397) of patients scored 0, 38% (n=384) scored 1, 22% (n=221) scored 2 or more.

The relationship between mFI-5 frailty score and clinicopathological variables, MUST risk, BMI, CT-derived body composition measurements, systemic inflammation, incidence of post-operative complications and thirty-day mortality in patients undergoing potentially curative surgery for colorectal cancer is shown in Table 9-3. On univariate analysis, the mFI-5 frailty score was significantly associated with age ($p<0.001$), tumour site ($p<0.001$), neo-adjuvant chemotherapy ($p<0.05$), BMI ($p<0.05$), low SMD ($p<0.001$), NLR ($p<0.05$), mGPS ($p<0.05$), SIG ($p<0.05$), incidence of post-operative complications ($p<0.001$) and thirty-day mortality ($p<0.05$, Table 9-3).

The relationship between clinicopathological variables, MUST risk, BMI, CT-derived body composition measurements, systemic inflammation, mFI-5 frailty score and incidence of post-operative complications in patients undergoing potentially curative surgery for colorectal cancer is shown in Table 9-4. On univariate analysis, age ($p<0.05$), sex ($p<0.05$), SIG ($p<0.05$) and mFI-5 frailty score ($p<0.001$) were significantly associated with the incidence of post-operative complications. On multivariate analysis, sex ($p<0.05$), SIG ($p<0.05$) and mFI-5 frailty score ($p<0.01$) remained significantly associated with the incidence of post-operative complications (Table 9-4).

The relationship between mFI-5 frailty score, SIG and incidence of post-operative complications in patients undergoing potentially curative surgery for colorectal cancer is shown in Table 9-5. On univariate analysis, SIG was associated with the incidence of post-operative complications ($p<0.05$). On univariate analysis, mFI-5 frailty score was significantly associated with the incidence of post-operative complications ($p<0.05$). In patients who were not inflamed (SIG 0), mFI-5 frailty score was significantly associated with the incidence of post-operative complications ($p<0.05$). In patients who were mFI-5 0, SIG was not associated with the incidence of post-operative complications ($p=0.243$, Table 9-5).

9.4 Discussion

The results of the present study showed that, in a large cohort of patients undergoing potentially curative surgery for colorectal cancer, the mFI-5 frailty score was found to be associated with age, tumour site, neo-adjuvant chemotherapy, BMI, SMD, NLR, mGPS, SIG the incidence of post-operative complications and thirty-day mortality. However, mFI-5 and SIG were independently associated with the incidence of post-operative complications. Therefore, the mFI-5 has clinical utility and would appear to capture the prognostic impact that some elements of nutritional and functional status have on the incidence of post-operative complications, but not that of the systemic inflammatory response.

Whilst an association between frailty and short-term outcomes (incidence of post-operative complications, length of stay and thirty-day mortality) has been widely reported in patients undergoing surgery for colorectal cancer, the basis of this relationship remains unclear. It has been postulated that an exaggerated systemic inflammatory response may be responsible for the adverse clinical outcomes in frail patients (Chapter 8). Indeed, Soysal and co-workers reported an association between frailty and systemic inflammation in a recent systematic review and meta-analysis, in keeping with the present observations (226). However, frailty was found to remain significantly associated with the incidence of post-operative complications in patients who were not inflamed (SIG 0, See Table 9-5). As such, the relationship between frailty, systemic inflammation and short-term outcomes in patients undergoing surgery for colorectal cancer remains unclear and requires further study.

Frailty is thought to encompass not only age, but a number of recognised domains including functional status, malnutrition, co-morbidity, cognition, socio-economic and psychological factors (12, 222). Indeed, the present study that found mFI-5 frailty scores were significantly associated with short-term clinical outcomes, even when younger patients (<65 years) were studied in insolation (Appendix C). The present observations are in keeping with those of Miller and co-workers, who in a cohort of 9, 252 patients undergoing proctectomy for colorectal cancer,

reported that frailty, but not age, was independently associated with adverse post-operative outcomes (205). Taken together, these results that frailty screening measures may have prognostic value in younger adults undergoing surgery for colorectal cancer, as an assessment of their robustness to the physiological stress of surgery. Furthermore, that simply screening for frailty in patients of advanced age is insufficient and that those who are functionally restricted, co-morbid or cachexic are also likely to be frail and at increased risk of adverse outcomes following surgery (Chapter 8).

In the present study, it was of interest that frailty, determined using the mFI-5 frailty score, was not associated with recognized prognostic host factors in colorectal cancer including malnutrition and low skeletal muscle mass (122, 155). Indeed, a loss of skeletal muscle mass is one of many causes of functional impairment, a hallmark of frailty (240). Furthermore, malnutrition has been reported to be prevalent in frail, older adults (237, 241). However, since frailty screening tools may capture many elements of ageing including nutritional status, physical function and now from this work systemic inflammation, it is likely that the contribution of these elements to a high frailty score will vary with the disease condition. Therefore, although mFI-5 is a convenient screening tool, it is important to define which element is the main driver of the frailty score so that this may be targeted in the patient. Specifically, if the present results are confirmed, frailty screening measures should be utilized in combination with other recognized prognostic host-assessments such as MUST, CT-derived body composition and systemic inflammatory status in patients undergoing surgery for colorectal cancer (122, 155).

There are a number of limitations to the present study. Firstly, the study was retrospective in nature and subject to sample bias. Specifically, the retrospective scoring of frailty using the mFI-5. However, in the present cohort, around 22% (n=227) of patients undergoing surgery for colorectal cancer had an mFI-5 ≥2. This is in keeping with the observations of Al-Khamis and co-workers, who found a similar prevalence of mFI-5 score of ≥2 (18%) in a cohort of 295,490 patients undergoing colorectal surgery (219). As such the present observations are likely to be reliable. Secondly, whilst functional impairment is a recognised hallmark of frailty, there is no objective measure of functional status utilised in the mFI-5. As

such, there is potential for significant variation in the level of physical function in patients deemed to have non-independent functional status. Associations between routine measures of physical function and the mFI-5 frailty index will therefore be informative. Lastly, the present study included only patients who underwent surgical resection with curative intent and not those with advanced inoperable disease. Further studies of frailty across other cancer subtypes and disease stages will be required to delineate the prognostic value of the mFI-5 frailty index to cancer outcomes.

In conclusion, mFI-5 frailty score was found to be significantly associated with age, CT-derived body composition, systemic inflammation and post-operative outcomes in patients undergoing potentially curative surgery for colorectal cancer. Incorporation of an objective assessment of functional status and systemic inflammation may improve the prognostic value of future frailty screening tools.

9.5 Tables

Table 9-1: Prevalence of mFI-5 frailty screening items of included patients (n=1,002)

Item	Patients (n=/%)
Congestive Heart Failure	21 (2%)
Chronic Obstructive Pulmonary Disease or recent pneumonia	66 (7%)
Hypertension (Requiring medication)	451 (45%)
Diabetes Mellitus	151 (15%)
Non-independent Functional Status	184 (18%)

Table 9-2: The mFI-5 frailty scores of included patients (n=1,002)

mFI-5 Frailty Score	Patients (n=/%)
0	397 (40%)
1	384 (38%)
2	180 (18%)
3	36 (4%)
≥4	5 (<1%)

Table 9-3: The relationship between mFI-5 frailty score and clinicopathological variables, MUST risk, BMI, CT-derived body composition measurements, systemic inflammation, incidence of post-operative complications and thirty-day mortality in patients undergoing potentially curative surgery for colorectal cancer (n=1,002)

	mFI-5= 0 (n=397)	**mFI-5= 1** (n=384)	**mFI-5 ≥2** (n=221)	**p value**
Age (<65/65-74/>74)	165/157/75	114/135/135	66/75/80	<0.001
Sex (Female/Male)	175/222	172/212	101/120	0.697
Tumour Site (Colon/Rectum)	209/188	246/138	147/74	<0.001
TNM Stage (I/II/III)	89/148/160	98/158/138	53/98/70	0.072
Neo-adjuvant chemotherapy (No/Yes)	325/68	338/45	194/25	0.024
MUST Risk[1] (Low/Medium/High)	331/30/32	302/36/36	177/25/15	0.630
BMI (<20/20-24.9/25-29.9/≥30kg/m^2)	23/114/147/113	28/122/118/116	7/56/72/86	0.034
High SFI (No/Yes)	81/316	82/302	36/185	0.299
High VFA (No/Yes)	111/286	113/271	47/174	0.128
Low SMI (No/Yes)	204/193	184/200	107/114	0.407
Low SMD (No/Yes)	163/234	112/272	59/162	<0.001
CT-SS (0/1/2)	204/61/132	184/39/161	107/19/95	0.068
NLR (<3/3-5/>5)	224/116/57	194/121/69	105/73/43	0.019
mGPS (0/1/2)	301/50/46	271/41/72	159/18/44	0.028
SIG (0/1/2/≥3)	187/107/58/45	155/94/80/55	85/59/41/36	0.006
Post-operative Complication (No/Yes)	274/123	214/170	126/95	<0.001
Thirty-day Mortality (No/Yes)	395/2	381/3	215/6	0.019

[1] 18 patients missing MUST assessment

Table 9-4: The relationship between clinicopathological variables, MUST risk, BMI, CT-derived body composition measurements, systemic inflammation, mFI-5 frailty score and the incidence of post-operative complications in patients undergoing potentially curative surgery for colorectal cancer (n=1,002)

	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Age (<65/65-74/>74)	1.28 (1.00-1.38)	0.047	-	0.241
Sex (Female/Male)	1.40 (1.08-1.81)	0.011	1.39 (1.07-1.80)	0.013
Tumour Site (Colon/Rectum)	1.13 (0.87-1.47)	0.347	-	-
Neo-adjuvant chemotherapy (No/Yes)	1.10 (0.76-1.58)	0.624	-	-
MUST risk (Low/Medium/High)	1.08 (0.87-1.33)	0.498	-	-
BMI (<20/20-24.9/25-29.9/≥30 kg/m^2)	1.03 (0.90-1.19)	0.668	-	-
High SFI (No/Yes)	1.09 (0.79-1.50)	0.619	-	-
High VFA (No/Yes)	1.07 (0.80-1.42)	0.668	-	-
Low SMI (No/Yes)	1.10 (0.85-1.42)	0.462	-	-
Low SMD (No/Yes)	1.13 (0.86-1.48)	0.384	-	-
CT-SS (0/1/2)	1.08 (0.94-1.24)	0.283	-	-
SIG (0/1/2/≥3)	1.17 (1.05-1.30)	0.004	1.14 (1.03-1.27)	0.014
mFI-5 Score (0/1/≥2)	1.33 (1.13-1.58)	<0.001	1.32 (1.11-1.56)	0.001

OR- Odds ratio, CI- Confidence interval

Table 9-5. The relationship between mFI-5 frailty score, SIG and incidence of post-operative complications in patients undergoing potentially curative surgery for colorectal cancer (n=1,002)

	mFI-5 0 (n=397)	**mFI-5 1 (n=384)**	**mFI-5 ≥2 (n=221)**	**mFI-5 (0-≥2)**	**p value**
SIG 0 (n=427)	51 (27%)	62 (40%)	33 (39%)	146 (34%)	0.024
SIG 1 (n=260)	36 (34%)	44 (47%)	26 (44%)	106 (41%)	0.121
SIG 2 (n=179)	22 (38%)	32 (40%)	17 (42%)	71 (40%)	0.719
SIG ≥3 (n=136)	14 (31%)	32 (58%)	19 (53%)	65 (48%)	0.039
SIG (0-≥3)	123 (31%)	170 (44%)	95 (43%)	388 (39%)	0.006
p value	0.243	0.080	0.219	0.001	

In each cell is the complication incidence

10 The relationship between LDH and the phenotypic and aetiological criterion of the GLIM diagnostic framework for cachexia in patients with advanced cancer

10.1 Introduction

LDH is an enzyme that is present in almost every tissue in the human body (242). In addition to acting as a functional checkpoint in single-stranded DNA metabolism and glucose restoration during gluconeogenesis, LDH is a key enzyme in anaerobic cell metabolism (243). Specifically, in the conversion of lactate to pyruvate during the Cori cycle, which is utilized by the liver for gluconeogenesis (244).

Elevated serum LDH levels have been reported to be associated with disease progression and metastasis in patients cancer (245). Moreover, have been reported to have prognostic value to treatment efficacy (246, 247) and survival (248, 249). The basis of such an association is thought to be the result of a combination of tumour necrosis due to hypoxia and enhanced glycolytic activity of the tumour (Warburg effect). As such, the role of LDH in cancer remains an area of interest and a potential therapeutic target in oncology (250, 251).

Cancer cachexia is a complex metabolic syndrome that is associated with dysregulated glucose metabolism (119). However, there is currently a paucity of studies examining the relationship between serum LDH concentration, an early biomarker of dysregulated glucose metabolism, and the phenotypic/aetiologic criterion of the GLIM diagnostic framework for cancer cachexia. Specifically, the relationship between LDH and a low skeletal muscle mass, the defining feature of cachexia. In this chapter, the relationship between serum LDH concentration and the diagnostic criterion of the GLIM framework and survival in patients with advanced cancer was examined.

10.2 Methods

10.2.1 Patients

Prospectively collected data from patients with advanced cancer, undergoing anti-cancer therapy with palliative intent, across nine sites in the UK and Ireland between 2011–2016, was retrospectively analysed (102, 166). Eligible adult patients with advanced disease (defined as locally advanced or with histological, cytological or radiological evidence of metastasis), across all cancer subtypes, who had recorded serum LDH values prior to entry to the study were assessed for inclusion. The study included patients with primary lung, GI, breast, gynaecological, urological and haematological malignancies.

The primary outcome of interest was survival at three months from entry to the study. The study had ethical approval in both the UK and Ireland (West of Scotland Ethics Committee UK: 18/WS/0001 (18/01/2018) and Cork Research Ethics Committee Ireland: ECM 4 (g) (03/03/2015) and was conducted in accordance with the Declaration of Helsinki, as previously described (102, 166). The study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies (134).

10.2.2 Methods

Clinicopathological characteristics were recorded for each patient prior to study entry. Tumour site was grouped as lung, GI or other. Performance status was determined using the ECOG-PS and assessed by a clinician or clinical researcher at entry to the study, as described in Chapter 3. ECOG-PS was grouped as 0-1/2/3-4. Serum LDH concentration was calculated from venous blood sample obtained at time of entry to study. LDH values were grouped as <250/250-500/>500 Units/L, based on threshold values reported to have prognostic value (252).

GLIM diagnostic criterion studied included involuntary weight loss, low BMI, low skeletal muscle mass, disease burden and systemic inflammation (128). Each patient had their weight and BMI recorded on entry to the study. Weight loss was

categorised as (≤/>5%) prior to study entry. A low BMI as <20 kg/m^2 in patients aged <70 years and <22kg/m^2 in patients aged >70 years. A low skeletal muscle mass was defined as a low SMI using the threshold values of Martin and co-workers (61). SMI was determined from CT images obtained at the level of the L3, as described in Chapter 3. Disease burden was classified as the presence/absence of metastasis on staging CT scan performed prior to entry to the study. The presence of systemic inflammation was determined using the NLR and mGPS, calculated from venous blood samples obtained on entry to the study, as described in Chapter 3. NLR values were grouped as <3/3-5/>5 and mGPS values as 0/1/2.

10.2.3 Statistical Analysis

Clinicopathological variables, LDH, ECOG-PS, weight loss, low BMI, low SMI, NLR, mGPS and 3-month survival were presented as categorical variables. Categorical variables were analysed using Chi square test for linear-by-linear association.

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 27.0 (SPSS Inc., Chicago, IL, USA).

10.3 Results

A total of 436 patients met the inclusion criteria (Figure 10-1). The clinicopathological characteristics of the included patients are shown in Table 10-1. 46% (n=200) of patients were male and 59% (n=258) were ≥65 years of age. The majority of patients had either lung (37%, n=162) or GI (28%, n=124) tumours. 61% (n=267) of patients received chemotherapy, 41% (n=179) received radiotherapy and 14% (n=59) received hormonal therapy. The median serum LDH concentration was 394 Units/L (1.8-2757) and 33% (n=146) had an LDH >500 Units/L. 41% (n=180) of patients were ECOG-PS 0/1. Of the 421 patients, 33% (n=139) had >5% weight loss. 33% (n=143) patients were categorised as having a low BMI. Of the 177 patients with CT-imaging facilitating body composition analysis, 55% (n=97) were categorised as having a low skeletal muscle mass. 81% (n=355) patients had metastatic disease on entry to the study. 44% (n=193) patients had an NLR>5 and 62% (n=270) patients had an mGPS≥1. The median survival from study entry was 8.7 months (0-22) and 65 % (n=284) of patients were alive at 3-months from entry to the study (Table 10-1).

The relationship between LDH and ECOG-PS, weight loss, low BMI, low SMI, metastatic disease, NLR, mGPS and 3-month survival in patients with advanced cancer is shown in Table 10-1. LDH was significantly associated with ECOG-PS ($p<0.001$), NLR ($p<0.05$), mGPS ($p<0.05$) and 3-month survival ($p<0.001$, Table 10-1).

The relationship between LDH, weight loss and 3-month survival in patients is shown in Table 10-2a. LDH was significantly associated with 3-month survival independent of weight loss ($p<0.05$). The relationship between LDH, low BMI and 3-month survival in patients with advanced cancer is shown in Table 10-2b. LDH was significantly associated with 3-month survival independent of BMI ($p<0.05$). The relationship between LDH, low SMI and 3-month survival in patients with advanced cancer is shown in Table 10-2c. LDH was significantly associated with 3-month survival independent of SMI ($p<0.05$). The relationship between LDH, metastatic disease and 3-month survival in patients with advanced cancer is shown in Table 10-2d. LDH was significantly associated with 3-month survival

independent of the presence of metastatic disease ($p<0.05$). The relationship between LDH, NLR and 3-month survival in patients with advanced cancer is shown in Table 10-2e. LDH was significantly associated with 3-month survival independent of NLR>5 ($p<0.05$). The relationship between LDH, mGPS and 3-month survival in patients with advanced cancer is shown in Table 10-2f. LDH was significantly associated with 3-month survival independent of mGPS ($p<0.01$).

10.4 Discussion

To our knowledge, the present study is one of the largest to date examining the relationship between LDH and other validated prognostic host factors (specifically the GLIM criteria) in patients with advanced cancer. It was of interest that LDH was shown to be significantly associated with performance status, systemic inflammation and survival but not weight loss, low BMI or low SMI. Given that an elevated LDH is considered an early biomarker of dysfunctional glucose metabolism, the present observations may represent the tip of the iceberg with regard to the profound metabolic changes that occur in patients with advanced cancer. Indeed, an elevated LDH was associated with the systemic inflammatory response which is recognised to have a catabolic effect on skeletal muscle in patients with cancer (253). Therefore, the present results suggest that an elevated LDH would be a useful additional aetiologic criterion in the GLIM diagnostic framework.

The results of the present study are consistent with the observations of Zhou and co-workers, who reported that an elevated LDH was significantly associated with mGPS, in a study of 359 patients with small cell lung cancer (254). The basis of this relationship is not clear. However, it has been reported that increased tumour and bone marrow glucose uptake was associated with systemic inflammation in different tumour types (255). Moreover, at the tumour microenvironment level, inhibitors of LDH appear to reverse inflammation induced changes (256, 257). Taken together, these observations appear to confirm that the intimate cellular connection between inflammation and metabolism proposed by Hotamisligil and co-workers occurs not only at the cellular level, but also at a systemic level (258). Therefore, it may be that the immune-metabolic changes that occur in the tumour microenvironment result in systemic increases in lactate and inflammation, which subsequently impact on skeletal muscle mass and performance status in patients with cancer. This hypothesis requires testing both in the tumour microenvironment and at a systemic level. For example, using immunohistochemistry to examine the relationship between LDH expression in the tumour microenvironment, biomarkers of systemic inflammation and CT-derived muscle measurements. Irrespective, the measurement of LDH and systemic

inflammation in routine clinical cancer care may alert the clinician to the presence of profound immune-metabolic changes in the patient and the increased likelihood of poor survival.

There are a number of limitations to the present study. Firstly, this study is retrospective in nature and subject to sample bias. Indeed, less than half (42%, n=177) of the included patients had eligible CT-imaging available for body composition analysis. Nevertheless, these routine available clinical results may be readily tested in future studies.

In conclusion, elevated LDH was associated with performance status, systemic inflammation and survival in patients with advanced cancer. If the present results are confirmed in subsequent studies, then an elevated LDH may be a useful additional aetiologic criterion in the GLIM framework. Moreover, may provide a therapeutic target in the treatment of cachexia in patients with advanced cancer.

10.5 Tables and Footnotes

Table 10-1: The relationship between LDH and ECOG-PS, weight loss, low BMI, low SMI, metastatic disease, NLR, mGPS and 3-month survival in patients with advanced cancer (n=436)

	LDH <250 Units/L (n=110)	LDH 250-500 Units/L (n=180)	LDH >500 Units/L (n=146)	p value
Age (<65/65-74/>74)	48/38/23	72/50/58	57/39/50	0.101
Sex (Female/Male)	52/58	106/74	78/68	0.412
Tumour Site (Lung/GI/Other)	51/20/39	66/50/64	45/54/47	0.266
Chemotherapy (Yes/No)	61/49	114/66	92/54	0.248
Radiotherapy (Yes/No)	39/71	80/100	60/86	0.427
Hormone Therapy (Yes/No)	13/97	20/160	26/120	0.136
ECOG-PS (0-1/2/≥3)	69/30/11	68/87/25	43/62/41	<0.001
Weight loss (>5%, No/Yes)[1]	70/37	116/57	96/45	0.662
Low BMI (No/Yes)	84/26	109/71	100/46	0.273
Low SMI (No/Yes)[2]	33/33	25/29	22/35	0.210
Metastatic disease (No/Yes)	20/90	44/136	17/129	0.118
NLR (<3/3-5/>5)	43/31/36	64/41/75	44/20/82	0.003
mGPS (0/1/2)	50/14/46	77/38/65	39/38/69	0.021
3-month survival (Yes/No)	93/17	121/59	70/76	<0.001

[1] 15 patients did not have sequential monitoring of weight

[2] 249 patients did not have eligible CT imaging at L3 for CT-body composition analysis

Table 10-2a: The relationship between LDH, weight loss and 3-month survival in patients with advanced cancer (n=421)

	LDH <250 Units/L (n=107)	**LDH 250-500 Units/L (n=173)**	**LDH >500 Units/L (n=141)**	**p value**
Weight loss ≤5% (n=282)	63 (57%)	92 (51%)	51 (35%)	<0.001
Weight loss >5% (n=139)	28 (25%)	26 (14%)	18 (12%)	0.002
p value	0.048	<0.001	0.146	

Each cell (n=/%)

Table 10-2b: The relationship between LDH, low BMI and 3-month survival in patients with advanced cancer (n=436)

	LDH ≤250 Units/L (n=110)	**LDH 250-500 Units/L (n=180)**	**LDH >500 Units/L (n=146)**	**p value**
Normal/high BMI (n=293)	78 (73%)	82 (47%)	54 (38%)	<0.001
Low BMI (n=143)	17 (16%)	39 (23%)	16 (11%)	0.008
p value	0.002	0.005	0.031	

Each cell (n=/%)

Table 10-2c: The relationship between LDH, low SMI and 3-month survival in patients with advanced cancer (n=177)

	LDH ≤250 Units/L (n=66)	**LDH 250-500 Units/L (n=54)**	**LDH >500 Units/L (n=57)**	**p value**
Normal/high SMI (n=80)	31 (47%)	18 (33%)	14 (25%)	0.006
Low SMI (n=97)	28 (42%)	22 (41%)	17 (30%)	0.001
p value	0.230	0.747	0.266	

Each cell (n=/%)

Table 10-2d: The relationship between LDH, metastatic disease and 3-month survival in patients with advanced cancer (n=436)

	LDH ≤250 Units/L (n=110)	**LDH 250-500 Units/L (n=180)**	**LDH >500 Units/L (n=146)**	**p value**
Non-metastatic disease (n=81)	17 (15%)	31 (17%)	9 (6%)	0.035
Metastatic disease (n=355)	76 (69%)	90 (50%)	61 (42%)	<0.001
p value	0.950	0.599	0.661	

Each cell (n=/%)

Table 10-2e: The relationship between LDH, NLR and 3-month survival in patients with advanced cancer (n=436)

	LDH <250 Units/L (n=110)	**LDH 250-500 Units/L (n=180)**	**LDH >500 Units/L (n=146)**	**p value**
NLR <3 (n=151)	41 (37%)	57 (32%)	31 (21%)	0.001
NLR 3-5 (n=92)	28 (25%)	25 (14%)	14 (10%)	0.057
NLR >5 (n=193)	24 (22%)	39 (22%)	25 (17%)	<0.001
p value	0.001	<0.001	<0.001	

Each cell (n=/%)

Table 10-2f. The relationship between LDH, mGPS and 3-month survival in patients with advanced cancer (n=436)

	LDH <250 Units/L (n=110)	**LDH 250-500 Units/L (n=180)**	**LDH >500 Units/L (n=146)**	**p value**
mGPS 0 (n=166)	49 (45%)	67 (37%)	30 (21%)	0.002
mGPS 1 (n=90)	12 (11%)	25 (14%)	17 (12%)	0.005
mGPS 2 (n=180)	32 (29%)	29 (16%)	23 (16%)	<0.001
p value	<0.001	<0.001	<0.001	

Each cell (n=/%)

10.6 Figures and Legends

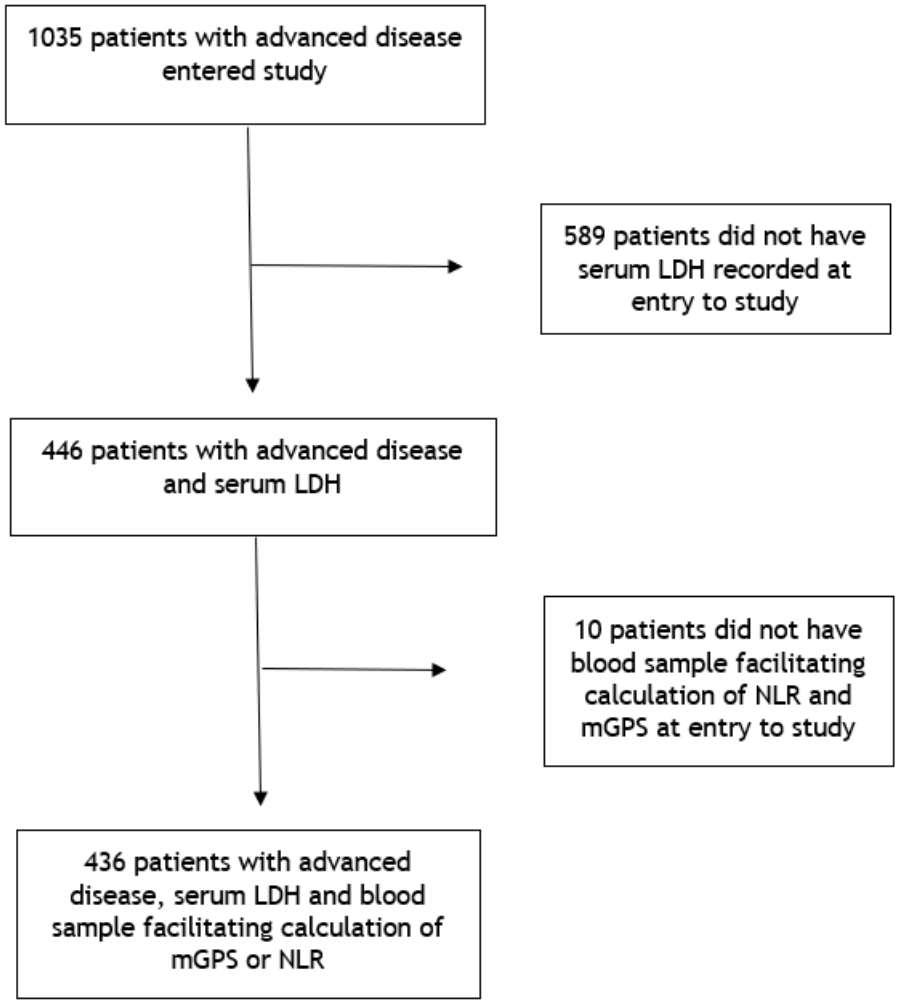


Figure 10-1: Flowchart of patients included in study

11 The relationship between CT-derived liver mass and clinicopathological characteristics and survival in patients undergoing potentially curative surgery for colonic cancer

11.1 Introduction

Whilst cancer progression is associated with a loss of skeletal muscle mass, liver mass is thought to be preserved/increase (259). CT is widely regarded as a reliable modality for the quantification of liver mass, with cohort studies reporting excellent correlation between CT-derived liver volume and the mass of resected specimens in patients undergoing hepatectomy for colorectal liver metastasis (129, 260) and liver transplantation (261). Therefore, CT may provide a readily available modality for the quantification and examination of liver mass in patients with cancer.

The paucity of studies examining liver mass in patients with cancer, quantified using CT-derived volumetry, is likely attributable to the absence of a standardised methodology (262). Moreover, the time-consuming nature of manual segmentation of sequential CT images for the quantification of the total liver volume (129), regarded to be the gold-standard methodology (263, 264). Therefore, at present, the relationships between liver mass and clinicopathological characteristics and survival outcomes in patients with cancer remains unclear.

We hypothesise that the maximal cross-sectional liver area on a single axial CT image, measured using manual delineation, may be a simple and readily quantified surrogate marker of liver mass in patients with cancer, analogous to how skeletal muscle mass is quantified using CT. In this chapter, the relationship between the maximal cross-sectional liver area on a single axial CT slice and CT-derived total liver volume, derived using manual segmentation was examined in patients undergoing potentially curative surgery for colonic cancer. Furthermore, the relationship between CT-derived liver mass and clinicopathological characteristics and overall survival was also examined.

11.2 Patients and Methods

11.2.1 Patients

Consecutive patients who underwent elective, potentially curative, right or extended right hemicolectomies for colonic cancer, between 1st March 2008 and 1st of April 2018, within NHS Greater Glasgow and Clyde, were identified from a prospectively maintained database. Patients who had TNM stage I-III disease and had recorded pre-operative height and weight, satisfactory CT imaging for body composition analysis, and pre-operative assessment of the systemic inflammatory response, within the preceding 3 months of surgery, were assessed for inclusion. Exclusion criteria were as follows; patients who had undergone previous hepatic resections, patients who had neo-adjuvant chemotherapy and patients who had liver metastasis, given they are likely confounding factors to liver volume (265-267).

Patients were operated on at Glasgow Royal Infirmary, a single tertiary referral teaching hospital. Prophylactic antibiotics were administered at the induction of anaesthesia. As per unit policy, subcutaneous low molecular weight heparin and pneumatic compression stockings were given to patients as venous thromboprophylaxis.

The primary outcome of interest was overall survival. All patients were followed up for a minimum of 3 years post-operatively. Vital status was obtained from the included patients' electronic case records. The date of last recorded follow-up or last review of electronic case records was 1st December 2022, which acted as the censor date. The present study was approved as part of surgical audit by the West of Scotland Research Ethics Committee, Glasgow. The need for individual patient consent waived by due to the retrospective observational nature of the study.

11.2.2 Methods

Routine demographic details including age, sex, height and weight were recorded. Age categories were grouped into <64, 65-74 and >74 years. BMI was categorized

as <18.5, 18.5-24.9, 25-29.9 and ≥30 kg/m^2. Body surface area (BSA, m^2) was calculated using Mosteller's formula and values categorized into tertiles (268). Patient comorbidity was classified using the ASA grading system (121), as described in Chapter 3. Furthermore, the presence of type 2 diabetes mellitus (T2DM) and liver disease (non-alcoholic fatty liver disease/cirrhosis) were also recorded.

CT-derived liver measurements including the maximal cross-sectional liver area on axial CT slice (cm^2) and total liver volume (cm^3) were calculated as described in Chapter 3. The median number of slices analysed to identify the CT slice containing the maximal liver area was 7 (5-9). The maximal cross-sectional liver area was then normalized for height^2 to create the LMI.

Measurements were made by one individual (JM). Another individual (AMG) performed an independent measurement of 30 patient images to assess inter-rater reliability using intra-class correlation coefficients (ICCC). The ICC of maximal cross-sectional liver area slice was 0.998.

11.2.3 Statistical Analysis

Correlations amongst maximal cross-sectional liver area on axial CT slice (cm^2) and total liver volume (cm^3) were examined using linear regression and results presented coefficient of determination (R^2).

LMI tertiles were calculated and patients were grouped into categories according to LMI value. The relationship between LMI and age, sex, BMI, BSA, ASA, T2DM, liver disease and overall survival were examined using the Chi square test for linear-by-linear association. Binary logistic regression of variables associated with LMI was performed. Variables that had a p value <0.1 at univariate analysis were included in multivariate binary logistic regression using a backward conditional model.

Survival data were analysed using univariate and multivariate Cox's proportional hazards model. Those variables associated with a degree of p<0.1 were entered into a backward conditional multivariate model. Overall survival was defined as

the time between the date of surgery and the date of death of any cause. Patients who died within 30-days of surgery were excluded from subsequent survival analysis. LMI was presented as both a continuous and categorical (tertiles) variable.

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 27.0 (SPSS Inc., Chicago, IL, USA).

11.3 Results

A total of 359 patients met the inclusion criteria. The clinicopathological characteristics of included patients are shown in Table 11-1. 51% (n=182) of patients were male and 73% (n=261) were aged 65 years or older. The median BMI of the cohort was 27 kg/m^2 and 65% (n=234) of patients had a BMI≥ 25 kg/m^2. The median BSA was 1.73 m^2 (1.51-1.94). 39% (n=141) of patients were ASA ≥3. 19% (n=69) patients had T2DM and 4% (n=15) a history of liver disease. The median follow-up was 79 (51-109) months (Table 11-1).

The median maximal cross-sectional liver area on axial CT slice was 178.7 cm^2 (163.7-198.4). The median total liver volume was 1509.1 cm^3 (857.8-3337.1). The relationship between maximal cross-sectional liver area (cm^2) and total liver volume (cm^3) is shown in Figure 11-1. The maximal cross-sectional liver area was found to strongly correlate with total liver volume in a randomly selected sample of 50 patients (R^2=0.749, Figure 11-1).

The median LMI was 66.8 cm^2/m^2 (62.0-71.6). The relationship LMI (tertiles) and age, sex, BMI, BSA, ASA, T2DM, liver disease and overall survival is shown in Table 11-2. On univariate analysis, LMI was significantly associated with age ($p<0.001$), BMI ($p<0.001$), BSA ($p<0.001$) and T2DM ($p<0.001$).

The relationship between LMI (lowest/middle vs. highest tertiles) and age, sex, BMI, BSA, ASA, and T2DM is shown in Table 11-3. On univariate analysis, LMI was significantly associated with age ($p<0.001$), sex ($p<0.05$), BMI ($p<0.001$), BSA ($p<0.001$), ASA ($p<0.05$) and T2DM ($p<0.001$). On multivariate analysis, age ($p<0.001$), sex ($p<0.05$), BMI ($p<0.001$) and T2DM ($p<0.05$) remained significantly associated with LMI (Table 11-3).

On univariate cox regression analysis, neither LMI (continuous) or LMI (tertiles) were significantly associated with overall survival (HR 1.00, 95%CI 0.98-1.01, p=0.582 and HR 0.90, 95%CI 0.74-1.09, p=0.290, respectively). Therefore, the results of survival analysis are not displayed in detail.

11.4 Discussion

The present study sought to investigate the utility of the maximal cross-sectional liver area, obtained by manual segmentation of a single axial CT slice, as a method for quantifying liver mass in patients with cancer. The present results show that there was a strong correlation between maximal cross-sectional liver area and total liver volume using the proposed methodology. Furthermore, show that the measurement of maximal cross-sectional liver area had excellent inter-rater reliability. Taken collectively, the observations support our hypothesis, that the maximal cross-sectional liver area is a reliable surrogate marker for the quantification of liver mass using CT and may readily facilitate the examination of the relationships with clinicopathological characteristics and clinical outcomes in patients with cancer.

Manual segmentation of the cross-sectional liver area on sequential CT images is still regarded by many as the gold-standard methodology for liver volumetry and the quantification of liver mass (263, 264). However, the absence of standardized methodology and time-consuming nature have limited the volume of studies examining liver mass in patients with cancer (129). The present results are of therefore of interest, reporting that a single measure obtained by manual segmentation of axial CT slices, obtained in less than five minutes using pre-existing software routinely available in clinical practice, was not only a reliable measure with excellent correlation of measurements between independent observers, but also had strong correlation with the total liver volume (Figure 11-1). Given that the median total liver volume observed in the present study was comparable with those reported by other contemporary studies of malignant and non-malignant disease, derived using manual segmentation of CT images (129, 264, 269, 270), as well as semi-automated measures (137, 271), the present methodology is likely to be reliable. Further study of other cohorts should readily confirm the present observations and external validity of this novel methodology.

On multivariate analysis, LMI was found to be significantly associated with age, male sex, BMI and T2DM in the present study. The present observations are therefore consistent with those of Vauthey and co-workers, who reported that

liver volume was correlated with body weight in study of 292 patients from four sites across North America and Europe, who underwent CT imaging for conditions unrelated to the hepatobiliary system and had no known hepatic abnormality (270). The results of the present study are also consistent with those of Harada and co-workers who reported that liver volume was negatively correlated with age, in a study of 374 patients who underwent abdominal CT imaging for a range of gastro-intestinal pathologies (272). Furthermore, like in the present study, Harada and co-workers also reported that male patients had significantly larger liver volumes compared with female patients (272). Lastly, the present observations are consistent with those of Martin and co-workers, who reported that T2DM was associated with MRI-derived liver volume in a study of 32,859 patients identified from a UK biobank (273). Taken collectively, the results suggest that the determinants of liver mass in patients with cancer are similar to those of patients without neoplasia.

In contrast to soft tissues such as muscle, the liver mass is largely considered to be preserved in cancer (274). However, compared to skeletal muscle and fat, there is a relative paucity of studies utilizing modern-day imaging techniques to examine the alterations to liver mass in patients with cancer. Moreover, the observations of studies utilizing CT-derived liver volumetry to examine the relationship between liver and skeletal muscle mass in patients with cancer have often been confounded by several factors including the administration of certain chemotherapy agents and the presence of primary/secondary tumours within the liver itself (265-267). As such, the present observations are informative, finding that the relationships between clinicopathological characteristics and liver mass is similar in patients with colonic cancer, who did not receive neo-adjuvant chemotherapy or have liver metastases. Whilst further study is required to validate the present observations, they provide a foundation from which CT-derived liver mass may be incorporated into future studies of cancer-associated wasting (37, 275).

The present study has a number of limitations. Firstly, this study was a single centre study, with a modest small sample size and therefore may be subject to sample bias. Secondly, whilst a 5mm slice thickness has been shown to be acceptable for CT-liver volumetry, a smaller slice thickness would reduce error

(130). Nevertheless, the present observations are comparable with those reported by other studies utilizing manual segmentation of CT images for liver volumetry (129, 264, 269, 270). Lastly, the absence of a fixed anatomical landmark for the quantification of liver mass, like those utilised in the measurement of soft tissues, is a limitation. Indeed, the correlation between the maximal cross-sectional liver area and total liver volume observed in the present study is not as strong as that reported by studies examining the correlation between a single slice area and multi-slice volumes of muscle/fat at L3 (276). However, the present study reports a strong correlation between the maximal cross-sectional liver area on a single axial CT slice and the total liver volume quantified using manual segmentation, considered the gold-standard methodology for liver volumetry (263). Therefore, this simple and reliable method may facilitate further study of liver mass in patients with cancer until automated, artificial intelligence-based software for CT-derived volumetry becomes validated and routinely available.

In conclusion, the simple, reliable method proposed in this study for quantifying liver mass using CT was found to have excellent correlation between observers and give results consistent with contemporary literature. This method may facilitate routine measurement of liver mass and allow examination of the relationships with skeletal muscle mass in patients with cancer.

11.5 Tables and Footnotes

Table 11-1: Clinicopathological characteristics of included patients (n=359)

Clinicopathological characteristic	n=
Age (<65/65-74/>74)	98/128/133
Sex (Female/Male)	177/182
BMI (<18.5/18.5-24.9/25-29.9/≥30 kg/m^2)	13/112/113/121
BSA (<1.51/1.51-1.94/>1.94 m^2)	119/120/120
ASA (1/2/≥3)	53/165/141
T2DM (No/Yes)	289/69
Liver Disease (No/Yes)	341/15
Median maximal cross-sectional liver area (cm^2)	178.7 (163.7-198.4)
Median LMI (cm^2/m^2)	66.8 (62.0-71.6)
Median total liver volume (cm^3)	1509.1 (857.8-3337.1)
Overall survival (Yes/No)	305/75

Table 11-2: The relationship LMI (tertiles) and age, sex, BMI, BSA, ASA, T2DM, liver disease and overall survival (n=359)

	LMI <61.9 cm^2/m^2 (n=119)	**LMI 61.9-71.6 cm^2/m^2 (n=120)**	**LMI >71.6 cm^2/m^2 (n=120)**	**p value**
Age (<65/65-74/>74)	25/36/58	30/44/46	43/48/29	<0.001
Sex (Female/Male)	61/58	67/53	71/49	0.106
BMI (<18.5/18.5-24.9/25-29.9 /≥30kg/m^2)	8/59/31/21	3/40/43/34	2/13/39/66	<0.001
BSA (<1.51/1.51-1.94 />1.94 m^2)	56/35/28	38/46/36	25/39/56	<0.001
ASA (1/2/≥3)	24/50/45	17/61/42	12/54/54	0.053
T2DM (No/Yes)	110/9	98/22	81/39	<0.001
Liver Disease (No/Yes)	115/4	116/4	113/7	0.347
Overall survival (Yes/No)	91/28	95/25	108/22	0.350

Table 11-3: The relationship between LMI (lowest/middle vs. highest tertiles) and age, sex, BMI, BSA, ASA and T2DM (n=359)

	Univariate OR (95% CI)	**p value**	**Multivariate OR (95% CI)**	**p value**
Age (<65/65-74/>74)	0.60 (0.45-0.79)	<0.001	0.53 (0.38-0.74)	<0.001
Sex (Female/Male)	1.67 (1.08-2.61)	0.023	2.10 (1.14-3.82)	0.017
BMI (<18.5/18.5-24.9/25-29.9 /≥30kg/m^2)	2.69 (2.00-3.61)	<0.001	3.04 (1.99-4.65)	<0.001
BSA (<1.51/1.51-1.94 />1.94 m^2)	1.81 (1.37-2.41)	<0.001	-	0.058
ASA (1/2/≥3)	1.40 (1.01-1.94)	0.043	-	0.058
T2DM (No/Yes)	3.34 (1.94-5.73)	<0.001	2.48 (1.33-4.62)	0.004

OR- Odds ratio, CI-Confidence interval

11.6 Figures and Legends

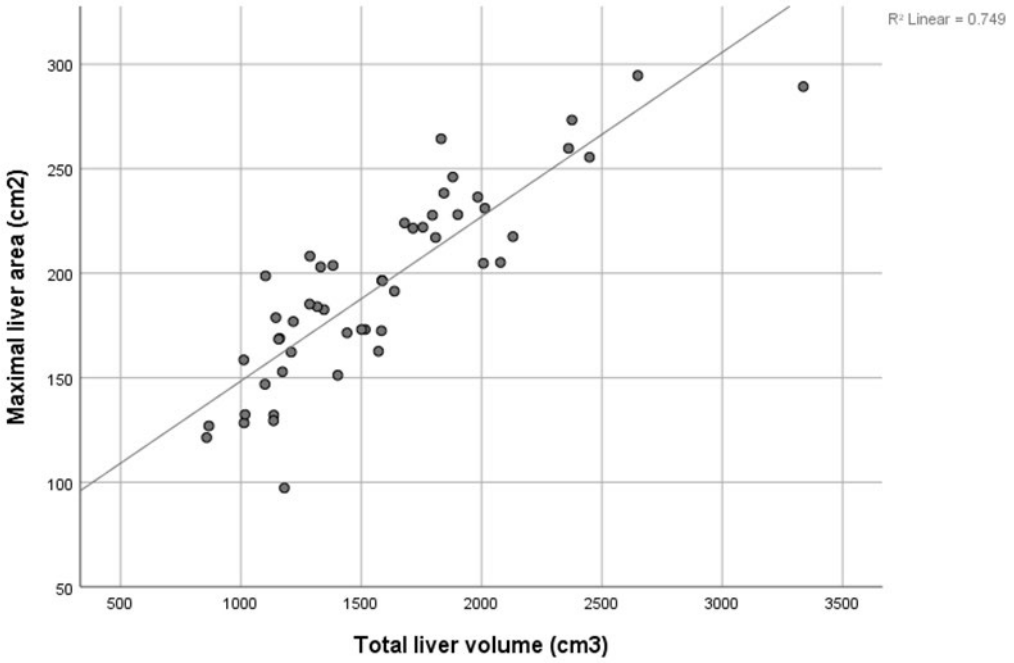


Figure 11-1: The relationship between maximal cross-sectional liver area (cm^2) and total liver volume (cm^3)

12 The relationship between CT-derived liver mass and CT-derived body composition, TNM stage, systemic inflammation and survival in patients undergoing potentially curative surgery for colonic cancer

12.1 Introduction

Cancer cachexia is a complex metabolic syndrome characterised by the loss of skeletal muscle mass (67). Thought to affect up to half of patients with advanced cancer, contemporary evidence suggests that cancer cachexia is responsible for up to 20% of cancer-related deaths (227). Furthermore, cancer cachexia has consistently been reported to be negatively associated with response to anti-cancer therapy and quality of life in patients in studies of with advanced cancer (179, 277).

Research examining the phenotypic changes in body composition that occur in patients with cancer cachexia has predominantly focused on the loss of skeletal muscle mass (53). However, cancer cachexia is considered a systemic phenomenon affecting the heart, liver, gastrointestinal tract and brain (114). Indeed, the liver is thought to be central to the phenotypic alterations in body composition experienced in cancer cachexia, inducing an acute-phase response in response to tumour-mediated inflammation, that drives proteolysis and the loss of skeletal muscle (278). Furthermore, to foster tumour growth and progression, the liver is actively co-opted to perform enhanced gluconeogenesis from the amino acids produced by skeletal muscle degradation. Consequently, there is a resulting increase in resting energy expenditure in patients with cancer cachexia, which may further contribute to loss of skeletal muscle mass (114, 275).

Despite the metabolic link between the two organs, only a handful of studies to date have examined this relationship at a systemic level, using CT-derived body composition to quantity liver and skeletal muscle mass (260). As such, the relationship between liver and skeletal muscle mass in patients with cancer remains unclear. Specifically, if the loss of skeletal muscle mass exhibited in

patients with cancer, and resultant protein flux, is associated with alterations in liver mass.

In this chapter, the relationship between CT-derived liver mass and CT-derived body composition measurements, TNM stage, systemic inflammation and overall survival in patients undergoing potentially curative surgery for colonic cancer was examined.

12.2 Methods

12.2.1 Patients

Consecutive patients who underwent elective, potentially curative, right or extended right hemicolectomies for colonic cancer, between 1st of March 2008 and 1st of April 2018, within NHS Greater Glasgow and Clyde, were identified from a prospectively maintained database. Patients who had TNM stage I-III disease and had recorded pre-operative height and weight, satisfactory CT imaging for body composition analysis, and pre-operative assessment of the systemic inflammatory within the preceding 3 months of surgery were assessed for inclusion. Exclusion criteria were as follows; patients who had undergone previous hepatic resections, patients who had neo-adjuvant chemotherapy and patients who had liver metastasis, given they are likely confounding factors to liver volume (137, 265-267).

Patients were operated on at Glasgow Royal Infirmary, a single tertiary referral teaching hospital. Prophylactic antibiotics were administered at the induction of anaesthesia. As per unit policy, subcutaneous low molecular weight heparin and pneumatic compression stockings were given to patients as venous thromboprophylaxis.

The primary outcome of interest was overall survival. All patients were followed up for a minimum of 3 years. Vital status was obtained from the included patients' electronic case records. The date of last recorded follow-up or last review of electronic case records was 1st December 2022, which acted as the censor date. The need for individual patient consent waived by due to the retrospective observational nature of the study.

12.2.2 Methods

Routine demographic details included age, sex and BMI. Age categories were grouped into <64, 65-74 and >74 years. BMI was categorized as <20, 20-24.9, 25-29.9 and ≥30 kg/m^2. Tumour site was identified from pre-operative CT imaging,

endoscopic and pathology reports. Tumours were staged using the fifth edition of the TNM classification, consistent with practice in the UK during the study period (157). Patient comorbidity was classified using ASA grading system, as described in Chapter 3. The MUST was used to determine the overall risk of malnutrition, as described in Chapter 3. Systemic inflammation was determined using the NLR and mGPS, calculated from pre-treatment venous blood samples, as described in Chapter 3. NLR values were grouped as <3/3-5/>5 and mGPS values as 0/1/2.

CT-derived body composition analysis was carried out as described in Chapter 3. A high SFI and VFA were defined using the threshold values of Ebadi and co-workers and Doyle and co-workers, respectively (124, 125). A low SMI was defined using the threshold values of Martin and co-workers (61) and Caan and co-workers (72). A low SMD was defined using the threshold values of Martin and co- workers (61) and Xiao and co-workers (11). The CT-SS was determined as described in Chapter 3.

CT-derived maximal cross-sectional liver area on axial CT-slice (cm^2), was calculated as described in Chapter 3. The median number of slices analysed to identify the CT-slice containing the maximal liver area was 7 (5-9). The maximal cross-sectional liver area was then normalized for $height^2$ to create the liver mass index (LMI).

12.2.3 Statistical Analysis

LMI values were categorized into tertiles and the relationship with age, sex, TNM stage, ASA, MUST risk, BMI, SFI, VFA, SMI, SMD, mGPS, NLR and overall survival were examined using the Chi square test for linear-by-linear association. Continuous variables were analysed using the Kruskal Wallis test.

Binary logistic regression of variables associated with LMI was performed. Variables that had a p value <0.1 at univariate analysis were included in multivariate binary logistic regression using a backward conditional model.

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 27.0 (SPSS Inc., Chicago, IL, USA).

12.3 Results

A total of 385 patients met the inclusion criteria. The clinicopathological characteristics of included patients are shown in Table 12-1. 51% (n=198) of patients were male and 73% (n=280) were aged 65 years or older. 16% (n=60) of patients had TNM stage I disease, 44% (n=170) had stage II and 40% (n=155) of patients had stage III disease. 40% (n=153) of patients were ASA grade ≥3. 20% (n=69) of patients were at risk of malnutrition (MUST risk medium-high). The median BMI of the cohort was 27 kg/m^2 and 65% (n=251) of patients had a BMI ≥25 kg/m^2. The median SFI was 79.5 cm^2/m^2 and 51% (n=198) of patients had a high SFI. The median VFA was 191.2 cm^2 and 75% (n=289) of patients had a high VFA. The median SMI was 44.5 cm^2/m^2 and 56% (n=217) of patients had a low SMI. The median SMD was 30.3 HU and 73% (n=281) of patients had a low SMD. 50% (n=191) of patients had an NLR≥3 and 35% (n=133) of patients had an mGPS≥1 (Table 12-1).

The median LMI was 66.7 cm^2/m^2 (58.7-75.6). The distribution of LMI values of included patients is shown in Figure 12-1. The relationship between LMI (tertiles) and age, sex, TNM stage, ASA, MUST risk, BMI, CT-derived body composition measurements, systemic inflammation and overall survival in patients undergoing potentially curative surgery for colonic cancer is shown in Table 12-2. On univariate analysis, LMI was significantly associated with age ($p<0.001$), ASA ($p<0.05$), MUST risk ($p<0.001$), BMI ($p<0.001$), median SFI ($p<0.001$), high SFI ($p<0.001$), median VFA ($p<0.001$), high VFA ($p<0.001$), median SMI ($p<0.001$) and low SMI ($p<0.001$).

The relationship between LMI (lowest/middle vs. highest tertiles) and age, sex, ASA, MUST risk, high SFI, high VFA and low SMI in patients undergoing potentially curative surgery for colonic cancer is shown in Table 12-3. On univariate analysis, high LMI was significantly associated with age ($p<0.05$), ASA ($p<0.05$), MUST risk ($p<0.05$), high SFI ($p<0.05$), high VFA ($p<0.001$) and low SMI ($p<0.001$). On multivariate analysis, age ($p<0.05$), sex ($p<0.05$), ASA ($p<0.05$), high VFA ($p<0.001$) and low SMI ($p<0.05$) remained significantly associated with a high LMI.

12.4 Discussion

To our knowledge, the present study is the first to examine the relationship between CT-derived liver mass and CT-derived body composition, TNM stage, systemic inflammation and survival in patients undergoing potentially curative surgery for colonic cancer. It was of interest that CT-derived liver mass was significantly associated with age, co-morbidity, malnutrition risk, BMI and CT-body composition measurements. Specifically, a higher LMI was associated with a higher SMI. Whilst liver mass is thought to be relatively preserved, on a background of skeletal muscle loss, as cancer progresses, the present results suggest that they may be closely associated in early-stage disease. Therefore, the present observations provide a foundation for future work examining the relationship between liver and skeletal muscle mass in patients with cancer.

In the present study, it was of interest that a higher CT-derived liver mass (LMI) was associated with a higher CT-derived skeletal muscle mass (SMI) in patients undergoing potentially curative surgery for colonic cancer. The results of the present study are in keeping with those of Lodewick and co-workers, who reported that a higher SMI was significantly associated with a higher liver mass (total liver volume), in a study of 80 patients undergoing pre-operative assessment for hepatic resection (260). Furthermore, with those of Dello and co-workers, who reported that a higher SMI was significantly associated with a higher liver mass (total liver volume) in a study of 40 patients undergoing partial hepatectomy for primary and secondary liver tumours (137). Whilst the studies differ in cancer type, disease stage and method used to quantify liver mass, taken collectively, the results suggest that liver and skeletal muscle mass are closely related in patients with cancer. However, further study across a range of tumour subtypes and disease stages is still required to determine the relationship between liver and skeletal muscle mass in patients with cancer.

In contrast to skeletal muscle mass, liver mass is largely considered to be preserved/increase with cancer progression (259). Lieffers and co-workers reported that liver mass increased, on a background of loss of skeletal muscle mass, as the patient neared death, in a longitudinal study of 34 patients with

advanced colorectal cancer (279). However, the observations may have been confounded by several factors including the administration of certain chemotherapy agents and burden of metastatic disease in the liver itself (265-267). Indeed, the authors reported that they were unable to differentiate between liver tissue and metastases in limitations of the study (279). With modern-imaging techniques facilitating the delineation of liver and tumour volume (137, 260), study of the relationship between CT-derived liver and skeletal muscle mass is now feasible in patients with advanced cancer, including those who have liver metastases. Longitudinal studies examining the relationship between CT-derived liver and skeletal muscle mass may help to determine if these change in opposite directions with cancer progression.

The present study has a number of limitations. Firstly, this study was a single centre study, with a modest small sample size and therefore may be subject to sample bias. Secondly, whilst the quantification of the total liver volume by manual segmentation of CT images is considered the gold-standard methodology for determining liver mass (263), the present study opted to use the maximal cross-sectional liver area of single axial CT slice as a surrogate measure of liver mass. Given this measure has been reported to be strongly correlated with the total liver volume in patients with primary operable colonic cancer (Chapter 11), it is unlikely to be a major confounding factor to the present analysis and future studies utilizing manual segmentation or semi-automated/ automated software to quantify total liver volume should readily confirm the present observations.

In conclusion, CT-derived liver mass was significantly associated with age, co-morbidity, malnutrition, BMI and CT-body composition measurements including SMI. The present results suggest that liver and skeletal muscle mass may be closely related in patients with early-stage disease, providing a foundation for future work examining their relationship in patients with cancer.

12.5 Tables and Footnotes

Table 12-1: Clinicopathological characteristics of included patients (n=385)

Clinicopathological characteristics	n=
Age (<65/65-74/>74)	105/137/143
Sex (Female/Male)	187/198
TNM stage (I/II/III)	60/170/155
ASA (1/2/≥3)	54/178/153
MUST risk (Low or Medium/High)[1]	281/69
BMI (<18.5/ 18.5-24.9 /25-29.9/≥30 kg/m^2)	14/120/128/123
Median LMI (cm^2/m^2)	66.7 (58.7-75.6)
Median SFI (cm^2/m^2)	79.5 (54.8-108.1)
High SFI (No/Yes)	187/198
Median VFA (cm^2)	191.2 (114.4-283.1)
High VFA (No/Yes)	96/289
Median SMI (cm^2/m^2)	44.5 (37.9-52.5)
Low SMI (No/Yes)	168/217
Median SMD (HU)	30.3 (24.1-36.6)
Low SMD (No/Yes)	104/281
NLR (<3/3-5/>5)	194/127/64
mGPS (0/1/2)	252/50/83
Overall Survival (Yes/No)	309/76

[1] 35 patients did not have MUST risk

Table 12-2: The relationship between LMI (tertiles) and age, sex, TNM stage, ASA, MUST risk, BMI, CT-derived body composition measurements, systemic inflammation and overall survival in patients undergoing potentially curative surgery for colonic cancer (n=385)

Clinicopathological Characteristic	**LMI <61.8** (cm^2/m^2, n=128)	**LMI 61.8-71.6** (cm^2/m^2, n=129)	**LMI >71.6** (cm^2/m^2, n=128)	**p value**
Age (<65/65-74/>74)	27/39/62	35/46/48	43/52/33	<0.001
Sex (Female/Male)	63/65	70/59	54/74	0.261
TNM stage (I/II/III)	19/58/51	21/57/51	20/55/53	0.929
ASA (1/2/≥3)	24/55/49	18/66/45	12/57/59	0.046
MUST risk (Low or Medium/ High)[1]	80/35	98/21	103/13	<0.001
BMI (<18.5/18.5-24.9/25-29.9/≥30 kg/m^2)	8/63/36/ 21	4/41/49/ 35	2/16/43/ 67	<0.001
Median SFI (cm^2/m^2)	62.9	82.0	94.5	<0.001
High SFI (No/Yes)	36/92	19/110	12/116	<0.001
Median VFA (cm^2)	140.9	177.0	247.4	<0.001
High VFA (No/Yes)	51/77	32/97	13/115	<0.001
Median SMI (cm^2/m^2)	40.4	43.5	49.7	<0.001
Low SMI (No/Yes)	36/92	32-97	13/115	<0.001
Median SMD (HU)	30.1	31.9	28.9	0.202
Low SMD (No/Yes)	30/98	38/91	36/96	0.399
NLR (<3/3-5/>5)	64/41/23	62/46/21	68/40/20	0.558
mGPS (0/1/2)	80/16/32	85/14/30	87/20/21	0.172
Overall Survival (Yes/No)	101/27	101/28	107/21	0.347

[1]35 patients did not have MUST risk

Table 12-3: The relationship between LMI (lowest/middle vs. highest tertiles) and age, sex, ASA, MUST risk, high SFI, high VFA and low SMI in patients undergoing potentially surgery for colonic cancer (n=385)

	Univariate OR (95% CI)	**p value**	**Multivariate OR (95% CI)**	**p value**
Age (<65/65-74/>74)	0.66 (0.50-0.86)	0.002	0.59 (0.42-0.83)	0.002
Sex (Female/Male)	1.47 (0.96-2.25)	0.078	1.73 (1.06-2.82)	0.028
ASA (1/2/≥3)	1.43 (1.04-1.97)	0.027	1.83 (1.25-2.67)	0.002
(Low or Medium/ High)	0.40 (0.21-0.77)	0.006	-	0.430
High SFI (No/Yes)	2.63 (1.35-5.12)	0.004	-	0.334
High VFA (No/Yes)	4.22 (2.25-7.93)	<0.001	4.04 (2.00-8.17)	<0.001
Low SMI (No/Yes)	0.44 (0.29-0.68)	<0.001	0.47 (0.29-0.78)	0.003

OR-Odds ratio, CI- Confidence interval

12.6 Figures and Legends

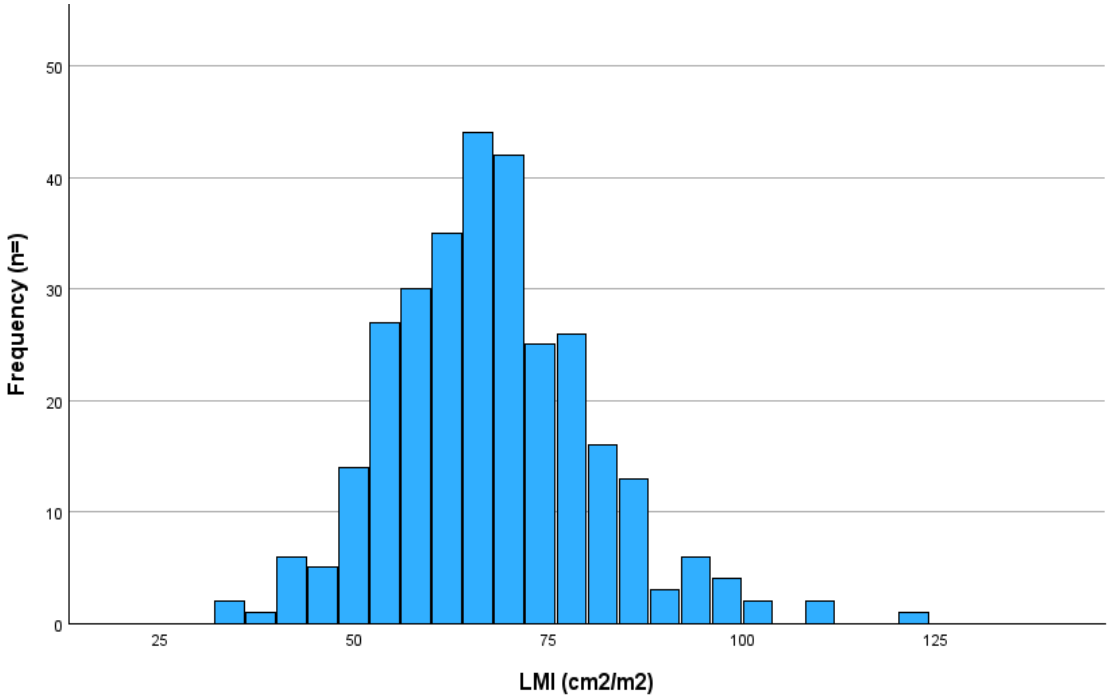


Figure 12-1: Distribution of LMI values of included patients (n=385)

13 Conclusions and Future Work

13.1 Conclusions

Whilst there is a significant volume of literature examining CT-derived skeletal muscle measurements in patients with cancer, the determinants and prevalence remain largely unknown. The results of Chapter 4 reported that a low SMI and a low SMD had a percentage prevalence of between 30-60% in the substantial cohort examined and that this was similar irrespective of threshold values used. Moreover, that a low SMI and SMD are endemic across a range of cancer subtypes and disease stages, challenging pre-existing beliefs surrounding the prevalence and determinants of CT-derived skeletal muscle measurements.

Chapters 5 and 6 examined the relationships between the CT-derived sarcopenia score (CT-SS), a score that combines SMI and SMD, and physical function, malnutrition, systemic inflammation and survival in patients with curative disease. The results of Chapter 5 reported that the CT-SS was significantly associated with malnutrition, systemic inflammation and poorer survival, irrespective of threshold values used to define a low SMI or SMD, in a large cohort of patients undergoing potentially curative surgery for colorectal cancer. Chapter 6 reported that CT-SS was associated with CPET performance, systemic inflammation and survival in a cohort of good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer. Taken collectively, the results of Chapters 5 and 6 suggest that the CT-SS may objectively characterize sarcopenia in patients with cancer and provide a measure by which it can be readily assessed in future studies. Further studies examining the relationship between the CT-SS and measures of physical function in patients with cancer are therefore warranted.

Whilst the results of Chapter 6 reported that the CT-SS was significantly associated with survival in good performance status (ECOG-PS 0/1) patients with oesophagogastric cancer, the CT-SS did not retain prognostic value when adjusted for mGPS. Similarly, the results of Chapter 7 reported that mGPS, but not CT-SS, was significantly associated with survival in good performance status (ECOG-PS 0/1) patients with advanced cancer. Taken collectively, the results suggest that

systemic inflammation may dominate the prognostic value of CT-derived skeletal muscle measurements in patients with cancer. Given that an association between the two variables has been reported in Chapters 5 through 7, determining if CT-derived skeletal muscle measure have independent prognostic value is of paramount importance to the utility of such measurements for prognostication in patients with cancer. Particularly as systemic inflammatory biomarkers are routinely available and readily quantified in clinical practice. Further study is therefore required to delineate the relationship between CT-derived skeletal muscle measurements, systemic inflammation and survival in patients with cancer.

Sarcopenia is considered a cause of frailty in older adults with cancer. However, the relationship between the CT-SS, frailty and clinical outcomes in patients with cancer is unclear. Specifically, if frailty is prognostic to clinical outcomes in patients with cancer, independent of CT-derived skeletal muscle measurements. Chapter 8 examined the prevalence and prognostic value of frailty screening tools in patients with colorectal cancer. This systematic review reported that frailty is not only prevalent in patients with colorectal cancer, but also has prognostic value to both short- and long-term clinical outcomes, across a range of frailty screening measures/tools. The results are confirmed in Chapter 9, that reported frailty was both prevalent and associated with short-term clinical outcomes in patients undergoing potentially curative surgery for colorectal cancer. Moreover, the results reported that whilst associated with CT-derived skeletal muscle measures, frailty remained independently associated with short-term clinical outcomes (post-operative complications) when adjusted for such measures. Therefore, the present results support the hypothesis that sarcopenia (low muscle mass and loss of function) is a cause of frailty in patients with cancer. Furthermore, suggest that the CT-SS may be a useful adjunct to frailty screening measures in patients with cancer, such as the Fried frailty phenotype, that includes low muscle strength as a diagnostic criterion.

Cancer cachexia is a complex metabolic syndrome associated with dysregulated glucose metabolism and the loss of skeletal muscle mass. However, the relationship between biomarkers of dysregulated metabolism, such as LDH, and low skeletal muscle mass, the defining feature of cancer cachexia, is unclear. Chapter 10 reported that an elevated LDH was significantly associated with

performance status, systemic inflammation and survival in patients with advanced cancer. However, also reported that there was no significant association between an elevated LDH and a low SMI. Whilst the present results do not suggest an association, further study is required to determine whether the loss of skeletal muscle mass is associated with dysregulated glucose metabolism in patients with cancer. Nevertheless, the present results suggest that an elevated LDH may be a useful additional aetiologic criterion in the GLIM diagnostic framework. Moreover, that LDH may provide a rationale therapeutic target in the treatment of cachexia in patients with advanced cancer.

Whilst skeletal muscle mass is considered to reduce with cancer progression, liver mass is thought to be preserved/ increase. CT-derived liver volumetry is considered a reliable, but time-consuming, method for the quantification of liver mass in patients with cancer. We hypothesized that the maximal cross-sectional liver area on an axial CT slice, derived using manual segmentation, may be an easily quantified surrogate measure of liver mass, analogous to how skeletal muscle mass is quantified using CT. Chapter 11 reported that the maximal cross-sectional liver area was strongly correlated with the total liver volume in patients undergoing potentially curative surgery for colonic cancer, suggesting that it was a reliable method for the quantification of liver mass using CT. Moreover, the results of Chapter 11 reported that CT-derived liver mass was significantly associated with age, sex, BMI and co-morbidity, suggesting that the determinants of liver mass are similar in patients with and without cancer. Chapter 12 reported that CT-derived liver mass was significantly associated with CT-derived SMI, suggesting that a higher SMI is associated with a higher liver mass in patients with early-stage disease. Therefore, the results are informative and provide a foundation for future work examining the relationship between skeletal muscle and liver mass in patients with cancer.

13.2 Future Work

The present work has highlighted several important issues to the utility of CT-derived muscle measurements in patients with cancer. These include:

- Whilst current threshold values for SMI and SMD have been adjusted for sex and BMI, the importance of adjusting for other determinants remains unclear. The present work suggests that age is a robust determinant of CT-derived body composition in patients with cancer. Therefore, establishing threshold values for low SMI and SMD that are adjusted for age would appear of imperative importance to differentiate between the physiological and pathological losses of skeletal muscle mass in older adults with cancer.

- In keeping with contemporary studies, the results of the present work suggest that whilst closely associated with a low SMI and SMD, systemic inflammation is likely to dominate the prognostic value of such measures. Given that systemic inflammation is a hallmark of cancer, and systemic inflammatory biomarkers are routinely recorded in current clinical practice, independent prognostic value would be the minimum pre-requisite to the inclusion of CT-derived skeletal muscle measure in clinical cancer care. Therefore, further study examining if CT-derived skeletal muscle measurements have prognostic value in patients with cancer, independent of systemic inflammatory status, is required.

- The present work suggests that the CT-SS provides an objective measure of sarcopenia, with studies reporting an association with measures of physical function (ECOG-PS and CPET) in patients with primary operable disease. Further examination of the relationship between the CT-SS and other measures of muscle strength, such as HGS, in patients with primary operable and advanced inoperable cancer, would be of interest.

- The present work confirms the association between CT-derived skeletal muscle measurements and frailty in older adults with cancer. Further examination of the relationship between CT-SS, an objective measure of sarcopenia, and other frailty screening measures in patients with cancer would be of interest given sarcopenia is considered a cause of frailty. Specifically, the Fried frailty phenotype which includes reduced muscle strength, thought to be captured by the CT-SS, as a diagnostic criterion.

- The present work reports that an elevated LDH was associated with systemic inflammation and survival in patients with advanced cancer. However, that there was no association with the phenotypic diagnostic criterion of the GLIM framework. Further study examining the utility an elevated LDH as an additional aetiologic criterion in the GLIM diagnostic framework would be of interest given that cancer cachexia is considered a metabolic syndrome associated with dysregulated glucose metabolism.

- The present work questions the importance that tumour burden has to the loss of skeletal muscle mass, with a similar prevalence of low SMI reported across a range of disease stages. However, the importance that tumour metabolism has to a low SMI is unclear. Therefore, further studies examining the relationship between objective biomarkers of the metabolic activity of the tumour, such as those derived from Positron Emission Tomography and a low SMI would be of interest.

- The present work utilized manual segmentation of CT images for the quantification of skeletal muscle and liver mass. However, the emergence of new artificial intelligence techniques such as deep learning has meant that rapid and reliable automated CT-body composition analysis is now feasible. Such advances will lead to large cohorts of patients in which the relationships and

prognostic value of CT-derived body composition measurements can be examined. Moreover, may facilitate the transition of CT-body composition analysis from a research tool to clinical practice.

- To date, it has been hypothesised that cancer progression is associated with a relative increase in liver mass on a background of skeletal muscle mass loss. The present work further adds to our understanding of this relationship reporting that liver and skeletal muscle mass are closely associated in patients with early-stage disease. Further longitudinal studies examining the relationship between liver mass, derived using the proposed methodology, and skeletal muscle mass in patients with cancer, across a range of tumour subtypes and disease stages, would be of interest.

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Appendices

Appendix A: Studies reporting CT-derived SMI

Study	Design	Country	Patient (n=)	SMI Threshold	Patients with low SMI n=/ (%)
Curative Colorectal cancer					
Aro et al (2020)	RCS	Finland	348	Martin	208 (59)
Dolan et al (2019)	RCS	UK	650	Martin	283 (44)
Okabe et al (2020)	RCS	Japan	193	Martin	121 (623)
Pędziwiatr et al (2016)	RCS	Poland	124	Martin	34 (27)
Schaffler et al (2020)	RCS	Austria	85	Martin	26 (30)
Souwer et al (2020)	Prospective	Netherlands	174	Martin	143 (82)
Sueda et al (2018)	RCS	Japan	211	Martin	105 (50)
van Roekel et al (2017)	RCS	Netherlands	104	Martin	29 (32)
Van Vugt et al (2017)	RCS	Netherlands	816	Martin	411 (50)
		Total patients (n=)	**2, 705**	**Median (IQR) (%)**	**50 (32-60)**
Choi et al (2018)	RCS	Korea	188	Prado	74 (39)
Han et al (2020)	RCS	Korea	1, 384	Prado	944 (68)
Malietzis et al (2016)	RCS	UK	805	Prado	485 (60)
Nakanishi et al (2017)	RCS	Japan	494	Prado	296 (60)

Reisinger et al (2015)	RCS	Netherlands	310	Prado	148 (48)
Wang et al (2020)	RCS	China	400	Prado	164 (41)
		Total patients (n=)	**3, 581**	**Median (IQR) (%)**	**54 (43-60)**
Huang et al (2015)	Prospective	China	142	Other	17 (12)
Hopkins et al (2019)	RCS	Canada	968	Other	266 (28)
Feliciano et al (2017)	RCS	USA	2, 470	Other	1136 (46)
Miyamoto et al (2015)	RCS	Japan	220	Other	55 (25)
Mosk et al (2018)	RCS	Netherlands	251	Other	61 (24)
Park et al (2018)	RCS	Korea	65	Other	25 (39)
Shirdel et al (2020)	RCS	Sweden	728	Other	241 (33)
Zhang et al (2020)	RCS	China	1, 058	Other	272 (26)
		Total patients (n=)	**5, 902**	**Median (IQR) (%)**	**27 (25-35)**
Non-curative Colorectal cancer					
Blauwhoff-Buskermolen et al (2016)	Prospective	Netherlands	67	Martin	38 (57)
Charette et al (2019)	RCS	Belgium	217	Martin	163 (75)
Chemama et al (2016)	RCS	France	97	Martin	58 (60)

da Cunha et al (2019)	RCS	Brazil	72	Martin	32 (44)
Kurk et al (2019)	RCS	Netherlands	333	Martin	171 (51)
Liu et al (2020)	RCS	Taiwan	182	Martin	85 (47)
		Total patients (n=)	**968**	**Median (IQR) (%)**	**54 (48-59)**
Agalar et al (2020)	Prospective	Turkey	65	Prado	20 (31)
Barret et al (2014)	Prospective	France	51	Prado	36 (71)
Eriksson et al (2017)	RCS	Sweden	97	Prado	63 (65)
Lieffers et al (2012)	RCS	Canada	234	Prado	91 (39)
Thoresen et al (2013)	Prospective	Norway	71	Prado	28 (40)
van Vugt et al (2015)	RCS	Netherlands	206	Prado	90 (44)
Vashi et al (2019)	RCS	USA	112	Prado	58 (52)
		Total patients (n=)	**968**	**Median (IQR) (%)**	**44 (39-59)**
Gökyer et al (2019)	RCS	Turkey	36	Other	23 (64)
Kobayashi et al (2017)	RCS	Japan	124	Other	24 (19)
Lodewick et al (2015)	RCS	Netherlands	171	Other	80 (47)
		Total patients (n=)	**331**	**Median (IQR) (%)**	**47 (33-55)**
Curative Oesophageal cancer					

Gabiatti et al (2019)	RCS	Brazil	123	Martin	57 (46)
Panje et al (2019)	RCS	Switzerland	61	Martin	31 (51)
		Total patients (n=)	**184**	**Median (IQR) (%)**	49 (47-50)
Anandavadivelan et al (2016)	RCS	Sweden	72	Prado	31 (43)
Elliot et al (2017)	RCS	Ireland	252	Prado	40 (16)
Grotenhuis et al (2016)	RCS	Netherlands	120	Prado	54 (45)
Oguma et al (2019)	RCS	Japan	194	Prado	28 (14)
Sato et al (2018)	RCS	Japan	48	Prado	34 (71)
Siegal et al (2018)	RCS	USA	173	Prado	127 (73)
Tan et al (2015)	RCS	UK	89	Prado	44 (49)
Xu et al (2019)	RCS	China	141	Prado	73 (52)
Yip et al (2014)	RCS	UK	35	Prado	9 (26)
Yoon et al (2020)	RCS	Korea	248 (Males only)	Prado	156 (63)
		Total patients (n=)	**1, 372**	**Median (IQR) (%)**	**47 (30-60)**
Benadon et al (2020)	RCS	France	104	Other	84 (81)
Harada et al (2015)	RCS	Japan	325	Other	107 (33)
Ozawa et al (2019)	RCS	Japan	82	Other	23 (28)
Paireder et al (2017)	RCS	Austria	130	Other	50 (38)

Saeki et al (2018)	RCS	Japan	157	Other	85 (54)
Tamandl et al (2016)	RCS	Austria	200	Other	130 (65)
		Total patients (n=)	**998**	**Median (IQR) (%)**	46 (34-62)
Non-curative Oesophageal cancer					
Dijksterhuis et al (2019)	RCS	Netherlands	88	Martin	43 (49)
		Total patients (n=)	**N/a**	**Median (IQR) (%)**	**N/a**
Mallet et al (2020)	RCS	France	97	Prado	54 (56)
Onishi et al (2019)	RCS	Japan	176	Prado	101 (57)
		Total patients (n=)	**273**	**Median (IQR) (%)**	**N/a**
Jarvinen et al (2018)	RCS	Finland	234	Other	199 (85)
Ma et al (2019)	RCS	Korea	198	Other	150 (76)
Nakashima et al (2018)	RCS	Japan	341	Other	170 (50)
Srpcic et al (2020)	RCS	Slovenia	139	Other	23 (17)
Sugawara et al (2020)	RCS	Japan	378	Other	186 (49)
		Total patients (n=)	**1, 290**	**Median (IQR) (%)**	**50 (49-76)**
Curative Gastric cancer					

Koch et al (2019)	RCS	Germany	83	Martin	30 (36)
Kudou et al (2017)	RCS	Japan	148	Martin	62 (42)
Nishigori et al (2018)	RCS	Japan	177	Martin	76 (43)
Palmela et al (2017)	RCS	Portugal	48	Martin	11 (23)
		Total patients (n=)	**456**	**Median (IQR) (%)**	**39 (33-42)**
Choi et al (2018)	RCS	Korea	98	Prado	39 (36)
O'Brien et al (2018)	RCS	Ireland	56	Prado	20 (35)
		Total patients (n=)	**154**	**Median (IQR) (%)**	**N/a**
Huang et al (2016)	Prospective	China	470	Other	47 (10)
Li et al (2019)	RCS	China	152	Other	45 (30)
Lou et al (2017)	Prospective	China	206	Other	14 (7)
Wang et al (2016)	Prospective	China	255	Other	32 (13)
Zhang et al (2018)	Prospective	China	156	Other	24 (15)
Zheng et al (2018)	RCS	China	532	Other	91 (17)
Zhou et al (2017)	Prospective	Japan	240	Other	69 (29)
Zhuang et al (2016)	RCS	China	937	Other	389 (42)
		Total patients (n=)	**2, 948**	**Median (IQR) (%)**	**16 (12-29)**
Non-curative Gastric cancer					

Hayashi et al (2016)	RCS	Japan	53	Martin	37 (70)
Kudou et al (2019)	RCS	Japan	86	Martin	26 (30)
Tegels et al (2015)	RCS	Netherlands	152	Martin	86 (58)
		Total patients (n=)	**291**	**Median (IQR) (%)**	**58 (44-64)**
Beuran et al (2018)	RCS	Romania	78	Prado	56 (72)
Sierzega et al (2019)	Prospective	Poland	138	Prado	60 (44)
		Total patients (n=)	**216**	**Median (IQR) (%)**	**N/a**
Lee et al (2018)	RCS	Korea	140	Other	67 (48)
Sakurai et al (2017)	RCS	Japan	569	Other	142 (25)
		Total patients (n=)	**709**	**Median (IQR) (%)**	**N/a**
Curative Hepatobiliary cancer studies					
Kamachi et al (2015)	RCS	Japan	92	Prado	61 (66)
Levogler et al (2015)	RCS	Netherlands	90	Prado	52 (58)
Voron et al (2015)	RCS	France	109	Prado	59 (54)
		Total patients (n=)	**291**	**Median (IQR) (%)**	**58 (56-62)**

Harimoto et al (2013)	RCS	Japan	186	Other	75 (40)
Itoh et al (2014)	RCS	Japan	190	Other	77 (41)
Yabusaki et al (2016)	RCS	Japan	195	Other	89 (46)
Takagi et al (2016)	RCS	Japan	254	Other	118 (47)
van Rijssen et al (2017)	RCS	Netherlands	166	Other	130 (78)
Shiba et al (2018)	RCS	Japan	68	Other	22 (32)
		Total patients (n=)	**1, 059**	**Median (IQR) (%)**	**43 (40-46)**
Non-curative Hepatobiliary cancer					
Antonelli et al (2018)	RCS	Italy	96	Martin	47 (49)
Meza-Junco et al (2013)	RCS	USA	116	Martin	35 (30)
		Total patients (n=)	**212**	**Median (IQR) (%)**	**N/a**
Parsons et al (2012)	RCS	USA	48	Prado	20 (42)
		Total patients (n=)	**N/a**	**Median (IQR) (%)**	**N/a**
Dello et al (2013)	RCS	Netherlands	40	Other	27 (68)
Endo et al (2020)	RCS	Japan	63	Other	22 (35)
Fujiwara et al (2015)	RCS	Japan	1, 257	Other	139 (11)
Ha et al (2018)	RCS	Korea	178	Other	62 (35)

Hamaguchi et al (2019)	RCS	Japan	606	Other	84 (14)
Iritani et al (2015)	RCS	Japan	217	Other	24 (11)
Kobayashi et al (2018)	RCS	Japan	102	Other	31 (30)
Kobayashi et al (2019)	RCS	Japan	465	Other	62 (13)
Lanza et al (2020)	RCS	Italy	142	Other	121 (85)
Lee et al (2019)	RCS	Korea	156	Other	99 (64)
Mardian et al (2019)	RCS	Indonesia	100	Other	31 (31)
Okumura et al (2017)	RCS	Japan	109	Other	69 (63)
Uojima et al (2020)	RCS	Japan	100	Other	59 (59)
Wu et al (2020)	RCS	Taiwan	120 (Male only)	Other	18 (15)
		Total patients (n=)	**3, 499**	**Median (IQR) (%)**	**33 (14-62)**
Curative Pancreatic cancer					
Griffin et al (2019)	RCS	Ireland	78	Martin	39 (50)
Linder et al (2019)	RCS	Germany	139	Martin	35 (25)
Nishida et al (2016)	RCS	Japan	266	Martin	132 (50)
Sandini et al (2016)	RCS	Italy	124	Martin	20 (24)
		Total patients (n=)	**607**	**Median (IQR) (%)**	**37 (25-50)**

El Amrani et al (2018)	RCS	USA	107	Prado	50 (47)
		Total patients (n=)	**N/a**	**Median (IQR) (%)**	**N/a**
Cho et al (2020)	RCS	Korea	299	Other	29 (10)
Choi et al (2015)	RCS	Korea	484	Other	103 (21)
Cooper et al (2015)	RCS	USA	89	Other	46 (52)
Okumura et al (2017)	RCS	Japan	301	Other	120 (40)
Stretch et al (2018)	RCS	Canada	123	Other	50 (41)
Sugimoto et al (2018)	RCS	USA	323	Other	80 (25)
Sui et al (2018)	RCS	Japan	354	Other	87 (25)
		Total patients (n=)	**1, 973**	**Median (IQR) (%)**	**25 (23-40)**
Non-curative Pancreatic cancer					
Basile et al (2019)	RCS	Italy	94	Martin	69 (73)
Rollins et al (2016)	RCS	UK	228	Martin	138 (61)
		Total patients (n=)	**322**	**Median (IQR) (%)**	**N/a**
Dalal et al (2012)	RCS	USA	41	Prado	26 (63)
Facciorusso et al (2020)	RCS	Italy	215	Prado	139 (64)
Gruber et al (2019)	RCS	Austria	133	Prado	78 (59)

Naumann et al (2019)	RCS	Germany	147	Prado	99 (67)
Pecorelli et al (2016)	RCS	Italy	202	Prado	132 (65)
Tan et al (2009)	RCS	USA	111	Prado	62 (56)
		Total patients (n=)	**849**	**Median (IQR) (%)**	**64 (60-65)**
Choi et al (2015)	RCS	Korea	484	Other	103 (21)
Ninomiya et al (2017)	RCS	Japan	265	Other	170 (64)
Kurita et al (2019)	RCS	Japan	82	Other	42 (51)
		Total patients (n=)	**831**	**Median (IQR) (%)**	**51 (36-58)**
Curative Breast cancer					
Deluche et al (2018)	RCS	France	119	Martin	58 (49)
Weinberg et al (2017)	RCS	USA	241	Martin	72 (34)
		Total patients (n=)	**360**	**Median (IQR) (%)**	**N/a**
Aleixo et al (2020)	RCS	USA	338	Prado	58 (17)
Del Fabbro et al (2012)	RCS	USA	129	Prado	18 (14)
Mazzuca et al (2018)	RCS	Italy	21	Prado	8 (38)
Omarini et al (2019)	RCS	Italy	407	Prado	48 (12)
		Total patients (n=)	**895**	**Median (IQR) (%)**	**16 (14-22)**

Caan et al (2018)	RCS	USA	3, 241	Other	1, 086 (34)
Ueno et al (2020)	RCS	Japan	82	Other	10 (12)
		Total patients (n=)	**3, 323**	**Median (IQR) (%)**	**N/a**
Non-curative Breast cancer					
Rier et al (2017)	RCS	Netherlands	166	Martin	111 (67)
		Total patients (n=)	**N/a**	**Median (IQR) (%)**	**N/a**
Prado et al (2009)	RCS	Canada	55	Prado	14 (26)
		Total patients (n=)	**N/a**	**Median (IQR) (%)**	**N/a**
Franzoi et al (2020)	RCS	Belgium	50	Other	20 (40)
Shachar et al (2017)	RCS	USA	40	Other	23 (58)
		Total patients (n=)	**90**	**Median (IQR) (%)**	**N/a**
Curative Lung cancer					
Kim et al (2016)	RCS	Korea	186	Other	128 (69)
Martini et al (2020)	RCS	France	234	Other	78 (33)
Suzuki et al (2016)	RCS	Japan	90	Other	38 (42)
		Total patients (n=)	**510**	**Median (IQR) (%)**	**42 (38-56)**
Non-curative Lung cancer					

Cortellini et al (2018)	RCS	Italy	81	Martin	28 (35)
Cortellini et al (2019)	RCS	Italy	23	Martin	14 (61)
		Total patients (n=)	**104**	**Median (IQR) (%)**	**N/a**
Srdic et al (2017)	Prospective	Croatia	100	Prado	47 (47)
Stene et al (2014)	RCS	Norway	35	Prado	26 (74)
		Total patients (n=)	**135**	**Median (IQR) (%)**	**N/a**
Sjøblom et al (2016)	RCT	Norway (Males only)	734	Other	213 (51)
Takada et al (2020)	RCS	Japan	103	Other	51 (50)
		Total patients (n=)	**837**	**Median (IQR) (%)**	**N/a**

IQR- Interquartile range, RCS- Retrospective cohort study, RCT-Randomized controlled trial

Appendix B: Studies reporting CT-derived SMD

Study	**Design**	**Country**	**Patient (n=)**	**SMD Threshold**	**Patients with low SMD (n=/%)**
Curative Colorectal cancer					
Aro et al (2020)	RCS	Finland	348	Martin	108 (31)
Pędziwiatr et al (2016)	RCS	Poland	124	Martin	48 (39)
Souwer et al (2020)	Prospective	Netherlands	174	Martin	152 (87)
Sueda et al (2018)	RCS	Japan	211	Martin	110 (52)
Van Vugt et al (2017)	RCS	Netherlands	816	Martin	523 (64)
Dolan et al (2019)	RCS	UK	650	Other	341 (53)
Hopkins et al (2019)	RCS	Canada	968	Other	537 (54)
Kroenke et al (2018)	RCS	USA	3262	Other	966 (30)
van Baar et al (2018)	RCS	Netherlands	715	Other	196 (27)
		Total patients (n=)	**7, 268**	**Median (IQR) (%)**	**52 (31-54)**
Non-curative Colorectal cancer					
Blauwhoff-Buskermolen et al (2016)	Prospective	Netherlands	67	Martin	43 (64)
Charette et al (2019)	RCS	Belgium	217	Martin	42 (19)

da Cunha et al (2019)	RCS	Brazil	72	Martin	51 (71)
Margadant et al (2016)	RCS	Netherlands	373	Other	92 (25)
		Total patients (n=)	**729**	**Median (IQR) (%)**	**45 (24-66)**
Curative Oesophageal cancer					
Gabiatti et al (2019)	RCS	Brazil	123	Martin	72 (59)
		Total patients (n=)	**N/a**	**Median (IQR) (%)**	**N/a**
Non-curative Oesophageal cancer					
Dijksterhuis et al (2019)	RCS	Netherlands	88	Martin	44 (50)
		Total patients (n=)	**N/a**	**Median (IQR) (%)**	**N/a**
Curative Gastric cancer studies					
Zhang et al (2018)	Prospective	China	156	Other	131 (84)
		Total patients (n=)	**N/a**	**Median (IQR) (%)**	**N/a**
Non-curative Gastric cancer					
Hayashi et al (2016)	RCS	Japan	53	Martin	31 (59)

		Total patients (n=)	**N/a**	**Median (IQR) (%)**	**N/a**
Curative Hepatobiliary cancer					
van Rijssen et al (2017)	RCS	Netherlands	166	Other	81 (49)
		Total patients (n=)	**N/a**	**Median (IQR) (%)**	**N/a**
Non-curative Hepatobiliary cancer					
Fujiwara et al (2015)	RCS	Japan	1, 257	Other	1069 (85)
Mardian et al (2019)	RCS	Indonesia	100	Other	65 (65)
Okumura et al (2017)	RCS	Japan	109	Other	53 (49)
		Total patients (n=)	**1, 466**	**Median (IQR) (%)**	**65 (57-75)**
Curative Pancreatic cancer					
Griffin et al (2019)	RCS	Ireland	78	Martin	40 (51)
Linder et al (2019)	RCS	Germany	139	Martin	36 (26)
Choi et al (2018)	RCS	Korea	484	Other	60 (33)
Okumura et al (2017)	RCS	Japan	301	Other	144 (48)
Stretch et al (2018)	RCS	Canada	123	Other	31 (25)

Van Dijk et al (2017)	RCS	Netherlands	186	Other	62 (33)
		Total patients (n=)	**1, 311**	**Median (IQR) (%)**	33 (28-44)
Non-curative Pancreatic cancer					
Rollins et al (2016)	RCS	UK	228	Martin	126 (55)
		Total patients (n=)	**N/a**	**Median (IQR) (%)**	**N/a**
Curative Breast cancer					
Aleixo et al (2020)	RCS	USA	338	Martin	178 (53)
Weinberg et al (2017)	RCS	USA	241	Martin	72 (34)
Caan et al (2018)	RCS	USA	3, 241	Other	1193 (37)
		Total patients (n=)	**3, 820**	**Median (IQR) (%)**	**37 (36-45)**
Non-curative Breast cancer					
Rier et al (2017)	RCS	Netherlands	166	Martin	99 (60)
Franzoi et al (2020)	RCS	Belgium	50	Other	43 (86)
		Total patients (n=)	**211**	**Median (IQR) (%)**	**N/a**
Non-curative Lung cancer					

Cortellini et al (2018)	RCS	Italy	81	Martin	23 (28)
Sjøblom et al (2016)	RCT	Norway	734 (Males only)	Other	74 (10)
		Total patients (n=)	**815**	**Median (IQR) (%)**	**N/a**

IQR- Interquartile range, RCS- Retrospective cohort study, RCT-Randomized controlled trial

Appendix C: The relationship between clinicopathological variables, MUST risk, BMI, CT-derived body composition measurements, systemic inflammation, mFI-5 frailty score and the incidence of post-operative complications in patients younger than 65 years of age, undergoing potentially curative surgery for colorectal cancer (n=345)

	Univariate OR (95% CI)	**p value**	**Multivariate OR (95% CI)**	**p value**
Sex (Female/Male)	1.13 (0.73-1.76)	0.587	-	-
Tumour Site (Colon/Rectum)	1.39 (0.89-2.17)	0.142	-	-
Neo-adjuvant chemotherapy (No/Yes)	1.18 (0.68-2.06)	0.562	-	-
MUST Risk (Low/ Medium/ High risk)	1.62 (1.08-2.44)	0.021	1.61 (1.07-2.43)	0.023
BMI (<20/20-24.9/25-29.9/≥30 kg/m^2)	1.05 (0.82-1.34)	0.714	-	-
High SFI (No/Yes)	1.09 (0.62-1.90)	0.767	-	-
High VFA (No/Yes)	1.09 (0.68-1.77)	0.717	-	-
Low SMI (No/Yes)	1.10 (0.70-1.73)	0.686	-	-
Low SMD (No/Yes)	0.99 (0.64-1.55)	0.979	-	-
SIG (0/1/2/≥3)	1.22 (1.01-1.48)	0.040	-	0.142
mFI-5 Score (0/1/≥2)	1.41 (1.06-1.88)	0.019	1.43 (1.07-1.91)	0.017

OR- Odds ratio, CI- Confidence interval