UTILITY OF BODY COMPOSITION SOFTWARE IN IDENTIFYING SARCOPENIA, AND THE SIGNIFICANCE OF SARCOPENIA IN PATIENTS WITH UPPER GASTROINTESTINAL MALIGNANCY

Enoch Yee Lok Wong

MBBS BMedSci FRACS

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ABSTRACT

Introduction

Sarcopenia is the age-related progressive loss of skeletal muscle mass, function and quality, and has been shown to have adverse effects on morbidity and mortality. Its importance has become increasingly recognised in the surgical population where its detection and recognition has historically been low. This project aims to investigate the use of body composition software in a population of patients undergoing surgical resection for upper gastrointestinal (UGI) malignancy and develop a protocol to identify sarcopenia. The prevalence of sarcopenia in this group and its impact on surgical outcomes will be examined.

Methods

All patients undergoing major UGI surgical resection (oesophagectomy, gastrectomy) for malignant disease at a single institution over a consecutive 6-year period (2013-2018) were examined. Demographic details and surgical outcomes including complications and survival were recorded. The preoperative CT scans of these patients were obtained and a protocol developed to assess the amount of skeletal muscle in these patients using a validated body composition software. The subsequent impacts of low skeletal muscle mass (sarcopenia) on outcomes were analysed.

Results

A total of 93 patients were analysed and preoperative CT scans (in digital/PACS format) were available for 77 of these patients. A robust, repeatable and accurate protocol was developed for assessing the skeletal muscle mass and muscle quality through the use of the body composition software. This protocol demonstrated a correlation coefficient of 0.9968 for repeated assessment of skeletal muscle mass. The use of this protocol in the cohort demonstrated a sarcopenia prevalence of approximately 46.7% based on the skeletal muscle index (SMI) and 33.8% based on muscle quality. Sarcopenia based on SMI was associated with shorter overall survival (OS) (5-year OS 37% vs 52% for sarcopenic vs non sarcopenic, p-value = 0.0485) but not associated with five-year disease-free survival (in the group in whom we had five-year data) or the overall complication rate (for the whole cohort). The difference in survival between the two groups seemed to relate to greater mortality within the first 12 months after surgery. No such associations were seen for sarcopenia when the diagnosis was based on muscle quality.

Discussion

A robust protocol has been designed to measure the skeletal muscle mass and muscle quality using body composition software. This protocol could potentially be used in a variety of settings. These results reinforce the effectiveness and utility of previously established standardised cut-offs for sarcopenia using body composition. A sarcopenia prevalence of 46.7% in this cohort of UGI surgical patients is significant as it represents a substantial but previously unrecognised subgroup who are at higher risk of poor outcomes. In this cohort, sarcopenia was associated with a decrease in 5-year OS. This protocol can easily be combined with other indices of sarcopenia, aiming to identify sarcopenic patients and then hopefully deliver effective interventions in order to improve their outcomes.

DECLARATION

This thesis is an original work of my research and contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature:

Print Name: Enoch Yee Lok Wong

Date: 03 January 2022

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KEY TERMS

Sarcopenia

Body composition

Tissue segmentation

Upper gastrointestinal - UGI

Gastric

Oesophagus

Malignancy

Computed tomography - CT

Skeletal muscle mass - SMM

Skeletal muscle index - SMI

Skeletal muscle radiation attenuation - SMRA

Hounsfield unit - HU

Picture archiving and communication system - PACS

Surgical outcomes

Complications

Survival

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1. BACKGROUND

Sarcopenia is a relatively new term in surgical oncology literature that is defined as the progressive, systematic loss of skeletal muscle mass, function and quality that is associated with aging. There are multiple methods for diagnosing sarcopenia, with body composition tools being increasingly utilised. The presence of sarcopenia has been shown to be associated with poorer outcomes for patients with malignancy.

This is an initial study investigating the use of body composition software in identifying sarcopenia in a population of patients with upper gastrointestinal (UGI) malignancies undergoing surgical resection at a single institution. The impact of sarcopenia on outcomes will also be investigated.

2. AIMS

This thesis attempts to answer the following questions:

a. To develop a standardised methodology and approach to the use of body composition software for tissue segmentation
b. To assess the utility of body composition software in identifying sarcopenia and its relationship to other nutritional markers.
c. To measure the prevalence of sarcopenia using the body composition software in a cohort of patients with UGI malignancy.
d. To determine whether sarcopenia diagnosed via body composition software might aid in prediction of surgical outcomes for patients with UGI malignancy.

3. INTRODUCTION

Sarcopenia is a progressive and generalised skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality.[1] It has been predominantly studied in the geriatric population but has been similarly shown to be a prognostic factor for cancer patients.[2]

All cancers are associated with some degree of anorexia as well as increased catabolism and inflammation that may cause cancer-related malnutrition.[3] Oesophageal and gastric cancers in particular can affect a patient's ability to swallow or digest food and therefore these patients are at increased risk for malnutrition. In addition, treatments for these cancers including chemotherapy, radiotherapy and surgery can compound the malnutrition via a variety of methods including malabsorption, loss of appetite and nausea. Malnutrition has been shown to play a role in the development of sarcopenia and there are significant overlaps between sarcopenia, malnutrition and cancer cachexia.

The optimal treatment for UGI malignancies is often multimodal and can involve significant morbidity. Management depends on the stage of the cancer diagnosis but also the ability for the patient to undergo treatment which is reflected by their physiology and underlying comorbidities. It is important to identify patients who are most likely to benefit from an aggressive treatment approach and those who may do poorly with such approaches due to underlying sarcopenia.

Sarcopenia is therefore both prevalent and relevant when assessing a patient with UGI cancer and may reflect one factor that can aid clinicians in decision making. With the routine use of axial based imaging in the form of computed tomography (CT) in the preoperative assessment and staging of patients with UGI malignancy, an opportunity was seen for further interrogation of already existing data of these patients. Sarcopenia may be able to be identified through the use of body composition software applied to routinely obtained preoperative CT imaging for cancer diagnosis and staging. ***This thesis describes the methods used to diagnose sarcopenia with the use of emerging software and the relevance it may play in surgical outcomes.***

3.1 UPPER GASTROINTESTINAL MALIGNANCY

3.1.1 Oesophageal cancer overview

Approximately 1400 people are diagnosed with oesophageal cancer in Australia each year.[4] There are 2 main types of oesophageal cancer; adenocarcinoma and squamous cell carcinoma. The overall 5-year survival rate for oesophageal cancer is 20%.[5]

3.1.2 Oesophageal cancer presentation and risk factors

Patients with oesophageal cancer classically present with progressive dysphagia and loss of weight. They may also present with odynophagia, heartburn, vomiting, gastrointestinal bleeding, hoarseness or chest pain. Risk factors for adenocarcinoma include increased age, male sex, obesity, gastro-oesophageal reflux disease (GORD), Barrett's disease and smoking. Risk factors for squamous cell carcinoma include increased age, smoking, alcohol intake, achalasia, drinking hot liquids and a history of corrosive ingestion.

3.1.3 Oesophageal cancer diagnosis, staging and investigation

Oesophageal cancer diagnosis can involve

- History and physical examination
- Baseline blood tests
- Gastroscopy
- Endoscopic ultrasound
- Contrast swallow
- Computed tomography (CT) – chest, abdomen and pelvis
- Positron emission tomography (PET) scan
- Preoperative workup including echocardiogram, respiratory function tests
- Staging laparoscopy (gastro-oesophageal junctional tumours only)
- Staging thoracoscopy (not routine)

3.1.4 Oesophageal cancer treatment

Curative treatment for oesophageal cancer typically involves neoadjuvant chemoradiotherapy followed by surgical resection in the form of oesophagectomy. Neoadjuvant chemoradiotherapy is usually in the form of the CROSS protocol[6] and consists of weekly carboplatin and paclitaxel for 5 weeks with concurrent radiotherapy (41.4Gy in 23 fractions).

Oesophagectomy can generally be performed as a 2 stage (abdomen and chest) or as a 3 stage (abdomen, chest and neck) procedure depending on the location of the cancer within the oesophagus. Both laparoscopic and open approaches can be utilized.

3.1.5 Gastric cancer overview

Approximately 2100 people are diagnosed with gastric cancer in Australia each year.[4] The Lauren system is the most widely used system for classification of gastric cancer and classifies adenocarcinoma (most common type) into a diffuse or intestinal subtype. The 5-year survival rate for gastric cancer is 32%.[5]

3.1.6 Gastric cancer presentation

Patients with gastric cancer can present with a variety of non-specific symptoms. These include abdominal pain, anorexia, nausea, vomiting, early satiety, loss of weight and gastrointestinal bleeding. Importantly, gastric cancer is asymptomatic in its earlier stages and so late presentation is common. Risk factors for gastric cancer include smoking, *Helicobacter pylori* infection, gastric atrophy and gastritis, high nitrate consumption, high intake of salted or smoked foods and genetic conditions such as familial adenomatous polyposis and hereditary diffuse gastric cancer.

3.1.7 Gastric cancer diagnosis, staging and investigation

Gastric cancer diagnosis can involve

- History and physical examination
- Gastroscopy
- Endoscopic ultrasound (not routine)
- Computed tomography (CT) – chest, abdomen and pelvis
- Preoperative workup including baseline blood tests
- Staging laparoscopy and peritoneal washings

3.1.8 Gastric cancer treatment

Curative treatment for gastric cancer typically involves surgical resection. The surgical resection performed depends on the location and extent of the cancer. Cancers in the distal portion of the

stomach can be treated with a subtotal or distal gastrectomy whereas cancers in the proximal stomach typically require a total gastrectomy.

Chemotherapy and radiotherapy may be used in a neoadjuvant or adjuvant setting depending on the stage of the cancer. It is important to note that patients with gastric cancer may present acutely with gastrointestinal bleeding or gastric outlet obstruction and this may necessitate an urgent operation, precluding the use of neoadjuvant therapy. In general however, most patients with gastric cancer that are of a locally advanced stage (Stage 2 or 3) would undergo surgical resection with curative intent and neoadjuvant treatment is routine for such patients.

3.2 SARCOPENIA

3.2.1 Overview

The human body can be broadly divided up into its main components of fat, soft tissue and bone through the use of body composition techniques. Soft tissue can be further subdivided into muscle and other organs with muscle mass making up approximately 40% of the total body mass (Figure 1). There are various direct and indirect techniques in body composition assessment in use today.[7] To varying degrees, these body composition techniques describe the nutritional status and overall health of an individual. In recent times, body composition analysis, specifically focussed on muscle mass has garnered increasing interest, particularly in our aging population.

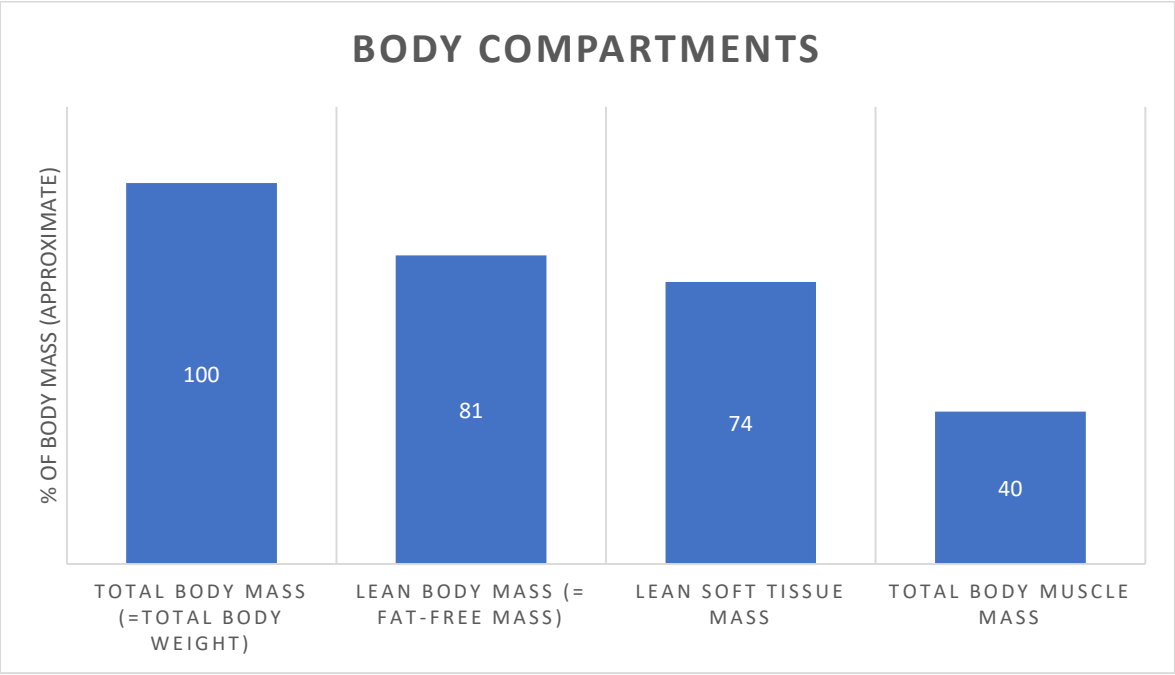


Figure 1. Body compartments reference[8]

The term sarcopenia derived from the Greek terms “sarc” for flesh and “penia” for loss, was first coined by Dr. Irwin Rosenberg[9] in the late 1980s to describe the age-related phenomenon of muscle loss related to increasing age. Since that time, understanding of sarcopenia has increased dramatically with greater recognition and emphasis placed upon muscle function and strength along with muscle loss. It can be understood as muscle failure, akin to other organ failure such as liver or renal failure. In sarcopenia, the main problem is a decrease in muscle mass and strength ultimately resulting in adverse health outcomes, functional decline and an increase in morbidity and mortality.

It is known that muscle mass and strength decrease with increasing age[10-12] and this loss can begin as early as the 4th decade of life.[13] Changes in body composition also occur with age and accompanying this loss of muscle mass is an increase in body fat. Sarcopenia becomes a disease entity when these changes begin to induce disability and is thought to be distinct from normal aging. Sarcopenia may be primary when it is related to the aging process and no other specific causes are found. Secondary sarcopenia is where this process is accelerated by acute or chronic problems such as infections, malignancy, organ failure, disability and inactivity.[14]

Other terms that have been used often interchangeably both prior and following the introduction of the term sarcopenia include malnutrition, frailty and cachexia (Figure 2). It is beyond the scope of this thesis to discuss all these terms as the primary focus is on sarcopenia but there is clearly overlap amongst these concepts[15,16] and it is important to mention these in brief.

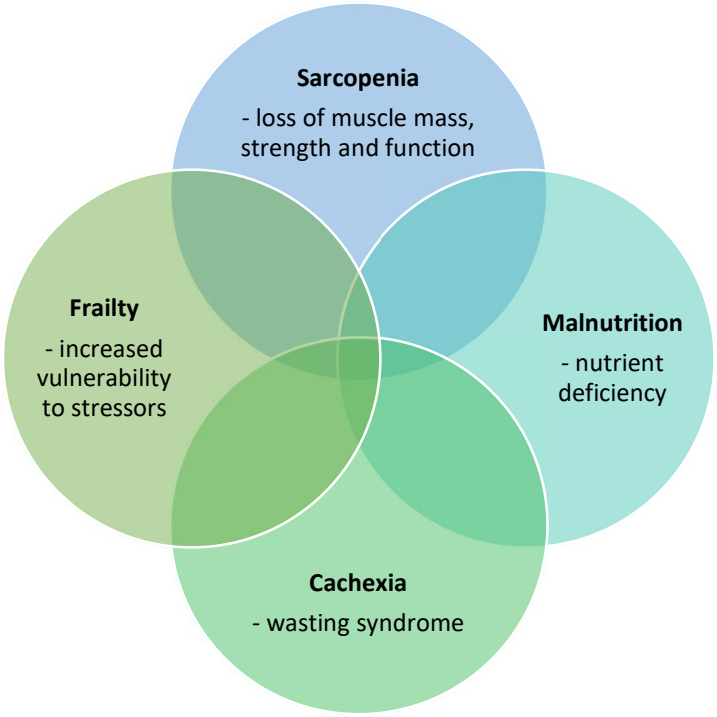


Figure 2. Conceptualisation of overlaps between sarcopenia, frailty, malnutrition and cachexia[17]

Malnutrition can refer to any deficiency in micro or macronutrient that can subsequently lead to specific health syndromes and also contribute to frailty, cachexia and sarcopenia. Weight loss, one of the simplest measures of malnutrition has long been understood to have an adverse effect on outcomes in patients.[18,19] Malnutrition is usually associated with unintentional weight loss and low body mass index, yet having a normal or elevated BMI does not necessarily mean a patient is well nourished, or does not have sarcopenia. In fact, studies have identified patients with elevated BMIs who are also sarcopenic.[18,20-22] This is known as sarcopenic obesity and it has been shown to have negative impacts on surgical complications and survival in cancer patients.[23] Particular attention is required in such patients as the loss in muscle may be offset somewhat by an increase in body fat in these patients. Therefore, breakdown and assessment of body composition in these patients becomes more important as weight loss and malnutrition do not necessarily reveal the entire picture of a patient's decline. Information about the patient may therefore be missed when merely looking only at weight loss and malnutrition.

Cachexia is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[24] It is usually related to an underlying acute or chronic illness, such as renal failure, cardiac failure and chronic obstructive pulmonary disease. Inflammation, anorexia and marked protein degradation are particular features of cachexia.[25] Where cachexia is due to cancer, it is known as cancer cachexia.

Frailty is a geriatric syndrome which makes an individual vulnerable when exposed to a stressor.[26] It is multidimensional in nature with both physical and psychosocial factors playing a role[27] in its development.

Internationally, sarcopenia was formally recognized as a disease affecting the muscle and was assigned ICD-10 code (M62.84) in 2016 allowing appropriate funding and research efforts to take place for this significant disease. Importantly, recent research has shown that sarcopenia is potentially reversible[28,29] and therefore, early identification and treatment for it can improve outcomes for patients. Historically the concept of sarcopenia originated in the geriatric population group and its role in the outcome for surgical patients and specifically surgical cancer patients has only recently gained wider exposure and understanding.

3.2.2 Pathophysiology

Clearly, the normal aging process plays a role in the reduction of lean muscle mass and muscle function witnessed as individuals grow older. Muscle mass alone is known to decline with age and this process accelerates in the latter stages of life.[30] The factors contributing to this loss include reduced muscle turnover and repair capacity, lower hormone excretion and a change in muscle fibre type from larger, faster contracting type 2 muscle fibres towards smaller, slower contracting type 1 muscle fibre types.[25]

However, sarcopenia is distinct in that it becomes a disease process when that low muscle mass and strength puts the individual at risk of functional decline with subsequent morbidity and mortality. The development of sarcopenia is likely a complex interplay between genetic and environmental factors (Fig 3). These factors include imbalances in anabolic and catabolic protein pathways, inflammation, endocrine dysfunction, disuse, malnutrition and chronic disease.[31]

At a molecular and cellular level, changes in mitochondrial integrity and decreased numbers of satellite cells (adult stem cell of skeletal muscle) contribute to decreased muscle regeneration and myogenesis.[32] Endocrine dysfunction occurs with changes in insulin sensitivity and reduction in hormones important in muscle mass maintenance such as insulin like growth factor 1, estrogen and particularly testosterone in men[13]. Neurological alterations with time can result in signalling pathway dysregulation, denervation and ultimately muscle atrophy and loss.[33]

Marked infiltration of fibrous and adipose tissue (myosteatosis) also occurs with increasing age[9] and this results in loss of lean muscle mass, but not necessarily in overall muscle size. This is one of the potential reasons that muscle strength decreases to a greater proportion than mass with age. Interestingly the combination of sarcopenia and obesity, sarcopenic obesity, demonstrated the strongest correlation for functional impairment, falls and disability.[20]

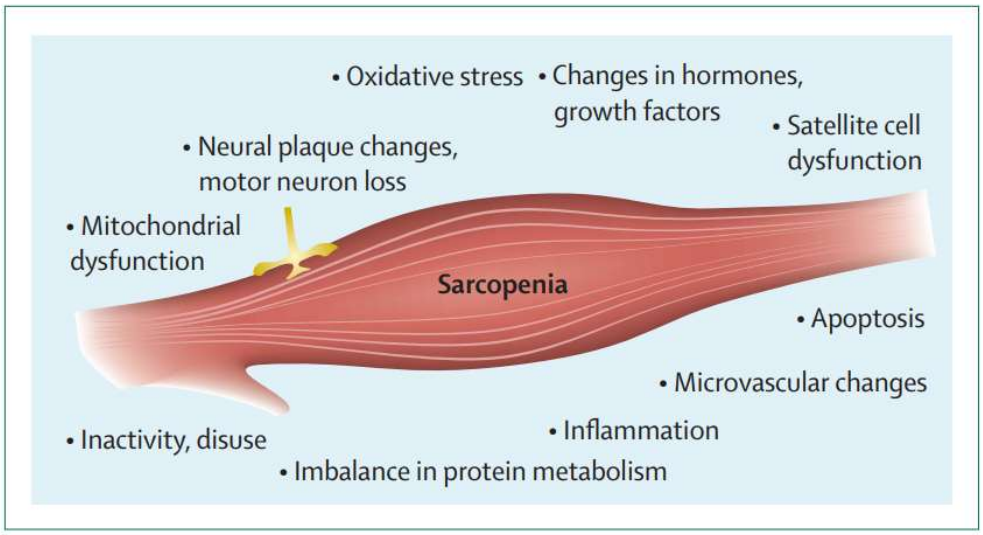


Figure 3. Multifactorial causes of sarcopenia[17]

With regard to UGI malignancy, presenting symptoms such as dysphagia, early satiety and anorexia often leads to poor oral intake and subsequent malnutrition. This may be compounded by the effects of excess catabolism and inflammation related to the neoplastic process. Clearly this can lead to the development of sarcopenia or worsen pre-existing sarcopenia.

Moreover, neoadjuvant treatment, either chemotherapy or radiotherapy alone, or combined also has impacts on metabolism, appetite and inflammation. Fatigue is a common complaint of patients undergoing chemotherapy or radiotherapy which also impacts the amount of physical activity undertaken.

It is known that surgical stress results in production of cytokines, that may lead to muscle catabolism, inflammation and oxidative stress providing further avenues for the development of sarcopenia.

A greater understanding of the pathophysiological processes in the development sarcopenia are vital in finding interventions that might reverse this problem.

3.2.3 Diagnosis

A diagnosis of sarcopenia employs a wide range of techniques to assess muscle mass, strength and function. Multiple definitions have been used as can be seen in Table 1 below.

Table 1 Comparison of sarcopenia definitions

Definition	Function	Muscle mass
SIG: cachexia-anorexia in chronic wasting disease [3]	Gait speed <0.8 m/s, OR other physical performance test	Low muscle mass (2SD)
EWGSOP [4]	Gait speed <0.8 m/s; grip strength 40 kg males, 30 kg females	Low muscle mass (not defined)
IWGS Sarcopenia Task Force [5]	Gait speed <1.0 m/s, grip strength	Low appendicular lean mass (<7.23 kg/m^2 in men, 5.67 in women)
Sarcopenia with limited mobility (SCWD) [6]	6 min walk <400 m, OR gait speed <1.0 m/s	Low appendicular lean mass/height^2
Asian Working Group for Sarcopenia [7]	Gait speed <0.8 m/s; grip strength 26 kg males, 18 kg females	Low appendicular lean mass/height^2
Foundation for the National Institutes of Health [8]	Gait speed <0.8 m/s; grip strength 26 kg males, 16 kg females	Appendicular lean mass/BMI

EWGSOP European Working Group of Sarcopenia in Older Persons, *SCWD* Sarcopenia, Cachexia and Wasting Disorders, *IANA* International Association of Nutrition and Aging)

Table 1. Sarcopenia definitions. From Morley et al 2014[34]

One of the criticisms of early studies into sarcopenia is that the definitions and the methods used for diagnosis were non-standardised, making analysis between studies challenging.[35,36] Hence in 2009, the European Working Group on Sarcopenia in Older People (EWGSOP) met to develop a formal consensus definition of sarcopenia that was suitable for use in research and clinical practice.[37] They published a

practical definition and consensus diagnostic criteria for age-related sarcopenia. Their initial criteria for the diagnosis of sarcopenia included both low muscle mass and low muscle function (strength or performance) but did require observation of low muscle mass. (Table 2).

Diagnosis is based on documentation of criterion 1 plus (criterion 2 or criterion 3)
1. Low muscle mass
2. Low muscle strength
3. Low physical performance

Table 2. Initial criteria for the diagnosis of sarcopenia (2010)

Establishment of a consensus definition went some way to standardising the assessment of sarcopenia thereby allowing subsequent studies to be compared and analysed. The emphasis was still on low muscle mass but with further research, it was found that muscle strength also seemed to be significant in predicting outcomes.[28,33,38,39]

In 2018, the EWGSOP met again and updated its definition (Table 3) with more importance placed on low muscle strength as strength has been shown in some studies to be even better than low muscle mass alone in predicting adverse outcomes.[1] Early studies on sarcopenia relied on the assumption that low muscle mass would directly lead to the decline in muscle strength and function. However, it has been shown that the decline between muscle mass and muscle strength is not entirely linear and that strength can decline to a greater extent than muscle mass.[25,40,41] It was suggested by Clark and Manini[33] that another term, dynapenia could even be used to describe age-related changes in muscle strength.

Despite this new emphasis on muscle strength, the diagnosis of sarcopenia continues to require a measurement of low muscle mass. The severity of sarcopenia can be further quantified if the low muscle strength and mass subsequently affect physical performance.

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

Table 3. Revised criteria for the diagnosis of sarcopenia (2018)

Two consensus articles (EWGSOP2 and ICFSR) on sarcopenia also recommend initial screening for sarcopenia in older adults using validated instruments. These include SARC-F questionnaire, the FRAIL scale, the Edmonton Frail Scale and Rockwood Clinical Frailty Scale. (Appendix A) To date, these have not been formally validated in the oncology patient group.

3.2.3.1 Muscle strength

Handgrip strength has been widely used as a marker of muscle strength and this is assessed using a calibrated handheld dynamometer (Appendix B). Handgrip strength has been shown to correlate with other measures of arm and leg strength but it should be noted that lower limb, rather than upper limb strength is more relevant for gait and overall physical function. Lower limb strength can be assessed via tools such as the chair-stand test (Appendix B) but the methods used to measure this are less well validated. Muscle strength assessment can be influenced by other factors such as cognition, motivation and fatigue. Nevertheless, grip strength is a quick, simple and inexpensive test of muscle strength. Low handgrip strength has been shown in a study by Sato et al[42] to be associated with morbidity after gastric cancer surgery.

3.2.3.2 Muscle quantity or quality

In regards to muscle mass, dual energy X-ray absorptiometry (DEXA) has been the most widely utilized and studied tool to date. DEXA uses 2 different energy levels of low dose radiation to measure bone, lean mass and fat mass[43] and is used in both research and clinical settings. Early studies utilising DEXA measured skeletal muscle mass (kg) and this was expressed as a skeletal muscle index (SMI) as mass divided by the square of the height in metres (kg/m^2).

Sarcopenia was then defined as being < 2 standard deviations below the mean of a young reference group.[44] A calculated cut off point <7.26 kg/m^2 for males and <5.45kg/m^2 for females has been used widely.[45] DEXA is used widely for measuring bone density in osteoporosis but its use in sarcopenia has been limited to research settings thus far. Depending on hydration status, DEXA has a tendency to overestimate muscle mass.

Bioimpedance analysis (BIA) is based on the differing electrical conduction abilities of water rich vs lipid rich tissues in the body. It utilizes specific equations to determine body composition and these equations were based on specific population groups with specified cut off values. Skeletal muscle mass may be estimated and similar to DEXA, a SMI can be calculated, this time based on the skeletal muscle

mass / body mass. A cut-off utilizing the number of standard deviations below a sex-specific mean for young adults (aged 18-39) has been used to define sarcopenia. However, because of the various equations used to calculate skeletal muscle mass, BIA currently lacks standardization[46] and more work is required to assess its utility in sarcopenia. In addition, BIA currently has no role in routine clinical use.

Cross sectional imaging in the form of computed tomography (CT) and magnetic resonance imaging (MRI) have also been used as non-invasive methods for measuring body composition. CT and MRI are an established part of clinical practice and CT in particular is routine in diagnosing and monitoring cancer patients. However, by focusing on other areas not normally used for diagnostic purposes such as the muscle or adipose tissue quantity, additional information can be gained from these scans.

Muscle quantity can be accurately measured due to the resolution of anatomical images obtained using CT. Lumbar muscle, psoas muscle, mid-thigh muscle and even masseter muscle cross-sectional area can be measured using either in-built or add-on software depending on which part of the body is being scanned. Like in DEXA, the quantified results can be adjusted for height giving a skeletal muscle index (SMI). This is performed by dividing the surface area measured by the square of the height in metres. Cut-off points defining low muscle mass have been proposed but can vary across different population groups.

Beyond this, on CT muscle quality may also be assessed to a degree by the degree of fat infiltration into the muscle and such infiltration has been shown to lower work performance.[47]

Similarly, MRI, apart from being useful and accurate in muscle volume analyses, has the ability to go beyond muscle mass measurement and can also assess for the presence of myosteatosis, which is a marker of poor muscle quality. Additionally, different MRI sequences such as magnetic resonance elastography (measuring stiffness of skeletal muscle), diffusion tensor imaging (analyses muscle microstructure) and magnetic resonance spectroscopy (provides information on insulin resistance, intramyocellular lipid) can provide even more approaches at analysing skeletal muscle, but this technology is not in routine use.[48]

Presently no standardised method for the measurement of muscle mass exists.[8]

The various strengths and weaknesses of the main assessment tools are summarised in Table 4.

Test	Strength	Weakness
DEXA	Low ionising radiation Allow measure of 3 body compartments Repeatable to measure changes	2 dimensional images Different software can yield differing results Affected by hydration status Does not measure truncal muscle mass Unable to quantify fat infiltration within muscle
CT	Ease of access Accurate muscle measurement including muscle density Routine use for cancer staging	Ionising radiation exposure Moderate cost
MRI	No ioinising radiation High resolution Accurate muscle measurement	High cost Affected by movement artefact Limited availability Significant technical expertise required
BIA	Non invasive Precise measure of body resistance Portable No training required	Indirect measure of muscle mass based on electrical conductivity Affected by hydration status and temperature May be affected by electrode quality and positioning Wide prediction error in measuring lean body mass Lack of standardisation

Table 4. Summary of main assessment tools for muscle quantity or quality

3.2.3.3 Physical performance

Physical performance is a composite measure of whole-body function, encompassing muscle and nervous function.[49] This is best measured with functional outcomes such as gait speed, the time up and go test (TUG), 400m walk test and the short physical performance battery (SPPB). Gait speed in particular has been shown to be able predict adverse outcomes including falls, need for institutionalization and mortality.[50]

These composite tests of performance however can be affected by not only muscle mass and strength but also by cognitive, neurological and other disorders and although standardized tests exist, are considered more subjective in nature.

3.2.4 Significance and impact

A diagnosis of sarcopenia has been demonstrated to affect mobility, function, nutritional status and is ultimately associated with adverse outcomes including impacts on daily activities and increased morbidity and mortality.[41,51,52] Rates of sarcopenia amongst community dwelling adults have been estimated from 5-48%.[10,53,54] The prevalence however, obviously varies depending on the population being tested with rates being higher in institutionalized patients compared with community patients.[31]

Its prevalence also increases with age and with an aging population, it has been estimated that sarcopenia may affect more than 200 million people in the next 40 years[37] making it a significant health problem.

Specifically, in regards to the oncology population, there are additional factors that would increase the risk of developing sarcopenia including the cancer itself, with resultant increased inflammation, catabolism and secondary effects such as loss of appetite and loss of weight, or even psychological distress leading to physical inactivity. Additionally, many of the treatments for cancer are cytotoxic and decreases in muscle mass has been shown to occur following neoadjuvant chemotherapy in UGI cancer.[55,56] It is therefore likely that its prevalence is even higher in this group patients compared with age matched controls.

The presence of sarcopenia has been shown to be associated with poorer outcomes across multiple oncology groups. This includes patients with colorectal[57], lung[58], pancreatic[59], breast[60] and UGI cancer. Its effects seem to be wide ranging but include higher overall and disease- specific mortality[61], increased complications and increased rates of treatment related toxicities.[62] Many other studies have clearly demonstrated that sarcopenia confers worse prognosis and this is applicable across a wide range of gastrointestinal cancers.[63-65]

At present the mechanisms by which sarcopenia affects surgical outcomes is not entirely clear. It has been shown that sarcopenia can reduce respiratory function, including reduced forced expiratory volume 1 second and forced vital capacity.[56] This has presumed impacts on the post operative patient with inability to clear secretions and decreased lung capacity resulting in increased rates of pneumonia and hypoxia. In support of this hypothesis, Sato et al[42] found that the incidence of pneumonia was

significantly higher in patients with low hand grip strength compared to those with higher hand grip strength.

Decreases in mobility secondary to sarcopenia may also affect the patient's ability to recover after major surgery. It has long been recognized that immobility following surgery is detrimental and has been associated with increased complications via venous thromboembolic events, cardiovascular complications and even death.[66] It is possible there are other currently unrecognized mechanisms that allow sarcopenia to contribute directly to morbidity and mortality but it is more likely that it is a combination of factors that ultimately lead to harm.

Most of the studies examining sarcopenia and its effects in cancer patients have used measures of low skeletal muscle mass as the basis of the diagnosis. Sarcopenia as measured by total psoas area and volume was useful as a predictor of 1 year mortality risk in a group of patients undergoing gastrointestinal surgery.[67] The combination of total psoas area and basic parameters such as age, haemoglobin and ECOG status seemed to identify patients at greatest risk for 1 year mortality in this cohort.

However, as has been discussed previously, the diagnosis has become more formalized and refined in its approach only recently. Low muscle mass though, is objective and easily measured in the cancer population group via CT. This concept of measuring low muscle mass and its utility will be explored in the next section.

3.2.5 Role of CT

Although DEXA and BIA have a role in providing information about lean mass and fat mass, neither is in routine clinical use for cancer patients and neither can accurately discriminate between lean and fat subcompartments.[68] In contrast, cancer patients are routinely staged using CT and this contains significant information related to the body composition of the patient that is usually not of prime interest from an oncological perspective. Generally, a staging CT for patients with UGI cancers would encompass the chest, abdomen and pelvis. This can be performed at multiple time points of the patient's cancer journey but is at least performed at the time of diagnosis, and depending on local protocols before or after any cancer specific treatments including neoadjuvant and adjuvant therapy or operative intervention. The images are usually stored in digitized format on an institution's picture archiving and communication system (PACS) and are therefore readily accessible and analysable.

CT is considered a gold standard in measuring specific muscle mass, muscle cross sectional area, muscle quality and adipose tissue[37,69] due to its high anatomical definition and ability to distinguish

different tissues via differing radiodensities. This is based on the X-ray attenuation value expressed on a linear scale of Hounsfield units (HU). Air is assigned a value of -1000 HU and water is assigned a value of 0 HU. Typically, bone has HU ranging from 700 to 3000, soft tissue 20 to 50, skeletal muscle -29 to 150, and adipose tissue -190 to -30. Visceral adipose tissue (-150 to -30 HU) tends to have a slightly higher attenuation compared with subcutaneous adipose tissue. Based on these attenuations, body composition analyses can be undertaken, dividing an axial slice of the body into its various components including muscle, visceral fat and subcutaneous fat (Figure 4).

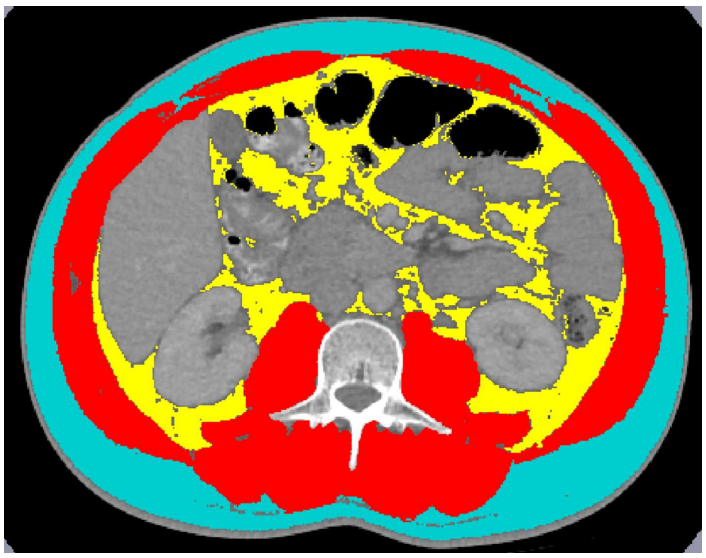


Figure 4. Example of CT body composition based on HU attenuation. Red – skeletal muscle; Yellow - visceral fat; Light blue - subcutaneous fat

A CT comprises a composite of 2-dimensional slices of differing thicknesses that then create a 3-dimensional representation of the object. Each image or slice is composed of a series of voxels, (akin to a pixel) that represents a specific area and attenuation value. In this way, the cross-sectional area in cm^2 can be calculated by measuring the number of tissue voxels multiplied by the surface area. It is clearly impractical to measure the total body muscle or fat from the myriad of images that a staging CT provides by measuring multiple individual slices. Therefore, surrogate measures of whole-body muscle mass utilising single axial slices have been established.

Shen et al[70] was one of the first to demonstrate a linear relationship of a single abdominal image to quantify whole body skeletal muscle and adipose tissue. They found that a single abdominal image, 5cm above the L4-5 intervertebral space as demonstrating the highest correlation between measured skeletal muscle and total body skeletal muscle. The measurement of whole body adipose tissue has similarly shown a relationship with single lumbar vertebral slices in other studies.[71]

Multiple other single axial levels across a CT scan that have been used as markers of body composition include other vertebral levels, the thoracic vertebrae[72], upper and lower limb musculature[43] and even cervical vertebrae.

However, the most widely accepted and studied level to perform measurements is the L3 level[73] and this would be in keeping with the findings of the early study performed by Shen et al. In a recent systematic review by Amini et al,[74] for the assessment of muscle mass, the most common muscle group used was total abdominal wall musculature. This was used in 142 / 330 (43%) of studies and amongst those studies, the most commonly used landmark was the L3 vertebra. At this level, the muscles included are psoas, erector spinae, quadratus lumborum, transversus abdominus, internal and external obliques and rectus abdominus which form the bulk of the truncal musculature.

Tewari et al [75] compared DEXA, CT and BIA in 47 patients who had either undergone major surgery or neoadjuvant chemotherapy for UGI cancer. For the CT measurement, a single image slice at the L3 vertebra was used to calculate the surface area of skeletal muscle and adipose tissue. This study found good correlation in measuring the fat free mass and fat mass between DEXA and analysis of CT scans. The correlation between CT and BIA was lower but still significant.

In diagnosing sarcopenia via low muscle mass on CT, there are a number of commonly used cut-off points for the SMI that have been described and this is known to be higher in male patients. DEXA, BIA and CT measurements were correlated in a cohort of patients by Mourtzakis et al.[76] They found that CT-based muscle analysis at L3 was strongly correlated to DEXA appendicular skeletal muscle mass and the DEXA cut-off values for sarcopenia of <7.26 kg/m^2 and < 5.45 kg/m^2 equated to an SMI on CT of <55.4 cm^2/m^2 and <38.9 cm^2/m^2 in males and females respectively.

Prado et al[77] used optimum stratification to determine sex-specific cut-offs for the L3 SMI with the highest association with mortality. They found that this cut-off was 52.4 cm^2/m^2 for males and 38.5 cm^2/m^2 for females. They defined patients with an SMI lower than these cut-offs as having sarcopenia, and found obesity (BMI > 30 kg/m^2) with sarcopenia was an independent predictor of poor survival, highlighting the emerging concept of sarcopenic obesity.

The use of BMI to adjust threshold values was evaluated in a large study looking at the SMI in over 1400 patients.[78] Like the study by Prado et al, optimal stratification was used to identify the threshold values that conferred significantly lower survival. It was identified that the threshold values for SMI differed for men (<43 cm^2/m^2 or < 53 cm^2/m^2) depending on whether the BMI was < 25 kg/m^2 or > 25 kg/m^2. In women, the cut-off for lower survival was <41 cm^2/m^2 regardless of BMI.

Another aspect of sarcopenia that may be measured by CT and has been mentioned is low muscle quality. It has been shown that skeletal muscle attenuation is inversely related to muscle fat content and can be used as an indirect measure of muscle content and quality.[79] This concept of myosteatosis or fat deposition within skeletal muscle goes beyond measurements of size and CT can also be of use in this domain. The mean HU of the skeletal muscle, known as the skeletal muscle radiation attenuation (SMRA) provides a picture of how dense this muscle is.

For example, in the figure below, the images are of 2 patients with similar age and BMI. (Figure 5) Although the shaded areas encompassing the paraspinal muscles are similar, the histogram breakdown of the tissues into various HU demonstrates a higher proportion of intermuscular fat attenuation. The mean SMRA of the patient above is 42.3 HU versus 20.4 HU in the patient below.

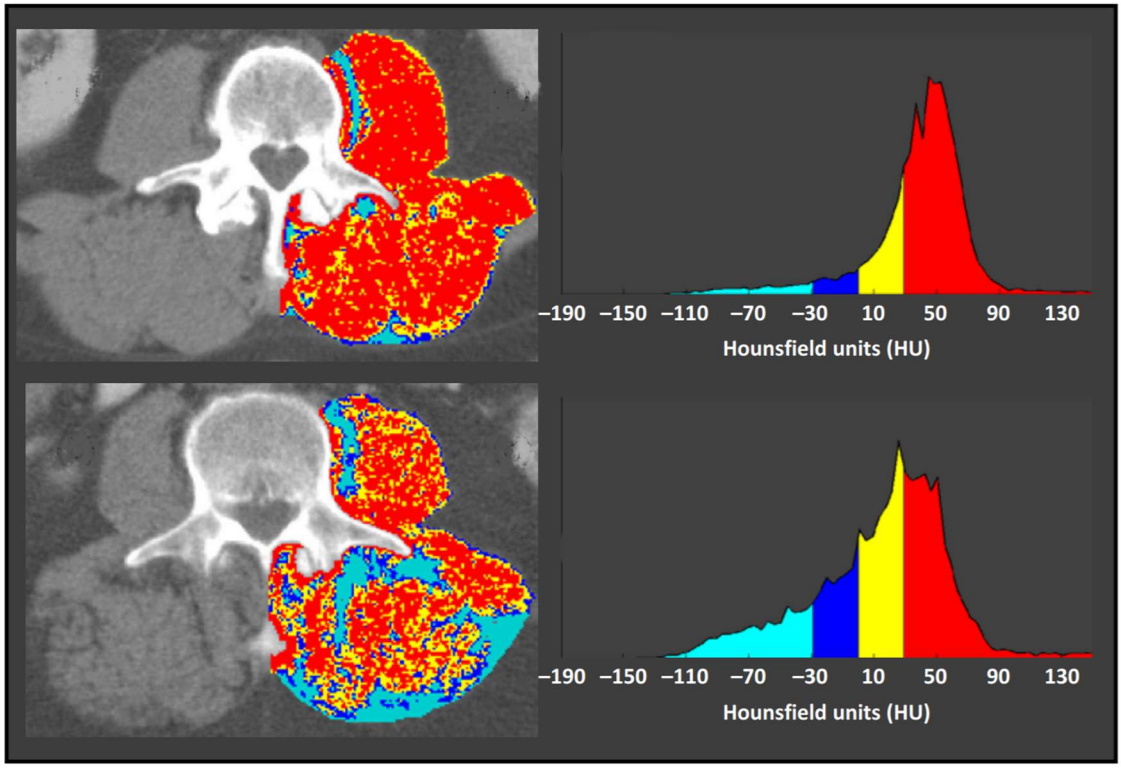


Figure 5. Skeletal muscle radiation attenuation and corresponding Hounsfield unit histogram for two patients with similar age and BMI but differing SMRA.[79] Note the peak in the histogram occurs at a lower Hounsfield unit in the second patient.

Establishing cut-off points for myosteatosis based on the HU is even less standardised than values for SMI. The majority of studies have used total abdominal wall musculature at the L3 level but total thigh musculature, psoas and other landmarks have been used. Only for total abdominal wall musculature

has there been repeated use of one cut-off which was established from Martin et al's large study. Like SMI, they established cut-offs dependent on BMI but not gender. In their study, if BMI > 25 kg/m^2, then the HU cut-off for sarcopenia was an SMRA < 33HU; if BMI < 25 kg/m^2, then the cut-off was an SMRA < 41 HU.

The distinction of using BMI as part of the cut-off is an important consideration. In population studies of SMI and SMRA[80] it has been shown that SMRA decreases with increasing BMI further lending support to the notion that sarcopenia goes beyond measuring muscle mass but also to muscle quality.

Another known method to measure the actual fat content contained within the muscle with the use of body composition software is to measure the intra-muscular adipose tissue (IMAT). The IMAT has also been shown in some studies to be a marker for prognosis and it may also be used as a surrogate for functional testing of muscle but does require more detailed knowledge of the anatomical boundaries of the musculature and also a further step in the body composition process to tag the appropriate tissue.

In summary the role of CT in body composition is underutilized but has been demonstrated in many of the studies mentioned to be valuable and accurate. It is rapid, inexpensive and widely available and is standard in staging patients with UGI cancer and would seemingly serve as a useful starting point at measuring sarcopenia in this population group. Additionally, CT is often repeated throughout the various phases of treatment and follow up for cancer patients providing the ability to detect change, either improvement or decline with various interventions.

Utilising a single axial CT slice estimate body composition has many advantages in that it is readily available, can be segmented into multiple different tissue classes and can potentially provide information on skeletal muscle density and attenuation.

3.2.6 Body composition software

A medical image analysis software SliceOmatic v 5.0 (SliceOmatic; TomoVision, Canada) that allows segmentation of tissues into different classes has been in use for over 20 years. SliceOmatic has both automated and manual functions allowing segmentation of cross-sectional imaging into different tissue classes, based on the HU for CT. It has been validated in multiple studies and is the software that has been used to generate commonly used reference ranges of sarcopenia.[77,78]

SliceOmatic was initially developed as a research tool designed to assist in computing anatomical volumes and tissue segmentation. It has the ability to open DICOM files maintaining the original

format without alterations in window and level values. An example of a DICOM file opened in its original format in SliceOmatic is seen in the figure below. (Figure 6)

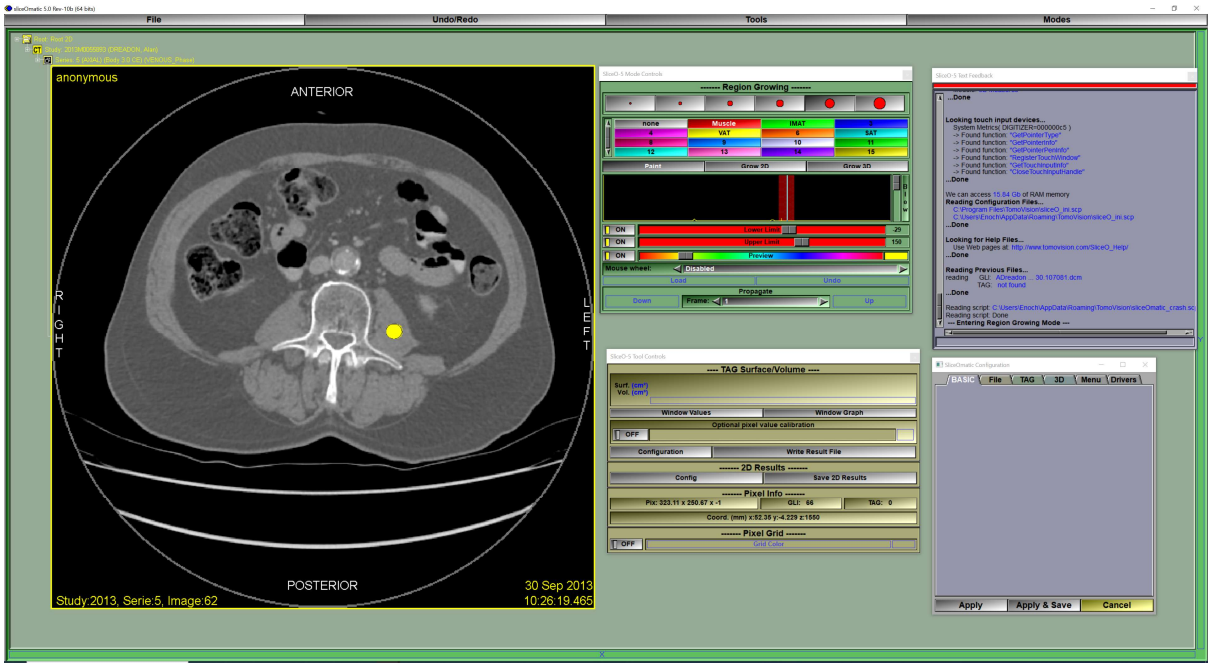


Figure 6. Example CT image open on SliceOmatic with tools allowing region growing and surface volume calculations shown.

Subsequent to the development and use of SliceOmatic, a number of other free and commercially available programs have been developed for quantifying skeletal muscle in the body and performing other body composition analysis. These include but are not limited to OsirisX, NIH Image J and FatSeg and Coreslicer.

Van Vugt et al performed a comparative study examining the inter-software correlation across four different programs including SliceOmatic.[81] This demonstrated that measurements of cross-sectional muscle area at the mid L3 slice were highly comparable between these programs. Multiple other studies[82-85] have demonstrated similar findings and concordance in measuring skeletal muscle area, visceral adipose tissue and subcutaneous adipose tissue across different programs. It appears that results of different software programs in body composition analysis are largely comparable.

Despite the development of different programs and their comparable results, SliceOmatic has been the most widely used and reported program in the literature.[74,86] In a systematic review examining the role of CT scans for body composition in patients with abdominal malignancy, all but two studies identified used SliceOmatic as the software for measuring low muscle mass.[87]

Some of the programs listed require significant technical expertise[85] and furthermore, there are concerns regarding confidentiality when using free, often web-based software programs in analysing patient scans. For these reasons, SliceOmatic was chosen as the software to use for this study. SliceOmatic requires the purchase of a licence, which is contained within a USB dongle delivered upon purchase. This enables the ability to utilize all the modes for tissue segmentation, save and review results and calculate tissue volumes.

3.2.7 Treatment

With the complex interplay of factors thought to lead to the development of sarcopenia, the treatments that have been investigated can be broadly classified into exercise, nutrition and pharmacological interventions or a combination of those approaches.

At present, resistance exercise has been the most extensively studied intervention and has demonstrated the ability to reverse sarcopenia.[88,89] Resistance training may be provided within prescribed programs that induces skeletal muscle contraction with progressive increases in intensity and/or volume.

Skeletal muscle is remarkable as it has a great ability to adapt and change according to its demands, even in elderly populations.[25,90] Both muscle size and strength has been demonstrated to improve in one study looking at resistance training in a small group of patients over 90 years old. This subsequently led to improvements in gait speed and functional mobility in this group of nonagenarians.

The International Clinical Practice Guidelines for Sarcopenia (IFCSR) strongly recommend resistance training as first-line therapy in managing sarcopenia.[91] In fact, there is a recommendation from the Clinical Oncology Society of Australia (COSA) that exercise be considered a key 'treatment' for all patients undergoing cancer treatment, irrespective of sarcopenia status.[92] Overall however, the quality of evidence for improved outcomes with resistance training remains low due to the fact that many of the studies investigating its role are heterogenous in nature, particularly with regard to the definition of sarcopenia used.

The evidence for nutritional intervention alone to treat sarcopenia is not supported by strong evidence.[26] For nutritional interventions, establishing direct links is difficult due to the complex interaction between eating patterns, diet, digestion and metabolism. Regardless, it seems intuitive that adequate caloric and protein intake would be of prime importance given that muscles are composed of proteins and their function is dependent on appropriate mitochondrial activity that

requires energy. International guidelines have clearly recommended protein supplementation or protein rich diets in older patients with sarcopenia.[91,93]

Specific amino acids play a vital role in muscle mass and function and act as substrates for new muscle growth. In some studies, leucine has been prescribed and has been shown to increase muscle mass. HMB, (β-hydroxy-β-methylbutyrate) an active metabolite of leucine has been used by athletes to enhance muscle hypertrophy, strength and overall performance. Its use in the sarcopenic population has shown some promise, although most studies to date have limited sample sizes.[94]

In population studies, low vitamin D has long been associated with frailty and falls although the mechanisms for its effect are not entirely clear. Its mechanisms continue to be explored with the discovery of vitamin D receptors on skeletal muscle and changes in in this receptor are thought to have a direct effect on muscle strength.[95] Vitamin D supplementation thus far, has yielded conflicting results in the treatment and prevention of sarcopenia. There are of course other indications for vitamin D supplementation in patients, distinct from reasons related to sarcopenia.

In many studies, nutritional interventions have often been used in conjunction with exercise training and nutritional interventions in this context, rather than in isolation, seem to deliver the most benefit. A meta-analysis by Yoshimura et al[88] has concluded that exercise and nutritional interventions have positive effects for treating sarcopenia, although the quality of evidence is very low. An important consideration in this regard though, is that severely undernourished patients are unlikely to respond purely to exercise training and therefore the addition of nutrition supplementation to exercise is likely to be of more benefit in this group.[96] It is important to understand the population group in order to target appropriate interventions to their requirements.

The use of pharmacologic approaches including testosterone and selective androgen receptor modulators have also shown some promise.[97] The selective ghrelin receptor agonist, anamorelin (ONO-7643) has been demonstrated to improve lean body mass, improve anorexia and nutritional state but did not improve motor function in a group of patients with non-small cell lung cancer.[98] This has not yet been specifically studied in the UGI cancer population group. Therefore at present, pharmacologic approaches are not in routine use and are not recommended for the management of sarcopenia in UGI malignancy. In particular, some exogenous hormone therapies used to combat sarcopenia have been associated with increased rates of malignancy and cardiovascular events.

Ongoing research is being undertaken to understand the development and progression of sarcopenia in order to establish new diagnostic techniques and better treatments for sarcopenia. This has primarily been aimed at broader geriatric populations and unfortunately not specifically targeted

toward the cancer population group. For example, the 'sarcopenia and physical frailty in older people: multi-component treatment strategies' (SPRINTT) project[99] is a randomized controlled trial aimed at a general level, implementing a multicomponent intervention involving exercise and nutrition to prevent mobility and disability, that is currently in progress. With increasing recognition of sarcopenia in the cancer population, it is hoped that more research will be undertaken to target this vulnerable group of patients.

3.3 RELEVANCE TO CURRENT STUDY

On the basis of the literature review above, it is clear that sarcopenia is highly relevant and prevalent, particularly in a population of patients with UGI malignancy. Its presence confers increased risks of morbidity and mortality following surgical resection and its importance and impact has only been recently reported on.

We postulate that many patients presenting with UGI malignancy undergoing surgical resection have undiagnosed sarcopenia and that this fact might not be apparent to clinicians undertaking surgery on such patients. Preoperative assessment of sarcopenia should be routine as it offers an opportunity for early identification and targeted treatments in order to improve outcomes for such patients. There are a number of methods such as questionnaires and functional tests to help diagnose sarcopenia but most of these do not form a routine part of the workup for patients with UGI malignancy.

All patients undergoing surgical resection for UGI malignancy undergo routine preoperative staging CT scans. These CT scans are intended to look for evidence of local or regional spread of the cancer but are also potentially useful in measuring muscle mass, one of the criteria for the diagnosis of sarcopenia. This represents an underutilized resource that has been shown in studies to be a valuable and significant prognostic marker.

We therefore sought to review the preoperative CT scans for in a cohort of patients undergoing UGI resections to determine the prevalence of sarcopenia and to examine its impacts on outcomes of these patients. We aim to develop a simple method for measuring muscle mass and quality as a surrogate for sarcopenia through the use of a validated body composition tool. Through the development of a method to diagnose low muscle mass, it is hoped that this will lead to further studies on interventions specifically targeting this at-risk group to improve their outcomes.

4. DESIGN

This is a retrospective study examining a consecutive population of patients undergoing major UGI surgery at a single institution over a 6-year period from January 2013 – December 2018.

Data including patient demographics, type of cancer, (neo)adjuvant treatments, histology, morbidity and mortality was collected along with data reflecting the nutritional status of the patient including BMI, weight, preoperative weight loss, albumin.

Body composition software allowing tissue segmentation into muscle and adipose tissue has not been used in our institution previously. A body composition software tool was obtained and used on patients' preoperative imaging. A standardised protocol for the software was designed to record the amount of skeletal muscle area and the skeletal muscle attenuation.

This study subsequently investigated the usability and utility of a standardised protocol for assessing sarcopenia and compared this with other markers of nutrition. The prevalence of sarcopenia in this particular patient population group was assessed. Statistical analyses were used to identify whether the presence of sarcopenia along with a combination of markers can be used to predict outcomes in major UGI malignancy.

Ethics approval for this study was obtained via the Office of Research and Ethics at Eastern Health with approval reference number QA19/30.

5. METHODS

5.1 PATIENT DETAILS

All patients undergoing oesophagectomy (two stage Ivor Lewis oesophagectomy, three stage oesophagectomy) and gastrectomy (total gastrectomy, total oesophagogastrectomy and partial gastrectomy) at a single tertiary institution over a six-year consecutive period (2013 – 2018) were reviewed. The inclusion period for the study of 2013 was chosen as this was the introduction of electronic medical records at our institution allowing easier access to patient information. A search through medical records via the terms oesophagectomy and gastrectomy was performed and a patient list generated.

Patients who underwent operations for a malignant indication were included. Patients who had undergone operations for weight loss surgery, benign disease such as bleeding and lesions such as gastrointestinal stromal tumours (GIST) were excluded. Basic demographics, operative details, histology details, neoadjuvant and adjuvant treatments, and outcomes including recurrence survival data was recorded. Follow up data was recorded from the initial date of operation until the patient died or any follow up until data closure in 2021, whichever occurred later.

Decisions for neoadjuvant and adjuvant therapy were based on multidisciplinary discussions in line with contemporaneous standards of care. In general, neoadjuvant treatment for oesophagectomy consisted of chemoradiotherapy as per the CROSS protocol.[6] Neoadjuvant treatment for gastrectomy consisted of a chemotherapy regimen. It initially consisted of epirubicin, cisplatin, fluorouracil (ECF) as per the MAGIC trial,[100] but was modified during the study period after 2018 to a protocol consisting of fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT) when emerging data demonstrated its superiority.[101]

5.2 OPERATIVE DETAILS

Operations were performed by an experienced unit of UGI surgeons. A senior UGI fellow would typically be present and would either perform the operation as primary operator under the supervision of an UGI surgeon or be first assistant. An accredited surgical registrar would also assist in portions of the operation and occasionally perform certain aspects of the operation, again under the supervision of an UGI surgeon or fellow.

All operations were performed at a single institution and all were performed as open operations (oesophagectomy – open abdominal and open thoracic, open thoracoabdominal and/or open neck, gastrectomy – open abdominal) as is the standard and expertise at the local institution.

5.3 PREOPERATIVE CT IMAGES

Preoperative CT scans of patients was identified via the PACS of the institution. For patients with multiple CT scans, the closest preoperative scan to the date of the operation was chosen. For some patients, preoperative imaging was not available but perioperative imaging was. This was defined as having a CT scan in the same admission as the operation. Patients without any of these defined imaging available were excluded for analysis of sarcopenia.

Images were exported as a Digital Imaging and Communications in Medicine (DICOM) file format, which is the standard medical imaging information protocol. It was necessary to export the whole series of images (usually containing approximately 800 images) as the DICOM format was not able to be maintained with export of a single image (the attenuation of the individual image would subsequently be altered, therefore the standard HU for tissue segmentation could not be used).

Mid-sagittal and axial images were linked in the image viewer in order to identify the mid 3rd lumbar vertebrae (L3) as shown in figure 7. Ideally, both tips of the transverse processes of L3 were visible on the single slice. A single image can be identified by the series and slice number in the series. The series and slice number of this axial image of the abdomen was then noted and selected for analysis from the previously downloaded series.

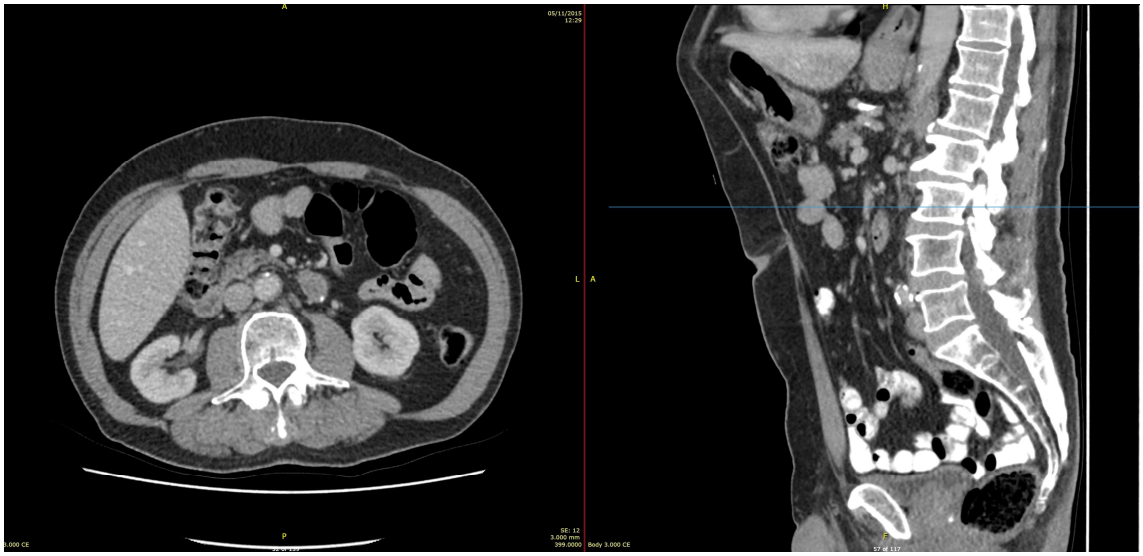


Figure 7. Linked axial and sagittal images to identify mid L3 level

5.4 BODY COMPOSITION SOFTWARE

The SliceOmatic software and its reason for use in this study was described above. A copy of the SliceOmatic licence was purchased from Tomovision and used to analyse all CT images available.

5.4.1 Tissue segmentation tools

There are various modes that SliceOmatic can use to compute tissue segmentation and 'tag' images in order to calculate an area. It is highlighted in the description for SliceOmatic that different modalities can be best segmented with different techniques. The available modes include:

Edit – a manual paint brush of varying size

Thresholding –applies a global threshold to the complete image based on the HU of individual pixels. This represents a type of automated tissue segmentation tool for SliceOmatic.

Region growing – based on thresholding, directly off the pixel values. This has a 'paint' mode and will tag the pixels within a given predetermined threshold. A 'Grow 2D' mode will grow a region starting from the cursor and all adjacent pixels falling within the reference range will be tagged.

Snake – this creates an outline of any tissue and is ideal for the circumference of the body. This allows the snake to be calculated as a length and the tissues within can also be filled.

Morpho – breaks the image up into small segments based on mathematical morphology in variation of the pixel values (tissue gradients). These regions can be merged together to create progressively larger regions separated by the various tissue gradients.

There is the potential for an additional plugin for the software to perform automatic segmentation of CT slices at the T4 or L3 level into muscle, subcutaneous, visceral and intra-abdominal fat but this proprietary technology has not been validated yet and was not used.

5.4.2 Protocol development

Each of the different methods were initially trialled to generate tissue classes and the difficulties encountered are also described. Ultimately a protocol utilising the region growing tool was used as this was felt to be the most efficient and accurate method of performing the body composition analysis.

Thresholding

This is an automated tool allowing a global threshold to be applied to a single image. Grey levels based on the HU are applied to the whole image and four different thresholds may be used. In theory, this is a useful tool to break down all the tissues for quick and easy body composition analysis.

A histogram box in this mode shows the number of pixels that occupy each HU. (Figure 8)

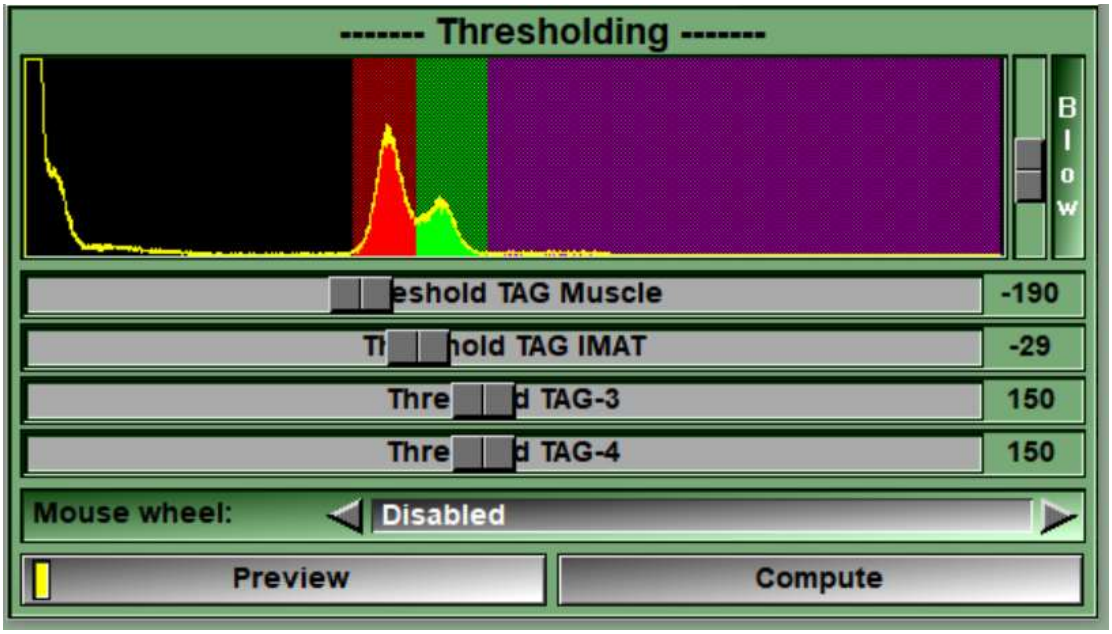


Figure 8. Histogram taken from SliceOmatic for a patient based on HU

This roughly corresponds to the various tissues contained within that slice of varying densities, ie. Adipose tissue < -30 HU, skeletal muscle and soft tissue between -29 - 150 HU and bone 250 - 1000HU. Up to 4 different classes of tissues can then be coloured differently depending on the range of HU used.

However, there is significant overlap of the HU of various tissues. For example, soft tissue, such as the liver has an unenhanced attenuation value of approximately 55 HU.[102] This clearly overlaps with skeletal muscle which is the intended target tissue for the analysis.

Upon using the initial value for skeletal muscle of -29 to 150 HU multiple other intra-abdominal tissues and organs were also tagged apart from skeletal muscle. An example is seen below. (Figure 9)

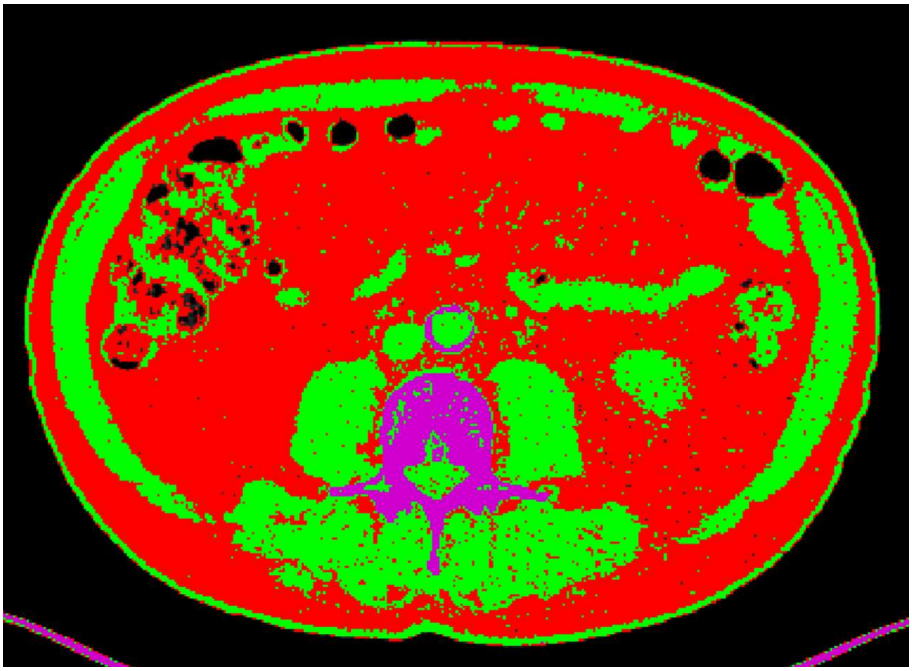


Figure 9. Example of body segmentation of L3 slice based on thresholding. Red – fat, HU -190 to -30. Green – muscle, HU -29 to 150. Purple – bone/other, HU >150.

Manual removal of unwanted tissues can be performed. The thresholding mode of analysis was thought to be probably more useful for tissues that do not have significant overlap in HU such as bone or perhaps in areas where there is a lesser variety of tissues. This mode has been used in assessing skeletal muscle in the thigh.[103]

Region growing

Region growing mode involves manually painting the desired area and can be used with a variety of sub-modes). Initially the semi-automated sub-mode grow 2D was used. A cursor was placed over the required tissue, ie. psoas muscle, with HU between -29 to 150. A region associated with the structure where the cursor selected would be filled in with adjacent pixels falling in the threshold range also being highlighted. In this way an area could be filled in rapidly. Depending on the size of the cursor used, this could either fill in a large block of tissue but this did result in some inadvertent highlighting of unintended tissues. This included the aorta and inferior vena cava which are frequently adjacent to the psoas muscle for example (*Figure 10)*. A larger cursor resulting in a smaller area to highlight and fill or manual adjustments could subsequently be made to remove these areas.

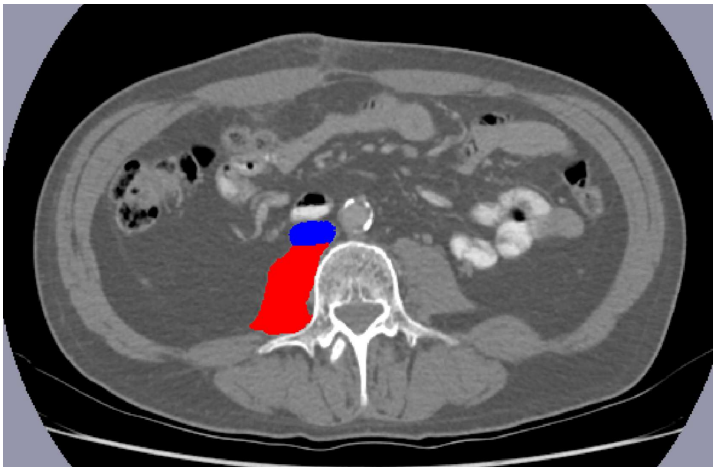


Figure 10. Exampled of incorrectly highlighted tissue. Inferior vena cava (blue) that could be easily tagged adjacent to right psoas muscle (red).

A further sub-mode of region growing, 'paint' provided greater control over the region of interest. A threshold value of -29 to 150 HU was provided for a circular cursor. The size of the circular cursor could be altered and therefore fine control could be attained, particularly over the areas where tissues were directly adjacent to one another. This method was performed manually beginning with a larger cursor for rapidly tagging tissue, then smaller cursors were used on areas requiring greater control.

Ultimately a combination of both 'grow 2D' and 'paint' was felt to provide the best balance between capturing all the necessary data but also efficiency. Larger areas could be filled and segmented rapidly utilising the grow 2D tool and finer areas requiring greater control were completed using the paint tool. For all measurements, -29 to 150 HU was used for measurement of skeletal muscle.

Morpho

Morpho breaks the image up into large or small areas of tissue with roughly similar HU. The shapes generated are based on watershed areas where the HU density changes. Large or small shapes could be computed based on the setting and each of these shapes then required filling by clicking in the area. Morpho seemed particularly useful and accurate when using the smallest shape but the requirement of clicking in each area which proved time consuming. Larger morpho shapes allowed tissues to be filled more quickly but there was often overlap with adjacent (non-skeletal muscle) soft tissue meaning. These could be manually removed but only according to the predefined shape in the Morpho mode. An example of a scan broken down by this method is seen below *(Figure 11a and 11b)*.

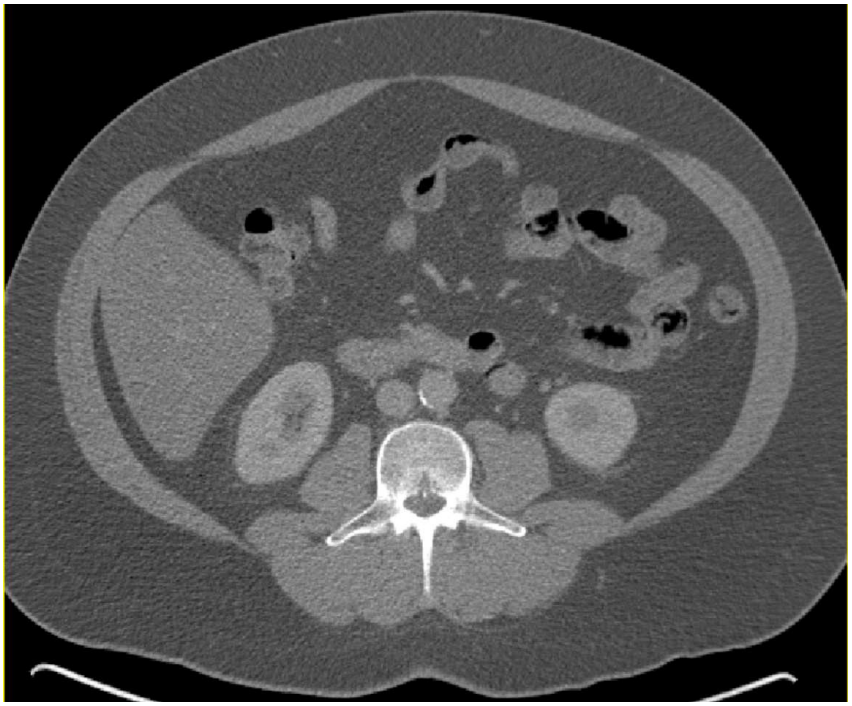


Figure 11a. Example of L3 slice prior to morpho tool

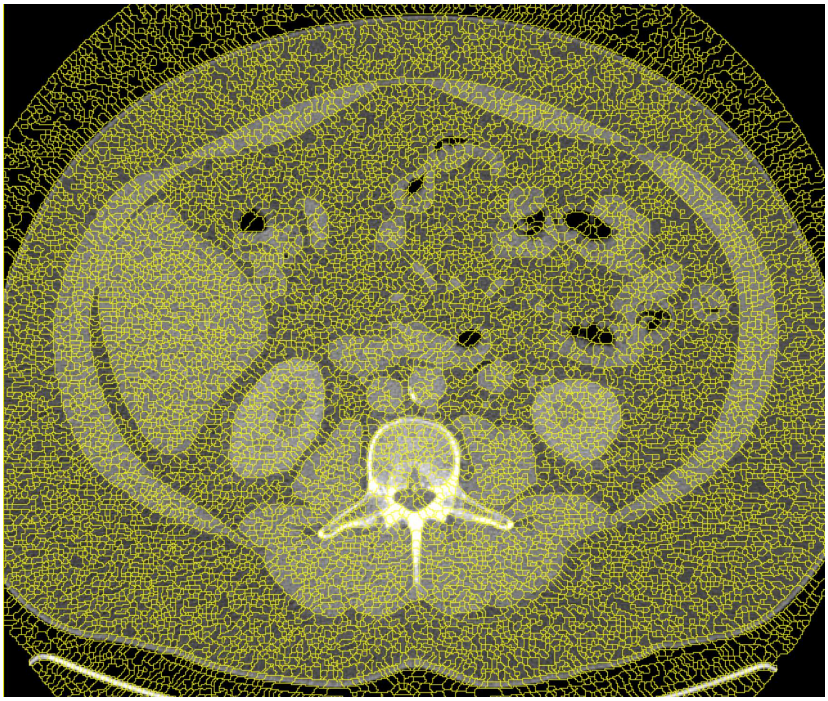


Figure 11b. Same image broken down via morpho. Each shape can then be selected to highlight the area required.

Snake

Snake was useful as a freehand tool but was found to be time consuming as each individual muscle generally required outlining with subsequent filling.

5.4.3 Measurement of skeletal muscle index and skeletal muscle radiation attenuation

All measurements were performed by the primary investigator (EW), a Fellow of the Royal Australasian College of Surgeons who had developed the SliceOmatic protocol described and had extensive experience of reviewing CT images and therefore sound understanding of radiologic anatomy.

Following tagging of the appropriate tissues using the region growing method described, SliceOmatic was able to provide measurements regarding the surface area in cm^2 of the relevant area. This was performed for each patient with the available CT slice. This area is known as the skeletal muscle area (SMA) or total abdominal musculature area (TAMA) at the L3 slice *(Figure 12a and 12b)*. A skeletal muscle index (SMI) was then calculated by dividing this area by the square of the patient's height (in m^2). The cut-offs for sarcopenia have been described previously. Figure 12b demonstrates a patient with sarcopenia and the significant loss of muscle can be seen marked via body composition.

The skeletal muscle radiation attenuation (SMRA) was based on the mean HU of all tagged voxels after selecting the appropriate musculature. A range (minimum and maximum HU) is also provided but this was not thought to be clinically relevant. As mentioned, intra-muscular fat (IMAT) can also be assessed as an indirect marker of muscle quality but this would require further steps after the initial tagging of muscle. In order to keep the protocol readily accessible for novice users, this process was omitted.

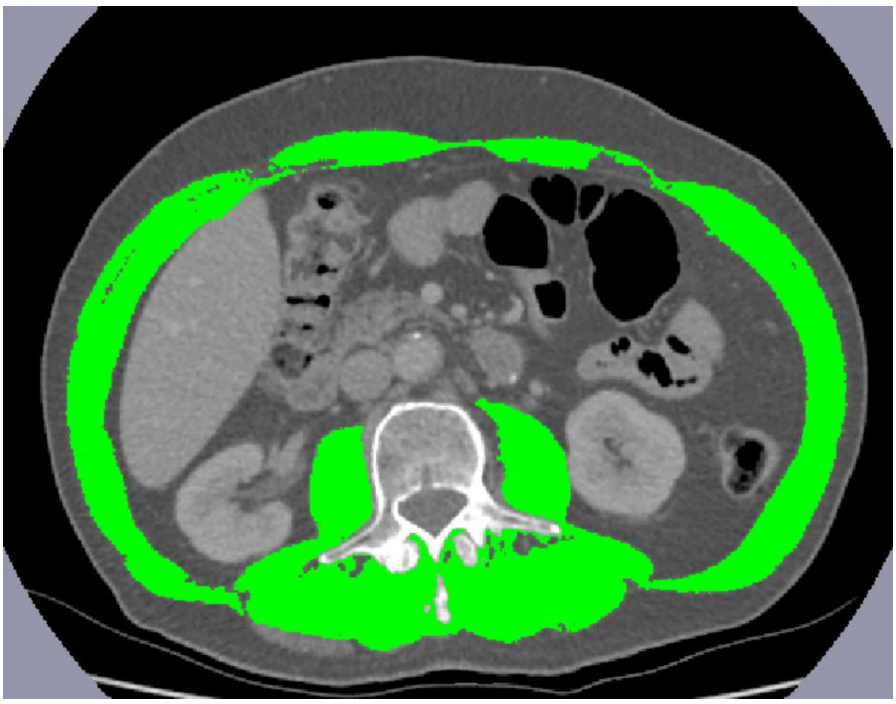


Figure 12a. Example of total abdominal musculature area (TAMA), taken at single L3 slice

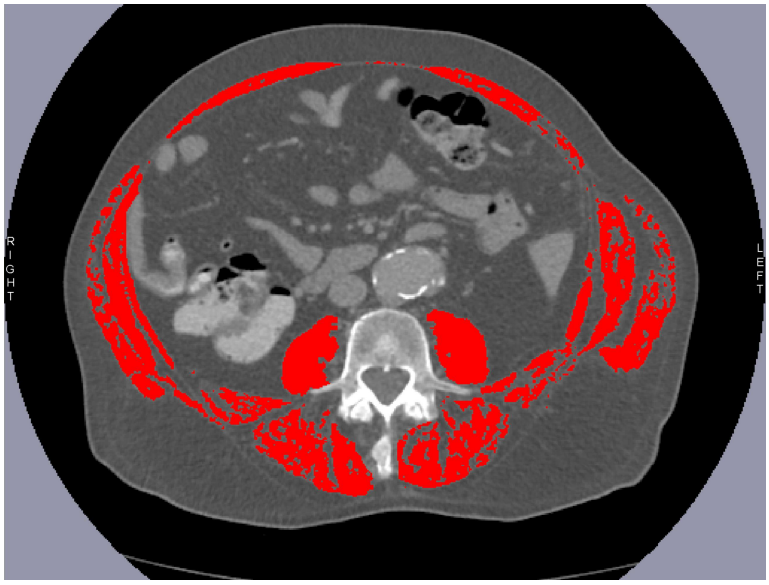


Figure 12b. An example of TAMA in a patient with sarcopenia; SMI 37 cm^2/m^2

5.5 VALIDATION OF RESULTS

For each patient, this measurement was repeated on the same CT slice. If the SMIs were both above or both below the cut-off measures for sarcopenia, then this was taken to be consistent and adequate for the diagnosis of sarcopenia or no sarcopenia. The average of these 2 measurements was used as the final SMI for that patient. Where one measurement was above and one was below the cut-off for sarcopenia, the procedure was completed a third time. The two closest measurements in agreeance were used as the true measures and the average of those 2 measurements was used as the final SMI. These results were also analysed for % variation between measurements.

It is understood that there may be a difference in the quality of the CT images, due to differing protocols in contrast use, voltage, scanning phases and thickness of slices provided. The assessment of the quality of the images was not the purpose of this study and the use of these images in such a protocol as described reflects 'real world' settings. In reality, the measurement of SMI and SMRA was not greatly impeded by this fact as the fundamental aim was to determine the accuracy and robustness of the described technique.

5.6 STATISTICAL ANALYSIS

The results were divided into patients undergoing oesophagectomy versus those undergoing gastrectomy and analysed both separately and also combined as a larger cohort of all malignant UGI patients undergoing surgical resection at our institution.

Quantitative data were presented as mean $\pm$ standard deviation. Data were compared using either the Wilcoxon Rank sum (Mann-Whitney U) test. Paired results were compared using ANOVA for multivariate analysis. Univariate regression was used to evaluate the effect of sarcopenia on morbidity, mortality and recurrence.

Concordance was measured using the Pearson correlation and Spearman-Rho test. Survival was estimated using a Kaplan-Meier survival analysis and differences in survival rates were tested with the log-rank test and with univariate and multivariate Cox Proportional Hazards regression analysis.

All statistical analyses were performed using STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). *P-value* less than 0.05 was considered to be statistically significant.

6. RESULTS

6.1 OVERVIEW

The initial aim of the study was to develop a standardised methodology for using body composition software to assess for the presence of sarcopenia in our surgical patients, using their routine staging CT scans. The next aim was to assess the significance of sarcopenia on patient outcomes.

The results section is therefore divided into two broad parts. The first primarily addresses the measurements of SMI and SMRA, and the accuracy and the concordance of those results using the protocol described. The second section analyses the patient cohort and examines whether sarcopenia or other factors were associated with surgical outcomes for these patients.

A total of 93 patients were identified over the study time period. Of these, 11 were excluded (surgery for benign disease or only having a 'wedge gastrectomy' performed) leaving a total of 82 patients to review. 38 patients underwent oesophagectomy and 44 patients underwent either partial or total gastrectomy. 5 patients in the gastrectomy group did not have any suitable/available imaging to analyse. The total number of scans analysed was 77 and this is represented in a flow diagram. (Figure 13)

Overall, the measurement of SMI and SMRA demonstrated high concordance using the protocol and methodology developed in sections 5.3, 5.4.2, 5.4.3 and 5.5 above. Subsequent analysis of sarcopenia based on SMI and SMRA showed that sarcopenia, tumour stage, and any recurrence were independent risk factors for survival.

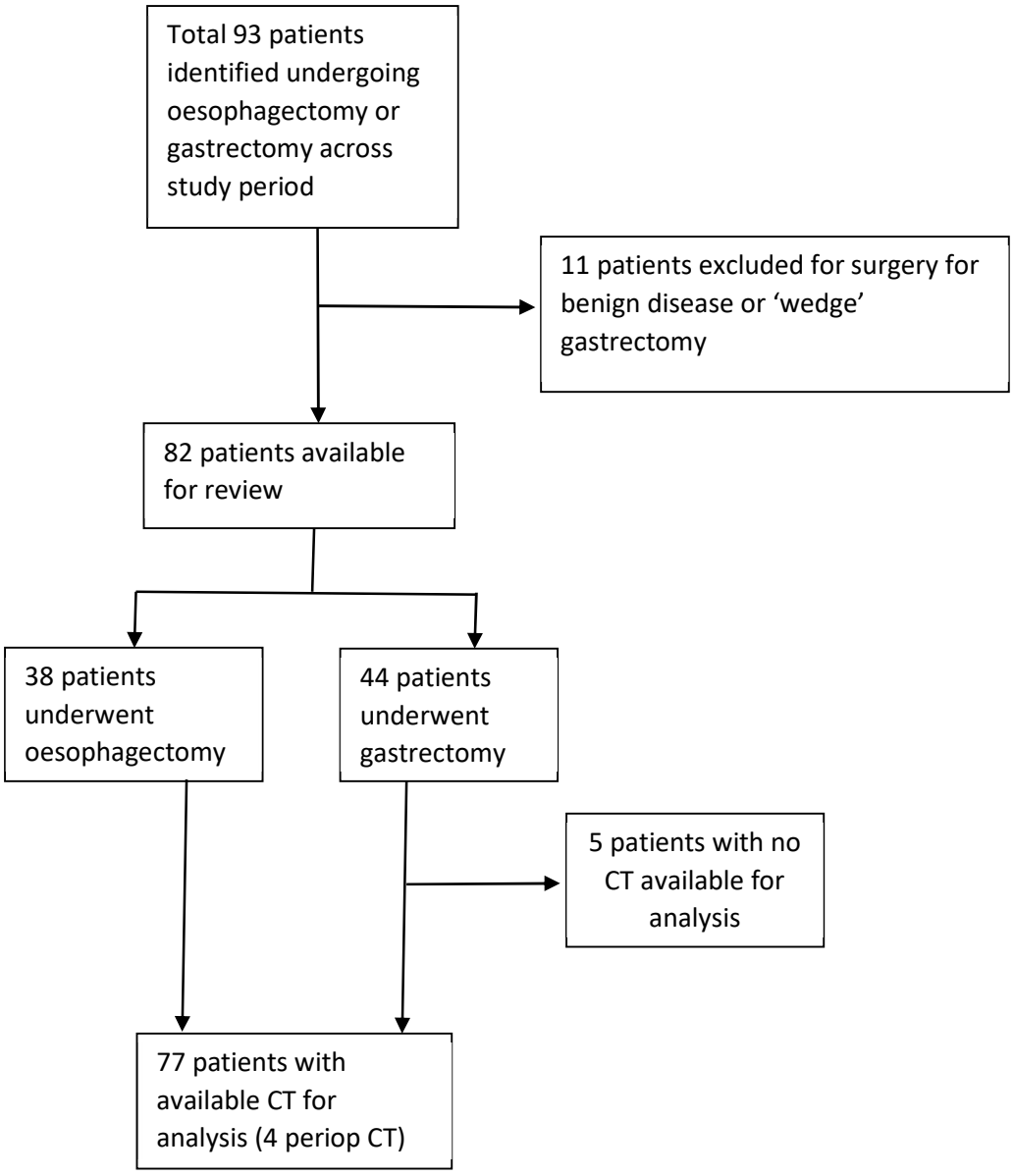


Figure 13. Flow diagram representing patient inclusion

6.2 MEASUREMENT OF SMI AND SMRA

6.2.1 SMI and SMRA measurements

Overall males had a significantly higher SMI than females. Across both oesophagectomy and gastrectomy patients, the mean SMI for females was 39.82 cm^2/m^2 and for males it was 50.39 cm^2/m^2. This was statistically significant (p-value = 0.02).

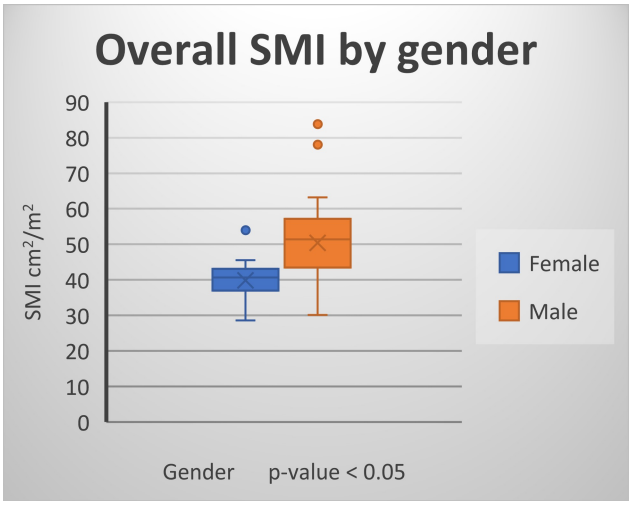


Figure 14. Overall SMI by gender – difference significant at p-value < 0.05 (Mann-Whitney U test)

For males, oesophageal cancer patients had a higher SMI compared with gastrectomy patients. (Mean SMI of 52.9 cm^2/m^2 vs 47.62 cm^2/m^2; p-value 0.0016) whereas the opposite was true in female patients. (Mean SMI of 36.0 cm^2/m^2 vs 41.7 cm^2/m^2; p-value 0.047). (Fig 15a and 15b)

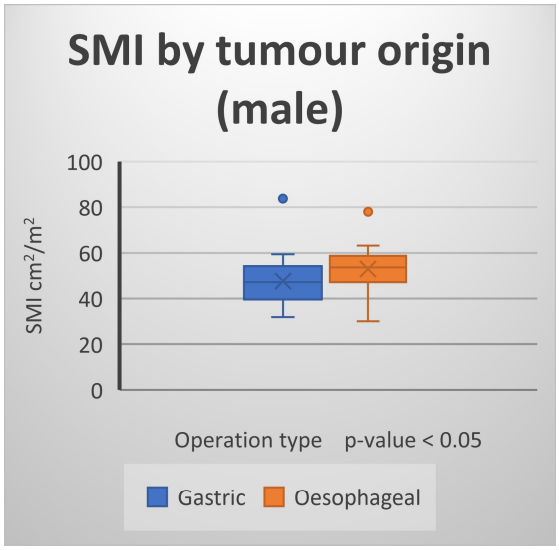


Figure 15a. SMI by tumour origin (male)

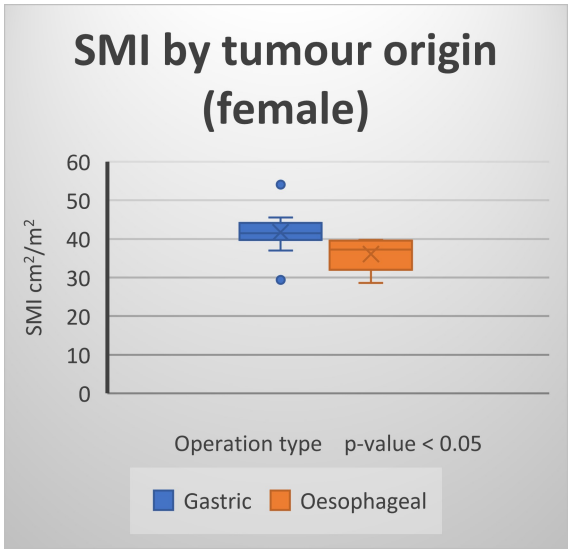


Figure 15b. SMI by tumour origin (female)

The SMRA was similar between oesophagectomy and gastrectomy patients with a mean of 39.85HU and 37.95HU respectively (p-value = 0.81). (Figure 16) In contrast to SMI, there was no statistically significant difference between the SMRA of male and female patients, regardless of operation type (p-value = 0.48). (Figure 17)

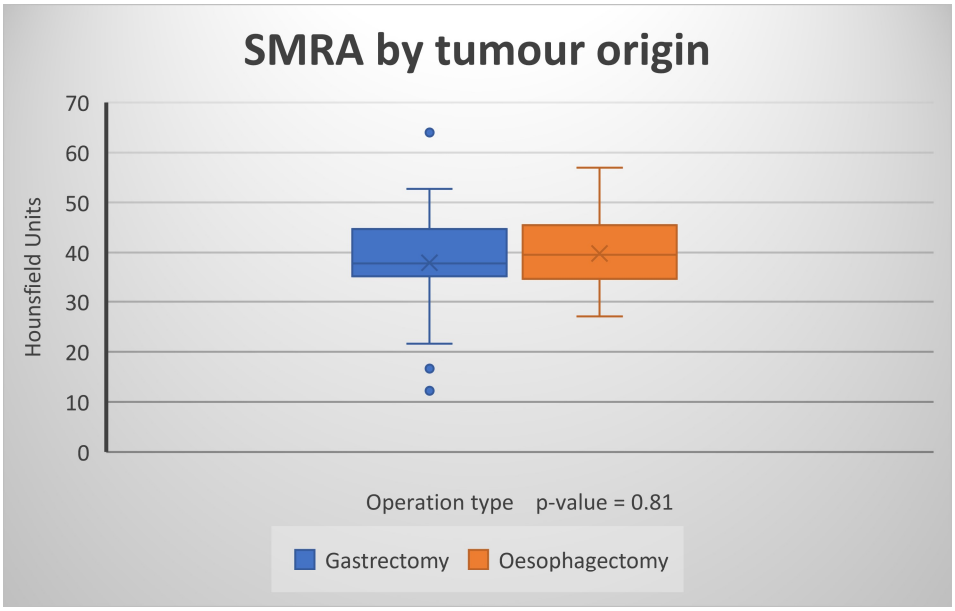


Figure 16. SMRA (skeletal muscle radiation attenuation) by tumour origin

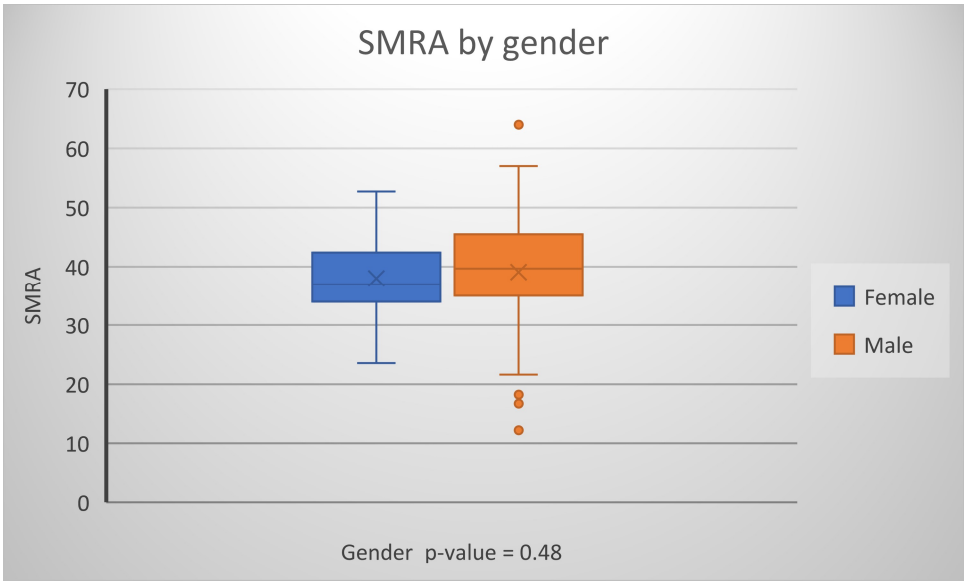


Figure 17. SMRA by gender

6.2.2 Concordance

The 2 separate SMI measurements for each scan were recorded and concordance rates between were analysed. There was a high Pearson's coefficient of correlation demonstrated between the measurements for the gastrectomy and oesophagectomy patients with an R value of .9965 and .9968 respectively. The actual recorded SMI for all the patients across the 2 repeated measurements are shown in a scatter plot in Figure 18 below.

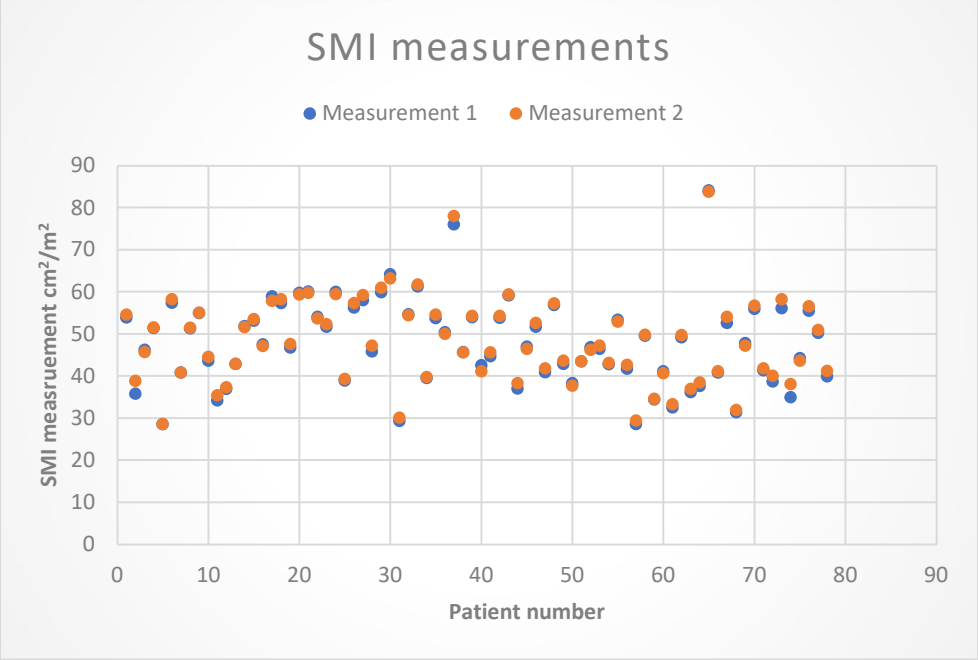


Figure 18. Scatter plot demonstrating SMI for each patient. The 1st measurement is represented by blue and the 2nd measurement is represented by orange.

The overall coefficient of correlation for the groups combined was 0.9968 with an R^2 value of .9937. This correlation is shown in the line of best fit (between the 2 measurements) in Figure 19 below.

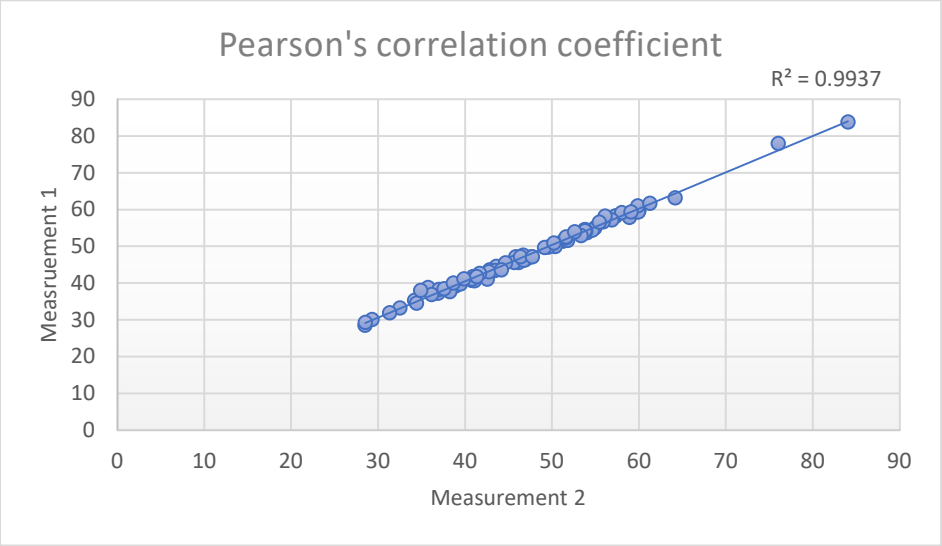


Figure 19. Linear graph representing Pearson's correlation coefficient between the 2 repeated measurements of SMI

The coefficient of variation was close across the 2 measurements of SMI. Between measurement 1 and measurement 2, there was an average overall difference in measurements of 1.86%.

Similarly, the SMRA demonstrated a high coefficient of correlation with an R value of .992 and R^2 of 0.984.

6.3 IMPACTS OF SARCOPENIA

6.3.1 Demographic details

Baseline data are presented for the 77 patients in Table 5 below and divided by operation type.

	Oesophagectomy (n = 38)	**Gastrectomy (n = 39)**	**Overall (n = 77)**	**P-value**
Age (years) Mean +/- SD	64	70	67 63 +/- 9.8	**0.017**
Gender F:M	5:33	10:29	15:62	0.25
BMI kg / m^2, mean	27	25.6	26.3	0.19
Obese: BMI > 30 kg / m^2	10	10	20	0.99
SMI cm^2 / m^2, mean - **Female** - **Male**	 36.0 52.9	 41.7 47.6	 39.8 50.4	 **0.047** **0.0016**
SMRA (HU), mean	39.85	37.95	38.8	0.18
Sarcopenia present (%)	18 (46%)	18 (46%)	36 (47%)	0.99
Number of days CT performed prior to operation [95% CI]	68 [50.5, 85.5]	35.9 [22.7, 49.2]	53 [40.5, 63.1]	**0.002**
ASA score, mean	2.7	2.7	2.7	0.76
LOS (days), median	14	10	12	**<0.05**
ICU LOS (days), mean	4	1.2	2.5	**<0.001**
Complications **- Anastomotic Leak** **- Return to theatre**	20 0 3	8 1 4	28 1 7	**0.005** - 0.99
Neoadjuvant therapy (%)	31 (81.5%)	10 (25.6%)	41 (53.2%)	**<0.001**
Adjuvant therapy (%)	9 (23.7%)	16 (41.0%)	25 (32.5%)	0.15

Histology				
- **Adenocarcinoma**	35	38	73	-
- **Squamous cell carcinoma**	2	-	2	
- **Other/not specified**	1	1	2	
Overall stage				
- **1**	9	11	20	0.39
- **2**	4	1	5	
- **3**	21	22	43	
- **4**	0	3	3	
R0 resection (%)	36 (94.7%)	39 (100%)	75 (97.4%)	0.99
30-day mortality (%)	1 (2.6%)	0 (0%)	1 (1.3%)	-
Recurrence in study period	16	15	31	0.99
Median survival in days	589	613.5	589	0.35

Table 5. Demographic data. BMI – body mass index; SMI – skeletal muscle index; SMRA – skeletal muscle radiation attenuation; HU – Hounsfield unit; ASA – American society of anaesthesiologists; LOS – length of stay; ICU LOS – intensive care unit length of stay

Overall, the average age of patients was 67 years old, with gastrectomy patients being older than oesophagectomy patients by approximately 6 years (p-value = 0.017). There were 62 male patients (80.5%) and average BMI at time of surgery was 26.23 kg/m^2 (95% CI 17 – 43kg/m^2). Average length of stay (LOS) was higher in the oesophagectomy group compared with patients undergoing gastrectomy (14 vs 10 days, p-value < 0.05) as was the ICU LOS (4 vs 1.2 days, p-value < 0.001). This will reflect the thoracic dissection required for oesophagectomy and also the protocols for commencing oral intake, which are different for the two groups.

Most patients (81.5%) in the oesophagectomy group received neoadjuvant therapy whereas a higher proportion of patients had adjuvant therapy following their gastrectomy (41.0%). Furthermore, patients in the oesophagectomy group had their scan analysed on average over 1 month earlier than that of patients with gastric cancer. The timing of these scans does reflect the frequent use of neoadjuvant treatment in these patients. The histology type was primarily adenocarcinoma and there

were no significant differences in pathological stage noted (p-value = 0.39). Median length of follow up was 19.4 months.

There was 1 death within 30 days in the cohort representing an overall 30-day mortality of 1.3%. This occurred in a patient 8 days following an oesophagectomy. The cause of death was cardiac arrest.

6.3.2 Prevalence of sarcopenia

There were 36/77 patients diagnosed with sarcopenia on SMI using the cut-off values established by Martin et al[78] giving an overall prevalence in our population of 46.7%. (Table 6) The prevalence of sarcopenia was slightly higher (49.4%) when using the cut-offs of Prado et al[77] (SMI < 52.5 cm^2/m^2 and < 38.5 cm^2/m^2 without respect to BMI in male and female patients respectively). When the highest cut-off criterion for sarcopenia by Mourtzakis et al[76] was applied (SMI < 55.4 cm^2/m^2 for male and SMI < 38.9 cm^2/m^2 for female), the prevalence decreased (36.4%) as would be expected with more stringent criteria.

There was no statistical difference between sarcopenic and non-sarcopenic patients for age, BMI, gender or between gastrectomy and oesophagectomy patients. There was a trend toward sarcopenic patients being older, but the difference in ages was only 3 years. The cut-off by Martin et al was primarily used for subsequent analyses, the reasons for this are detailed in the Discussion below.

Of the sarcopenic patients, 10/36 (27.8%) were classed as obese, ie. sarcopenic obesity (Sarcopenia and BMI > 30 kg/m^2).

	Overall (n = 77)	**Non Sarcopenic (n = 41)**	**Sarcopenic (n = 36)**	**p-value**
Age, mean [IQR]	67 [57, 73]	66 [53, 73]	69 [63, 74]	0.06
BMI kg/m^2, mean [IQR]	26 [23, 30]	26 [24, 30]	26 [22, 30]	0.31
Gender (F:M)	15:62	7:34	8:28	0.58
Gastrectomy: Oesophagectomy	39:38	21:20	18:18	0.99
Neoadjuvant treatment	41 (53%)	18 (44%)	23 (64%)	0.11
Adjuvant treatment	25 (32%)	13 (32%)	12 (33%)	0.99

LOS (days), mean [IQR]	12 [10, 17]	12 [8, 18]	13 [10, 16]	0.53
ICU LOS (days), mean [IQR]	2 [0,4]	1 [0,1]	2 [1,3]	0.30
Overall complications	28 (36%)	18 (44%)	10 (28%)	0.16
Recurrence	31 (40%)	13 (32%)	18 (50%)	0.11
Overall mortality in study period	33 (43%)	13 (32%)	20 (56%)	**0.04**

Table 6 Sarcopenia associations based on Martin et al cut-offs. BMI – body mass index; LOS – length of stay; ICU – intensive care unit. (Age, BMI, LOS and ICU LOS expressed as medians)

With regards to diagnosing sarcopenia via SMRA, we found that the prevalence was 33.8% (26/77) overall. There was no requirement for the SMRA cut-off to be adjusted for gender but the female:male ratio was 6:20. There was no statistically significant difference for sarcopenia based on SMRA with regards to other basic demographic data including age, BMI and operation type.

There appeared to be a correlation between SMI and SMRA (Figure 20), but the correlation between these 2 results was low on Spearman Rho calculation (R_s 0.30, p-value < 0.05). SMRA classified as sarcopenic 3 patients, who were not classified sarcopenic via SMI.

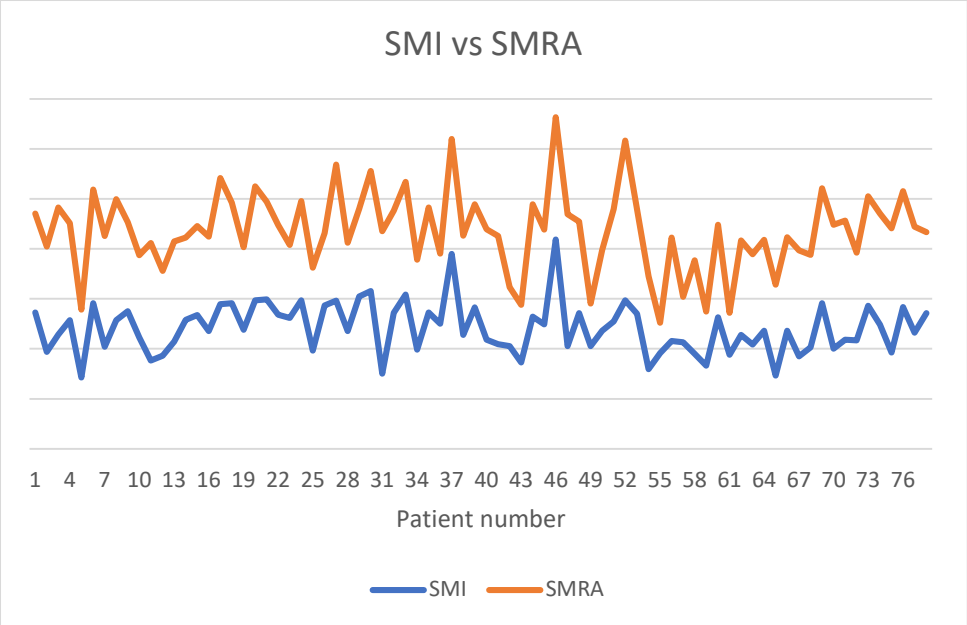


Figure 20. Overall trend between SMI and SMRA for each patient, SMI – blue, SMRA – orange. (not to scale)

6.3.3 Length of stay and complications

The overall complication rate was 36% with significantly more complications occurring in oesophagectomy patients (20/38 patients, 53%) than gastrectomy patients (8/39 patients, 21%) (p-value < 0.05). The presence of sarcopenia was not associated with an increase in complications with complications occurring in 10/36 (28%) sarcopenic versus 18/41 (44%) non-sarcopenic patients (p-value = 0.16). No statistically significant difference was detected for LOS, ICU LOS, readmission rates or return to theatre between sarcopenic and non-sarcopenic patients.

There was only 1 patient with an (1.3%) anastomotic leak in the entire cohort. This occurred in a patient following total gastrectomy who was confirmed on imaging to have a leak on day 3. The patient was returned to theatre for repair of the leak. Subsequently, the patient also required a further return to theatre for a small bowel obstruction.

2/39 patients in the oesophagectomy group had chyle leaks (5.2%) both requiring return to theatre for repair. Other complications included respiratory (14.3%), cardiac (9.1%), superficial site infection (6.5%), thromboembolic (5.2%) and non-specified (3.9%). 9 (11.7%) patients (6 oesophagectomy, 3 gastrectomy) required readmission within 30 days of discharge.

Complications occurred in 3/10 (30%) patients with sarcopenic obesity and 7/26 (26.9%) patients with sarcopenia alone.

The overall complications are summarised in Table 7 below.

Complications	**Oesophagectomy (n = 38)**	**Gastrectomy (n = 39)**	**Overall (n = 77)**
Anastomotic leak	0	1	1
Return to theatre	4	4	8
Respiratory	9	2	11
Cardiac	5	2	7
Superficial site infection	2	3	5
Deep site infection	0	1	1
Thromboembolic	3	1	4
Other	2	1	3
Readmission within 30 days	6	3	9
Overall	20	8	28

			p-value < 0.05

Table 7. Summary of complications; Note some patients had multiple complications

6.3.4 Survival

The 5-year overall survival (OS) was 43% with a median of 2.03 years. On univariate analysis, higher T, N and overall stage conferred worse OS (HR of 2.67, 2.60, and 1.86 respectively). Disease recurrence and adjuvant therapy were also predictors of worse survival. Sarcopenia showed a trend to worse OS. However, this was not statistically significant (p-value = 0.053). On multivariate Cox-regression analysis, disease recurrence and overall stage of cancer remained significant for conferring worse OS. On this analysis, sarcopenia was also found to be a statistically significant independent predictor for worse OS with an odds ratio of 2.17 (p-value = 0.03). See Table 8.

	Odd Ratios	**p-value**
Recurrence	**2.95 [1.33, 6.51]**	**0.008**
Sarcopenia	**2.17 [1.06, 4.45]**	**0.03**
Stage (T3/T4 vs T1/2)	**1.57 [1.06, 2.31]**	**0.025**
Neoadjuvant	1.20 [0.57, 2.51]	0.63
Adjuvant	0.82 [0.38, 1.78]	0.62

Table 8. Multivariate Cox-regression analysis for overall survival

None of age, sex, BMI, LOS, or complications had a significant influence on survival in univariate or multivariate analyses.

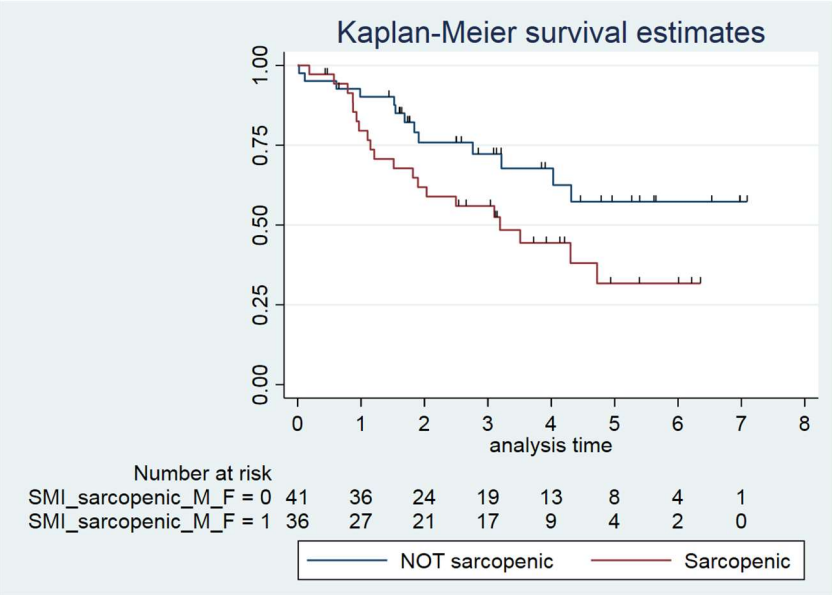
The 5-year OS was 57% in the non-sarcopenic group versus 32% in the sarcopenic group. This was statistically significant (p-value = 0.0485). The overall survival by year is shown in Table 9. A Kaplan-Meier survival curve (Figure 21) demonstrates an early drop off in survival for patients with sarcopenia occurring in the first year.

There was no association between the obese sarcopenic group and overall survival with the Kaplan-Meier survival curve between sarcopenia and sarcopenic obesity essentially mirroring one another for the first 2 years. (Figure 22)

Overall survival

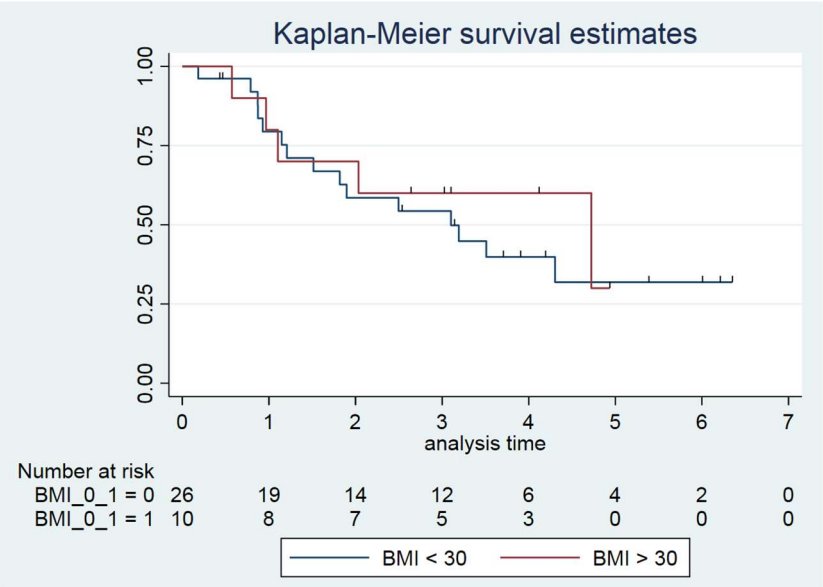
	Overall	Sarcopenic	NOT sarcopenic
Year 1	85% [75%, 92%]	80% [62%, 90%]	90% [76%, 96%]
Year 2	69% [57%, 79%]	62% [44%, 76%]	76% [58%, 87%]
Year 3	65% [52%, 75%]	56% [38%, 71%]	72% [54%, 84%]
Year 4	56% [43%, 68%]	44% [27%, 61%]	68% [48%, 81%]
Year 5	45 [31%, 58%]	32% [14%, 51%]	57% [36%, 74%]

Table 9. Overall survival table by year. Overall p-value 0.0485



p-value = 0.0485

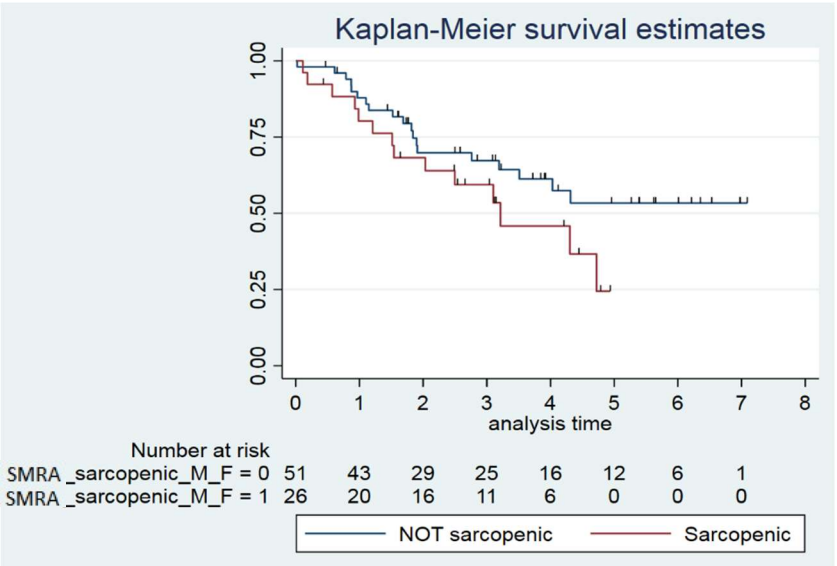
Figure 21. Kaplan-Meier overall survival curve between sarcopenic (red) versus non sarcopenic (blue) groups. Sarcopenia diagnosis based on SMI cut-offs as found in Martin et al.[78]



p–value = 0.68

Figure 22. Kaplan-Meier overall survival curve for sarcopenic obesity patients. Sarcopenic obesity, BMI > 30 (red) versus sarcopenia alone, BMI < 30 (blue)

When using the SMRA criterion for diagnosing sarcopenia, a trend still existed for worse 5-year OS in the sarcopenic population (36%) versus the non-sarcopenic population (53%). (Figure 23) This was not statistically significant. Sarcopenia based on SMRA was not demonstrated to be a statistically significant factor for OS on either uni- or multivariate analyses.

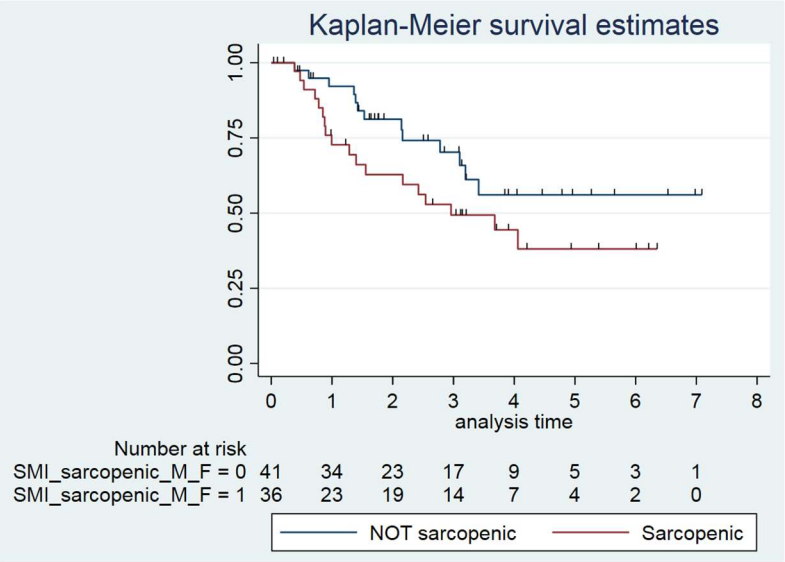


p-value = 0.14

Figure 23. Kaplan-Meier survival curve between sarcopenic (red) versus non-sarcopenic (blue) groups. Diagnosis based on SMRA cut-offs as found in Martin et al.[78]

6.3.5 Recurrence

Overall, 31 patients are known to have developed recurrence during the follow up period. With patients coming from other centres and the private setting, 5-year follow up data availability was incomplete (four patients lost to follow up). Follow However, disease-free survival (DFS) was 47% in those who had follow up out to 5 years. There was a negative correlation between sarcopenia and DFS with 5-year DFS of 38% and 56% in sarcopenic and non-sarcopenic patients respectively but this was not statistically significant (p-value = 0.11). Although the DFS quoted here was higher than the OS quoted in 6.3.4, this is not a contradiction because this figure represents a subset of that particular group in who 5 year data regarding recurrence was available. The Kaplan-Meier curve is shown in Figure 24 for DFS. The overall stage of the patient was the only significant factor affecting DFS (OR 1.77, p-value = 0.009) on multivariate analysis. Again there was no statistically significant association between the obese sarcopenic group and the non-obese sarcopenic. When sarcopenia was diagnosed via SMRA, there was no significant difference in recurrence seen between the sarcopenic and non-sarcopenic groups.



p-value = 0.11

Figure 24. Kaplan-Meier curve for 5-year DFS in sarcopenic (red) versus non-sarcopenic (blue) groups. Sarcopenia diagnosis based on SMI cut-offs as found in Martin et al.[78] (Black vertical dash represents patient censoring)

7. DISCUSSION

7.1 OVERVIEW

Sarcopenia is an increasingly recognised disease process of prognostic significance in both cancer and non-cancer populations. In the UGI cancer population sarcopenia has been associated with increased postoperative complications, increased toxicity when undergoing neoadjuvant treatment and shorter overall and disease-free survival.[63] Therefore better recognition and diagnosis of sarcopenia is a necessary first step in the hoped-for improvement in patient outcomes through effective treatment of this condition.

Patients with a new diagnosis of cancer will all routinely have staging CT scans. It is not routine to perform body composition analysis on these scans but software exists for this purpose. Body composition software provides extra information about patients, that is otherwise not utilised. In particular, it has the ability to provide information on the quantity and quality of the musculature, both of which are prerequisites for the diagnosis of sarcopenia. Our study demonstrates that useful data can be derived from these routine scans, using relatively simple, and readily available software.

CT-based diagnosis of sarcopenia is distinct from previously described functional methods[17] that can detect the condition. CT-based diagnosis can accurately measure muscle mass, whereas functional tests look at muscle performance – it seems likely that these two approaches will be adjunctive in the future.

It will be necessary to establish appropriate cut-offs for SMI and SMRA through studies such as ours, looking not only at the distribution of results but the association between measurements of SMI and SMRA and patient outcomes. In our cohort, there was a significant association between sarcopenic detected on SMI and overall survival rates, using previously described cut-offs.[78] Sarcopenic patients represent a group who are readily identifiable on the protocol established and who represent a vulnerable group of patients undergoing major UGI surgery. CT based diagnosis could be utilised to guide treatment decisions, or allow interventions to be targeted in order to improve outcomes.

7.2 DEVELOPMENT OF METHODOLOGY AND UTILITY OF BODY COMPOSITION SOFTWARE

7.2.1 Methodology

Multiple body composition software programs to evaluate CT scans exist and are readily available. With the commencement of this study, a number of different software were considered. SliceOmatic appeared to be most widely reported software in use in the literature,[74] with many of the reference

ranges for sarcopenia based on studies that used SliceOmatic for measurements. Therefore, as a starting point, it was chosen to be used for this study.

Pandemic related restrictions meant that formal instruction or tutorial was not possible in terms of learning to use SliceOmatic. However at https://www.tomovision.com/products/sliceomatic.html (accessed December 2021) tutorials are available that go through the basics of opening DICOM files, and tagging and segmenting different tissues. This is free and readily available.

An instruction manual is included with purchase of the licence and is also available online. This manual goes through the capabilities of each tool and various modes of tissue segmentation, but gives no indication of the ideal modes to use for different purposes. The development of a standardised methodology was done predominantly through experimentation with different tissue segmentation tools of the program, as discussed in the methods section. No changes were made to the HU cut-offs of different tissue types. Interestingly, the grow2D and paint mode that was settled on is also the protocol by which at least two other studies[84,104] had performed their comparative study between body composition software. Dennis et al[103] described a step-by-step approach to segment and measure a CT image of the thigh into fat, muscle and bone. However, this was not suitable for measuring the abdominal musculature as in this study. Other studies that have utilised SliceOmatic for body composition in the abdomen do not specifically describe their protocol.

Selecting the appropriate CT slice for analysis does require some knowledge of anatomy. The L3 level is easily determined by linking an axial and sagittal CT slice together. The L5 S1 level is a fairly easy landmark to find on the sagittal film and therefore L3 can be easily found. Alternatively, the last vertebra with ribs representing thoracic vertebra 12 (T12) can be followed from above, although lumbar ribs can be present in rare circumstance which would alter the measurement down to the L3 vertebra.

Although the ideal in most cases is to obtain an axial slice containing the 2 transverse processes of the L3 vertebrae, this is not always possible. In reality, it is highly unlikely that with modern CT with slice thicknesses of 3-5mm, that such a difference would result in measurement of a separate vertebral level. Regardless, a study examining the SMI of all vertebral levels from T10 to L5 found that L2 and L4 levels had the highest concordance with L3.

Once the axial slice has been identified, segmenting the tissues is comparatively straightforward with the help of body composition software. The main tissues of interest to be segmented on a CT have been largely defined, that is skeletal muscle with HU of -29 to 150. With the use of SliceOmatic, it is relatively easy to select the appropriate HU and only highlight tissues based on voxels falling within

the units selected. Other tissues that may be of interest may also be selected, ie, adipose tissue -190 to -30 HU. However, again some basic knowledge of anatomy, particularly with regard to the abdominal musculature is required for this, but could be easily taught. (Figure 25)

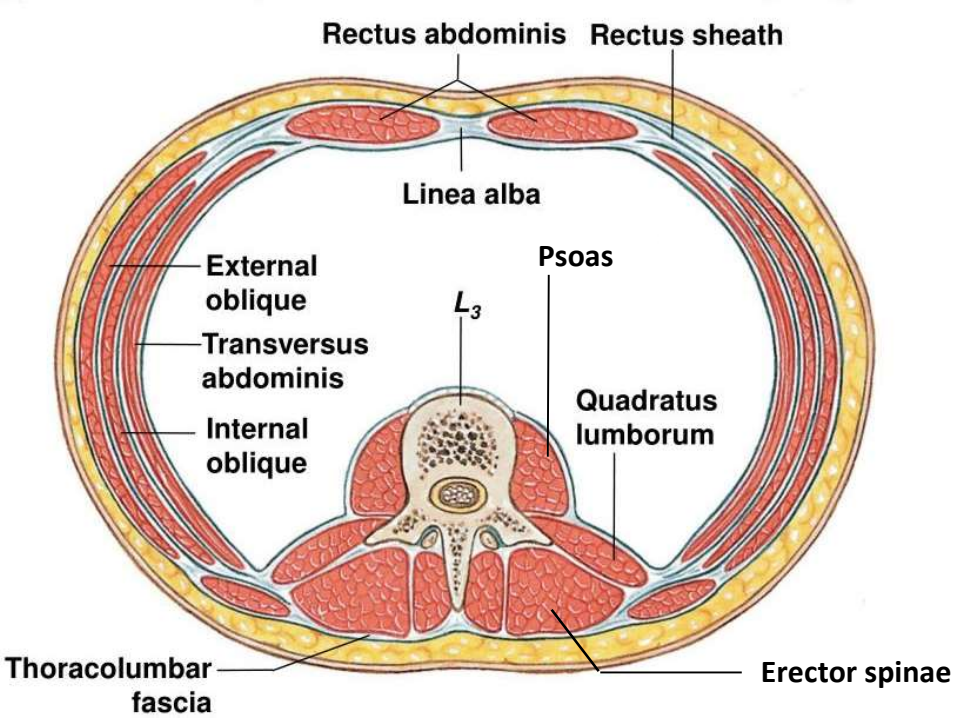


Figure 25. Diagram showing muscles measured at the L3 slice[105]

It is vital when assessing the abdominal musculature that a standardised approach is taken and this study outlines at least one method to assess the SMI at an L3 slice, starting from the initial CT scan. In this way, this protocol can be extrapolated and applied to any other setting where a CT scan is performed and its raw images can be downloaded.

Furthermore, segmentation of other tissues of interest such as subcutaneous fat and intra-abdominal and intra-muscular adipose tissue may be performed utilising this protocol but with different HU cut-offs. Of course, some training may be required of users to understand some intra-abdominal structures but in general, fat should be of significantly lower HU density than organs within the abdomen and therefore would not be incorporated into the measurements. Increases in intra-abdominal adipose tissue and subcutaneous adipose tissue have shown varying impacts of surgical outcomes in the oncology patient group, but the measurement of it may be useful for other purposes such as documentation of weight loss in bariatric surgery.

7.2.2 Reliability and concordance

With any test, inter-observer variability will be an issue. A protocol needs to be robust enough to allow for accurate testing. It was noted during development through the use of the various tagging modes that it was easy to highlight extraneous tissue apart from muscle, from nearby organs or attenuated fat. Particularly around the psoas musculature, adjacent organs such as the kidney, IVC and aorta frequently contain contrast meaning they may have HU that overlap closely with muscle.

Inflammation to tissues can similarly increase the HU, particularly of the underlying adipose tissue. It is therefore vital that an appropriate assessment of where the muscle edge starts and finishes is undertaken prior to the tagging process. Figure 26 demonstrates a relatively easy error that could be performed during the tagging process. This highlights the need for these software tools to have a manual option or at least a manual check function to look for such errors.

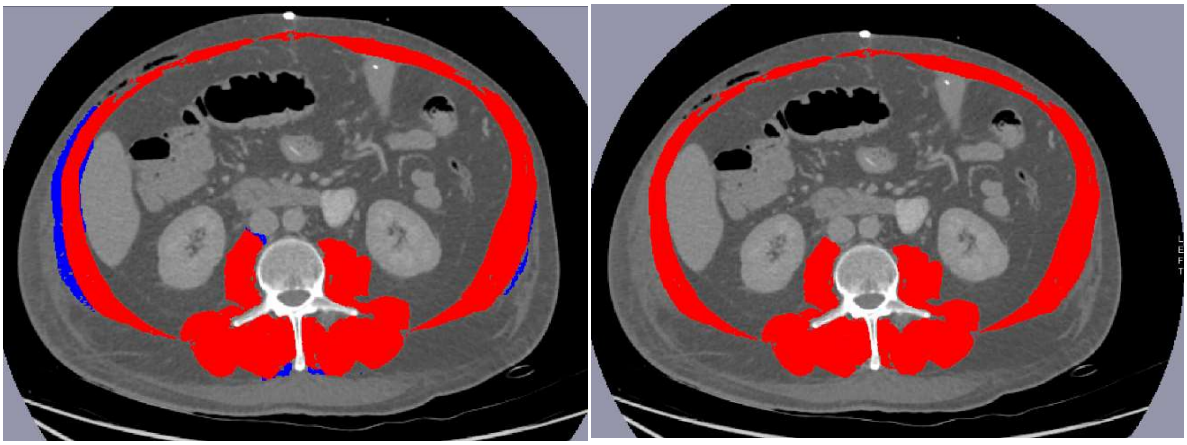


Figure 26. Example of how extra shaded areas (highlighted in blue) that could easily be inadvertently tagged. These tissues represent inflammation in the surrounding subcutaneous adipose tissue increasing its density to mimic that of skeletal muscle.

With establishment and adherence to the described protocol, it has been shown that repeated measurements demonstrated excellent correlation. The Pearsons correlation coefficient for the 2 separate measurements of SMI for both groups was 0.9968 indicating a very low intra-observer variation. In normal settings, an R^2 value above 0.7 is generally seen as having high correlation. The protocol is highly reproducible and precise, even in novice users with little formal training in the use of the software. The inadvertent highlighting of adjacent tissues to a minor degree does not seem to significantly alter between repeated measurements.

Inter-observer variability has also been shown to be low in several studies, although this was not formally examined in this study. Van Vugt et al was able to demonstrate almost perfect inter-observer agreement (intra-class correlation coefficient ≥ 0.999) between 2 medically trained observers with knowledge about radiologic anatomy and body composition software.[104] Similarly, both Takahashi et al[106] and Irving et al[85] confirmed high inter-observer coefficients of reliability.

7.2.3 Utility

Despite its high initial startup cost ($~5500AUD), SliceOmatic has a number of advantages. There are multiple modes for tagging selected tissue, different HU ranges may be selected individually and it easily quantifies the region of interest both in terms of surface area, volume and HU density. There are also likely other features of the software that may be useful but that were not required for the purposes of this study. SliceOmatic has been also compared with multiple other software programs and they seem to produce similar cross-sectional areas and measurements of the tissues of interest. Importantly this has been shown to be true in both expert and novice users of the body composition software.[106] In reality, it appears that most body composition analysis programs produce comparable results and can provide useful additional information not normally analysed from routine, readily available imaging.

7.3 TOWARD AUTOMATIC SEGMENTATION

A number of studies have examined the role for automation to decrease the amount of manual work required to assess body composition from CT images[106-108] with some promising results.

SliceOmatic can have an additional module added on known as the ABACS (Automated Body composition Analyzer using Computed tomography image Segmentation) module that provides automatically the HU and labelled tags to highlight the appropriate tissues. This provides semi-automation where preset programs are able to assist a manual user and should in theory facilitate more rapid analysis.

Increasingly, artificial intelligence (AI) may also be utilized for body composition analysis and work in this field is rapidly evolving. Largely these AI approaches are based around neural networks which require initial calibration,[109] but if found to be accurate and useful have great potential to expand the field of body composition.

AI may have the potential to not only analyse a single slice, but even multiple slices across multiple vertebral levels to give an even greater understanding of the body composition of patients. The time taken to analyse scans will be greatly reduced through automation and in theory, inter- and intra-observer variation will be reduced to zero although the ranges on which the neural pathways are based still rely on a likely manually generated reference range.

7.4 PREVALENCE OF SARCOPENIA

7.4.1 Overview

The overall prevalence of sarcopenia was 33.8 – 49.4% in the cohort depending on the SMI cut-offs used. This did not vary depending on whether the patient underwent an oesophagectomy or a gastrectomy. There was a trend toward sarcopenic patients being older although this was not statistically significant.

These sarcopenic patients represent a previously unrecognised subset of patients undergoing major UGI resection who are at particular risk. The presence of sarcopenia was not correlated with gender, BMI, ASA score, tumour stage, nor perhaps surprisingly, neoadjuvant therapy.

Sarcopenia has been shown to worsen or even develop during the course of neoadjuvant treatment for oesophageal or gastric cancer. Certainly, muscle mass[110] and function[111] has been shown to decline in patients undergoing neoadjuvant chemotherapy for oesophageal cancer and this was associated with poor outcomes. Patients with greater muscle loss during neoadjuvant treatment seem to have a significantly lower rates of overall survival.[110]

In a study of 261 patients by Elliott et al[112] patients actually developed sarcopenia during neoadjuvant chemoradiotherapy for locally advanced oesophageal cancer. The rate of sarcopenia increased from 15.9% to 30.8% preoperatively as measured by skeletal muscle index on CT assessment associated with a loss of 3kg lean body mass. Interestingly, in the study by Elliott et al, fat mass appeared to be preserved during the course of treatment, despite overall weight loss, suggesting a direct effect of neoadjuvant chemoradiation on skeletal muscle – perhaps an effect that goes beyond poor oral intake, and tumour-related catabolism.

Interventions during this period of neoadjuvant treatment have been suggested[111] but to date, no studies have been reported demonstrating improvements in relation to sarcopenia in this population group.

This research program was retrospective and while we analysed pre-operative scans for each patient we did not formally analyse whether the CT was performed prior, during or after neoadjuvant therapy. It is noted that in general, the number of days the CT was performed prior to the operation date was higher for patients undergoing oesophagectomy (68 days), in keeping with a higher number of these patients undergoing neoadjuvant therapy. Given the longer time that these patients had CT assessment performed prior to their operation, it is likely that for many, the CT analysis was performed prior to neoadjuvant treatment and perhaps no restaging CT was performed. No formal protocol existed at the time for restaging imaging to be performed during or after neoadjuvant treatment and this was done at the discretion of clinicians.

A sarcopenia prevalence of 33.8 – 49.4% compares favourably with two recent systematic reviews for all cancer types[113,114] and other published literature specific to gastric (10-62%)[115] and oesophageal cancers (16-75%)[116,117] although clearly there is variability in its prevalence, which could of course be partly related to differing diagnostic criteria. The prevalence in the cancer population is significantly higher than studies conducted in the general population,[118,119] where it is about 10%.

An important issue in this broad area is the actual definition of sarcopenia. Several similar but not identical definitions are in use for both SMI and SMRA, and a standardized approach would make it easier to accurately compare future studies.

It is impractical however to compare this population of patients with UGI malignancy with a healthy population as a control group as healthy individuals are not appropriate controls. Intuitively, it might be that all cancer patients are at risk of sarcopenia, and that oesophageal and gastric cancer patients are at higher risk due to potential nutritional issues associated with the tumours and their treatments. However, there is more work required in that area as well, and moreover this project was aimed at how to measure sarcopenia, not at comparing rates of sarcopenia across cancer diagnoses.

The research program aimed to assess the possibility and utility of using body composition software in assessing sarcopenia in UGI cancer patients, and then to examine the effect of sarcopenia on clinical outcomes in these patients. References ranges and definitions were adopted based upon review of the literature, and there was no advantage anticipated by trying to find age-matched but healthy patients who had CT scans available for analysis as a more direct set of “controls”.

7.4.2 Establishing cut-offs for sarcopenia

Clearly the prevalence of sarcopenia is dependent on how it is measured and defined. It is important to note that currently, there is no universal definition for sarcopenia as measured by skeletal muscle

mass or index on CT. Initially, low muscle mass or quantity was the focus for identification of patients with sarcopenia. Baumgartner et al[52] was one of the first to examine skeletal muscle mass and its health impacts in a large cohort of elderly patients in the late 1990's. At the time, no established references for low muscle mass were available. In their study, muscle mass was either measured directly via dual-energy X-ray absorptiometry (DEXA) or calculated using an equation involving various anthropometric measurements developed for the purposes of measuring muscle mass. Sarcopenia was defined as a SMI with a cut-off value of greater than 2 standard deviations below the sex-specific means for young adults aged 18-40. Baumgartner et al found that prevalence of sarcopenia increased with age, affecting > 50% of people over 80 years. Furthermore, the presence of sarcopenia in these individuals was independently associated with functional impairment and disability in their cohort.

7.4.2.1 SMI

When the first consensus definition for sarcopenia was released by EWGSOP in 2010, the main cut-offs provided were for SMI found on DEXA and BIA. Even at this time, 3 similar, but slightly different, cut-off points of SMI were used to diagnose sarcopenia.[37] No cut-off points for sarcopenia were provided for SMI based on CT although CT was mentioned as a gold standard in muscle mass measurement.

It is not practical in the retrospective clinical setting of this project to compare sarcopenia as diagnosed on CT with investigations used more commonly in research settings such as DEXA and BIA, as the patients had not had DEXA or BIA. Of course, these comparisons have already been made in other population groups as has been discussed.

One significant issue is, in fact, despite L3 SMI cut-offs found on CT quoted frequently in the literature as being diagnostic of sarcopenia, there is no current consensus on what the cut-offs actually should be. Much of the literature bemoans this fact – it is clear that low muscle mass and by default sarcopenia, easily detected on routine CT, is consistently associated with worse surgical outcomes. In spite of the heterogeneity in definition of sarcopenia, studies still conclude that CT would seem the sensible 'primary method for body composition assessment owing to its routine use in this patient cohort.'[3]

SMI cut-offs that are used most frequently in the literature are provided by 3 main studies (Table 10) but they differ slightly in their measurement and derivation and this is worth discussing.

SMI Cut-off for sarcopenia	Female	Male	Sarcopenia prevalence (%)
Mourtzakis et al[76]	< 38.9 cm^2/m^2	<55.4 cm^2/m^2	33.4%
Prado et al[77]	< 38.5 cm^2/m^2	< 52.8 cm^2/m^2	49.4%
Martin et al[78]	< 41 cm^2/m^2	< 43 cm^2/m^2 if BMI < 25 < 51 cm^2/m^2 if BMI > 25	47.6%

Table 10. Differing SMI cut-offs according to the 3 major quoted studies and relative prevalence of sarcopenia in our cohort.

Mourtzakis et al actually correlated measures of skeletal muscle at L3 with formal whole-body fat-free mass measured via DEXA and found a linear relationship between the two. Equations were formulated allowing CT based methods of measuring skeletal muscle to be converted into DEXA generated results. Cut-offs for SMI on CT were calculated then at <55.4 cm^2/m^2 and < 38.9 cm^2/m^2 when using diagnostic ranges of sarcopenia based on appendicular skeletal muscle mass of <7.26 kg/m^2 and < 5.45 kg/m^2 for males and females respectively.

The studies by Prado and Martin both used optimal stratification to determine the cut-off value with the most prognostic significance. In brief, optimal stratification is a statistical method that can divide a modest sample size into homogenous strata and then examines the boundary at which the sample provides a clinically meaningful discrimination value.[120,121] In short, different cut-offs are assessed to determine what boundaries will have the greatest predictive value on outcome. The rationale for using techniques such as optimal stratification to define cut-off points is that the relationship with survival for a particular variable is not known.

To date, the study by Martin et al is the largest by some margin, (>1400 patients). They found that the criteria to determine sarcopenia were related to the patient's BMI. According to their study, the SMI cut-off most associated with low survival for a male patient with BMI < 25 kg/m^2 is <43 cm^2/m^2 and < 51 cm^2/m^2 for a male patient with BMI > 25 kg/m^2. Interestingly, these SMI cut-off values for sarcopenia correspond roughly with the 5^{th} centile for SMI in a standard healthy Caucasian population.[80]

The higher SMI cut-off by Mourtzakis et al yielded a lower prevalence of sarcopenia in our cohort and subsequently showed no correlation with survival. This SMI cut-off was, essentially arbitrarily

proposed at two standard deviations below a reference range found in healthy populations and it may be less useful than a cut off based on clinical outcomes (eg Martin et al), in particular for patients with a known malignancy. The authors did not report correlations between their their proposed SMI cut-off and outcomes in their original cohort of cancer patients, although this was not the aim of that article.

In our study, it was found the cut-offs from Prado and Martin's studies had an association with decreased overall survival, and the relationship was statistically significant using the criteria proposed by Martin et al. These cut-offs appear likely to be the more useful, indicating, as they do, a group of now-identifiable patients with poorer outcomes.

Aside from these 3 main cut-off criteria, other studies have generated their own SMI cut-offs by dividing groups into tertiles and using the lowest tertile as a cut-off or using a cut-off based on 2 standard deviations below the mean. Many other variations of this exist, creating further heterogeneity in the proposed cut-off criteria in the literature.

In Amini's[74] recent systematic review on the topic of CT assessment for muscle mass and myosteatosis, they highlight the need for further standardisation. They conclude that the emerging trend of utilising CT will require some form of standardisation and this is echoed in other works including the update provided by the EWSGOP for the consensus definitions for sarcopenia.[17,73]

7.4.2.2 SMRA

The utility of using muscle quality to diagnose sarcopenia is also severely diminished by the lack of a consensus definition. The SMRA is the most commonly used indirect method on CT to measure muscle fat content. However, no actual cut-off criteria have been used widely in the literature apart from the those published by Martin et al. Therefore, the criteria from that reference was utilised in this study. Interestingly, unlike SMI, the cut off for SMRA is not dependent on gender although it is true that females in general have a higher proportion of body fat overall, compared with males. What is not clearly known though is whether this proportion of body fat affects the SMRA. Aubrey et al[79] reports that being male may have an effect of +3.8HU to the SMRA and perhaps even up to +14.7. Despite this possibility, the SMRA cut-off currently remains the same for both male and females. Of note, BMI is less relevant in this approach as BMI can remain normal or perhaps even elevated, despite a patient having low SMRA (Figure 5).

Utilising Martin et al's cut-off in our cohort, sarcopenia on SMRA criteria was diagnosed in a significant, albeit smaller, proportion of patients and it is possible that, in particular, some female patients were

assessed as non-sarcopenic, when perhaps sex-specific cut-offs for SMRA would have detected these patients to have sarcopenia.

Another issue regarding use of the SMRA to detect sarcopenia is the different contrast related phases that can be achieved of performing CT scan. It is unclear whether the phase of the CT impacts the SMRA, and further technical knowledge of the radiological basis of HU measurement would likely be required to ascertain this.

Recently, a combination of skeletal muscle area (psoas area) and SMRA was reported[122] to be most predictive of complications and prognosis following gastrectomy. It is possible that a combination of CT obtained measurements, perhaps even in combination with other recorded measurements may have an even greater predictive value in our cohort, but this will require further analyses.

7.5 IMPACTS OF SARCOPENIA

There are multiple potential impacts of sarcopenia on surgical outcomes that have been described in the literature. Sarcopenia has also been demonstrated to be associated with postoperative complications,[123] and poor prognosis[117,124] although some isolated studies have failed to demonstrate any negative short nor long term impacts.[125] A meta-analysis has demonstrated that sarcopenia may be associated with an increased risk of up to 30-40% for major complications after gastrointestinal tumour resection.[126]

In our study, sarcopenia had a negative impact on OS and this was statistically significant. There was a similar correlation to DFS but this was not statistically significant. No relationship between sarcopenia and overall complication rate, readmission rate or return to theatre was seen in this study.

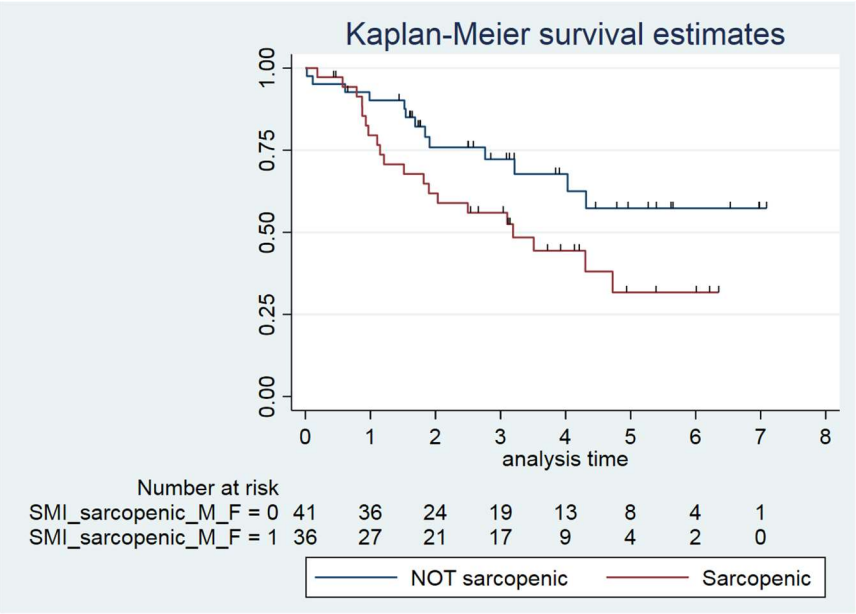
7.5.1 Impact on overall and disease-free survival

With regards to OS, multiple studies and meta-analyses have consistently shown sarcopenia to be an independent risk factor for poor survival. In our study, sarcopenia gave an odds ratio of 2.17 for poorer overall survival and this was statistically significant. Our data seem reliable in that the other statistically significant factors affecting overall survival (overall stage and recurrence) are well recognised and validated risk factors.

Additionally the impact of sarcopenia on survival found in this study closely mimics those reported in a recent meta-analysis performed by Deng et al[117] for patients undergoing oesophagectomy. Sarcopenic patients in this analysis demonstrated a lower 3-year OS rate of 51.6% vs 65.4%, $p < 0.001$).

Sarcopenia was found to be an independent risk factor for OS with a hazard ratio of 1.58 ($p < 0.001$). One of the recommendations arising from this meta-analysis suggested the routine preoperative assessment of sarcopenia given its significance in predicting survival.

Interestingly the patterns of decreased survival described by Deng et al are also similar to the findings in the current study, in that they report a difference in 3-year survival rates of approximately 10-15% that is then preserved out to the 5-year follow up. It is clear from the Kaplan-Meier curve in Figure 21 that there is an early drop off in survival for sarcopenic patients in the first year. Thereafter, the difference between the 2 curves is maintained and tend to run in parallel. It appears that the difference in OS in our population occurs in the initial 1-2 years after operation.



p-value = 0.0485

Figure 21 reproduced. Kaplan-Meier survival curve between sarcopenic (red) versus non sarcopenic (blue) groups. Sarcopenia diagnosis based on SMI cut-offs as found in Martin et al.[78]

It is hypothesised on the basis of this finding that the effects of sarcopenia are felt more or exacerbated by surgery and the perioperative period. The patients might then do worse in this initial period after surgery and then perhaps return to baseline. It is also true that this project did not have the capacity to determine whether patients remained sarcopenic, or whether they regained lost muscle mass after recovering from surgery and adjuvant treatment. Huang et al[127] found that sarcopenia found on CT was able to predict 1 year mortality in a cohort of elderly (≥ 65yo) patients undergoing gastrectomy.

What is unclear from our data and the literature is whether it is possible to (and how to potentially) identify this subgroup of sarcopenic patients at seemingly higher risk in the period following surgery. Greater support in the perioperative period may be required for some patients, and in others futile surgery may even be avoided altogether. More research is required to help risk-stratify these sarcopenic patients further.

Sarcopenia has also been shown to affect disease-free survival although this was not born out in our data. Our follow up period was thought to be of sufficient length (mean > 2 years overall) and robust enough (careful review of all points of hospital contact a patient) for most recurrence to be detected. The overall stage of the patient was the only factor that affected disease free survival with a higher stage giving an odds ratio of 1.77.

Clearly the use of neoadjuvant and adjuvant therapy affects overall and disease-free survival. Neither were demonstrated to be independent predictors of survival although it is noted that only a minority of patients undergoing gastrectomy in our cohort underwent neoadjuvant treatment and a minority of patients undergoing oesophagectomy underwent adjuvant treatment. This merely reflects the local practice of our institution at the time and further analysis of these smaller groups of patients are likely insufficient to make valid observations.

Overall, the results of this study support the finding that sarcopenia is an independent risk factor for OS, giving the second highest risk after developing recurrence (OR 2.17 vs 2.95). Cancer recurrence is largely based on tumour biology but recurrence can be altered by treatments such as adjuvant therapy. In much the same way, although sarcopenia may already be determined prior to the patient's diagnosis based on their physical traits, underlying comorbidities and lifestyle, identification of it may allow the provision of treatments that could improve or even delay the progression of sarcopenia and thus improve survival. It is also possible that sarcopenia is an early manifestation of poor-prognosis tumour biology, although that is an untested hypothesis at this stage.

7.5.2 Impact on complications

Reports suggesting sarcopenia as a predictor for complications in patients undergoing oesophagectomy or gastrectomy are mixed. Rinninella et al[128] performed a meta-analysis of gastric cancer patients with low muscle mass as measured at L3 specifically and found a higher risk of postoperative complications and severe complications and increased length of stay. On the other hand, a meta-analysis conducted by Boshier et al[3] on oesophagectomy patients found no significant difference with post-operative complications (Clavien-Dindo ≥ II) in sarcopenic patients.

Most studies reporting an association group the complications quite broadly. In the current study, the overall complication rate was 36% and no significant differences were noted between sarcopenic and non-sarcopenic patients. The most common complications were of a respiratory (14.3%) or cardiac (9.1%) nature and these results compare favourably with international benchmarks (Low 2019). The study was likely underpowered to detect complication rates in our cohort given the relatively low incidence of morbidity.

Furthermore, given the low number of complications, associations with specific operation type were unable to be detected. For example, higher rates of postoperative pneumonia have been demonstrated in sarcopenic patients undergoing oesophagectomy.[3,129] Patients undergoing oesophagectomy are particularly prone to developing respiratory complications, because dissection into the thoracic cavity is required for patients. Single lung ventilation is usually required for the duration of the thoracic component of the operation with resultant lung collapse. Respiratory complications were not more likely to occur in our sarcopenic patient group undergoing oesophagectomy as compared with other non-sarcopenic patients.

The most feared complication of UGI surgery is anastomotic leak and one of the early was concerns that sarcopenia may be a risk factor for this. In our study, there was only one leak in the entire cohort of patients precluding any meaningful analysis between groups, whereas anastomotic leak rates may be higher (up to 18%)[130] in studies reporting this association. Dedicated research has further failed to confirm any association. Anastomotic leak rates may perhaps be more affected by factors other than sarcopenia such as technical precision or operative approach.

The lack of association between sarcopenia and complications in our study probably also explains the lack of association with length of stay, given recovery of patients will like be impacted by any perioperative morbidity.

Studies have shown that the presence of sarcopenia impacts on a patient's ability to tolerate neoadjuvant therapy and may result in dose-limiting toxicities. No difference in rates of neoadjuvant therapy were seen in sarcopenic versus non-sarcopenic oesophageal cancer patients in our study. However, there may be a proportion of patients who initially underwent neoadjuvant therapy who then failed to progress to surgical resection due to the impacts of sarcopenia, but these patients would not have been captured and analysed on our inclusion criteria.

7.6 RELATIONSHIP OF SARCOPENIA TO OTHER MARKERS OF NUTRITION

7.6.1 Weight loss

Weight loss is known to occur in patients with malignancy and in particular, patients with UGI malignancy. Martin et al[78] have already reported on weight loss of ~8% of body weight to be a significant factor in survival for cancer patients. However, weight loss, or more specifically a lack thereof, does not indicate a patient is not at risk of poor outcomes.

Awad et al[55] demonstrated that significant reductions in skeletal muscle occurred and the incidence of sarcopenia actually increased with neoadjuvant therapy for patients with oesophageal cancer. This is despite the body weight remaining fairly static during this period, implying that sarcopenia is clinically insidious and not easily detected without explicit investigation, such as through the use of body composition software.

In our cohort the patient's weight was well recorded at the time of operation, but weight was not well recorded at time of diagnosis or of first review. Often weight loss was documented to have occurred but not quantified. Furthermore, at our institution, we receive a number of patients from either the private setting or from rural and regional areas where the documentation of weight loss was unavailable. Therefore the data regarding weight loss did not allow meaningful analysis with the rest of the data that was far more standardised and readily available. This severely limited any associations to be made between weight loss, sarcopenia and surgical outcomes. However, from the results, BMI either elevated or depressed, was not associated with sarcopenia, implying sarcopenia as a distinct and separate entity from weight alone. A prospective approach to recording a patient's weight at each visit or review will be helpful in confirming any relationship between sarcopenia, weight and weight loss.

Other means of assessing for weight loss in our cohort were contemplated however. In one study looking at patients with oesophageal cancer,[110] even though sarcopenia itself was not a risk factor for survival, a decrease in SMI of ~3% during neoadjuvant treatment was associated with worse survival. The loss of SMI corresponded to up to a 6kg loss of weight.

At the time of analysis, there was no standardised protocol regarding repeated imaging to be performed during or following the completion of neoadjuvant therapy and subsequently it is difficult to know, even indirectly from a decrease in SMI, what the relationship of weight loss to sarcopenia and surgical outcomes in our cohort. There were a number of patients who did have two scans (one prior and one following neoadjuvant treatment) but this was quite variable. Therefore, we were only able to assess one scan and utilised the one closest to the date of surgery as a standard.

This is of particular importance in the oesophagectomy group whose rates of neoadjuvant therapy were (expectedly) much higher. It is possible that the analysis was primarily performed on the CT done

at the time of diagnosis and perhaps sarcopenia may have developed during neoadjuvant treatment as has been shown in the literature. Therefore, there may be patients who were initially classified as not sarcopenic but subsequently developed sarcopenia during treatment that were missed. This may have two effects in that the outcomes of this missed sarcopenic group would be poor but this data would be included as non-sarcopenic, hence dragging down the outcomes of the non-sarcopenic group whilst simultaneously improving the outcomes for the sarcopenic group. Such an effect would make it harder to detect an adverse effect of sarcopenia in this group of patients, and in the whole group.

The protocol at our institution has become more formalised in recent times, such that patients will now receive a scan at the commencement and at the conclusion of neoadjuvant treatment. This may allow more formal assessment of the impacts and changes that occur in body composition after neoadjuvant treatment.

7.6.2 Biochemical markers

One key marker that was not consistently available in our cohort was the preoperative albumin. Preoperative blood tests including albumin levels would be part of the workup for major surgery. However, with the transition to an electronic medical record in 2017 at our institution, many of the blood tests performed prior to this time point were no longer readily accessible. Furthermore, patients that had come from regional areas had blood tests performed at outside institutions again limiting access to this information. For this reason, albumin measurement was not part of the study as the data were too incomplete to be of value in analyses.

7.6.3 Sarcopenic obesity

Body mass index (BMI) is a classic marker of overall nutrition and part of the standard assessment of patients. It can be broken down into different classes. (Table 11)

BMI (kg / m^2)	**Weight status**
< 20	Underweight
20 – 25	Normal (healthy)
25 – 30	Overweight
> 30	Obese

Table 11. Weight status classification. BMI - Body Mass Index

In the obese state, fat deposition can occur within skeletal muscle affecting its function. Patients can therefore still have impaired muscle function, a hallmark of sarcopenia, but yet have preserved muscle size and preserved or even elevated BMI. This is especially important due to the obesity epidemic occurring across the planet, particularly in the western world, but also due to the fact that weight and BMI are historically used as markers of malnutrition and cachexia. Using BMI alone to assess body composition can provide an incomplete assessment of a patient and miss vital information. Patients may have elevated BMI and presumably then be well nourished, yet be sarcopenic based on skeletal muscle indices. This group of patients are commonly referred to as having sarcopenic obesity.

Importantly, this subset of sarcopenic patients who are obese has been shown to have poor outcomes in patients with cancer.[77] In our study, there was no difference in OS, DFS or complication rate for patients with sarcopenic obesity, probably due to the fact that these numbers were quite small (10 obese sarcopenic, 26 non-obese sarcopenic). Greater patient numbers and further investigation may be required to explore this association further.

7.7 LIMITATIONS

There are a number of limitations that are appreciated in this study

Selection bias

Clearly the patients undergoing major UGI resection in our institution have already been identified by experienced surgeons to be capable of withstanding such morbid surgery. It is possible that there are a significant number of patients with UGI malignancy not coming forward for surgery that have sarcopenia and therefore the prevalence could be much higher. However, the results of our study reflect routine clinical practice where patients undergo other clinical assessments that may determine their ability to withstand major surgery. Despite being deemed suitable for surgery, the results of the study demonstrate that sarcopenia is still prevalent in this population with its presence found to be a significant risk factor for survival. Moreover, as surgeons we are interested in any index that can allow us to assess prognosis and risk, and that may allow us a therapeutic intervention (eg supplemental nutrition).

Retrospective design

This study, being retrospective in nature has some inherent limitations that are applicable to all retrospective studies. This includes certain errors in chart reviews and recording necessary variables.

In particular, due to the retrospective design, there may be other confounders that were not measured that may have an impact on the outcomes.

Availability of preoperative CT images

As discussed within the methods section, not all patients had a preoperative CT available although this number was small (four patients). Those patients without preoperative imaging all had perioperative imaging available during their inpatient stay which was used for analysis. It is understood that there may have been further development and worsening of sarcopenia demonstrated on a perioperative as opposed to a preoperative scan which may affect the results. However, none of these patients had neoadjuvant treatment meaning they had gone directly to surgery, minimizing the potential for further development of sarcopenia that would subsequently impact on findings.

Measurement errors

Due to the (at least partially) manual performance of measuring the skeletal muscle area despite a standardised technique, there will be inherent intraobserver variability. Depicted in the figure below (Figure 27a and 27b) is a patient example where extra tissue could easily be included in repeat analyses. The area depicted in blue are within the same HU range as skeletal muscle and therefore portions or all of these tissues could be included into the total skeletal muscle area. A careful analysis of the initial image is required, and in certain cases, due to skeletal muscle being directly adjacent to viscera or other organs, an estimation of where the line of differentiation is required. This would usually only involve a small number of cases and overall a small proportion of the total skeletal muscle area. There were only eight patients that required a third measurement and it was established that the coefficient of variation was small. Hence the techniques developed empirically at the commencement of this project do seem to be effective and accurate. An analysis of inter-observer variation will be part of a future project.

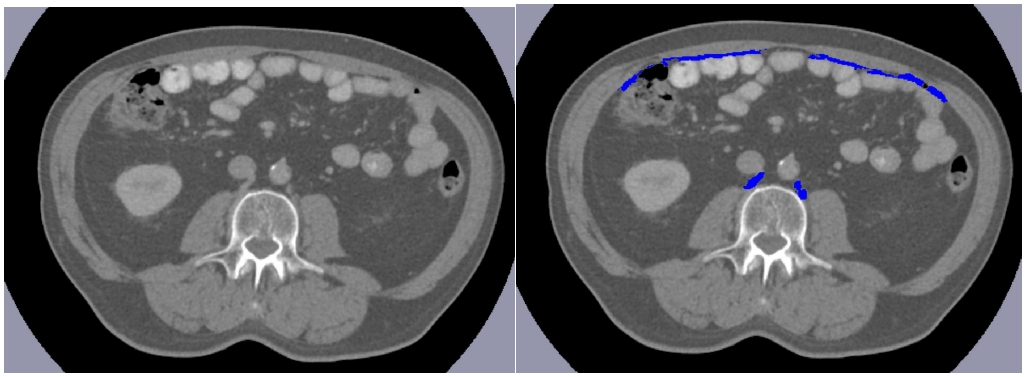


Figure 27a, 27b. Identical L3 slice with small bowel adjacent to anterior abdominal wall and lymph node adjacent to psoas muscles.

With no consensus cut-off for SMI, it may be useful to have a range for the cut-off values that can be adjusted depending on the aim for future studies. For example, in order to capture all patients with sarcopenia in a given population, it may be useful to set the cut-off value higher, whereas if only the patients with more significant sarcopenia were the intended targets, then the value could be lower. The published cut-off ranges for sarcopenia are slightly different but across a larger population, these differences may not be clinically significant as this would only apply to a small group of patients.

Lack of functional data

Importantly the consensus definition for sarcopenia changed subtly around the time this study was conducted. More interest and emphasis has been placed into using functional data to help identify patients with probable sarcopenia. Over the course of the study, functional tests did not form part of our algorithm for workup of such patients, and therefore the utility of these could not be analysed.

Statistical analyses

UGI cancer is a rare cancer in comparison to others in Australia and the number of patients undergoing curative resection is limited. Therefore the numbers incorporated in this study, despite running over several years, are relatively small. In addition, for many of the analyses, oesophagectomy and gastrectomy patients were combined – this is not uncommon in the UGI cancer literature, but is generally seen as a necessity rather than a virtue. Some analyses, particularly in regard to the impacts of sarcopenia on serious complication rates such as anastomotic leak were not meaningful due to the small numbers. The complication rates, especially for 30-day mortality and anastomotic leak, compare very favourably with other centres around the world.

7.8 FUTURE DIRECTIONS

Some of the questions this study raises in regards to body composition is when, in what context and by whom the analysis will be performed. With the increasing use of electronic systems for storing films, it would be relatively straightforward to perform retrospective analyses of historical patients. Equally, prospective measurements may be performed for patients and this in fact may potentially

become part of the process of tumour-staging and patient assessment, influencing decision-making and treatment approaches.

With the formal development of the study protocol, it is anticipated that an appropriately trained individual with access to the SliceOmatic software and licence and access to CT scans would be able to accurately segment tissues and assess for sarcopenia.

The effects of sarcopenia are seen in a wide range of patient groups and therefore, the use of body composition software to determine this could be useful in multiple settings. The protocol may be easily applied to other cancer populations who undergo routine staging with CT as sarcopenia such as colorectal, hepatopancreaticobiliary and urological malignancies.

It is important to recognise that for future research, the functional aspects of sarcopenia have gained greater significance and may be important to incorporate into a diagnostic algorithm. It would be relatively straightforward to incorporate the SARC-F questionnaire (Appendix B), handgrip strength with a standardised dynamometer and perhaps even some basic functional tests such as the chair stand test (Appendix A) or TUG that may be able to further stratify and prognosticate patients. There is potential to do this on our surgical unit.

Ultimately, the aim of diagnosing sarcopenia in this group of patients is to identify those at risk and find interventions that may be able to improve their outcome. In this regard, there are some promising results in community populations for resistance training to improve sarcopenia[131] (Borst 2004). A recent randomized clinical trial has shown the benefits of exercise and nutrient prehabilitation for patients undergoing UGI surgery but this was not specifically aimed at patients with sarcopenia.[132] So far, no studies in the UGI cancer population have been performed targeting sarcopenia in this group of patients. However it is hoped that with greater recognition and understanding of this important condition and its effects that more research efforts will be directed to its treatment.

8. CONCLUSION

In summary, sarcopenia is a complex disease best understood as muscle failure secondary to loss of both muscle mass and function. It can be diagnosed on routine scans performed for staging cancer patients and can be assessed via body composition software. A protocol to diagnose sarcopenia has been established and appears robust and accurate. Via this protocol, sarcopenia was found to be highly prevalent in a population of patients undergoing major UGI resection. Sarcopenia was shown to be a negative risk factor for overall survival. This study adds to the growing literature on this topic with the further strengthening of the role of establishing standardised cut-offs for sarcopenia diagnosed via body composition on CT. Further studies utilizing and refining this protocol for body composition can be performed in order to identify at risk patients. More studies are needed to identify appropriate interventions for sarcopenia in patients undergoing major UGI cancer operations in an effort to improve their outcomes and survival.

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APPENDIX A

Functional assessment questionnaires and screening tools for sarcopenia

Table 3
SARC-F screen for sarcopenia

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1–3 falls = 1 4 or more falls = 2

From Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc 2013;14:531; with permission.

SARC-F questionnaire

Frail Scale

Component	Question
Fatigue	How much time during the previous 4 weeks did you feel tired? (all of the time, most of the time = 1 points)
Resistance	Do you have any difficulty walking up 10 steps alone without resting and without aids? (yes = 1 point)
Ambulation	Do you have any difficulty walking several hundred years alone with without aids? (yes = 1 point)
Illness	How many illnesses do you have out of a list of 11 total? (5 or more = 1 point)
Loss of Weight	Have you had weight loss of 5% or more? (yes = 1 point)

Frail Scale scores range from 0-5, one point for each component, 0=best to 5=worst
Robust = 0 points
Pre-Frail = 0-1 points
Frail = 3-5 points

FRAIL scale

The Edmonton Frail Scale:				Score: ___/17
Frailty domain	Item	0 point	1 point	2 points
Cognition	Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of 'ten after eleven'	No errors	Minor spacing errors	Other errors
General health status	In the past year, how many times have you been admitted to a hospital?	0	1–2	≥2
	In general, how would you describe your health?	'Excellent', 'Very good', 'Good'	'Fair'	'Poor'
Functional independence	With how many of the following activities do you require help? (meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications)	0–1	2–4	5–8
Social support	When you need help, can you count on someone who is willing and able to meet your needs?	Always	Sometimes	Never
Medication use	Do you use five or more different prescription medications on a regular basis?	No	Yes	
	At times, do you forget to take your prescription medications?	No	Yes	
Nutrition	Have you recently lost weight such that your clothing has become looser?	No	Yes	
Mood	Do you often feel sad or depressed?	No	Yes	
Continence	Do you have a problem with losing control of urine when you don't want to?	No	Yes	
Functional performance	I would like you to sit in this chair with your back and arms resting. Then, when I say 'GO', please stand up and walk at a safe and comfortable pace to the mark on the floor (approximately 3 m away), return to the chair and sit down'	0–10 s	11–20 s	One of >20 s patient unwilling, or requires assistance
Totals	Final score is the sum of column totals			

Edmonton Frail Scale

Clinical Frailty Scale

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3 Managing Well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4 Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9 Terminally Ill – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia,** recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia,** they cannot do personal care without help.

Clinical Frailty Scale

APPENDIX B

Muscle strength assessment

Hand held dynamometer example

From Wikipedia

Chair stand test

Participants must sit and stand as many times in 30 seconds as possible. Scores vary according to gender and age