A window beneath the skin: how computed tomography assessment of body composition can assist in the identification of hidden wasting conditions in oncology that profoundly impact outcomes

L. E. Daly¹,²†, C. M. Prado³ and A. M. Ryan¹,⁴*

¹School of Food and Nutritional Sciences, College of Science, Engineering and Food Science, University College Cork, Ireland
²APC Microbiome Institute, University College Cork, Cork, Ireland
³Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada
⁴Cork Cancer Research Centre, University College Cork, Cork, Ireland

Advancements in image-based technologies and body composition research over the past decade has led to increased understanding of the importance of muscle abnormalities, such as low muscle mass (sarcopenia), and more recently low muscle attenuation (MA), as important prognostic indicators of unfavourable outcomes in patients with cancer. Muscle abnormalities can be highly prevalent in patients with cancer (ranging between 10 and 90%), depending on the cohort under investigation and diagnostic criteria used. Importantly, both low muscle mass and low MA have been associated with poorer tolerance to chemotherapy, increased risk of post-operative infectious and non-infectious complications, increased length of hospital stay and poorer survival in patients with cancer. Studies have shown that systemic antineoplastic treatment can exacerbate losses in muscle mass and MA, with reported loss of skeletal muscle between 3 and 5% per 100 d, which are increased exponentially with progressive disease and proximity to death. At present, no effective medical intervention to improve muscle mass and MA exists. Most research to date has focused on treating muscle depletion as part of the cachexia syndrome using nutritional, exercise and pharmacological interventions; however, these single-agent therapies have not provided promising results. Rehabilitation care to modify body composition, either increasing muscle mass and/or MA should be conducted, and its respective impact on oncology outcomes explored. Although the optimal timing and treatment strategy for preventing or delaying the development of muscle abnormalities are yet to be determined, multimodal interventions initiated early in the disease trajectory appear to hold the most promise.

Sarcopenia: Muscle attenuation: Cancer: Cachexia: Body composition: Survival

Over the past decade, there has been a growing interest in the measurement of body composition in patients with cancer. This has largely been in response to advancements in image-based technologies, including gold standard computed tomography (CT) that allow the precise quantification of both muscle and adipose tissue. This research has led to increased understanding of the importance of abnormal body composition...
Cancer is a disease associated with ageing. As a result, the aetiology of muscle loss in patients with cancer can be two-fold. Firstly, resulting from the age-related decline in muscle mass (sarcopenia), and secondly due to the metabolic changes induced by malignancy and cancer cachexia. Muscle loss related to sarcopenia begins relatively early in life, as muscle mass begins to decline from the age of 40 at a rate of 6% per decade\(^6\) and accelerates to a rate of 25–40% per decade above age 70 years\(^6\). The precise definition of sarcopenia remains controversial and a topic of much debate today; however, a generally accepted criterion in geriatric populations is a level of muscle mass greater than two standard deviations below that of a healthy young reference population\(^7\).

Cancer cachexia is a multifactorial syndrome that is characterised by the loss of muscle with or without the loss of fat mass leading to progressive functional impairment\(^8\). It is driven by a variable combination of reduced food intake and abnormal metabolism\(^8\). Systemic inflammation is commonly described as part of the pathogenesis of cancer cachexia, and may suppress appetite, increase body’s metabolic needs and energy expenditure, and accelerate muscle protein catabolism in patients\(^8\)–\(^10\). Cancer cachexia represents a spectrum of conditions and can range in severity and clinical presentation from pre-cachexia, identified by early clinical and metabolic signs (e.g. anorexia and impaired glucose tolerance) to refractory cachexia, where extensive muscle and fat depletion is evident, and patients are often immunocompromised\(^8\). Recognition of these stages of cachexia is important as these stages have different implications in the anabolic therapy response.

Reduced skeletal MA is a relatively newly characterised and distinctive abnormality in patients with cancer\(^11\). It represents a ‘qualitative’ measure of skeletal muscle, as low radiation attenuation is reflective of intramuscular adipose tissue infiltration, and therefore, poor ‘quality’ skeletal muscle\(^11\). It has been speculated that low MA precedes the development of sarcopenia, as the increase in lipid content occurs before a decline in muscle mass\(^12\)–\(^15\). Importantly, in recent years, low MA is emerging as an important prognostic indicator in patients with cancer, and in some cases, a better prognostic indicator compared with muscle mass alone\(^12\)–\(^18\).

Low muscle mass and low MA can occur at any given BMI (kg/m\(^2\))\(^1\)–\(^15\), and now with 40–60% of cancer patients presenting with overweight and obesity\(^19\), identification of these conditions is becoming increasingly difficult. Patients may therefore not appear malnourished as muscle depletion is often hidden behind mantles of adipose tissue and can often go undiagnosed and untreated. Body composition assessment is therefore crucial within this patient group.

This review will focus on the diagnostic criteria, prevalence and clinical consequences associated with CT-defined muscle abnormalities (low muscle mass and low MA) in relation to chemotherapy tolerance, post-operative outcomes and survival in oncology patients. We will examine the changes in body composition that occur in patients undergoing active anti-cancer treatment, and finally, we will briefly examine the evidence behind current treatments aimed at restoring muscle mass and MA, with a particular emphasis on nutritional interventions, physical activity, pharmacological agents and multimodal treatments.

### Measurement of skeletal muscle in oncology

The three most commonly used methods to measure body composition in patients with cancer are bioelectrical impedance analysis, dual-energy x-ray absorptiometry and CT. Each technique has its advantages and disadvantages, and methods differ in terms of cost, reliability, validity, availability and training required\(^21\). CT images are considered a gold standard method for body composition assessment, and allow the precise quantification of tissue area, volume and attenuation. Unlike bioelectrical impedance analysis or dual-energy x-ray absorptiometry, CT can measure body composition at a tissue-organ level, particularly total and regional adipose and skeletal muscle tissues. The use of CT for body composition assessment in non-cancer populations is limited by the high radiation dose, high cost and lack of availability. However, in oncology, CT scans are obtained routinely during diagnostic and surveillance purposes, and therefore represent a unique and exploitable opportunity to assess body composition within this patient group.

Measuring muscle mass by CT is usually done by measuring total skeletal muscle area (SMA) at the third lumbar vertebra (L3). Using a commercially available image analysis software (e.g. Sliceomatic (Tomovision), OsiriX (Pixmeo), Image J (National Institutes of Health), among others), muscle and adipose tissues can be evaluated based on Hounsfield unit (HU) thresholds. Muscles in this area include the psoas, paraspinal muscles (rector spinea, quadratus lumborum) and the abdominal wall muscles (transversus abdominus, external and internal oblique, rectus abdominus). Measurements are commonly taken at the third lumbar vertebra, as the SMA obtained at this level is a good correlate for whole body muscle in healthy individuals (r 0.92)\(^22\). From this skeletal muscle index (SMI; total SMA (cm\(^2\))/height (m\(^2\))) can be calculated and patients are often compared on this basis. Mean MA is typically derived by averaging HU of the SMA at the third lumbar vertebra. Although SMI and MA are continuous variables and could be modelled as such to predict survival/outcome, many clinicians find the interpretation of continuous prognostic covariates difficult, and prefer categorical or binary covariates based on a threshold/cut point to stratify patients into distinct risk groups when making treatment decisions.

### Defining low muscle mass (sarcopenia) in patients with cancer

Many oncolgical studies define sarcopenia based solely on low muscle mass, and studies often lack information on muscle strength or physical function. Therefore, the criteria to define sarcopenia in this group differ from...
those proposed in geriatric populations(23,24). In the oncology setting, consensus-based cut points to define low muscle mass or sarcopenia are lacking, and a variety have been devised. Studies(25–28) have defined sarcopenia based on cut points developed by Baumgartner et al.(7) in elderly individuals (2-SD below a healthy reference population), by converting the original dual-energy x-ray absorptiometry cut points (<7.26 kg/m² for men and <5.45 kg/m² for women) to corresponding CT cut points using published regression equations(29). These cut points are SMI <55.4 cm²/m² for men and <38.9 cm²/m² for women(29), and are those used in the cancer cachexia consensus definition(8). To date, no healthy population reference values for muscle mass obtained from CT exist.

Studies have employed a statistical technique known as optimal stratification, which is used to identify threshold values associated with elevated risk of poor outcome (e.g. mortality) to define sarcopenia. Using this technique, Prado et al.(19) identified cut points for SMI that best predicted survival in a cohort of 250 obese (BMI >30 kg/m²) cancer patients. These cut points are <52.4 cm²/m² for men and <38.5 cm²/m² for women(19), and have been widely applied in the literature. In 2013, Martin et al.(1) identified both sex- and BMI-specific cut points for SMI that best predicted survival (men: <43 cm²/m² if BMI ≥24.9 kg/m² and <53 cm²/m² if BMI ≥25 kg/m²; women: <41 cm²/m²) in a large cohort of 1473 patients with lung and gastrointestinal (GI) cancer, which are more applicable to non-obese cohorts. More recently, in 2017, Caan et al.(30) identified sex, BMI and cancerspecific cut points for survival in a very large cohort of early-stage colorectal cancer patients (n 3262; men: <52.3 cm²/m² if BMI <30 kg/m² and <54.3 cm²/m² if BMI ≥30 kg/m²; women: <38.6 cm²/m² if BMI <30 kg/m² and <46.6 cm²/m² if BMI ≥30 kg/m²)(30).

In addition to sex and BMI, ethnicity should be considered when applying cut points to a specific cohort. Fujiwara et al.(31) defined CT-derived cut points for a large (n 1257) homogenous cohort of Japanese patients with mixed stage (I–IV) hepatocellular carcinoma that best predicted survival (<36.2 cm²/m² for men and <29.0 cm²/m² for women), providing a reference population for these individuals. Notably, these cut points are lower(31,32) compared with those derived from large Caucasian populations.(1,34)

Using optimal stratification methodology, several other studies have reported cut points for SMI associated with mortality in a number of cancer cohorts (see Table 1), these range 36–55.8 cm²/m² for men and 29–46.6 cm²/m² for women. Several factors influence patient’s muscle mass (ethnicity, age, sex, physical activity and magnitude of adiposity)(33,34); hence, published cut points may not be applicable to all cancer populations. For example, cut points published by Prado et al.(19) were devised in a cohort of obese patients with cancer, and may have limited relevance when applied to populations with varying prevalence of obesity, but have subsequently been used in studies comprised of predominantly non-obese individuals.(35–40)

Other studies have defined sarcopenia based on more data-orientated approaches, dichotomizing SMI based on predetermined percentiles, such as quartiles(41), tertiles(17,42) or based on the median(43,44). Studies focused solely on one muscle group, the psoas muscle, generating a psoas muscle index, often considered patients within the lowest quartile of psoas muscle index to be sarcopenic.(45–47) However, no studies have related psoas muscle area to whole body measures, and it has only been weakly correlated with total lumbar muscle area(48). Therefore, it has been argued that the use of the psoas muscle as a sentinel muscle for the diagnosis of sarcopenia is flawed(49). Other investigations have included additional measures of physical function (hand grip strength and/or gait speed) in conjunction with skeletal muscle from CT scan analysis when defining sarcopenia in patients with cancer(50–52). The rationale for including the measures of both muscle mass and function is that muscle strength does not depend solely on muscle mass, and the relationship between muscle strength and mass is not linear(53). Hence, several expert groups have proposed the use of both muscle mass and function to define sarcopenia in older adults.(23,24,52)

**Prevalence of low muscle mass (sarcopenia) in patients with cancer**

As discussed previously, comparison among studies reporting the prevalence of sarcopenia is often difficult because of inconsistent methodology used to evaluate body composition (dual-energy x-ray absorptiometry, bioelectrical impedance analysis, CT), and diagnostic criteria/cut points used to define sarcopenia. Table 2 summarises the prevalence of sarcopenia among patients with cancer using the same methodology (CT defined SMI) but using varying published cut points. The prevalence of sarcopenia is highly variable across primary cancer sites, and has been shown to range from 11 to 90 %.(31,53). Of note is the heterogeneity in the prevalence of sarcopenia among cohorts of the same primary cancer site and stage, e.g. 19–71 % in advanced colorectal cancer(54,55), 33–90 % in metastatic kidney cancer(56–58) and 21–89 % in advanced pancreatic cancer(57,58). This large variability could be attributed to the varying cut points used to define sarcopenia; limitations related to sample size; or patient characteristics such as age, sex, ethnicity, BMI and concurrent co-morbidities, thus limiting the ability to draw conclusions as to the true prevalence according to the cancer site. Sarcopenia appears to be the most prevalent in patients with any stage of pancreatic or lung cancer, while in other cancer types (e.g. gastric and breast), it appears to be more frequent in advanced stage disease compared with earlier loco regional disease. Sarcopenia can be present at any given BMI, and the prevalence of sarcopenic obesity (sarcopenia and obesity (BMI ≥30 kg/m²)) has been shown to vary between 1 and 29 % in studies including individuals from all BMI categories, and between 15 and 36 % in studies including obese individuals only(59).

**Low muscle attenuation in patients with cancer**

Similar to the measures of SMI, no widely agreed upon cut points are available for defining low MA.
Impact of muscle abnormalities on clinical outcomes

Notwithstanding the controversies in determining and defining low muscle mass and low MA in oncology, it has been well established and reported over the past decade that these muscle abnormalities are unequivocally associated with negative clinical outcomes in patients with cancer.

Muscle abnormalities and tolerance to chemotherapy

Chemotherapy can often be associated with severe toxicity (grades III–IV) that can result in dose delays, dose reductions and treatment termination, referred to as dose-limiting toxicities (DLT). DLT may lead to hospitalisations and can be life threatening. Exploratory studies provided the initial evidence of an association between low muscularity and increased incidence of severe toxicity/DLT to chemotherapy, and subsequent work has confirmed these observations in multiple cancer sites and treatments (Fig. 1). In advanced disease, low muscularity has been associated with poorer tolerance to chemotherapy in patients with breast(71,72), renal(56,73,74), liver(75), lung(76), colorectal(55,77), thyroid(78) and melanoma(79) skin cancer(4,79). Sarcopenia, in patients with peritoneal metastasis from colorectal cancer, was associated with significantly more chemotherapy toxicities (57 v. 26 %, \(P = 0.004\)) and particularly neutropenia (36 v. 17 %, \(P = 0.04\)) in a cohort of 97 patients receiving hyperthermic intraperitoneal chemotherapy.

Even in early-stage disease (stages I–III), sarcopenia is associated with poorer tolerance to chemotherapy(28,80). Interestingly, in patients with early-stage breast cancer (\(n = 151\)) and receiving anthracycline- and taxane-based chemotherapy, with every five-unit decrease in SMI, the risk of any grade III–IV toxicity increased by 27 % (relative risk 1.27 (95 % CI 1.09, 1.49), \(P = 0.002\))(82). In a large study of patients with non-metastatic colon cancer (\(n = 533\)) treated with adjuvant FOLOX treatment, patients with low muscle mass (lowest sex-specific tertile) were twice as likely to experience dose reductions (OR 2.28, \(P = 0.01\)), dose delays (OR 2.24, \(P = 0.002\)) and early discontinuation of treatment (OR 2.34, \(P = 0.03\))(2). Although the majority of studies have consistently demonstrated an association between low muscle mass and increased incidence of severe toxicity/DLT (twenty-six of thirty-two studies; see Supplementary material for summary of each study), fewer small studies found contradictory findings(85–88).

Emerging data suggest low MA to be also associated with poorer tolerance to antineoplastic agents(4,66,83). In metastatic melanoma patients (\(n = 84\), we have previously shown that patients with low MA more frequently experienced high-grade toxicities (75 v. 31 %, \(P = 0.001\)) and immune-related toxicities to ipilimumab (54 v. 23 %, \(P = 0.017\)) compared with those without low MA. More importantly, these patients were more susceptible to experience a DLT (37.5 v. 10.4 %, \(P = 0.011\))(8). In patients with metastatic prostate cancer treated with

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**Table 1.** Cut points for skeletal muscle index (SMI) at the third lumbar vertebra (L3) associated with mortality in patients with cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Tumour site/stage</th>
<th>n</th>
<th>Males SMI (cm²/m²)</th>
<th>Females SMI (cm²/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prado et al.(19)</td>
<td>Canada</td>
<td>Respiratory and GI/stages I-IV*</td>
<td>250</td>
<td>&lt;52.4</td>
<td>&lt;38-5</td>
</tr>
<tr>
<td>Van Vliet et al.</td>
<td>The Netherlands</td>
<td>Colorectal cancer with liver metastasis</td>
<td>196</td>
<td>&lt;43.75</td>
<td>&lt;41.1</td>
</tr>
<tr>
<td>Martin et al.(1)</td>
<td>Canada</td>
<td>Lung and GI/stages I-IV</td>
<td>1473</td>
<td>&lt;43.0 (BMI &lt;25 kg/m²)</td>
<td>&lt;41.0</td>
</tr>
<tr>
<td>Lanic et al.</td>
<td>France</td>
<td>Diffuse large B-cell lymphoma</td>
<td>82</td>
<td>&lt;55.5</td>
<td>&lt;38.9</td>
</tr>
<tr>
<td>Fujikawa et al.</td>
<td>Japan</td>
<td>Hepatocellular carcinoma/stages I-IV</td>
<td>217</td>
<td>&lt;36.0</td>
<td>&lt;29.0</td>
</tr>
<tr>
<td>Kimura et al.</td>
<td>Japan</td>
<td>Lung cancer/stage III-IV</td>
<td>134</td>
<td>&lt;41.0</td>
<td>&lt;38.0</td>
</tr>
<tr>
<td>Choi et al.</td>
<td>Korea</td>
<td>Pancreatic cancer/advanced</td>
<td>484</td>
<td>&lt;42.2</td>
<td>&lt;33.9</td>
</tr>
<tr>
<td>Coelen et al.</td>
<td>The Netherlands</td>
<td>Perihilar cholangiocarcinoma/stages I-IV</td>
<td>100</td>
<td>&lt;46.8</td>
<td>&lt;39.1</td>
</tr>
<tr>
<td>Cann et al.</td>
<td>USA</td>
<td>Colorectal cancer/stages I-III</td>
<td>3262</td>
<td>&lt;52.3 (BMI &lt;30 kg/m²)</td>
<td>&lt;38.6 (BMI &lt;30 kg/m²)</td>
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<tr>
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<td></td>
<td></td>
<td>&lt;54.3 (BMI ≥30 kg/m²)</td>
<td>&lt;46.6 (BMI ≥30 kg/m²)</td>
</tr>
</tbody>
</table>

GI, gastrointestinal.

*Obese individuals only (BMI >30 kg/m²).

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(using optimal stratification) that related to poor survival in a large cohort of lung and GI cancer patients (\(n = 1473\); <41 HU for BMI 25 kg/m² and <33 for BMI ≥25 kg/m²)(1). Since then, cancer-specific cut points for low MA that relate optimally to survival have been reported for lung(18,60), ovariand(61) periangbular(16), pancreatic(63) gastro-oesophageal(28) and large B-cell lymphoma(15). These range from <28 to 44.1 HU in men(16,18,60) and <23.8 to 40.5 HU in women(16,18,60–62). Other studies have defined low MA based on the sample sex-specific median(44,64), tertile(17) or quartile(65).

The prevalence of low MA among patients with cancer varies greatly, and is dependent on the cohort under investigation and cut point used, but has been shown to range from 10 to 86 % (18,66). Using the cut points devised by Martin et al.(1), which have been applied most widely in the literature, the prevalence of low MA has been reported to be between 46 and 53 % in two large cohorts of patients with cancer (mixed tumour sites and stages (I–IV))(1,67). In the setting of advanced disease, the prevalence of low MA has been reported to be 33 % in melanoma(4) 55 % in pancreatic(68), 59 % in gastric(13), 60 % in breast(14) and 86 % in prostate cancer(66). While in patients with operable colorectal cancer, low MA is present in 58–78 % of patients(69,70).
Table 2. Prevalence of sarcopenia according to cancer site, country and definition used

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Stage/n</th>
<th>% Sarcopenic*</th>
<th>Sarcopenia definition†</th>
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<tr>
<td><strong>Colorectal cancer</strong></td>
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<td>Van Vledder et al.</td>
<td>The Netherlands</td>
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<tr>
<td>Liefers et al.</td>
<td>Canada</td>
<td>Stages II–IV/234</td>
<td>39</td>
<td>1</td>
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<tr>
<td>Thoresen et al.</td>
<td>Norway</td>
<td>Advanced/50</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Barret et al.</td>
<td>France</td>
<td>Metastatic/51</td>
<td>71</td>
<td>2</td>
</tr>
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<td>Thoresen et al.</td>
<td>Norway and Canada</td>
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<td>39</td>
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<tr>
<td>Miyamoto et al.</td>
<td>Japan</td>
<td>Stages I–III/220</td>
<td>25</td>
<td>6</td>
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<tr>
<td>Reisinger et al.</td>
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<td>48</td>
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<tr>
<td>Buskeromolen et al.</td>
<td>The Netherlands</td>
<td>Metastatic/67</td>
<td>57</td>
<td>3</td>
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<tr>
<td>Chemarina et al.</td>
<td>France</td>
<td>Advanced/97</td>
<td>40</td>
<td>3</td>
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<td>Malietzis et al.</td>
<td>UK</td>
<td>Resectable/763</td>
<td>65</td>
<td>3</td>
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<tr>
<td>Cann et al.</td>
<td>USA</td>
<td>Stages I–III/326</td>
<td>42</td>
<td>12</td>
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<tr>
<td>McSorley et al.</td>
<td>UK</td>
<td>Resectable/322</td>
<td>47</td>
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<tr>
<td><strong>Oesophageal/oesophagogastric cancer</strong></td>
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<td>Awad et al.</td>
<td>UK</td>
<td>Stages I–III/47</td>
<td>57</td>
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<td>Yip et al.</td>
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<td>Tamandji et al.</td>
<td>Austria</td>
<td>Non-metastatic/200</td>
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<td>Tan et al.</td>
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<td>Anandavadielvan et al.</td>
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<td>Resectable/120</td>
<td>45</td>
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<td>Nishigori et al.</td>
<td>Japan</td>
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<td>Elliott et al.</td>
<td>Ireland</td>
<td>Resectable/252</td>
<td>16</td>
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<td><strong>Gastric cancer</strong></td>
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<td>Hayashi et al.</td>
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<td>Palmela et al.</td>
<td>Portugal</td>
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<td>23</td>
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<td>Kudou et al.</td>
<td>Japan</td>
<td>Stages I–III/148</td>
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<tr>
<td>Baracos et al.</td>
<td>Canada</td>
<td>NSC/stages III–IV/441</td>
<td>47</td>
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<td>Stene et al.</td>
<td>Norway</td>
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<td>71</td>
<td>1</td>
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<td>Arrieta et al.</td>
<td>Mexico</td>
<td>NSC/metastatic/84</td>
<td>69</td>
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<td>Kim et al.</td>
<td>Korea</td>
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<td>Antoun et al.</td>
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<td>Sharma et al.</td>
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<td>Auclin et al.</td>
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NSC, non-small cell; SC, small cell; GI, gastrointestinal; NR, not recorded; GIST, gastrointestinal stromal tumour.
*Prevalence of sarcopenia in both sexes combined.
† Sarcopenia definitions stratified as follows:
1. Skeletal muscle index (SMI) <52.4 cm²/m² for males; <38.5 cm²/m² for females
2. SMI <55.4 cm²/m² for males; <39.9 cm²/m² for females (Baumgartner sarcopenia cut points for elderly healthy subjects(7) converted to CT cut points using regression equations(26).
3. SMI <43 cm²/m² BMI <24.9 kg/m² and <53 cm²/m² BMI >25 kg/m² for males; <41 cm²/m²/m² for females(7).
4. SMI <43.75 cm²/m² for males; <41.1 cm²/m² for females(84).
5. SMI <55.8 cm²/m² for males; <38.9 cm²/m² for females(80).
6. SMI <49.9 cm²/m² and for women <42.1 cm²/m² (lowest quartile)(41).
7. SMI <42.2 cm²/m² for males; <33.9 cm²/m² for females(7).
8. SMI <36.5 cm²/m² for males; <29.0 cm²/m² for females(19).
9. SMI <36.0 cm²/m² for males; <29.0 cm²/m² for females(10).
10. SMI <41.5 cm²/m² (median) for females(13).
11. SMI <46.8 cm²/m² for males; <39.1 cm²/m² for females(34).
12. SMI <52.3 cm²/m² for men and <38.6 cm²/m² for men with a BMI <30 kg/m² and <54.3 cm²/m² for men and <46.6 cm²/m² for women with a BMI ≥30 kg/m²(37).

**docetaxel (n = 63), a combination of both low muscle mass and low MA was associated with an increased risk of DLT (59 vs. 29%, P = 0.021) [165]. Similarly, in early-stage disease, Shachar et al. (182) demonstrated that in breast cancer (n = 151), the risk of hospitalisations due to chemotherapy toxicity increased 19% with every five-unit decrease in MA (relative risk 1.19 [95% CI 1.00, 1.43], P = 0.05).

In increased toxicity in patients with sarcopenia may be attributed to alterations in the distribution, metabolism and clearance of systemic chemotherapy drugs [80]. The practice of administration of cytotoxic chemotherapy based on body surface area, and targeted therapy as a flat dose, ignores several sources of inter-individual variation. Using body surface area as the only method to individualise chemotherapy drug dose is insufficient to avoid severe toxicity, but the continued use mainly relies on the lack of other more precise methods for dose individualisation [185]. It is recently acknowledged that variability in body composition (lean mass, fat mass and total body water) of cancer patients may be a source of disparities in the metabolism of cytotoxic agents resulting in increased toxicity (173,80,90). The rationale is that body weight comprises two major compartments, lean mass and fat mass, which may be the two major sites of distribution of hydrophilic and lipophilic drugs, respectively [86,91]. Therefore, changes in body composition may lead to changes in the volume of distribution and adversely impact the effectiveness and tolerance of cancer therapies.

Administration of hydrophilic chemotherapy drugs that are mainly distributed to the lean mass compartment in sarcopenic patients would result in a disproportionately small volume of the drug distribution in relation to their body weight or body surface area [71,80]. This has been hypothesised to lead to considerable variation in milligram of chemotherapeutic agent per kg lean mass, and a higher dose per kg lean mass is associated with more frequent severe toxic side effects [6,80,92,93]. In patients with advanced non-small-cell lung cancer (n = 424), when the dose of non-platinum drugs was expressed as mg/kg lean mass, a 3-fold range was observed, and the dose of non-platinum chemotherapeutic agent per kg lean mass was a significant predictor of haematologic toxicity. Every 1% increase in drug dose per kg lean mass above the mean was associated with a 3% increased risk of grade III–IV haematologic toxicity, while patients with
doses >20% above the mean were at almost double the risk of experiencing a grade III–IV haematologic toxicity (93). Pharmacokinetic data have supported this hypothesis, with sarcopenic patients experiencing higher plasma concentrations of antineoplastic drugs, and experiencing more toxicity (75,78). The same hypothesis holds true for toxicity to lipophilic drugs. In a study of ovarian cancer patients receiving doxorubicin and trabectedin, the risk of DLT decreased with increased fat mass:lean mass ratio. As lipophilic drugs are mainly distributed in the adipose tissue, leaner individuals would present with reduced volume of distribution for the drug and consequently increase their risk for DLT (91).

In addition to the pharmacokinetic hypothesis to explain the increased toxicity in sarcopenic patients, other mechanisms have been suggested. Low levels of lean mass and altered concentration of plasma proteins (e.g. albumin) may affect the distribution of highly protein-bound drugs, and may explain the increased toxicity of the vandetanib (78), sorafenib (75) and eprubin (80). Systemic inflammation is known to inhibit hepatic enzymes and may contribute to higher drug exposure, and subsequently excess toxicity in patients with sarcopenia (75,78). In addition, sarcopenic patients are generally more susceptible to acute medical events and perhaps chemotherapy toxicity may be an additional generalised intolerance (84). Whether altered chemotherapy dosing based on lean mass in patients receiving treatment is effective in preventing toxicity is currently being investigated (ClinicalTrials.gov identifier: NCT01624051).

Sarcopenia and survival

The impact of sarcopenia on survival in oncology was first identified in a cohort of 250 obese lung and GI cancer patients by Prado et al. in 2008 (19). Within this study, sarcopenic obese patients had a lower median overall survival compared with their non-sarcopenic counterparts (11.3 vs. 21.6 months, P < 0.001), and sarcopenic obesity independently predicted survival when adjusted for known prognostic covariates (hazard ratio (HR) 4.2 (95% CI 2.4–7.2), P < 0.0001) (19). Since then, sarcopenia has repeatedly been shown to be independently prognostic of reduced survival in a number of cancer sites and stages including pancreatic (95), kidney (96,97), liver (98–100), lung (101), oesophageal (102), colorectal (103), urothelial (104), and lung and GI cancers (1). Its important prognostic ability was reported in a study of 196 patients following resection for colorectal cancer liver metastases, whereby sarcopenic patients had a median survival of 24 months, which was in stark contrast to 60 months in those without sarcopenia (P < 0.001) (54). In patients with hepatocellular carcinoma (n 116), similar results were obtained with a median survival of 16 months in patients with sarcopenia compared with 28 months in those without sarcopenia (P = 0.003) (98). More recently, a large cohort of stage I–III colorectal cancer patients...
(n 3262) showed that sarcopenic patients had a 27 % higher risk of overall mortality than their non-sarcopenic counterparts(30).

The impact of sarcopenia on survival has been extensively reviewed previously(104–106) and of note is a recent systematic review and meta-analysis(104), which examined the prognostic value of sarcopenia in 7843 patients with solid tumours from a total of thirty-eight studies. Sarcopenia was found to be associated with poor overall survival (HR 1.44 (95 % CI 1.32–1.56), P < 0.001), the effect of which remained in various tumour types and across disease stages. Additionally, sarcopenia was associated with cancer-specific survival (HR 1.93 (95 % CI 1.38–2.70), P < 0.001), as well as disease-free survival (HR 1.16 (95 % CI 1.00–1.30), P = 0.014). However, it is noteworthy to mention the limitations of this study. The authors included several studies in the review that contained duplicated data, and this is prohibited in a meta-analysis as it may lead to overestimation of an effect(107). In addition, the studies were largely heterogeneous in terms of the tumours considered, stage of disease, treatments and cut points used to define sarcopenia, which ranged from 29 to 42.1 cm²/m² in women and 36 to 55.4 cm²/m² in men(104).

In spite of the abundance of evidence supporting the role of sarcopenia as an important and independent prognostic factor in cancer, this finding has not always been consistently reported and several studies have reported no impact on survival(16–18,37,68,88). It is possible that the impact of sarcopenia may vary depending on cancer diagnosis, treatment and overall prognosis. For example, in colorectal cancer patients, sarcopenia was shown to be predictive of survival in patients undergoing curative resection(41), but not in patients with unresectable disease receiving chemotherapy(108). Alternatively, this may be a consequence of the choice of cut points to define sarcopenia in many of these studies. As discussed earlier, cut points obtained in different studies are highly dependent on the methodology and the population from which they were devised, and when used in dissimilar populations, they may represent a suboptimal approach in identifying the true prevalence of low muscle mass and its relationship to survival within these cohorts.

Muscle quality v. quantity

Low MA, often referred to as myosteatosis, is emerging as an important prognostic indicator in patients with cancer and in some cases more superior to predicting survival compared with muscle mass alone(12–18). The first report by Sabel et al.(109) in melanoma patients showed poorer disease-free survival (P = 0.04) and distant disease-free survival (P = 0.0002) in patients with the lowest tertile of psoas MA. Antoun et al.(64) corroborated these findings in a cohort of metastatic renal cell carcinoma patients, and reported that the median survival of patients with a MA below the median (<38 HU in men; <36 HU in women) was half that of those with MA above the median (29 v. 14 months, P = 0.001). In a large cohort of 1473 patients with lung and GI cancer, Martin et al.(17) reported that patients with a MA below the identified cut point (<41 HU for BMI <25 kg/m² and <33 HU for BMI ≥25 kg/m²) were at a 36 % increased risk of mortality (HR 1.36 (95 % CI 1.19–1.55), P < 0.001). Recently, low MA has been shown to be prognostic of reduced survival in a variety of different tumours, including lung(18,60), kidney(64), breast(14), gastric(13), pancreatic(15,65), perianampullary(16), cholangiocarcinoma(68), lymphoma(124) and melanoma(109). In a cohort of 734 patients with advanced lung cancer, Sjøblom et al.(18) reported that even minor changes in MA are associated with mortality risk. An incremental increase of 1 HU was associated with a 2 % reduction in the risk of death (HR 0.98 (95 % CI 0.97–0.99), P < 0.001). Accordingly, the mortality risk reduction of a 5 HU and 10 HU increase in MA were 8 % and 16 %, respectively(18).

Sarcopenia, low muscle attenuation and post-operative outcomes

Sarcopenia has also been identified as a predictor of post-operative infections, complications, readmissions, longer length of hospital stay and higher health care costs(3,100,110–114). Elliott et al.(40) demonstrated that sarcopenia, in a cohort of 252 patients with oesophageal cancer undergoing resection, was independently associated with increased risk of major postoperative complications (grade ≥IIb; OR 5.30 (95 % CI 1.94–14.45), P = 0.001) and pulmonary complications (OR 2.17 (95 % CI 1.12–4.23), P = 0.023). Similarly, in patients with colorectal cancer undergoing cytoreductive surgery for peritoneal carcinomatosis (n 206), sarcopenia was associated with severe post-operative complications, and sarcopenic patients underwent significantly more reoperations (26 v. 12 %, P = 0.012)(15). Consequently, length of hospital stay has shown to be significantly longer in patients with sarcopenia(40,46,96,110,111,115). Following colorectal cancer surgery (n 234), the length of hospital stay for sarcopenic patients was 15.9 d compared with 12.3 d in patients without sarcopenia (P = 0.038)(110). Ultimately, adverse post-operative outcomes in patients with sarcopenia lead to increased health care costs. In a Western-Europe healthcare system, sarcopenia was independently associated with increased hospital costs of €4061 per patient (P = 0.015) in a study of 452 patients who underwent cancer surgery of the alimentary tract(115).

Akin to sarcopenia, low MA is emerging as a predictor of poor post-operative outcomes(16,44,69,116). In patients with colon cancer undergoing open resection (n 91), low MA was an independent risk factor for one or more complications (P < 0.001)(84). Van Rijssen et al.(16) reported similar findings, whereby patients with low MA experienced significantly more major post-operative complications (58 v. 37 %, P = 0.005) following resection for perianampullary cancer (n 166) compared with those without low MA. Examining MA as a continuous variable, Sabel et al.(109) reported that a 10 HU decrease in psoas MA was associated with an 8.1 % increase in complication rate in patients with stage III melanoma (n 101). In line with this, low MA was associated with prolonged length of hospital stay following colorectal cancer surgery(116).
surgery in a large cohort of 805 patients (7 \& 6 d (P = 0.034))\(^{(70)}\), and to a greater extent following pancreatic cancer resection, whereby patients with low MA (post-neoadjuvant chemoradiotherapy) had a mean length of stay of 42 d compared with 23 d in those without low MA (P = 0.001)\(^{(85)}\).

**Muscle loss during chemotherapy**

The precision associated with CT analysis of body composition (1-1.5 %) has allowed recent investigations to focus on the nature and magnitude of changes in body composition during the disease trajectory in patients with cancer. Studies have consistently shown that losses in muscle mass and MA are exacerbated by antineoplastic treatment\(^{(61,88,117)}\). In oesophagogastric cancer patients, neoadjuvant chemotherapy treatment which is typically delivered over a 6-8-week period can decrease SMA by 9.59 cm\(^2\) (P < 0.0001), which is the equivalent to a loss of 2.9 kg of lean mass\(^{(118)}\). These results have been corroborated in a study of 252 oesophageal cancer patients, whereby the prevalence of sarcopenia almost doubled (15.9-30.8 %) during a course of neoadjuvant chemotherapy\(^{(46)}\).

In patients with cancer, muscle is lost at a very high rate of 3-5 % per 100 d during systemic chemotherapy\(^{(4,36,43,95)}\), and losses are exponentially increased with progressive disease and proximity to death\(^{(117,120)}\). In a recent study of metastatic colorectal cancer patients (n = 63), on average patients lost muscle at a rate of 6.1 % during 3 months of chemotherapy\(^{(88)}\), it is noteworthy that the rate of decline is 24-fold more rapid than that observed in healthy ageing adults who tend to lose muscle at a rate of 1-1.4 % per year\(^{(6,121)}\).

Alterations in muscle mass may be a consequence of some cancer-directed therapies. Sorafenib, a multi-kinase inhibitor, has been shown to provoke muscle wasting in metastatic renal cell carcinoma patients, through the downstream suppression of PI3K, AKTm and mTOR, key mediators in activating muscle protein synthesis by amino acids and other stimuli\(^{(38)}\). Abiraterone\(^{(122)}\) and MK-0646 (anti-insulin-like growth factor 1 receptor)\(^{(123)}\) have also been reported to stimulate muscle loss through maximal androgen suppression and inhibition of anti-insulin-like growth factor 1 receptor, respectively. In contrast, two chemotherapy agents (vandetanib and selumetinib) have resulted in significant muscle gain in patients with advanced cancer\(^{(78,154)}\).

Loss of muscle during systemic anti-cancer treatment is associated with increased mortality in patients with pancreatic\(^{(56,125)}\), lung\(^{(37,126)}\), colorectal\(^{(88,108)}\), ovarian\(^{(43)}\), melanoma\(^{(49)}\) and foregut cancer\(^{(127)}\) (see Table 3 for a summary of available studies reporting that muscle loss during treatment is prognostic of reduced survival). Loss of muscle >2 %/100 d has been independently associated with reduced survival in ovarian cancer patients receiving neoadjuvant chemotherapy \(n = 123; HR = 1.77 (95 \% CI 1.02, 3.09), P = 0.043\)\(^{(43)}\), and we have previously reported that in patients with advanced cancers of the foregut, those with a skeletal muscle loss >6 %/100 d are at more than double the risk of mortality \(HR = 2.66 (95 \% CI 1.42, 4.97), P = 0.002\)\(^{(127)}\). Importantly, skeletal muscle depletion during chemotherapy has also been associated with reductions in physical function in elderly patients with advanced non-small-cell lung cancer\(^{(128)}\).

**Strategies to improve muscle mass and attenuation**

Currently, there is no consensus treatment for attenuating or reversing the muscle wasting caused by sarcopenia and/or cachexia in patients with cancer. Research to date has focused on strategies to treat sarcopenia in the context of cancer cachexia using nutritional, exercise and pharmacological interventions. However, these single-agent therapies have not provided promising results, and perhaps multifaceted treatment strategies may be more effective in treating cachexia. Ideally, interventions for cachexia should be initiated in the early stages of weight loss (i.e. pre-cachexia); however, patients are often referred for cachexia interventions late in their disease trajectory (i.e. refractory cachexia). At this stage, patients are in a catabolic state and respond poorly to anti-cancer treatment\(^{(8)}\). Experts have speculated that the failure of treatments to show benefit at clinical evaluation may not have been because of the drugs ability to ameliorate or treat cancer cachexia, but because they were introduced to patients too late\(^{(129)}\).

Rehabilitation care to modify body composition, either increasing muscle mass and/or MA should be conducted, and its respective impact on oncology outcomes explored. Previous investigations have shown that intramuscular adipose tissue was responsive to exercise in non-cancer individuals\(^{(130)}\), and that cancer patients have anabolic potential\(^{(117)}\). Current evidence in evaluating the efficacy of prehabilitation on postoperative outcomes among cancer patients is still limited\(^{(131,132)}\). Future clinical trials are warranted to test whether the window of time between cancer diagnosis and initiation of treatment is an opportunity to commence interventions to increase muscle mass and MA.

**Nutritional interventions**

A meta-analysis of oral nutritional interventions in malnourished patients with cancer identified thirteen randomised controlled trials and included 1414 patients. The analysis, conducted by Baldwin et al.\(^{(133)}\), concluded that oral nutritional interventions had no significant effect on body weight, energy intake or mortality compared with standard care. Given the wide range of pathophysiological alterations that occur in cancer, complex and individualised targeted strategies incorporating modulations of the metabolic components of cachexia (e.g. inflammation) may be required to allow nutrition interventions to be more effective\(^{(134)}\). To date, n-3 fatty acids, such as EPA have received a lot of attention for the treatment of cancer cachexia due to their potent anti-inflammatory properties. In cancer, plasma n-3 fatty acid levels appear to be depleted in patients with sarcopenia and may contribute to accelerate muscle mass\(^{(135)}\). The results of several small clinical trials suggested that
using EPA supplements or oral nutritional supplements containing EPA in patients with advanced cancer improved appetite, energy intake, body weight, lean mass and/or physical activity. The n-3 fatty acid supplementation has also been shown to be effective in reducing intramuscular adipose tissue while maintaining muscle mass (compared with standard care) in a small cohort of patients with non-small-cell lung cancer, supporting what is observed in preclinical experimental animal models. However, the clinical evidence supporting n-3 fatty acids remains inconclusive. Three systematic reviews published in 2007, 2009 and 2012 concluded that there was insufficient evidence to support a recommendation for n-3 fatty acids to treat muscle depletion and cancer cachexia. Due to the inconsistencies in the reported effects of n-3 fatty acids, the ESPEN oncology nutrition guidelines issue only a weak recommendation for their use to stabilise or improve appetite, food intake, lean mass and body weight.

Achieving adequate protein intake is an essential component to achieving muscle anabolism; however, no optimal amino acid and protein requirements have been established to prevent or treat sarcopenia in patients with cancer. Current recommendations suggest intakes of 1–1.5 g/kg/d in patients with cancer, however, many patients fail to reach these requirements. Moreover, recent research has suggested that protein requirements should be based on the measures of lean mass as opposed to body weight.

### Physical activity

A recent meta-analysis has shown resistance exercise to be effective in increasing muscle strength and mass in...
cancer patients undergoing neoadjuvant and adjuvant therapy, with mean increases in lower limb strength of 26.2 kg ($P = 0.00001$) and lean mass by 0.8 kg ($P < 0.00001$)\textsuperscript{(180)}. In a study of early-stage breast cancer patients receiving adjuvant chemotherapy, resistance exercise resulted in the reversal of sarcopenia and dynapenia in 43 and 59% of patients, respectively\textsuperscript{(151)}. To date, most studies have been conducted in early-stage breast and prostate cancer and evidence of the effect of physical activity on muscle mass and strength in patients with advanced disease and cancer cachexia is lacking\textsuperscript{(152,153)}. A recent Cochrane systematic review\textsuperscript{(153)}, which aimed to examine the impact of exercise on lean mass in patients with cancer cachexia, showed disappointing results. The authors screened more than 3000 individual articles, but found no trials that met the inclusion criteria for analysis\textsuperscript{(153)}. Initial findings indicate that exercise is safe and well tolerated in patients with advanced disease\textsuperscript{(154)} and improves physical performance and several domains of quality of life\textsuperscript{(155)}, but further work is needed. Evidence of interventions aimed at improving MA in patients with cancer are scarce; however, evidence in older adults suggests that exercise may represent a countermeasure to improve MA, as studies have shown that muscle fatty infiltration is amenable to change after 12 weeks of thrice-weekly resistance training\textsuperscript{(130)}.

Recently, a few studies have demonstrated that exercise interventions are capable of improving cancer outcomes. Cho et al.\textsuperscript{(156)} reported that preoperative exercise significantly improved operative risk factors and decreased the frequency of serious postoperative complications in gastric cancer patients. In breast cancer, a supervised moderate- to high-intensity exercise programme during adjuvant chemotherapy was associated with a beneficial effect on chemotherapy completion rates with a significantly smaller proportion of patients requiring dose adjustments compared with usual care (12 v. 34%)\textsuperscript{(157)}. The impact of exercise prehabilitation on cancer outcome warrants further investigation.

**Pharmacological agents**

To date, no pharmacotherapies have been approved to specifically treat the cancer cachexia syndrome. Non-steroidal anti-inflammatory drugs have been suggested as a potential treatment for cancer cachexia, with the aim of reducing systemic inflammation. In a recent systematic review of thirteen studies, eleven showed either improvement or stabilisation in weight or lean mass in patients with cancer\textsuperscript{(158)}; however, the evidence is still insufficient to recommend non-steroidal anti-inflammatory drugs to treat cancer cachexia outside of clinical trials. Promising results have been obtained for anamorelin (a ghrelin receptor agonist); phase III trials (ROMANA 1 and ROMANA 2) have shown that anamorelin significantly increases lean mass and improves anorexia/cachexia symptoms compared with placebo over a 12-week intervention period. However, muscle function (measured by hand grip strength) failed to improve during the intervention\textsuperscript{(159)}. Food and drug administration regulators generally require improvements in lean mass and functional outcomes as co-primary endpoints for the approval of new medications to treat cancer cachexia. As a result, anamorelin has not received the food and drug administration’s approval to date. Phase III trials have recently been completed for enobosarm, a selective androgen receptor modulator (NCT01355484), and MABp1, an anti II-1 alpha monoclonal antibody (NCT01767857), the results of which are yet to be published.

**Multimodal interventions**

Results so far suggest that single-agent therapies may be insufficient to counteract cancer cachexia and that early multimodal interventions may be necessary to combat its multifactorial and complex pathogenesis. A multimodal approach including the use of individualised nutritional interventions to promote energy balance and ensure optimal protein intake, decreasing inflammation and hyper metabolic stress with the aid of anti-inflammatory agents (non-steroidal anti-inflammatory drugs s and EPA) and increasing physical activity to stabilise/increase muscle mass, strength and physical performance has been recommended\textsuperscript{(118)}. One such intervention currently under investigation is the MENAC trial (Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia), whereby phase II feasibility studies have yielded encouraging results and suggest multimodal interventions are feasible and safe in patients with cancer\textsuperscript{(160)}. The phase III trial (NCT02330926) is currently being conducted across a number of international sites.

**Conclusion**

In summary, the evidence reviewed here shows that muscle abnormalities are highly prevalent in adult patients with cancer, across cancer sites and stages, and overweight and obesity do not preclude their presence. However, the heterogeneity in the diagnostic criteria limits the ability to accurately compare the reported prevalence rates between different cohorts and study findings overall. Efforts are required to standardise muscle measurements from CT images, as well as the diagnostic criteria for sarcopenia and low MA in patients with cancer. Nonetheless, the clinical importance of muscle abnormalities in these patients is evident, given their associations with negative clinical outcomes, such as poorer tolerance to chemotherapy, increased risk of post-operative complications and infections, increased length of hospital stays and poor prognosis.

In an age of increasingly personalised medicine, CT scans, obtained as part of routine patient care, provide valuable individualised information on muscle mass and MA with well-established prognostic implications. Incorporating routine assessment of muscle abnormalities from CT images into clinical practice has the potential to play a major role in stratifying patients at risk of poorer clinical outcomes, who may benefit from targeted interventions. At present, no effective medical intervention to improve muscle mass and MA exists; however,
in recent years, substantial progress has been made, with the results of several clinical trials awaited in the near future. The optimal timing and treatment strategy for preventing or delaying the development of muscle abnormalities are yet to be determined, but multimodal interventions appear to hold the most promise.

**Supplementary material**

The supplementary material for this article can be found at https://doi.org/10.1017/S0029665118000046

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**Conflict of interest**

None.

**Authorship**

L. E. D. reviewed the literature and wrote the manuscript. A. M. R. and C. M. P. participated in writing and revising the manuscript. All authors approved the final manuscript.

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