Proceedings of the Nutrition Society (2021), **80**, 73–91 doi:10.1017/S0029665120007855
 First published online 3 November 2020

The Nutrition Society Winter Meeting was held at the Royal Society of Medicine London on 2–4 December 2019

Conference on 'Diet and digestive disease'
Cuthbertson Award Lecture

Impact of musculoskeletal degradation on cancer outcomes and strategies for management in clinical practice

Aoife M. Ryan[1,2]* and Erin S. Sullivan[1]

[1]*School of Food & Nutritional Sciences, College of Science, Engineering & Food Science, University College Cork, Cork, Republic of Ireland*

[2]*Cork Cancer Research Centre, University College Cork, Cork, Republic of Ireland*

The prevalence of malnutrition in patients with cancer is one of the highest of all patient groups. Weight loss (WL) is a frequent manifestation of malnutrition in cancer and several large-scale studies have reported that involuntary WL affects 50–80 % of patients with cancer, with the degree of WL dependent on tumour site, type and stage of disease. The study of body composition in oncology using computed tomography has unearthed the importance of both low muscle mass (sarcopenia) and low muscle attenuation as important prognostic indications of unfavourable outcomes including poorer tolerance to chemotherapy; significant deterioration in performance status and quality of life (QoL), poorer post-operative outcomes and shortened survival. While often hidden by excess fat and high BMI, muscle abnormalities are highly prevalent in patients with cancer (ranging from 10 to 90 %). Early screening to identify individuals with sarcopenia and decreased muscle quality would allow for earlier multimodal interventions to attenuate adverse body compositional changes. Multimodal therapies (combining nutritional counselling, exercise and anti-inflammatory drugs) are currently the focus of randomised trials to examine if this approach can provide a sufficient stimulus to prevent or slow the cascade of tissue wasting and if this then impacts on outcomes in a positive manner. This review will focus on the aetiology of musculoskeletal degradation in cancer; the impact of sarcopenia on chemotherapy tolerance, post-operative complications, QoL and survival; and outline current strategies for attenuation of muscle loss in clinical practice.

Cancer: Cachexia: Survival: Nutrition: Sarcopenia

Involuntary weight loss (WL) is a hallmark feature of cancer-associated malnutrition, the prevalence of which has frequently been shown to be one of the highest of all hospital patient groups[1–3]. Several large scale studies over the past 40 years have reported that involuntary WL affects 50–80 % of patients with cancer with the degree of WL dependent on tumour site, type and stage of disease[4–7].

Malnutrition and involuntary WL at the time of diagnosis and deterioration of nutritional status during treatment, are associated with poor outcomes. A recent large international cohort of 8160 patients with cancer suggesting that WL of as little as 2·4 % predicts survival independent of disease, site, stage or performance score[6]. In addition to the adverse impact on survival, WL has historically been associated with severe chemotherapy-related toxicity[8–12]; and leads to a significant deterioration in a patients' performance status, psychological well-being and overall quality of life (QoL)[13,14].

Abbreviations: BSA, body surface area; CT, computed tomography; ESPEN, The European Society for Clinical Nutrition and Metabolism; MA, muscle attenuation; NIS, nutrition impact symptoms; PAL, physical activity level; QoL, quality of life; RD, registered dietitian; WL, weight loss.

***Corresponding author:** Aoife M. Ryan, email a.ryan@ucc.ie

Aetiology of malnutrition in cancer

The aetiology of malnutrition in cancer is multifactorial and includes the effect of nutrition impact symptoms (NIS) on oral intake, as well as complex metabolic alterations inherent in the disease process[15]. The pathophysiology includes derangement of metabolic and hormonal processes due to inflammatory mediators produced by the tumour microenvironment, which can impair appetite and promote an inflammatory state associated with increased energy requirements and anabolic resistance[16,17]. Therefore, reduced dietary intake, increased requirements, altered substrate utilisation and anabolic resistance, combined with the reduced anabolic stimulus in the form of exercise, all contribute to malnutrition in cancer.

Nutrition impact symptoms

As well as abnormal metabolism of nutrients, patients with cancer often experience a reduction in oral intake and absorption due to nutrition impact symptoms such as anorexia, dysgeusia, nausea, constipation diarrhoea, dysphagia, malabsorption and early satiety. NIS are caused by both the disease itself and cancer treatments. Underlying causes range from the mass-effect of tumours (in the case of pain and dysphagia), as well as more complex, centrally mediated mechanisms such as attenuated orexigen production (caused by systemic inflammation), to iatrogenic conditions such as radiation enteritis[18]. NIS are strongly associated with malnutrition, specifically anorexia and WL[19]. Most NIS reported are of gastrointestinal origin, for example; nausea, vomiting, constipation, taste and smell changes, dumping syndrome and dysphagia. However, pain, fatigue, reduced functional capacity, financial concerns[20–22] and depression are also noted by many patients. These varying symptoms all have a profound impact on QoL[23] and performance status[24]. The impact of NIS on performance status is of particular concern as reduced activity levels feed the cycle of cachexia. in that, reduced stimulus to the muscles can lead to muscle atrophy alongside the muscle wasting associated with a lack of substrate and anabolic resistance[25].

Metabolic derangements and increased energy expenditure

While reduced oral intake is a significant contributor to WL in cancer, a recent review showed that in studies where nutritional intake is controlled, WL persists in many patients[26], suggesting that factors such as hypermetabolism and anabolic resistance contribute to cancer-related WL[27]. The presence of cancer in the body causes a variety of metabolic and endocrine changes (such as inflammation, anabolic resistance, proteolysis, lipolysis and futile cycling) induced by the tumour and activated immune cells. Complex interactions between inflammation (pro-inflammatory cytokines), neuro-hormonal changes and potential proteolytic and lipolytic factors produced by the host and the tumour, fuel WL and loss of lean mass[15]. Hypermetabolism is also thought to be a significant contributor to energy deficits, with resultant WL. Depending on the tumour burden, and the level of anaerobic metabolism, an additional 418–5858 kJ (100–1400 kcals) can be required daily[28]. In addition, significantly increased production of acute-phase proteins and cytokines is an energy-intensive process[15] and receptors for many cytokines are expressed in the feeding centres of the hypothalamus, therefore inflammation-mediated changes in the hypothalamic-pituitary axis result in illness behaviour[16], including aberrations in appetite signalling and inhibition of orexigens resulting in poor oral intake[29]. Additional factors such as the browning of adipose tissue[30], changes in carbohydrate metabolism (Cori cycle upregulation), changes in fat metabolism (fatty acid cycling), increased insulin resistance[31] and the demand for amino acids to drive the inflammatory response, results in increased muscle proteolysis and reductions in lean mass, which affects both skeletal muscle and muscular organs, such as the heart[15]. Furthermore, upregulation of the ubiquitin-proteasome pathway leads to increased muscle degradation[32].

Increase in sedentary behaviour

A doubly-labelled water study quantifying the physical activity level (PAL) of healthy adults found that the PAL of a sedentary adult is 1·4–1·5[33]. Compared to this, patients with cancer have been shown in a number of studies to be significantly more inactive that this, with Moses *et al.* reporting on twenty-four pancreatic cancer patients with cachexia, who had a mean PAL of 1·24[34] and Gibney *et al.* who found that lung cancer patients had a PAL of 1·36[35]. These values correspond better with the severely disabled than any healthy, sedentary population. Community living spinal cord injury patients have been demonstrated to have a PAL of 1·32[36] and young patients with cerebral palsy a PAL of 1·23[37]. These findings attest to the marked impact of advanced cancer and cachexia on the physical function and QoL of such patients. Levels of physical activity this low may exacerbate muscle wasting and it is well understood in any individual that a lack of physical activity will cause deconditioning and deterioration in muscle mass.

Weight loss and changes in body composition following a cancer diagnosis

The end results of the factors discussed earlier is involuntary WL which is a hallmark feature cancer-associated malnutrition. Often referred to as cancer cachexia, it is now accepted to be a multifactorial syndrome characterised predominantly by the ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutrition support[38]. Moderate-to-severe WL is present in 30–70 % of cancer patients[2,4–7,39]. In the largest study to-date of 8160 patients with locally advanced or metastatic disease, 73 % experienced involuntary WL[6]. Table 1 summarises the prevalence of >5 % WL (a key component of the diagnostic criteria of cancer cachexia[38]) according to tumour site in the scientific literature. WL has

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

Table 1. Prevalence of patients with >5% weight loss according to primary tumour location in the scientific literature

Primary cancer	Percentage with >5% weight loss in 6 months
Pancreatic[40–44]	41–53
Gastric[230–233]	42–75
Colorectal[60,234–238]	32–48
Oesophageal[239–244]	33
Lung[134,238,245–252]	44–49
Breast[51,238,253,254]	24

consistently been shown to be most frequent in patients with cancers in the upper gut and lung[40–44].

While involuntary WL is reported by the majority of patients with cancer, a significant proportion remain overweight or obese by international standards, thus appearing well-nourished[45]. Recent studies have reported that between 40 and 60 % of cancer patients are overweight or obese (BMI >25 kg/m^2) even in the setting of metastatic disease[6,7,46–48]. In a recent pooled analysis of twenty-two randomised trials that included 11 724 patients with cancer, 67 % were shown to be overweight or obese at the time of their cancer diagnosis[49]. As a result, many patients with cancer-related malnutrition are diagnosed with malnutrition late in the course of their disease as nutritional screening instruments such as the Malnutrition Universal Screening Tool, and others, are primarily based on BMI and do not identify these patients as malnourished until they have lost significant weight. Neither BMI nor percentage WL can capture changes in body composition and specifically changes in muscle mass[45]. Muscle loss is the most clinically relevant phenotypic feature of cancer cachexia and identifying those with muscle loss can become a huge challenge in overweight and obese patients[39]. It is also important to note that although muscle loss is commonly associated with cancer, cancer is a disease associated with ageing, and therefore the aetiology of muscle loss in patients with cancer can be 2-fold, first resulting from the age-related decline in muscle mass and second due to cytokine-mediated degradation of muscle and adipose depots, hypermetabolism and anorexia associated with cancer cachexia[15]. Distinguishing the exact cause of muscle loss can be difficult.

Lean mass

Computed tomography is now considered a gold standard method of body composition assessment and is of particular convenience in oncology research as these scans are readily available because they are used as part of routine medical care. Axial computed tomography images at the level of L3 are analysed to determine muscle mass, muscle radiodensity and adipose tissue mass (total, subcutaneous and visceral) and excellent inter-observer reliability has been shown[50]. Regression formulae are available to estimate whole-body compartments using these data. Computed tomography allows the precise quantification of both muscle and adipose tissue and has led to a large volume of research which has increased our understanding of the importance of abnormal body composition phenotypes, such as low muscle mass (sarcopenia), and more recently low muscle attenuation (MA) as important prognostic indicators of unfavourable outcomes in patients with cancer[6,11,51,52].

Sarcopenia

Sarcopenia is defined by The European Working Group on Sarcopenia in Older People as 'a syndrome of progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death'[53,54]. While muscle loss is a normal part of ageing, this syndrome can also occur in association with disease, such as cancer. A generally accepted cut-point is skeletal muscle mass 2 standard deviations below that of a healthy, young population[55].

Sarcopenia is now known to relate to asthenia, fatigue, impaired physical function, increased chemotherapy toxicity, impaired QoL and reduced survival[6,13,45,56]. Recent studies have shown that cancer, and its treatment, exacerbate muscle loss and that patients continually lose muscle mass while on treatment[11,57,58]. While healthy adults over the age of 40 years have been shown to lose muscle at a rate of 1–1·4 %/year[59], cancer patients have been shown to have a 24-fold higher rate of muscle loss than that observed in healthy ageing adults[57,60]. In studies examining the rate of muscle loss in cancer patients, rates of 3·9 %/100 days have been reported in foregut cancer[57], 3·1 %/100 days in pancreatic cancer[61] 3·3 %/100 days in metastatic melanoma[11] and 5·2 %/100 days in ovarian cancer[58].

Prevalence of cancer cachexia and sarcopenia in oncology

The prevalence of cancer cachexia and sarcopenia can vary widely depending on the method of assessment and diagnostic criteria used[62]. From the literature, it can be estimated that the prevalence of cancer cachexia (based on WL >5 % as per the recent consensus definition[38]) can vary between 13 and 61 % depending on the tumour site (Table 1), and between 38 and 70 % of patients are considered to have sarcopenia (based on three of the most commonly used diagnostic criteria) (see Fig. 1). The prevalence of sarcopenia is highest in the lung (median 70 %, range 47–79 %)[63–66] and pancreatic cancer (median 56 %, range 44–89 %)[41,61,67–73] however, it is noteworthy that the majority of studies report a prevalence of above 40 % at most other sites in the body.

Our group recently estimated the incidence and prevalence of cachexia and sarcopenia in the UK and Ireland[74]. We estimated that across the Republic of Ireland and UK at least 128 892 cancer patients are affected by WL >5 % annually (34 %) and that there are 716 124 cancer survivors who have suffered >5 % WL at some point in their disease trajectory. Furthermore, we estimated that there are at least 133 707 annual cases of cancer patients with sarcopenia (35 %) and 771 589 cancer survivors alive who have been affected by sarcopenia during their disease trajectory.

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

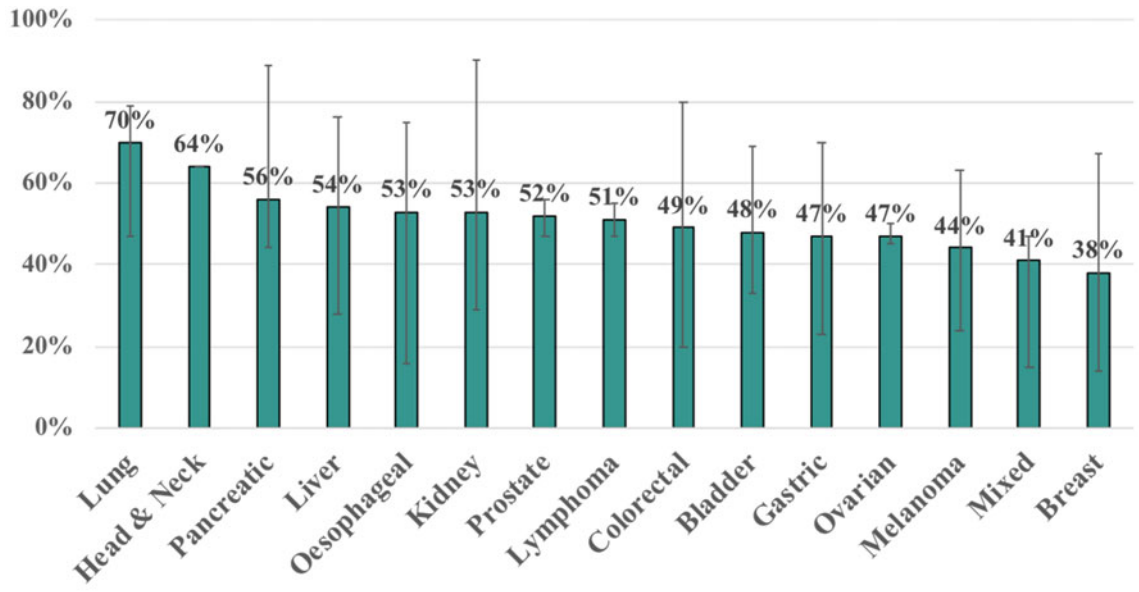

Fig. 1. Prevalence of sarcopenia in patients with cancer according to the primary tumour location in the literature (all stages).[63–68,136,41,61,69–73,111,180,256–260,90,94,261–264,12,113,265–270,95,271–275,52,60,149,150,276,277,185,260,278–280,86–88,281,282,283–287,91,288–293,11,47,57,58,92,162,164,268,294,295,7,93,96,100,165,296–299].

Prevalence of sarcopenia defined using three of the most common definitions for defining low muscle mass is displayed in Table 1. These definitions are as follows; Prado *et al.*[92]: Skeletal muscle index (SMI)<52·4 cm^2/m^2 in men and <38·5 cm^2/m^2 in women; Martin *et al.*[47]: SMI <43·0 cm^2/m^2 in men with a BMI <25 kg/m^2 and <53·0 cm^2/m^2 in men with a BMI >25 kg/m^2 and SMI <41·0 cm^2/m^2 in women; Baumgartner *et al.*[55] converted dual-energy X-ray absorptiometry cut points by Mourtzakis *et al.*[300] as SMI <55 4 cm^2/m^2 in men and <38·9 cm^2/m^2 in women.

The rates of muscle wasting seen in cancer populations are of huge public health importance, given that cancer cachexia and sarcopenia have been reported to be unequivocally associated with negative clinical outcomes in patients with cancer including poorer tolerance to anti-cancer treatment, poorer overall QoL, increased risk of post-operative complications and poorer overall survival[6,13,56,62].

Skeletal degradation in cancer treatment

As well as the ongoing loss of muscle mass, several anti-cancer therapies (both hormonal and non-hormonal) promote bone loss through direct dysregulation of bone turnover and indirectly through hypogonadism and nephrotoxicity. The rate of bone loss from cancer therapy can be ten times higher than in the general population[75–79] but is highest in breast and prostate cancer[75] due to commonly administered therapies such as endocrine therapy (breast cancer) and androgen deprivation therapy (prostate cancer). Chemotherapy drugs (cisplatin, doxorubicin, cyclophosphamide, ifosfamide, FOLFIRI, carboplatin, methotrexate and targeted therapies) cause reduced bone volume and radiation therapy, orchiectomy and oophorectomy also result in bone loss. The onset of bone loss from premature menopause is sudden (within 6 months of treatment) and significant (21 % decreased density *v.* age-matched menstruating women[80]). For men with prostate cancer on androgen deprivation therapy loss of bone starts within 6–9 months with annual declines of between 2 and 8 %[81–83]. Reduction in bone quality is also further exacerbated by inactivity. Muscle weakness and exercise intolerance can persist from months to years after remission[84,85]. Excess bone resorption can lead to fractures and spinal cord compression[75].

Why malnutrition matters: impact on tolerance to systemic chemotherapy

Chemotherapy can often be associated with severe toxicity that can result in dose delays, dose reductions and treatment termination, referred to as dose limiting toxicities. Moderate to severe toxicities can lead to interruption, deferral or even cessation of treatment. Severe toxic events can result in hospitalisations and can even be life-threatening. Recent evidence suggest that variability in body composition of cancer patients may be a source of disparities in the metabolism of cytotoxic agents resulting in increased toxicity[86–88].

To date, in excess of forty studies have examined the relationship between low lean mass (sarcopenia) and the prevalence of dose limiting toxicity in patients with cancer (we have previously reviewed these[89]). The relationship between sarcopenia and increased chemotherapy toxicity has been reported in both early and late-stage disease, at almost all cancer sites and with many modalities of cytotoxic agents (cytotoxic single agents, regimens, targeted agents and immunotherapies)[90–93]. Although the relationship between low lean mass and poorer tolerance to treatment has been observed in the majority of studies, a few smaller studies have reported no association[60,71,94–99].

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

Low lean mass can lead to increased toxic side effects to chemotherapy through alterations in the distribution, metabolism and clearance of chemotherapy drugs[100]. The widespread use of body surface area (BSA), relying on height and weight alone[101], in dosing chemotherapy drugs presents a problem as there are large discrepancies in muscle mass between people of the same BSA, resulting in potential under or over-dosing when calculations are based on a simple BSA formula[102–104]. A 4–10-fold variation in drug clearance is possible in individuals with a similar BSA and there is concern that this approach to dosing is invalid[105,106]. Bodyweight comprises two major components (lean and fat mass) then these are the two major sites of distribution of hydrophilic and lipophilic drugs[107,108]. Therefore, variability in individual lean mass or fat mass may lead to changes in the volume of distribution of drugs and therefore adversely affect the tolerance of cytotoxic drugs[62]. In sarcopenic obesity, tolerance is further compromised in individuals where the combination of excessive fat mass and low lean mass may significantly impact the tolerance of hydrophilic drugs by resulting in a disproportionally small volume of drug distribution in relation to their body weight or BSA[100,107]. Variations in lean and fat mass can therefore lead to considerable variation in the milligram of chemotherapy drug per kilogram lean mass with higher doses per kilogram lean mass shown to be associated with more frequent and severe toxic side effects[107,109,110]. This hypothesis is supported by pharmacokinetic data, with sarcopenic patients experiencing higher plasma concentrations of antineoplastic drugs and experiencing more toxicity[111,112]. For lipophilic drugs such as doxorubicin or trabectedin, individuals with a low-fat mass may also present with toxicity due to a reduced volume of distribution[108].

It is also important to note that sarcopenic patients are excessively fragile and highly susceptible to acute medical events that exacerbate chemotherapy-related toxicity[113]. In addition, for those patients with systemic inflammation, this has been shown to decrease liver cytochrome activities and drug clearance and may modify drug exposure. Low concentrations of circulation plasma proteins (e.g. albumin), which is commonly seen in those with malnutrition or systemic inflammation (or both) may also affect the distribution of highly protein-bound drugs such as vandetanib, sorafenib and epirubicin[108,111,112]. As imaging techniques in body composition become more widely used, this may represent an opportunity for a more personalised approach to chemotherapy dosing.

Why malnutrition matters: impact on performance status and quality of life

The adverse impact of WL on QoL has long been recognised in patients with cancer and WL has been associated with deterioration in patients' performance status and psychosocial well-being[40,114,115]. In a recent systematic review examining the impact of WL and QoL, a negative relationship between %WL and QoL was reported in twenty-three of twenty-seven studies included in the analysis[13]. However, the mode by which WL exerts its influence on QoL is not fully understood but may relate to muscle atrophy associated with cachexia and WL leading to fatigue or reduced functional capacity[116]. The negative impact on QoL is unsurprising, considering cancer-related malnutrition is a major cause of fatigue[117,118], reduced functional ability[116] and a source of emotional distress[117,119]. Our group recently reported on a cohort of 1027 patients with advanced cancer and showed that WL >10 % was associated with poorer QoL in almost all functional and symptom domains[14]. In particular, WL in excess of 10 % in the preceding 3 months was independently associated with poorer physical function, fatigue and appetite loss and overall poorer QoL summary scores.

While there is no doubt that WL impacts negatively on QoL, inconsistent reports on the relationship between muscle parameters and QoL have been published in the literature[97,120–122]. Parsons and colleagues reported no significant associations between low Skeletal muscle index and symptom burden or functional life domains assessed by the MD Anderson Symptom Inventory, in a cohort of 104 patients with advanced cancer[97]. However, in a study of 734 advanced lung cancer patients, low Skeletal muscle index was non-linearly associated with lower global QoL, physical function and role function, and associated with more symptoms (fatigue and pain), while low MA was associated with poor physical function and more dyspnoea[122]. Sarcopenia has also been associated with greater depression symptoms and more fatigue in patients with advanced cancer[120,121]. It may be that low Skeletal muscle index, at a single time point, is not reflective of a dynamic measure of loss and may be influenced by a patient's intrinsic level of muscularity. Perhaps the loss of muscle over time may better reflect poor QoL and further research is needed in this area.

The mode by which WL exerts its influence on QoL is not fully understood but may relate to muscle atrophy associated with cachexia and WL leading to fatigue or reduced functional capacity. Recent work has suggested that the complex interplay between metabolic disruption and pro-inflammatory cytokines (i.e. IL-6, IL-8 and TNF-α) in cancer cachexia often leads to physical, biochemical and nutritional deterioration which subsequently leads to poor QoL[123]. It is thought that the systemic inflammatory response has a direct role in the development of cancer-associated symptom clusters, including pain, fatigue, mood, anorexia and physical function[124]. Systemic inflammation and loss of lean mass are also thought to drive cancer-related fatigue, which is thought to affect up to 80 % of cancer patients[125] both during and after treatment cessation[125–128]. Severe and persistent fatigue, along with muscle mass wasting has been shown to inhibit QoL by considerably reducing functional capacity to fully participate in daily living tasks[125]. Individual proinflammatory cytokines have been associated with clinical symptoms, e.g., IL-6 and C-reactive protein with anorexia[129], IL-1ra with fatigue[129] and IL-6 with major depression[130,131]. Our group recently reported that systemic

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

inflammation has a negative impact on QoL that is independent of Eastern Cooperative Oncology Group performance status[14] which is consistent with previous reports indicating that the systemic inflammatory response is associated with poorer QoL, even in those with a good performance score[132].

Importantly, interventions aimed at targeting nutritional status and attenuating weight have proven successful in improving aspects QoL in patients with cancer[133]. In addition, novel cachexia treatments, such as Anamorelin, an oral ghrelin-receptor agonist with appetite enhancing and anabolic activity have shown a favourable clinical response in alleviating anorexia-cachexia symptoms[134]. Research is warranted to determine if attenuating the systemic inflammatory response is capable of producing clinically relevant improvements in symptoms that may represent a new therapeutic approach to symptom management in patients with advanced cancer.

Impact on survival

The impact of sarcopenia on survival in cancer has been extensively studied over the past decade. Most studies report a significant decrease in overall survival in patients with sarcopenia compared with those without sarcopenia, irrespective of the primary cancer site and stage (see Fig. 2). Figure 1 displays a forest plot depicting the summary results of meta-analyses examining the role of sarcopenia in survival in cancer. To-date sarcopenia (diagnosed by computed tomography) has been shown to be independently associated with poorer survival in all those sites included in the meta-analysis in Fig. 2 as well as in head and neck[135–140], prostate cancer[141], cholangiocarcinoma[142–146], lymphoma[147–151] and leukaemia[152]. In a recent systematic review and meta-analysis of thirty-eight studies that included 7843 patients with solid tumours, low muscle cross-sectional area was observed in 27·7 % of patients with cancer and associated with poorer overall survival (hazard ratio (HR) 1·44, 95 % CI 1·32, 1·56), cancer-specific survival (HR 1·93, 95 % CI 1·38, 2·70), as well as disease-free survival (HR 1·16, 95 % CI 1·00, 1·30) but not with progression-free survival (HR 1·54, 95 % CI 0·90, 2·64)[153]. This meta-analysis demonstrated that the adverse effects of low lean mass on overall survival were similar in both metastatic (HR 1·37, 95 % CI 1·21, 1·56) and non-metastatic disease (HR 1·54, 95 % CI 1·31, 1·79), and this relationship was observed across different primary tumour sites. Recently, in two of the largest observational cohort studies to date, Caan and colleagues[154,155] demonstrated the prognostic value of low muscle mass in non-metastatic breast (*n* 3241) and colorectal cancer (*n* 3262). Low lean mass was present in 34 and 42 % of patients, respectively, and was independently associated with a 27–41 % higher risk of overall mortality (colon: HR 1·24, (95 % CI 1·09, 1·48); Breast: HR 1·41 (95 % CI 1·18, 1·69)][154,155].

In addition to low muscle area (sarcopenia), low MA (density; indicative of fatty infiltration of muscle tissue) is also associated with poorer survival in a variety of tumours including non-small cell lung cancer[156], colorectal[157–159], endometrial[160], renal[161], ovarian cancer[162] and melanoma[163]. Importantly, in some cases, low MA appears to superior in predicting mortality compared with low lean mass alone[156,164–167]. However, it has also been demonstrated that the risk of mortality associated with low lean mass and low MA can be independent of each other[146,168,169].

Lastly, the combination of sarcopenia and obesity has been shown to have particularly poor clinical outcomes. This may be related to the combined negative effects of both conditions or may be related to poor detection of sarcopenia in a cohort whose muscle loss is masked by excess adiposity. Sarcopenic obesity specifically has been associated with poorer survival in a number of cohorts[92,170].

Why malnutrition matters: impact of muscle loss during treatment and survival

Notwithstanding the impact of sarcopenia on survival, several studies have emphasised that patients continually lose muscle mass while on treatment and that this is associated with an increased risk of mortality in a number of cancers. Patients with advanced pancreatic cancer (*n* 97) who experienced the early loss of skeletal muscle (>10 % within 3 months of diagnosis) were at increased risk of poorer overall survival and progression-free survival compared to patients who did not experience muscle loss to the same degree (HR 2·16 (95 % CI 1·23, 3·78), $P = 0{\cdot}007$ and HR 2·31 (95 % CI 1·30, 4·09), $P = 0{\cdot}004$)[171]. In patients with surgically resected stage I-III colorectal cancer (*n* 1924), those who experienced the largest decrease in muscle mass (≥2 standard deviations or the equivalent to ≥11·4 % loss) and the largest decline in mean MA (≥2 SD; ≥20·2 % loss) from baseline were at a significantly increased risk of mortality (HR 2·15, 95 % CI 1·59, 2·92), $P < 0{\cdot}001$ and HR 1·61 95 % CI 1·20, 2·15, $P = 0{\cdot}002$, respectively), and these findings were independent of changes in body mass or other body composition parameters[158]. To date, losses in muscle have been shown to be prognostic of reduced survival in pancreatic[72,171], oesophageal[172], gastric[173], lung[174], colorectal[60,175,176], ovarian[58], melanoma[11] and foregut cancers[57].

Why malnutrition matters: impact on surgical outcomes

In cancer patients undergoing surgery, length of stay and post-operative complications are important indicators of surgical morbidity. Sarcopenia has been independently associated with adverse post-operative outcomes including infections, complications, the longer length of hospital stay and risk of readmission following gastrectomy[177,178], pancreatectomy[179], oesophagectomy[180,181], cystectomy[182]pneumonectomy[183,184] and colectomy[185–187]. Even in those without complications, length of stay has been shown to be significantly longer in patients with muscle abnormalities[188–190].

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

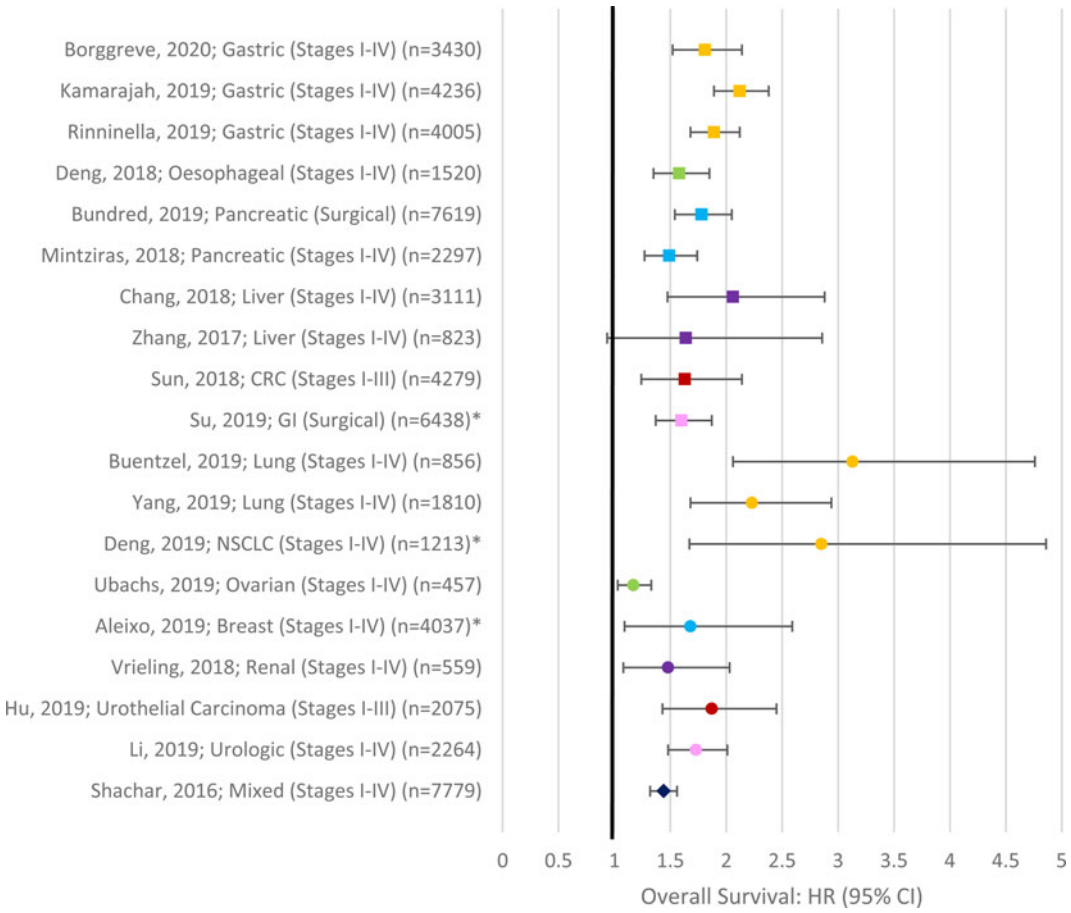

Fig. 2. (Colour online) Forest Plot depicting summary results of meta-analyses examining the role of sarcopenia in survival in cancer. Asterisks denote studies which did not confirm the inclusion of multivariate data in the meta-analysis[153,301–304,305–310,170,311–315].

Potential therapies for malnutrition in cancer

Despite much evidence that impaired nutritional status is associated with poor outcomes, the evidence-base regarding the optimal management of malnutrition in cancer and the ability to improve nutritional status to improve clinical outcomes is lacking[191]. While the treatment of malignancy is the primary method of reversing the metabolic environment which perpetuates cachexia, supportive care is required while this process ensues. In the early stages of cancer cachexia, malnutrition may be reversible; however, in later stages of the disease, it has been difficult to attain significant improvements in nutritional status, although it has been suggested that with the right combination of therapies, even patients with advanced disease may exhibit anabolic potential.

Dietetic management

Nutritional interventions have been a mainstay of cachexia management to date. Nutritional counselling, consisting of dietary advice and ongoing education is the first line for treatment of malnutrition[191]. While a food-first approach to a high-protein, high-energy diet is recommended, nutrition support, starting with the use of oral nutritional supplements is frequently required to augment volitional intake where appetite is limited. Furthermore, artificial nutrition in the form of enteral or parenteral nutrition may be required due to dysphagia, obstruction of the gastrointestinal tract or severe malabsorption[192]. The European Society for Clinical Nutrition and Metabolism (ESPEN) released consensus guidelines in 2017 for the nutritional management of cancer patients[191]. Despite limited evidence that nutritional interventions improve clinical outcomes, ESPEN strongly recommends, with moderate evidence, that nutritional interventions be employed in those at risk of malnutrition, aiming to increase oral intake, by providing dietary advice, management of metabolic derangements and nutrition impact symptoms, as well as the provision of oral nutritional supplementation where needed. ESPEN recommend that patients' total energy expenditure be assumed as 105–126 kJ/kg (25–30 kcal/kg) body weight daily, unless the direct measurement is available. Given that cancer patients can be hypo-, normo- or hypermetabolic, and displaying varying levels of anabolic resistance, it seems reasonable, in the absence of direct measurements, to take a pragmatic approach, and adjust requirements according to clinical response to the initial estimation.

Apart from energy requirements, meeting protein needs is also a priority in order to maintain lean mass

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

and support recovery throughout the cancer journey. ESPEN recommend 1–1·5 g protein/kg body weight in cancer patients but suggest that research is necessary to determine whether a higher level such as 2 g/kg may be beneficial[191]. PRIMe (ClinicalTrials.gov ID: NCT 02788955) is a feasibility study (*n* 40) comparing isoenergetic diets in colorectal cancer with either 1 g protein/kg body weight or 2 g protein/kg body weight and assessing the impact of the varying protein intakes on muscle mass and physical functioning.

A number of individual studies have demonstrated positive impacts of nutritional interventions on relevant outcomes. A number of studies have demonstrated that dietitian-led clinics and intensive dietary counselling can reduce nutrition-related admissions[193,194] and reduce the length of stay[195]. Improved energy and protein intake[196,197] and weight[198,199] were noted in some studies and these increases led to improved QoL, functioning and nutritional status[200].

A recent national survey led by our research group in Ireland examined the attitudes and experiences of patients with cancer (*n* 1085) to nutrition[201]. Overall 45 % reported problems with diet and eating, 44 % had experienced involuntary WL (mean loss reported 10·4 kg, range 1–44 kg) and 52 % reported they had noticed muscle loss. The majority (67 %) wanted more information on diet with 51 % reported they were concerned about their nutritional status and confused by what to eat. Worryingly one in three with involuntary WL had not been able to access a registered dietitian (RD) for individual advice. Despite ESPEN recommendation that all patients receive routine nutritional screening and intervention early in the course of malnutrition[191], access to RD for cancer patients is poor. For example, evidence-based guidelines from Australia recommend that all patients receiving radiotherapy to the gastrointestinal tract or head and neck area are routinely referred to dietitians[202], however, a service provision audit in the UK found that only 69 % of head and neck cancer patients see a dietitian, with those having oral tumours the most likely to be referred[203]. Generally speaking, there is a lack of dietitians providing care to those affected by cancer. In Ireland, as of 2016, there were thirty-six RD working in cancer care, of which only five are practising outside the capital city of Dublin, which provides only one dietitian to every 1389 active cancer patients[204]. This represents all dietitians who cover oncology as part of their role and does not constitute the number of dedicated oncology dietitians. In the USA, there are approximately 1·7 full-time equivalent dietitians per outpatient cancer centre, corresponding to 1 RD to 1202 patients[205]. In Ontario, Canada, there are few dietitians practising in oncology and palliative care, with 1·1–1·6 full-time equivalent full-time equivalent RD per 100 inpatient beds and 0·2–1·4 full-time equivalent/100 patients in the outpatient setting[206]. There is also a lack of specialist dietitians in oncology, with only 370 board-certified oncology specialist dietitians in the USA[207].

When malnourished patients are seen by dietitians the mainstay dietary treatment, particularly for those with poor appetite is a 'little and often, high protein high energy diet'. This diet constitutes a food-first approach which involves counselling patients and their carers on foods that are naturally high in protein and energy and providing meal and snack options to achieve this. Our group has developed several cookbooks to bring this advice to life over the past number of years and these are available as free downloadable e-books at www.breakthroughcancerresearch.ie/books. These resources are written in lay language and provide simple high protein high energy meal options. For some patients with continued problems with poor appetite and early satiety, oral nutritional supplements and/or enteral feeding will be necessary to support their nutritional status during cancer treatment.

Systemic inflammation

As observed by Sir David Cuthbertson in 1942[208] in reference to the post-shock metabolic response 'it is doubtful whether, during the early catabolic phase, any dietary measure can effectively suppress the catabolic destruction of protein'. One could argue the same is true for cancer where systemic inflammation is present. Systemic inflammation is present in 30–50 % of advanced cancer populations[209] and is an independent factor reducing survival[210]. Over the years several pharmaceutical and dietary factors have been examined to reduce inflammation including corticosteroids, non-steroidal inflammatory drugs, statins and *n*-3 fatty acids. Corticosteriods appear to increase appetite and QoL for a limited period of time but the optimal dose, duration or timing of intervention is not clear. There is good evidence that non-steroidal anti-inflammatory drugs can lead to increases in body weight in cachexia and a plausible mechanism is the attenuation of cachexia-related inflammation and subsequent modulation of the anabolic resistance associated with cancer cachexia. However, non-steroidal anti-inflammatory drugs do have some risks, such as gastrointestinal bleeding, and so further evidence is needed to prove efficacy and safety in cancer cachexia management[211]. *n*-3 Fatty acids have been associated with weight stabilisation[212,213], improved QoL[214,215] and increased chemo-sensitivity[216] in some studies.

Physical activity

Physical activity and more specifically, structured exercise, has been suggested as part of the management of cancer cachexia[217]. Exercise has been shown to be safe in individuals living with and beyond cancer[218] and can promote QoL in patients on active treatment[219] and during the survivorship period[220]. Moreover, the specific QoL domains impacted by exercise are those which are commonly impaired in cancer cachexia (physical functioning, role functioning, fatigue and body image/self-esteem)[219,220]. Of note, it has been shown that the most QoL benefit is gained from supervised exercise programmes[221] and that those patients with the lowest baselines experience the most improvement in fatigue, QoL, aerobic fitness and physical function, indicating that the patients who are most inactive could benefit from any increase in exercise[222].

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

Based on the current evidence, the American College of Sports Medicine position is that exercise is safe and beneficial for cancer patients and their guidelines provide evidence-based recommendations in terms of safety measures, and exercise prescription specifics across many tumour types, with a focus on the prescription of physical activity using the frequency, intensity, time, type framework. The recommended target to achieve the documented benefits of exercise programmes in cancer is ≥30 min moderate-intensity aerobic exercise ≥3 times per week for at least 8–12 weeks and resistance training ≥2 times per week (≥2 sets of eight–fifteen repetitions ≥60 % one-repetition maximum)[223,224]. Likewise, the Clinical Oncology Society of Australia has a position statement, as of 2018, which states that all members of the multidisciplinary team should promote physical activity amongst cancer patients and that patients should be encouraged to return to normal levels of activity as soon as possible after diagnosis and that they should aim for ≥150 min moderate-intensity or 75 min vigorous-intensity aerobic exercise per week and 2–3 sessions of resistance exercise per week (moderate to vigorous-intensity exercises targeting the major muscle groups)[225].

Multimodal approaches

When the multifactorial nature of malnutrition in cancer is considered, it seems reasonable that a multimodal approach to treatment may fare better than a unimodal approach. By targeting multiple aetiologies, there is some evidence that multimodal therapies may have a better chance of attenuating the progression of cachexia[226]. Multimodal management of cancer cachexia should incorporate general interventions such as nutrition counselling, symptom management and exercise as well as focused interventions that address specific aetiological components of the cancer cachexia syndrome, such as fish oil or non-steroidal anti-inflammatory drug to address increased inflammation or corticosteroids to improve appetite[227].

Early intervention is of the utmost importance as refractory cachexia remains a challenge, still considered irreversible and associated with a terminal prognosis[38]. The European School of Oncology Task Force's official position is that research should focus on the identification and management of cachexia early in the disease course when it is amenable to treatment[123]. Furthermore, it has been suggested that a 'parallel pathway' approach should be adopted to ensure that cachexia is managed alongside cancer itself, recognising their inherent connection and avoiding the sentiment that cachexia is an inevitable endpoint associated with advanced disease, but rather focusing on optimising clinical outcomes by preventing the development of malnutrition[228].

A systematic review by Hall *et al*. showed that the current literature base for combined nutrition and exercise programmes in advanced cancer is lacking in strong evidence. While studies to date have shown variable improvements in QoL, overall function, fatigue, endurance/strength, depression and nutritional status, the results are inconsistent across studies and they are often underpowered[229]. The strongest evidence in favour of these trials is only of moderate quality and it suggests that physical endurance and strength, as well as mood, can be improved by these interventions. Further well-designed studies are needed in order to verify the utility of multimodal approaches.

MENAC, a large multi-centre phase III trial (A randomised, open-label trial of a ***m***ultimodal intervention (***e***xercise, ***n***utrition and ***a***nti-inflammatory medication) plus standard care *v.* standard care alone to prevent/attenuate ***c***achexia in advanced cancer patients undergoing chemotherapy) is currently underway (ClinicalTrials.gov ID: NCT02330926)[230]. Identification of a successful cachexia treatment would mark significant progress in the field of oncology nutrition, and given the impact of nutrition of survival and tolerance to treatment, the oncology field as a whole.

Conclusions

WL and abnormalities of body composition are common across all cancer sites and stages and the aetiology of malnutrition in cancer is multifactorial and complex. It is associated with poorer QoL as well as increased morbidity and mortality and is often considered an inevitable part of the cancer trajectory. Irrespective of baseline BMI, muscle and fat wasting are associated with poorer outcomes; however, simple screening tools using weight and BMI alone miss a large proportion of patients with altered body composition who are at risk nutritionally and therefore, techniques to adequately identify patients at risk of malnutrition must be developed and widely implemented in order to facilitate early-intervention and a parallel pathway.

Despite the widespread fatalism with respect to cancer cachexia, patients do retain anabolic potential and although nutritional interventions, to date, have not been shown to increase survival, it may be that these interventions have not been successful in addressing the malnutrition as a primary outcome and thus, the benefit of survival has not been borne out. With more successful therapies, including multimodal and interdisciplinary approaches, it may be that nutritional interventions can improve not only QoL but also the length of life. Management of cancer-related malnutrition must focus on early-intervention with multimodal approaches in order to tackle the multifactorial nature of cachexia pathophysiology.

Further research into the pathogenesis and consequences of cancer-related malnutrition may lead to a better understanding of potential targets for treatment. However, while a number of promising therapies for cachexia are under investigation, the field lacks currently licensed treatments and so interventional research must be prioritised in order to provide an evidence base for the treatment of the condition which is now well documented as causing poor outcomes.

In conclusion, prompt identification of patients with cancer-related malnutrition must be optimised and development of an effective, evidence-based treatment strategy

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

is of the utmost importance as it stands to improve longevity and QoL for cancer survivors.

Acknowledgements

The authors would like to acknowledge the Health Research Board Clinical Research Facility at Mercy University Hospital Cork where a lot of the research mentioned in the article was conducted and their statistician Dr Darren Dahly for his ongoing help and support of our research.

Financial Support

The free cookbooks for cancer patients mentioned in this article received financial support from Breakthrough Cancer Research (Irish Registered Charity). The national survey mentioned in this article on attitudes of Irish cancer patients to nutrition was in part supported by the Irish Society of Clinical Nutrition & Metabolism (IrSPEN)

Conflict of Interest

None

Authorship

A. R. delivered the Cuthbertson Medal Lecture. A. R. and E. S. co-wrote the paper.

References

1 Raja R, Lim AV, Lim YP *et al.* (2004) Malnutrition screening in hospitalised patients and its implication on reimbursement. *Intern Med J* **34**, 176–181.
2 Tangvik RJ, Tell GS, Guttormsen AB *et al.* (2015) Nutritional risk profile in a university hospital population. *Clin Nutr* **34**, 705–711.
3 Kruizenga H, van Keeken S, Weijs P *et al.* (2016) Undernutrition screening survey in 564,063 patients: patients with a positive undernutrition screening score stay in hospital 1·4 d longer. *Am J Clin Nutr* **103**, 1026–1032.
4 Bozzetti F & Group SW (2009) Screening the nutritional status in oncology: a preliminary report on 1,000 outpatients. *Support Care Cancer* **17**, 279–284.
5 Dewys WD, Begg C, Lavin PT *et al.* (1980) Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med* **69**, 491–497.
6 Martin L, Senesse P, Gioulbasanis I *et al.* (2015) Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol* **33**, 90–99.
7 Ní Bhuachalla É, Daly LE, Power DG *et al.* (2018) Computed tomography diagnosed cachexia and sarcopenia in 725 oncology patients: is nutritional screening capturing hidden malnutrition? *J Cachexia Sarcopenia Muscle* **9**, 295–305.
8 Andreyev HJ, Norman AR, Oates J *et al.* (1998) Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer* **34**, 503–509.
9 Ross PJ, Ashley S, Norton A *et al.* (2004) Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? *Br J Cancer* **90**, 1905–1911.
10 Di Fiore F, Lecleire S, Pop D *et al.* (2007) Baseline nutritional status is predictive of response to treatment and survival in patients treated by definitive chemoradiotherapy for a locally advanced esophageal cancer. *Am J Gastroenterol* **102**, 2557–2563.
11 Daly LE, Power DG, O'Reilly Á *et al.* (2017) The impact of body composition parameters on ipilimumab toxicity and survival in patients with metastatic melanoma. *Br J Cancer* **116**, 310–317.
12 Cushen SJ, Power DG, Teo MY *et al.* (2017) Body composition by computed tomography as a predictor of toxicity in patients with renal cell carcinoma treated with Sunitinib. *Am J Clin Oncol* **40**, 47–52.
13 Wheelwright S, Darlington AS, Hopkinson JB *et al.* (2013) A systematic review of health-related quality of life instruments in patients with cancer cachexia. *Support Care Cancer* **21**, 2625–2636.
14 Daly LE, Dolan RD, Power DG *et al.* (2020) Determinants of quality of life in patients with incurable cancer. *Cancer* **126**, 2872–2882.
15 Argiles JM, Busquets S, Stemmler B *et al.* (2015) Cachexia and sarcopenia: mechanisms and potential targets for intervention. *Curr Opin Pharmacol* **22**, 100–106.
16 Baracos VE, Martin L, Korc M *et al.* (2018) Cancer-associated cachexia. *Nat Rev Dis Primers* **4**, 17105.
17 Baracos VE (2018) Cancer-associated malnutrition. *Eur J Clin Nutr* **72**, 1255–1259.
18 Schiessel DL & Baracos VE (2018) Barriers to cancer nutrition therapy: excess catabolism of muscle and adipose tissues induced by tumour products and chemotherapy. *Proc Nutr Soc* **77**, 394–402.
19 Del Fabbro E, Hui D, Dalal S *et al.* (2011) Clinical outcomes and contributors to weight loss in a cancer cachexia clinic. *J Palliat Med* **14**, 1004–1008.
20 Nicolini A, Ferrari P, Masoni MC *et al.* (2013) Malnutrition, anorexia and cachexia in cancer patients: a mini-review on pathogenesis and treatment. *Biomed Pharmacother* **67**, 807–817.
21 Kubrak C, Olson K, Jha N *et al.* (2010) Nutrition impact symptoms: key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. *Head Neck* **32**, 290–300.
22 Omlin A, Blum D, Wierecky J *et al.* (2013) Nutrition impact symptoms in advanced cancer patients: frequency and specific interventions, a case-control study. *J Cachexia Sarcopenia Muscle* **4**, 55–61.
23 Tong H, Isenring E & Yates P (2009) The prevalence of nutrition impact symptoms and their relationship to quality of life and clinical outcomes in medical oncology patients. *Support Care Cancer* **17**, 83–90.
24 Attar A, Malka D, Sabate JM *et al.* (2012) Malnutrition is high and underestimated during chemotherapy in gastrointestinal cancer: an AGEO prospective cross-sectional multicenter study. *Nutr Cancer* **64**, 535–542.
25 Antoun S & Raynard B (2018) Muscle protein anabolism in advanced cancer patients: response to protein and amino acids support, and to physical activity. *Ann Oncol: Official J Euro Soc Medical Oncol/ESMO* **29**, ii10–ii17.
26 Martin L & Kubrak C (2018) How much does reduced food intake contribute to cancer-associated weight loss? *Curr Opin Support Palliat Care* **12**, 410–419.

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

27 Vazeille C, Jouinot A, Durand JP *et al.* (2017) Relation between hypermetabolism, cachexia, and survival in cancer patients: a prospective study in 390 cancer patients before initiation of anticancer therapy. *Am J Clin Nutr* **105**, 1139–1147.
28 Friesen DE, Baracos VE & Tuszynski JA (2015) Modeling the energetic cost of cancer as a result of altered energy metabolism: implications for cachexia. *Theor Biol Med Model* **12**, 17.
29 Grossberg AJ, Scarlett JM & Marks DL (2010) Hypothalamic mechanisms in cachexia. *Physiol Behav* **100**, 478–489.
30 Chu K, Bos SA, Gill CM *et al.* (2019) Brown adipose tissue and cancer progression. *Skeletal Radiol* **49**, 635–639.
31 Dev R, Bruera E & Dalal S (2018) Insulin resistance and body composition in cancer patients. *Ann Oncol: Official J Euro Soc Medical Oncol/ESMO* **29**, ii18–ii26.
32 Muscaritoli M, Bossola M, Doglietto GB *et al.* (2006) The ubiquitin/proteasome system in cancer cachexia. In *Cachexia and Wasting: A Modern Approach*, pp. 503–508 [G Mantovani, SD Anker, A Inui, JE Morley, FR Fanelli, D Scevola, MW Schuster and S-S Yeh, editors]. Milano: Springer Milan.
33 Black AE, Coward WA, Cole TJ *et al.* (1996) Human energy expenditure in affluent societies: an analysis of 574 doubly-labelled water measurements. *Eur J Clin Nutr* **50**, 72–92.
34 Moses AW, Slater C, Preston T *et al.* (2004) Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. *Br J Cancer* **90**, 996–1002.
35 Gibney E, Elia M, Jebb SA *et al.* (1997) Total energy expenditure in patients with small-cell lung cancer: results of a validated study using the bicarbonate-urea method. *Metab, Clin Exp* **46**, 1412–1417.
36 Mollinger LA, Spurr GB, el Ghatit AZ *et al.* (1985) Daily energy expenditure and basal metabolic rates of patients with spinal cord injury. *Arch Phys Med Rehabil* **66**, 420–426.
37 Stallings VA, Zemel BS, Davies JC *et al.* (1996) Energy expenditure of children and adolescents with severe disabilities: a cerebral palsy model. *Am J Clin Nutr* **64**, 627–634.
38 Fearon K, Strasser F, Anker SD *et al.* (2011) Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* **12**, 489–495.
39 Ryan AM, Power DG, Daly L *et al.* (2016) Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. *Proc Nutr Soc* **75**, 199–211.
40 Bachmann J, Heiligensetzer M, Krakowski-Roosen H *et al.* (2008) Cachexia worsens prognosis in patients with resectable pancreatic cancer. *J Gastrointest Surg* **12**, 1193–1201.
41 Wesseltoft-Rao N, Hjermstad MJ, Ikdahl T *et al.* (2015) Comparing two classifications of cancer cachexia and their association with survival in patients with unresected pancreatic cancer. *Nutr Cancer* **67**, 472–480.
42 Krishnan S, Rana V, Janjan NA *et al.* (2006) Prognostic factors in patients with unresectable locally advanced pancreatic adenocarcinoma treated with chemoradiation. *Cancer* **107**, 2589–2596.
43 Olson SH, Xu Y, Herzog K *et al.* (2016) Weight loss, diabetes, fatigue, and depression preceding pancreatic cancer. *Pancreas* **45**, 986–991.
44 Nemer L, Krishna SG, Shah ZK *et al.* (2017) Predictors of pancreatic cancer-associated weight loss and nutritional interventions. *Pancreas* **46**, 1152–1157.
45 Bozzetti F (2017) Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. *Ann Oncol: Official J Euro Soc Medical Oncol/ESMO* **28**, 2107–2118.
46 Gioulbasanis I, Martin L, Baracos VE *et al.* (2015) Nutritional assessment in overweight and obese patients with metastatic cancer: does it make sense? *Ann Oncol* **26**, 217–221.
47 Martin L, Birdsell L, Macdonald N *et al.* (2013) Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* **31**, 1539–1547.
48 Ramos Chaves M, Boleo-Tome C, Monteiro-Grillo I *et al.* (2010) The diversity of nutritional status in cancer: new insights. *Oncologist* **15**, 523–530.
49 Greenlee H, Unger JM, LeBlanc M *et al.* (2017) Association between body mass index and cancer survival in a pooled analysis of 22 clinical trials. *Cancer Epidemiol Biomarkers Prev: Pub Am Assoc Cancer Res cosponsored Am Soc Prev Oncol* **26**, 21–29.
50 Aubrey J, Esfandiari N, Baracos VE *et al.* (2014) Measurement of skeletal muscle radiation attenuation and basis of its biological variation. *Acta Physiol* (*Oxf*) **210**, 489–497.
51 Cespedes Feliciano EM, Kroenke CH, Bradshaw PT *et al.* (2017) Postdiagnosis weight change and survival following a diagnosis of early-stage breast cancer. *Cancer Epidemiol Biomarkers Prev: Pub Am Assoc Cancer Res cosponsored Am Soc Prev Oncol* **26**, 44–50.
52 van Vugt JL, Braam HJ, van Oudheusden TR *et al.* (2015) Skeletal muscle depletion is associated with severe postoperative complications in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* **22**, 3625–3631.
53 Cruz-Jentoft AJ, Baeyens JP, Bauer JM *et al.* (2010) Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on sarcopenia in older people. *Age Ageing* **39**, 412–423.
54 Cruz-Jentoft AJ, Bahat G, Bauer J *et al.* (2019) Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* **48**, 16–31.
55 Baumgartner RN, Koehler KM, Gallagher D *et al.* (1998) Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* **147**, 755–763.
56 Prado CM, Cushen SJ, Orsso CE *et al.* (2016) Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. *Proc Nutr Soc* **75**, 188–198.
57 Daly LE, Ní Bhuachalla É, Power DG *et al.* (2018) Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer. *J Cachexia Sarcopenia Muscle* **9**, 315–325.
58 Rutten IJ, van Dijk DP, Kruitwagen RF *et al.* (2016) Loss of skeletal muscle during neoadjuvant chemotherapy is related to decreased survival in ovarian cancer patients. *J Cachexia Sarcopenia Muscle* **7**, 458–466.
59 Frontera WR, Zayas AR & Rodriguez N (2012) Aging of human muscle: understanding sarcopenia at the single muscle cell level. *Phys Med Rehabil Clin N Am* **23**, 201–207, xiii.
60 Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA *et al.* (2016) Loss of muscle mass during chemotherapy Is predictive for poor survival of patients with metastatic colorectal cancer. *J Clin Oncol* **34**, 1339–1344.
61 Tan BH, Birdsell LA, Martin L *et al.* (2009) Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res* **15**, 6973–6979.

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

62 Daly LE, Prado CM & Ryan AM (2018) 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. *Proc Nutr Soc* **77**, 135–151.
63 Baracos VE, Reiman T, Mourtzakis M *et al.* (2010) Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am J Clin Nutr* **91**, 1133S–1137S.
64 Arrieta O, De la Torre-Vallejo M, López-Macías D *et al.* (2015) Nutritional status, body surface, and low lean body mass/body mass index are related to dose reduction and severe gastrointestinal toxicity induced by Afatinib in patients with non-small cell lung cancer. *Oncologist* **20**, 967–974.
65 Stene GB, Helbostad JL, Amundsen T *et al.* (2014) Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. *Acta Oncol* **54**, 340–348.
66 Kim EY, Kim YS, Park I *et al.* (2015) Prognostic significance of CT-determined sarcopenia in patients with small-cell lung cancer. *J Thorac Oncol* **10**, 1795–1799.
67 Sandini M, Patino M, Ferrone CR *et al.* (2018) Association between changes in body composition and neoadjuvant treatment for pancreatic cancer. *JAMA Surg* **153**, 809–815.
68 El Amrani M, Vermersch M, Fulbert M *et al.* (2018) Impact of sarcopenia on outcomes of patients undergoing pancreatectomy: a retrospective analysis of 107 patients. *Medicine* **97**, e12076.
69 Di Sebastiano KM, Yang L, Zbuk K *et al.* (2013) Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia. *Br J Nutr* **109**, 302–312.
70 Cooper AB, Slack R, Fogelman D *et al.* (2015) Characterization of anthropometric changes that occur during neoadjuvant therapy for potentially resectable pancreatic cancer. *Ann Surg Oncol* **22**, 2416–2423.
71 Rollins KE, Tewari N, Ackner A *et al.* (2015) The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. *Clin Nutr* **35**, 1103–1109.
72 Dalal S, Hui D, Bidaut L *et al.* (2012) Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: a pilot study. *J Pain Symptom Manage* **44**, 181–191.
73 Carrara G, Pecorelli N, De Cobelli F *et al.* (2017) Preoperative sarcopenia determinants in pancreatic cancer patients. *Clin Nutr* **36**, 1649–1653.
74 Sullivan ES, Daly LE, Power DG *et al.* (2020) Epidemiology of cancer-related weight loss and sarcopenia in the UK and Ireland: incidence, prevalence, and clinical impact. *JCSM Rapid Commun* **3**, 91–102.
75 Sturgeon KM, Mathis KM, Rogers CJ *et al.* (2019) Cancer- and chemotherapy-induced musculoskeletal degradation. *JBMR Plus* **3**, e10187.
76 Higano C, Shields A, Wood N *et al.* (2004) Bone mineral density in patients with prostate cancer without bone metastases treated with intermittent androgen suppression. *Urology* **64**, 1182–1186.
77 Eastell R, Adams JE, Coleman RE *et al.* (2008) Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol* **26**, 1051–1057.
78 Shapiro CL, Manola J & Leboff M (2001) Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. *J Clin Oncol* **19**, 3306–3311.
79 Maillefert JF, Sibilia J, Michel F *et al.* (1999) Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. *J Urol* **161**, 1219–1222.
80 Cann CE, Martin MC, Genant HK *et al.* (1984) Decreased spinal mineral content in amenorrheic women. *JAMA: J Am Medical Assoc* **251**, 626–629.
81 Berruti A, Dogliotti L, Terrone C *et al.* (2002) Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J Urol* **167**, 2361–2367; discussion 2367.
82 Diamond TH, Bucci J, Kersley JH *et al.* (2004) Osteoporosis and spinal fractures in men with prostate cancer: risk factors and effects of androgen deprivation therapy. *J Urol* **172**, 529–532.
83 Diamond TH, Higano CS, Smith MR *et al.* (2004) Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: recommendations for diagnosis and therapies. *Cancer* **100**, 892–899.
84 Winters-Stone KM, Bennett JA, Nail L *et al.* (2008) Strength, physical activity, and age predict fatigue in older breast cancer survivors. *Oncol Nurs Forum* **35**, 815–821.
85 Nicolson GL & Conklin KA (2008) Reversing mitochondrial dysfunction, fatigue and the adverse effects of chemotherapy of metastatic disease by molecular replacement therapy. *Clin Exp Metastasis* **25**, 161–169.
86 Kurk SA, Peeters PHM, Dorresteijn B *et al.* (2018) Impact of different palliative systemic treatments on skeletal muscle mass in metastatic colorectal cancer patients. *J Cachexia Sarcopenia Muscle* **9**, 909–919.
87 van Vugt JLA, Coebergh van den Braak RRJ, Lalmahomed ZS *et al.* (2018) Impact of low skeletal muscle mass and density on short and long-term outcome after resection of stage I-III colorectal cancer. *Eur J Surg Oncol* **44**, 1354–1360.
88 van der Kroft G, Bours DMJL, Janssen-Heijnen DM *et al.* (2018) Value of sarcopenia assessed by computed tomography for the prediction of postoperative morbidity following oncological colorectal resection: a comparison with the malnutrition screening tool. *Clin Nutr ESPEN* **24**, 114–119.
89 Ryan AM, Prado CM, Sullivan ES *et al.* (2019) Effects of weight loss and sarcopenia on response to chemotherapy, quality of life, and survival. *Nutrition* **67–68**, 110539.
90 Tan BH, Brammer K, Randhawa N *et al.* (2015) Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. *Eur J Surg Oncol* **41**, 333–338.
91 Palmela C, Velho S, Agostinho L *et al.* (2017) Body composition as a prognostic factor of neoadjuvant chemotherapy toxicity and outcome in patients with locally advanced gastric cancer. *J Gastric Cancer* **17**, 74–87.
92 Prado CM, Lieffers JR, McCargar LJ *et al.* (2008) Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* **9**, 629–635.
93 Shachar SS, Deal AM, Weinberg M *et al.* (2017) Skeletal muscle measures as predictors of toxicity, hospitalization, and survival in patients with metastatic breast cancer receiving taxane-based chemotherapy. *Clin Cancer Res* **23**, 658–665.
94 Yip C, Goh V, Davies A *et al.* (2014) Assessment of sarcopenia and changes in body composition after neoadjuvant

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

chemotherapy and associations with clinical outcomes in oesophageal cancer. *Eur Radiol* **24**, 998–1005.
95 Auclin E, Bourillon C, De Maio E *et al.* (2017) Prediction of everolimus toxicity and prognostic value of skeletal muscle index in patients with metastatic renal cell carcinoma. *Clin Genitourin Cancer* **15**, 350–355.
96 Veasey Rodrigues H, Baracos VE, Wheler JJ *et al.* (2013) Body composition and survival in the early clinical trials setting. *Eur J Cancer* **49**, 3068–3075.
97 Parsons HA, Tsimberidou AM, Pontikos M *et al.* (2012) Evaluation of the clinical relevance of body composition parameters in patients with cancer metastatic to the liver treated with hepatic arterial infusion chemotherapy. *Nutr Cancer* **64**, 206–217.
98 Srdic D, Plestina S, Sverko-Peternac A *et al.* (2016) Cancer cachexia, sarcopenia and biochemical markers in patients with advanced non-small cell lung cancer-chemotherapy toxicity and prognostic value. *Support Care Cancer* **24**, 4495–4502.
99 Versteeg KS, Blauwhoff-Buskermolen S, Buffart LM *et al.* (2018) Higher muscle strength Is associated with prolonged survival in older patients with advanced cancer. *Oncologist* **23**, 580–585.
100 Prado CM, Baracos VE, McCargar LJ *et al.* (2009) Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res* **15**, 2920–2926.
101 Du Bois D & Du Bois EF (1989) A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* **5**, 303–311; discussion 312–303.
102 Stobäus N, Küpferling S, Lorenz ML *et al.* (2013) Discrepancy between body surface area and body composition in cancer. *Nutr Cancer* **65**, 1151–1156.
103 McLeay SC, Morrish GA, Kirkpatrick CMJ *et al.* (2012) The relationship between drug clearance and body size systematic review and meta-analysis of the literature published from 2000 to 2007. *Clin Pharmacokinet* **51**, 319–330.
104 Prado CM, Antoun S, Sawyer MB *et al.* (2011) Two faces of drug therapy in cancer: drug-related lean tissue loss and its adverse consequences to survival and toxicity. *Curr Opin Clin Nutr Metab Care* **14**, 250–254.
105 Takimoto CH (2009) Maximum tolerated dose: clinical endpoint for a bygone era? *Target Oncol* **4**, 143–147.
106 Baker SD, Verweij J, Rowinsky EK *et al.* (2002) Role of body surface area in dosing of investigational anticancer agents in adults, 1991–2001. *J Natl Cancer Inst* **94**, 1883–1888.
107 Prado CM, Baracos VE, McCargar LJ *et al.* (2007) Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin Cancer Res* **13**, 3264–3268.
108 Prado CM, Baracos VE, Xiao J *et al.* (2014) The association between body composition and toxicities from the combination of Doxil and trabectedin in patients with advanced relapsed ovarian cancer. *Appl Physiol Nutr Metab* **39**, 693–698.
109 Sjøblom B, Benth J, Grønberg BH *et al.* (2017) Drug dose per kilogram lean body mass predicts hematologic toxicity from carboplatin-doublet chemotherapy in advanced non-small-cell lung cancer. *Clin Lung Cancer* **18**, e129–e136.
110 Sjøblom B, Grønberg BH, Benth J *et al.* (2015) Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. *Lung Cancer* **90**, 85–91.
111 Mir O, Coriat R, Blanchet B *et al.* (2012) Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. *PLoS ONE* **7**, e37563.
112 Massicotte MH, Borget I, Broutin S *et al.* (2013) Body composition variation and impact of low skeletal muscle mass in patients with advanced medullary thyroid carcinoma treated with vandetanib: results from a placebo-controlled study. *J Clin Endocrinol Metab* **98**, 2401–2408.
113 Antoun S, Lanoy E, Albiges-Sauvin L *et al.* (2014) Clinical implications of body composition assessment by computed tomography in metastatic renal cell carcinoma. *Expert Rev Anticancer Ther* **14**, 279–288.
114 Blum D, Omlin A, Baracos VE *et al.* (2011) Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer. *Crit Rev Oncol Hematol* **80**, 114–144.
115 Ravasco P, Monteiro-Grillo I, Vidal PM *et al.* (2004) Cancer: disease and nutrition are key determinants of patients' quality of life. *Support Care Cancer* **12**, 246–252.
116 Fearon KC, Voss AC, Hustead DS *et al.* (2006) Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *Am J Clin Nutr* **83**, 1345–1350.
117 Evans WJ & Lambert CP (2007) Physiological basis of fatigue. *Am J Phys Med Rehabil* **86**, S29–46.
118 Ryan JL, Carroll JK, Ryan EP *et al.* (2007) Mechanisms of cancer-related fatigue. *Oncologist* **12**, Suppl. 1, 22–34.
119 Hopkinson JB, Brown JC, Okamoto I *et al.* (2012) The effectiveness of patient-family carer (couple) intervention for the management of symptoms and other health-related problems in people affected by cancer: a systematic literature search and narrative review. *J Pain Symptom Manage* **43**, 111–142.
120 Neefjes ECW, van den Hurk RM, Blauwhoff-Buskermolen S *et al.* (2017) Muscle mass as a target to reduce fatigue in patients with advanced cancer. *J Cachexia Sarcopenia Muscle* **8**, 623–629.
121 Nipp RD, Fuchs G, El-Jawahri A *et al.* (2017) Sarcopenia is associated with quality of life and depression in patients with advanced cancer. *Oncologist* **23**, 97–104.
122 Bye A, Sjøblom B, Wentzel-Larsen T *et al.* (2017) Muscle mass and association to quality of life in non-small cell lung cancer patients. *J Cachexia Sarcopenia Muscle* **8**, 759–767.
123 Aapro M, Arends J, Bozzetti F *et al.* (2014) Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European school of oncology task force. *Ann Oncol* **25**, 1492–1499.
124 McSorley S, Dolan R, Roxburgh C *et al.* (2017) How and why systemic inflammation worsens quality of life in patients with advanced cancer. *Expert Rev Quality of life in Cancer Care* **2**, 167–175.
125 Baguley BJ, Skinner TL & Wright ORL (2018) Nutrition therapy for the management of cancer-related fatigue and quality of life: a systematic review and meta-analysis. *Br J Nutr* **122**, 527–541.
126 Bower JE, Ganz PA, Tao ML *et al.* (2009) Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. *Clin Cancer Res* **15**, 5534–5540.
127 Bower JE & Lamkin DM (2013) Inflammation and cancer-related fatigue: mechanisms, contributing factors, and treatment implications. *Brain Behav Immun* **30**, Suppl, S48–57.
128 Wang XS, Zhao F, Fisch MJ *et al.* (2014) Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors. *Cancer* **120**, 425–432.

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

129 Paulsen O, Laird B, Aass N *et al.* (2017) The relationship between pro-inflammatory cytokines and pain, appetite and fatigue in patients with advanced cancer. *PLoS ONE* **12**, e0177620.
130 Du YJ, Zhang HY, Li B *et al.* (2013) Sputum interleukin-6, tumor necrosis factor-alpha and Salivary cortisol as new biomarkers of depression in lung cancer patients. *Prog Neuro-Psychopharmacol Biol Psychiatry* **47**, 69–76.
131 Breitbart W, Rosenfeld B, Tobias K *et al.* (2014) Depression, cytokines, and pancreatic cancer. *Psycho-oncology* **23**, 339–345.
132 Laird BJ, Fallon M, Hjermstad MJ *et al.* (2016) Quality of life in patients with advanced cancer: differential association with performance Status and systemic inflammatory response. *J Clin Oncol* **34**, 2769–2775.
133 Baldwin C, Spiro A, Ahern R *et al.* (2012) Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* **104**, 371–385.
134 Temel JS, Abernethy AP, Currow DC *et al.* (2016) Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *Lancet Oncol* **17**, 519–531.
135 Cho Y, Kim JW, Keum KC *et al.* (2018) Prognostic significance of sarcopenia with inflammation in patients with head and neck cancer who underwent definitive chemoradiotherapy. *Front Oncol* **8**, 457.
136 Fattouh M, Chang GY, Ow TJ *et al.* (2018) Association between pretreatment obesity, sarcopenia, and survival in patients with head and neck cancer. *Head Neck* **41**, 707–714.
137 Chargi N, Bril SI, Emmelot-Vonk MH *et al.* (2019) Sarcopenia is a prognostic factor for overall survival in elderly patients with head-and-neck cancer. *Eur Arch Otorhinolaryngol* **276**, 1475–1486.
138 Jung AR, Roh JL, Kim JS *et al.* (2019) Prognostic value of body composition on recurrence and survival of advanced-stage head and neck cancer. *Eur J Cancer* **116**, 98–106.
139 Ganju RG, Morse R, Hoover A *et al.* (2019) The impact of sarcopenia on tolerance of radiation and outcome in patients with head and neck cancer receiving chemoradiation. *Radiother Oncol* **137**, 117–124.
140 Stone L, Olson B, Mowery A *et al.* (2019) Association between sarcopenia and mortality in patients undergoing surgical excision of head and neck cancer. *JAMA Otolaryngol--Head & Neck Surg* **145**, 647–654.
141 Ohtaka A, Aoki H, Nagata M *et al.* (2019) Sarcopenia is a poor prognostic factor of castration-resistant prostate cancer treated with docetaxel therapy. *Prostate Int* **7**, 9–14.
142 Coelen RJ, Wiggers JK, Nio CY *et al.* (2015) Preoperative computed tomography assessment of skeletal muscle mass is valuable in predicting outcomes following hepatectomy for perihilar cholangiocarcinoma. *HPB* (*Oxford*) **17**, 520–528.
143 Kitano Y, Yamashita YI, Saito Y *et al.* (2019) Sarcopenia affects systemic and local immune system and impacts postoperative outcome in patients with extrahepatic cholangiocarcinoma. *World J Surg* **43**, 2271–2280.
144 Hahn F, Muller L, Stohr F *et al.* (2019) The role of sarcopenia in patients with intrahepatic cholangiocarcinoma: prognostic marker or hyped parameter? *Liver Int* **39**, 1307–1314.
145 Yugawa K, Itoh S, Kurihara T *et al.* (2019) Skeletal muscle mass predicts the prognosis of patients with intrahepatic cholangiocarcinoma. *Am J Surg* **218**, 952–958.
146 Okumura S, Kaido T, Hamaguchi Y *et al.* (2017) Impact of skeletal muscle mass, muscle quality, and visceral adiposity on outcomes following resection of intrahepatic cholangiocarcinoma. *Ann Surg Oncol* **24**, 1037–1045.
147 Go SI, Park S, Kang MH *et al.* (2019) Clinical impact of prognostic nutritional index in diffuse large B cell lymphoma. *Ann Hematol* **98**, 401–411.
148 Go SI, Park MJ, Song HN *et al.* (2016) Prognostic impact of sarcopenia in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Cachexia Sarcopenia Muscle* **7**, 567–576.
149 Camus V, Lanic H, Kraut J *et al.* (2014) Prognostic impact of fat tissue loss and cachexia assessed by computed tomography scan in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Eur J Haematol* **93**, 9–18.
150 Lanic H, Kraut-Tauzia J, Modzelewski R *et al.* (2014) Sarcopenia is an independent prognostic factor in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Leuk Lymphoma* **55**, 817–823.
151 Nakamura N, Hara T, Shibata Y *et al.* (2015) Sarcopenia is an independent prognostic factor in male patients with diffuse large B-cell lymphoma. *Ann Hematol* **94**, 2043–2053.
152 Nakamura N, Ninomiya S, Matsumoto T *et al.* (2019) Prognostic impact of skeletal muscle assessed by computed tomography in patients with acute myeloid leukemia. *Ann Hematol* **98**, 351–359.
153 Shachar SS, Williams GR, Muss HB *et al.* (2016) Prognostic value of sarcopenia in adults with solid tumours: a meta-analysis and systematic review. *Eur J Cancer* **57**, 58–67.
154 Caan BJ, Meyerhardt JA, Kroenke CH *et al.* (2017) Explaining the obesity paradox: the association between body composition and colorectal cancer survival (C-SCANS study). *Cancer Epidemiol, Biomarkers Prev: Pub Am Assoc Cancer Res, Cosponsored Am Soc Preventive Oncol* **26**, 1008–1015.
155 Caan BJ, Cespedes Feliciano EM, Prado CM *et al.* (2018) Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. *JAMA Oncol* **4**, 798–804.
156 Sjøblom B, Grønberg BH, Wentzel-Larsen T *et al.* (2016) Skeletal muscle radiodensity is prognostic for survival in patients with advanced non-small cell lung cancer. *Clin Nutr* **35**, 1386–1393.
157 Kroenke CH, Prado CM, Meyerhardt JA *et al.* (2018) Muscle radiodensity and mortality in patients with colorectal cancer. *Cancer* **124**, 3008–3015.
158 Brown JC, Caan BJ, Meyerhardt JA *et al.* (2018) The deterioration of muscle mass and radiodensity is prognostic of poor survival in stage I-III colorectal cancer: a population-based cohort study (C-SCANS). *J Cachexia Sarcopenia Muscle* **9**, 664–672.
159 van Baar H, Beijer S, Bours MJL *et al.* (2018) Low radiographic muscle density is associated with lower overall and disease-free survival in early-stage colorectal cancer patients. *J Cancer Res Clin Oncol* **144**, 2139–2147.
160 de Paula NS, Rodrigues CS & Chaves GV (2018) Comparison of the prognostic value of different skeletal muscle radiodensity parameters in endometrial cancer. *Eur J Clin Nutr* **73**, 524–530.
161 Antoun S, Lanoy E, Iacovelli R *et al.* (2013) Skeletal muscle density predicts prognosis in patients with metastatic renal cell carcinoma treated with targeted therapies. *Cancer* **119**, 3377–3384.

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

162 Ataseven B, Luengo TG, du Bois A *et al.* (2018) Skeletal muscle attenuation (Sarcopenia) predicts reduced overall survival in patients with advanced epithelial ovarian cancer undergoing primary debulking surgery. *Ann Surg Oncol* **25**, 3372–3379.

163 Sabel MS, Lee J, Cai S *et al.* (2011) Sarcopenia as a prognostic factor among patients with stage III melanoma. *Ann Surg Oncol* **18**, 3579–3585.

164 Hayashi N, Ando Y, Gyawali B *et al.* (2016) Low skeletal muscle density is associated with poor survival in patients who receive chemotherapy for metastatic gastric cancer. *Oncol Rep* **35**, 1727–1731.

165 Rier HN, Jager A, Sleijfer S *et al.* (2017) Low muscle attenuation is a prognostic factor for survival in metastatic breast cancer patients treated with first line palliative chemotherapy. *Breast* **31**, 9–15.

166 Chu MP, Lieffers J, Ghosh S *et al.* (2017) Skeletal muscle density is an independent predictor of diffuse large B-cell lymphoma outcomes treated with rituximab-based chemoimmunotherapy. *J Cachexia Sarcopenia Muscle* **8**, 298–304.

167 Van Rijssen LB, van Huijgevoort NC, Coelen RJ *et al.* (2017) Skeletal muscle quality is associated with worse survival after pancreatoduodenectomy for periampullary, nonpancreatic cancer. *Ann Surg Oncol* **24**, 272–280.

168 Charette N, Vandeputte C, Ameye L *et al.* (2019) Prognostic value of adipose tissue and muscle mass in advanced colorectal cancer: a post hoc analysis of two non-randomized phase II trials. *BMC Cancer* **19**, 134.

169 Sueda T, Takahasi H, Nishimura J *et al.* (2018) Impact of low muscularity and myosteatosis on long-term outcome after curative colorectal cancer surgery: a propensity score-matched analysis. *Dis Colon Rectum* **61**, 364–374.

170 Mintziras I, Miligkos M, Wachter S *et al.* (2018) Sarcopenia and sarcopenic obesity are significantly associated with poorer overall survival in patients with pancreatic cancer: systematic review and meta-analysis. *Int J Surg* **59**, 19–26.

171 Basile D, Parnofiello A, Vitale MG *et al.* (2019) The IMPACT study: early loss of skeletal muscle mass in advanced pancreatic cancer patients. *J Cachexia Sarcopenia Muscle* **10**, 368–377.

172 Yoon HG, Oh D, Ahn YC *et al.* (2020) Prognostic impact of sarcopenia and skeletal muscle loss during neoadjuvant chemoradiotherapy in esophageal cancer. *Cancers* (*Basel*) **12**, 925.

173 Park HS, Kim HS, Beom SH *et al.* (2018) Marked loss of muscle, visceral Fat, or subcutaneous Fat after gastrectomy predicts poor survival in advanced gastric cancer: single-center study from the CLASSIC trial. *Ann Surg Oncol* **25**, 3222–3230.

174 Nattenmuller J, Wochner R, Muley T *et al.* (2017) Prognostic impact of CT-quantified muscle and fat distribution before and after first-line-chemotherapy in lung cancer patients. *PLoS ONE* **12**, e0169136.

175 Takeda Y, Akiyoshi T, Matsueda K *et al.* (2018) Skeletal muscle loss is an independent negative prognostic factor in patients with advanced lower rectal cancer treated with neoadjuvant chemoradiotherapy. *PLoS ONE* **13**, e0195406.

176 Miyamoto Y, Baba Y, Sakamoto Y *et al.* (2015) Negative impact of skeletal muscle loss after systemic chemotherapy in patients with unresectable colorectal cancer. *PLoS ONE* **10**, e0129742.

177 Lou N, Chi CH, Chen XD *et al.* (2017) Sarcopenia in overweight and obese patients is a predictive factor for postoperative complication in gastric cancer: a prospective study. *Eur J Surg Oncol* **43**, 188–195.

178 Zhang Y, Wang JP, Wang XL *et al.* (2018) Computed tomography-quantified body composition predicts short-term outcomes after gastrectomy in gastric cancer. *Curr Oncol* **25**, e411–e422.

179 Cao Q, Xiong Y, Zhong Z *et al.* (2019) Computed tomography-assessed sarcopenia indexes predict major complications following surgery for hepatopancreatobiliary malignancy: a meta-analysis. *Ann Nutr Metab* **74**, 24–34.

180 Elliott JA, Doyle SL, Murphy CF *et al.* (2017) Sarcopenia: prevalence, and impact on operative and oncologic outcomes in the multimodal management of locally advanced esophageal cancer. *Ann Surg* **266**, 822–830.

181 Ida S, Watanabe M, Yoshida N *et al.* (2015) Sarcopenia is a predictor of postoperative respiratory complications in patients with esophageal cancer. *Ann Surg Oncol* **22**, 4432–4437.

182 Mao W, Ma B, Wang K *et al.* (2020) Sarcopenia predicts prognosis of bladder cancer patients after radical cystectomy: a study based on the Chinese population. *Clin Transl Med* **10**, e105.

183 Madariaga MLL, Troschel Cand Med FM, Best Cand Med TD *et al.* (2019) Low thoracic skeletal muscle area predicts morbidity after pneumonectomy for lung cancer. *Ann Thorac Surg* **109**, 907–913.

184 Kawaguchi Y, Hanaoka J, Ohshio Y *et al.* (2019) Sarcopenia predicts poor postoperative outcome in elderly patients with lung cancer. *Gen Thorac Cardiovasc Surg* **67**, 949–954.

185 Lieffers JR, Bathe OF, Fassbender K *et al.* (2012) Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. *Br J Cancer* **107**, 931–936.

186 Tsaousi G, Kokkota S, Papakostas P *et al.* (2017) Body composition analysis for discrimination of prolonged hospital stay in colorectal cancer surgery patients. *Eur J Cancer Care* (*Engl*) **26** [Epublication].

187 Zhang S, Tan S, Jiang Y *et al.* (2018) Sarcopenia as a predictor of poor surgical and oncologic outcomes after abdominal surgery for digestive tract cancer: a prospective cohort study. *Clin Nutr* **38**, 2881–2888.

188 Martin L, Hopkins J, Malietzis G *et al.* (2018) Assessment of Computed Tomography (CT)-defined muscle and adipose tissue features in relation to short-term outcomes after elective surgery for colorectal cancer: a multicenter approach. *Ann Surg Oncol* **25**, 2669–2680.

189 van Vugt JLA, Buettner S, Levolger S *et al.* (2017) Low skeletal muscle mass is associated with increased hospital expenditure in patients undergoing cancer surgery of the alimentary tract. *PLoS ONE* **12**, e0186547.

190 Gani F, Buettner S, Margonis GA *et al.* (2016) Sarcopenia predicts costs among patients undergoing major abdominal operations. *Surgery* **160**, 1162–1171.

191 Arends J, Bachmann P, Baracos V *et al.* (2017) ESPEN Guidelines on nutrition in cancer patients. *Clin Nutr* **36**, 11–48.

192 Arends J (2018) Struggling with nutrition in patients with advanced cancer: nutrition and nourishment-focusing on metabolism and supportive care. *Ann Oncol: Official J Euro Soc Medical Oncol/ESMO* **29**, ii27–ii34.

193 Kiss NK, Krishnasamy M, Loeliger J *et al.* (2012) A dietitian-led clinic for patients receiving (chemo)radiotherapy for head and neck cancer. *Support Care Cancer* **20**, 2111–2120.

194 Hall BT, Englehart MS, Blaseg K *et al.* (2014) Implementation of a dietitian-led enteral nutrition support clinic results in quality improvement, reduced readmissions, and cost savings. *Nutr Clin Pract* **29**, 649–655.

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

195 De Waele E, Mattens S, Honore PM *et al.* (2015) Nutrition therapy in cachectic cancer patients. The Tight Caloric Control (TiCaCo) pilot trial. *Appetite* **91**, 298–301.
196 Uster A, Ruefenacht U, Ruehlin M *et al.* (2013) Influence of a nutritional intervention on dietary intake and quality of life in cancer patients: a randomized controlled trial. *Nutrition* **29**, 1342–1349.
197 Poulsen GM, Pedersen LL, Osterlind K *et al.* (2014) Randomized trial of the effects of individual nutritional counseling in cancer patients. *Clin Nutr* **33**, 749–753.
198 Isenring E, Capra S, Bauer J *et al.* (2003) The impact of nutrition support on body composition in cancer outpatients receiving radiotherapy. *Acta Diabetol* **40**, Suppl. 1, S162–164.
199 Isenring EA, Capra S & Bauer JD (2004) Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* **91**, 447–452.
200 Ravasco P, Monteiro-Grillo I, Vidal PM *et al.* (2005) Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy. *J Clin Oncol* **23**, 1431–1438.
201 Sullivan ES, Rice N, Kingston E *et al.* (2019) The patient voice: An Irish survey of nutrition attitudes & access to dietetic care throughout the cancer journey. *Annals of Oncology* **30** (suppl 5), v718 v746
202 Isenring E, Zabel R, Bannister M *et al.* (2013) Updated evidence-based practice guidelines for the nutritional management of patients receiving radiation therapy and/or chemotherapy. *Nutr Diet* **70**, 312–324.
203 Bradley PJ, Zutshi B & Nutting CM (2005) An audit of clinical resources available for the care of head and neck cancer patients in England. *Clin Oncol* (*R Coll Radiol*) **17**, 604–609.
204 Irish Nutrition & Dietetic Institute (2015) Irish Nutrition & Dietetic Institute Submission to the National Cancer Strategy 2016-2025. Available at: https://www.indi.ie/34-members/special-interest-groups/haematology-and-oncology/568-indi-submission-to-the-national-cancer-control-programme-the-role-of-nutrition-dietetics-in-cancer-services.html
205 Trujillo E, Claghorn K, Dixon S *et al.* (2019) Inadequate nutrition services in outpatient cancer centers: Results of a National Survey. *J Oncol* **2019**, 7462940.
206 Dietitians of Canada Ontario Clinical Nutrition Leaders Action group (CNLAG) (2018) Dietitian staffing levels in Ontario Hospitals. Available at: https://www.dietitians.ca/DietitiansOfCanada/media/Documents/Resources/2018-12-18-2018-Dietitian-staffing-levels-in-Ontario-hospitals_Executive-Summary.pdf
207 O'Sullivan Maillet J, Brody RA, Skipper A *et al.* (2012) Framework for analyzing supply and demand for specialist and advanced practice registered dietitians. *J Acad Nutr Diet* **112**, S47–55.
208 Cuthbertson D (1942) Post-shock metabolic response. *The Lancet* **239**, 433–437.
209 Shinko D, Diakos CI, Clarke SJ *et al.* (2017) Cancer-Related systemic inflammation: the challenges and therapeutic opportunities for personalized medicine. *Clin Pharmacol Ther* **102**, 599–610.
210 McMillan DC (2013) The systemic inflammation-based Glasgow prognostic score: a decade of experience in patients with cancer. *Cancer Treat Rev* **39**, 534–540.
211 Solheim TS, Fearon KC, Blum D *et al.* (2013) Non-steroidal anti-inflammatory treatment in cancer cachexia: a systematic literature review. *Acta Oncol* **52**, 6–17.
212 Ryan AM, Reynolds JV, Healy L *et al.* (2009) Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. *Ann Surg* **249**, 355–363.
213 Persson C, Glimelius B, Ronnelid J *et al.* (2005) Impact of fish oil and melatonin on cachexia in patients with advanced gastrointestinal cancer: a randomized pilot study. *Nutrition* **21**, 170–178.
214 Lewis C, Xun P, Fly AD *et al.* (2015) Fish oil supplementation and quality of life in stage II colorectal cancer patients: a 24-month follow-up study. *Nutr Cancer* **67**, 1239–1246.
215 Werner K, Kullenberg de Gaudry D, Taylor LA *et al.* (2017) Dietary supplementation with n-3-fatty acids in patients with pancreatic cancer and cachexia: marine phospholipids versus fish oil - a randomized controlled double-blind trial. *Lipids Health Dis* **16**, 104.
216 Camargo CQ, Mocellin MC, Brunetta HS *et al.* (2019) Fish oil decreases the severity of treatment-related adverse events in gastrointestinal cancer patients undergoing chemotherapy: a randomized, placebo-controlled, triple-blind clinical trial. *Clin Nutr ESPEN* **31**, 61–70.
217 Maddocks M, Murton AJ & Wilcock A (2012) Therapeutic exercise in cancer cachexia. *Crit Rev Oncog* **17**, 285–292.
218 Turner RR, Steed L, Quirk H *et al.* (2018) Interventions for promoting habitual exercise in people living with and beyond cancer. *Cochrane Database Syst Rev***9**, CD010192.
219 Mishra SI, Scherer RW, Snyder C *et al.* (2012) Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev* **8**, CD008465.
220 Mishra SI, Scherer RW, Geigle PM *et al.* (2012) Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev* **8**, CD007566.
221 Sweegers MG, Altenburg TM, Chinapaw MJ *et al.* (2018) Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med* **52**, 505–513.
222 Buffart LM, Sweegers MG, May AM *et al.* (2018) Targeting exercise interventions to patients with cancer in need: an individual patient data meta-analysis. *J Natl Cancer Inst* **110**, 1190–1200.
223 Campbell KL, Winters-Stone KM, Wiskemann J *et al.* (2019) Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. *Med Sci Sports Exerc* **51**, 2375–2390.
224 Schmitz KH, Courneya KS, Matthews C *et al.* (2010) American college of sports medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* **42**, 1409–1426.
225 Cormie P, Atkinson M, Bucci L *et al.* (2018) Clinical oncology society of Australia position statement on exercise in cancer care. *Med J Aust* **209**, 184–187.
226 Solheim TS, Vagnildhaug OM, Laird BJ *et al.* (2019) Combining optimal nutrition and exercise in a multimodal approach for patients with active cancer with risk of losing weight rationale and practical approach. *Nutrition* [Epublication 27 Jun 2019].
227 Del Fabbro E (2015) Current and Future Care of Patients with the Cancer Anorexia-Cachexia Syndrome. *Am Soc Clin Oncol Educ Book* **2015**, e299-237.
228 Muscaritoli M, Molfino A, Gioia G *et al.* (2011) The "parallel pathway": a novel nutritional and metabolic

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

approach to cancer patients. *Intern Emerg Med* **6**, 105–112.
229 Hall CC, Cook J, Maddocks M *et al.* (2019) Combined exercise and nutritional rehabilitation in outpatients with incurable cancer: a systematic review. *Support Care Cancer* **27**, 2371–2384.
230 Solheim TS, Laird BJA, Balstad TR *et al.* (2018) Cancer cachexia: rationale for the MENAC (Multimodal-Exercise, Nutrition and Anti-Inflammatory Medication for Cachexia) trial. *BMJ Support Palliat Care* **8**, 258–265.
231 Climent M, Munarriz M, Blazeby JM *et al.* (2017) Weight loss and quality of life in patients surviving 2 years after gastric cancer resection. *Eur J Surg Oncol* **43**, 1337–1343.
232 Gavazzi C, Colatruglio S, Sironi A *et al.* (2011) Importance of early nutritional screening in patients with gastric cancer. *Br J Nutr* **106**, 1773–1778.
233 Pacelli F, Bossola M, Rosa F *et al.* (2008) Is malnutrition still a risk factor of postoperative complications in gastric cancer surgery? *Clin Nutr* **27**, 398–407.
234 Correia M, Cravo M, Marques-Vidal P *et al.* (2007) Serum concentrations of TNF-alpha as a surrogate marker for malnutrition and worse quality of life in patients with gastric cancer. *Clin Nutr* **26**, 728–735.
235 Berstad P, Haugum B, Helgeland M *et al.* (2013) Preoperative body size and composition, habitual diet, and post-operative complications in elective colorectal cancer patients in Norway. *J Hum Nutr Diet* **26**, 359–368.
236 Burden ST, Hill J, Shaffer JL *et al.* (2010) Nutritional status of preoperative colorectal cancer patients. *J Hum Nutr Diet* **23**, 402–407.
237 Zacharakis M, Xynos ID, Lazaris A *et al.* (2010) Predictors of survival in stage IV metastatic colorectal cancer. *Anticancer Res* **30**, 653–660.
238 van der Werf A, van Bokhorst QNE, de van der Schueren MAE *et al.* (2018) Cancer cachexia: identification by clinical assessment versus international consensus criteria in patients with metastatic colorectal cancer. *Nutr Cancer* **70**, 1322–1329.
239 Pressoir M, Desné S, Berchery D *et al.* (2010) Prevalence, risk factors and clinical implications of malnutrition in French comprehensive cancer centres. *Br J Cancer* **102**, 966–971.
240 van der Schaaf MK, Tilanus HW, van Lanschot JJ *et al.* (2014) The influence of preoperative weight loss on the postoperative course after esophageal cancer resection. *J Thorac Cardiovasc Surg* **147**, 490–495.
241 Martin L, Jia C, Rouvelas I *et al.* (2008) Risk factors for malnutrition after oesophageal and cardia cancer surgery. *Br J Surg* **95**, 1362–1368.
242 Hynes O, Anandavadivelan P, Gossage J *et al.* (2017) The impact of pre- and post-operative weight loss and body mass index on prognosis in patients with oesophageal cancer. *Eur J Surg Oncol* **43**, 1559–1565.
243 Lakenman P, Ottens-Oussoren K, Witvliet-van Nierop J *et al.* (2017) Handgrip strength is associated with treatment modifications during neoadjuvant chemoradiation in patients with esophageal cancer. *Nutr Clin Pract* **32**, 652–657.
244 Deans DA, Tan BH, Wigmore SJ *et al.* (2009) The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer. *Br J Cancer* **100**, 63–69.
245 Shen S, Araujo JL, Altorki NK *et al.* (2017) Variation by stage in the effects of prediagnosis weight loss on mortality in a prospective cohort of esophageal cancer patients. *Dis Esophagus* **30**, 1–7.
246 Morio K, Minami T, Sozu T *et al.* (2016) Weight loss associated with platinum-based chemotherapy in patients with advanced lung cancer. *Chemotherapy* **61**, 256–261.
247 Sanders KJ, Hendriks LE, Troost EG *et al.* (2016) Early weight loss during chemoradiotherapy Has a detrimental impact on outcome in NSCLC. *J Thorac Oncol* **11**, 873–879.
248 Alexander M, Evans SM, Stirling RG *et al.* (2016) The influence of comorbidity and the simplified comorbidity score on overall survival in non-small cell lung cancer-A prospective cohort study. *J Thorac Oncol* **11**, 748–757.
249 Alexander M, Wolfe R, Ball D *et al.* (2017) Lung cancer prognostic index: a risk score to predict overall survival after the diagnosis of non-small-cell lung cancer. *Br J Cancer* **117**, 744–751.
250 Kawai H, Saito Y & Suzuki Y (2017) Gender differences in the correlation between prognosis and postoperative weight loss in patients with non-small cell lung cancer. *Interact Cardiovasc Thorac Surg* **25**, 272–277.
251 Colinet B, Jacot W, Bertrand D *et al.* (2005) A new simplified comorbidity score as a prognostic factor in non-small-cell lung cancer patients: description and comparison with the Charlson's index. *Br J Cancer* **93**, 1098–1105.
252 Kiss N, Isenring E, Gough K *et al.* (2014) The prevalence of weight loss during (chemo)radiotherapy treatment for lung cancer and associated patient- and treatment-related factors. *Clin Nutr* **33**, 1074–1080.
253 Russell K, Healy B, Pantarotto J *et al.* (2014) Prognostic factors in the radical nonsurgical treatment of stage IIIB non-small-cell lung cancer. *Clin Lung Cancer* **15**, 237–243.
254 Caan BJ, Kwan ML, Hartzell G *et al.* (2008) Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer. *Cancer Causes & Control: CCC* **19**, 1319–1328.
255 Bradshaw PT, Ibrahim JG, Stevens J *et al.* (2012) Postdiagnosis change in bodyweight and survival after breast cancer diagnosis. *Epidemiology* **23**, 320–327.
256 Harimoto N, Shirabe K, Yamashita YI *et al.* (2013) Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. *Br J Surg* **100**, 1523–1530.
257 Voron T, Tselikas L, Pietrasz D *et al.* (2015) Sarcopenia impacts on short- and long-term results of Hepatectomy for Hepatocellular Carcinoma. *Ann Surg* **261**, 1173–1183.
258 Kamachi S, Mizuta T, Otsuka T *et al.* (2016) Sarcopenia is a risk factor for the recurrence of hepatocellular carcinoma after curative treatment. *Hepatol Res: the official J Japan Soc Hepatol* **46**, 201–208.
259 Nault JC, Pigneur F, Nelson AC *et al.* (2015) Visceral fat area predicts survival in patients with advanced hepatocellular carcinoma treated with tyrosine kinase inhibitors. *Dig Liver Dis* **47**, 869–876.
260 Black D, Mackay C, Ramsay G *et al.* (2017) Prognostic value of computed tomography: measured parameters of body composition in primary operable gastrointestinal cancers. *Ann Surg Oncol* **24**, 2241–2251.
261 Anandavadivelan P, Brismar TB, Nilsson M *et al.* (2016) Sarcopenic obesity: a probable risk factor for dose limiting toxicity during neo-adjuvant chemotherapy in oesophageal cancer patients. *Clin Nutr* **35**, 724–730.
262 Grotenhuis B, Shapiro J, van Adrichem S *et al.* (2016) Sarcopenia/muscle mass is not a prognostic factor for short- and long-term outcome after esophagectomy for cancer. *World J Surg* **40**, 2698–2704.
263 Reisinger KW, Bosmans JW, Uittenbogaart M *et al.* (2015) Loss of skeletal muscle mass during neoadjuvant

chemoradiotherapy predicts postoperative mortality in esophageal cancer surgery. *Ann Surg Oncol* **22**, 4445–4452.
264 Awad S, Tan BH, Cui H *et al.* (2012) Marked changes in body composition following neoadjuvant chemotherapy for oesophagogastric cancer. *Clin Nutr* **31**, 74–77.
265 Paireder M, Asari R, Kristo I *et al.* (2017) Impact of sarcopenia on outcome in patients with esophageal resection following neoadjuvant chemotherapy for esophageal cancer. *Eur J Surg Oncol* **43**, 478–484.
266 Tamandl D, Paireder M, Asari R *et al.* (2016) Markers of sarcopenia quantified by computed tomography predict adverse long-term outcome in patients with resected oesophageal or gastro-oesophageal junction cancer. *Eur Radiol* **26**, 1359–1367.
267 Sato S, Kunisaki C, Suematsu H *et al.* (2018) Impact of sarcopenia in patients with unresectable locally advanced esophageal cancer receiving chemoradiotherapy. *In vivo* **32**, 603–610.
268 Nishigori T, Okabe H, Tanaka E *et al.* (2016) Sarcopenia as a predictor of pulmonary complications after esophagectomy for thoracic esophageal cancer. *J Surg Oncol* **113**, 678–684.
269 Sharma P, Zargar-Shoshtari K, Caracciolo JT *et al.* (2015) Sarcopenia as a predictor of overall survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. *Urol Oncol* **33**, 339.e317–323.
270 Psutka SP, Boorjian SA, Moynagh MR *et al.* (2016) Decreased skeletal muscle mass is associated with an increased risk of mortality after radical nephrectomy for localized renal cell cancer. *J Urol* **195**, 270–276.
271 Huillard O, Mir O, Peyromaure M *et al.* (2013) Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients. *Br J Cancer* **108**, 1034–1041.
272 Antoun S, Birdsell L, Sawyer MB *et al.* (2010) Association of skeletal muscle wasting with treatment with sorafenib in patients with advanced renal cell carcinoma: results from a placebo-controlled study. *J Clin Oncol* **28**, 1054–1060.
273 Fukushima H, Nakanishi Y, Kataoka M *et al.* (2016) Prognostic significance of sarcopenia in patients with metastatic renal cell carcinoma. *J Urol* **195**, 26–32.
274 Cushen SJ, Power DG, Murphy KP *et al.* (2016) Impact of body composition parameters on clinical outcomes in patients with metastatic castrate-resistant prostate cancer treated with docetaxel. *Clin Nutr* **13**, e39–e45.
275 Mason RJ, Boorjian SA, Bhindi B *et al.* (2018) The association between sarcopenia and oncologic outcomes after radical prostatectomy. *Clin Genitourin Cancer* **16**, e629–e636.
276 Xiao DY, Luo S, O'Brian K *et al.* (2016) Impact of sarcopenia on treatment tolerance in United States veterans with diffuse large B-cell lymphoma treated with CHOP-based chemotherapy. *Am J Hematol* **91**, 1002–1007.
277 Thoresen L, Frykholm G, Lydersen S *et al.* (2012) The association of nutritional assessment criteria with health-related quality of life in patients with advanced colorectal carcinoma. *Eur J Cancer Care* (*Engl*) **21**, 505–516.
278 van Roekel EH, Bours MJL, Te Molder MEM *et al.* (2017) Associations of adipose and muscle tissue parameters at colorectal cancer diagnosis with long-term health-related quality of life. *Qual Life Res* **26**, 1745–1759.
279 Thoresen L, Frykholm G, Lydersen S *et al.* (2013) Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal results. *Clin Nutr* **32**, 65–72.
280 Chemama S, Bayar MA, Lanoy E *et al.* (2016) Sarcopenia is associated with chemotherapy toxicity in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal cancer. *Ann Surg Oncol* **23**, 3891–3898.
281 McSorley ST, Black DH, Horgan PG *et al.* (2017) The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer. *Clin Nutr* **37**, 1279–1285.
282 Reisinger KW, van Vugt JL, Tegels JJ *et al.* (2015) Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. *Ann Surg* **261**, 345–352.
283 Broughman JR, Williams GR, Deal AM *et al.* (2015) Prevalence of sarcopenia in older patients with colorectal cancer. *J Geriatr Oncol* **6**, 442–445.
284 Nakanishi R, Oki E, Sasaki S *et al.* (2018) Sarcopenia is an independent predictor of complications after colorectal cancer surgery. *Surg Today* **48**, 151–157.
285 Malietzis G, Johns N, Al-Hassi HO *et al.* (2016) Low muscularity and myosteatosis Is related to the host systemic inflammatory response in patients undergoing surgery for colorectal cancer. *Ann Surg* **263**, 320–325.
286 Eriksson S, Nilsson JH, Strandberg Holka P *et al.* (2017) The impact of neoadjuvant chemotherapy on skeletal muscle depletion and preoperative sarcopenia in patients with resectable colorectal liver metastases. *HPB* (*Oxford*) **19**, 331–337.
287 Barret M, Antoun S, Dalban C *et al.* (2014) Sarcopenia is linked to treatment toxicity in patients with metastatic colorectal cancer. *Nutr Cancer* **66**, 583–589.
288 Jarvinen T, Ilonen I, Kauppi J *et al.* (2018) Loss of skeletal muscle mass during neoadjuvant treatments correlates with worse prognosis in esophageal cancer: a retrospective cohort study. *World J Surg Oncol* **16**, 27.
289 Mayr R, Fritsche HM, Zeman F *et al.* (2018) Sarcopenia predicts 90-day mortality and postoperative complications after radical cystectomy for bladder cancer. *World J Urol* **36**, 1201–1207.
290 Kocher NJ, Jafri S, Balabhadra S *et al.* (2018) Is sarcopenia and sarcopenic obesity associated with clinical and pathological outcomes in patients undergoing radical nephroureterectomy? *Urol Oncol* **36**, 156.e117–156.e122.
291 Hirasawa Y, Nakashima J, Yunaiyama D *et al.* (2016) Sarcopenia as a novel preoperative prognostic predictor for survival in patients with bladder cancer undergoing radical cystectomy. *Ann Surg Oncol* **23**, 1048–1054.
292 Fukushima H, Yokoyama M, Nakanishi Y *et al.* (2015) Sarcopenia as a prognostic biomarker of advanced urothelial carcinoma. *PLoS ONE* **10**, e0115895.
293 Psutka SP, Carrasco A, Schmit GD *et al.* (2014) Sarcopenia in patients with bladder cancer undergoing radical cystectomy: impact on cancer-specific and all-cause mortality. *Cancer* **120**, 2910–2918.
294 Kumar A, Moynagh MR, Multinu F *et al.* (2016) Muscle composition measured by CT scan is a measurable predictor of overall survival in advanced ovarian cancer. *Gynecol Oncol* **142**, 311–316.
295 Valentine H, François G, Nora K *et al.* (2017) Sarcopenic overweight is associated with early acute limiting toxicity of anti-PD1 checkpoint inhibitors in melanoma patients. *Invest New Drugs* **35**, 436–441.
296 Del Fabbro E, Parsons H, Warneke CL *et al.* (2012) The relationship between body composition and response to neoadjuvant chemotherapy in women with operable breast cancer. *Oncologist* **17**, 1240–1245.

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press

297 Weinberg MS, Shachar SS, Muss HB *et al*. (2018) Beyond sarcopenia: characterization and integration of skeletal muscle quantity and radiodensity in a curable breast cancer population. *Breast J* **24**, 278–284.
298 Mazzuca F, Onesti CE, Roberto M *et al*. (2018) Lean body mass wasting and toxicity in early breast cancer patients receiving anthracyclines. *Oncotarget* **9**, 25714–25722.
299 Deluche E, Leobon S, Desport JC *et al*. (2018) Impact of body composition on outcome in patients with early breast cancer. *Support Care Cancer* **26**, 861–868.
300 Mourtzakis M, Prado CM, Lieffers JR *et al*. (2008) A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* **33**, 997–1006.
301 Hu X, Dou WC, Shao YX *et al*. (2019) The prognostic value of sarcopenia in patients with surgically treated urothelial carcinoma: a systematic review and meta-analysis. *Eur J Surg Oncol* **45**, 747–754.
302 Li J, Deng Y, Zhang M *et al*. (2019) Prognostic value of radiologically determined sarcopenia prior to treatment in urologic tumors: a meta-analysis. *Medicine* **98**, e17213.
303 Deng HY, Zha P, Peng L *et al*. (2019) Preoperative sarcopenia is a predictor of poor prognosis of esophageal cancer after esophagectomy: a comprehensive systematic review and meta-analysis. *Dis Esophagus* **32**.
304 Zhang G, Meng S, Li R *et al*. (2017) Clinical significance of sarcopenia in the treatment of patients with primary hepatic malignancies, a systematic review and meta-analysis. *Oncotarget* **8**, 102474–102485.
305 Yang M, Shen Y, Tan L *et al*. (2019) Prognostic value of sarcopenia in lung cancer: a systematic review and meta-analysis. *Chest* **156**, 101–111.
306 Chang KV, Chen JD, Wu WT *et al*. (2018) Association between loss of skeletal muscle mass and mortality and tumor recurrence in hepatocellular carcinoma: a systematic review and meta-analysis. *Liver Cancer* **7**, 90–103.
307 Sun G, Li Y, Peng Y *et al*. (2018) Can sarcopenia be a predictor of prognosis for patients with non-metastatic colorectal cancer? A systematic review and meta-analysis. *Int J Colorectal Dis* **33**, 1419–1427.
308 Su H, Ruan J, Chen T *et al*. (2019) CT-assessed sarcopenia is a predictive factor for both long-term and short-term outcomes in gastrointestinal oncology patients: a systematic review and meta-analysis. *Cancer Imaging* **19**, 82.
309 Vrieling A, Kampman E, Knijnenburg NC *et al*. (2018) Body composition in relation to clinical outcomes in renal cell cancer: a systematic review and meta-analysis. *Eur Urol Focus* **4**, 420–434.
310 Aleixo GFP, Williams GR, Nyrop KA *et al*. (2019) Muscle composition and outcomes in patients with breast cancer: meta-analysis and systematic review. *Breast Cancer Res Treat* **177**, 569–579.
311 Bundred J, Kamarajah SK & Roberts KJ (2019) Body composition assessment and sarcopenia in patients with pancreatic cancer: a systematic review and meta-analysis. *HPB: Official J Int Hepato Pancreato Biliary Assoc* **21**, 1603–1612.
312 Rinninella E, Cintoni M, Raoul P *et al*. (2019) Muscle mass, assessed at diagnosis by L3-CT scan as a prognostic marker of clinical outcomes in patients with gastric cancer: a systematic review and meta-analysis. *Clin Nutr* **39**, 2045–2054.
313 Buentzel J, Heinz J, Bleckmann A *et al*. (2019) Sarcopenia as prognostic factor in lung cancer patients: a systematic review and meta-analysis. *Anticancer Res* **39**, 4603–4612.
314 Ubachs J, Ziemons J, Minis-Rutten IJG *et al*. (2019) Sarcopenia and ovarian cancer survival: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle* **10**, 1165–1174.
315 Borggreve AS, den Boer RB, van Boxel GI, *et al*. (2020) The predictive value of low muscle mass as measured on CT scans for postoperative complications and mortality in gastric cancer patients: a systematic review and meta-analysis. *J Clin Med* **9**, 199.

Proceedings of the Nutrition Society

https://doi.org/10.1017/S0029665120007855 Published online by Cambridge University Press