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Cuthbertson Award Lecture

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

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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.

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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

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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.

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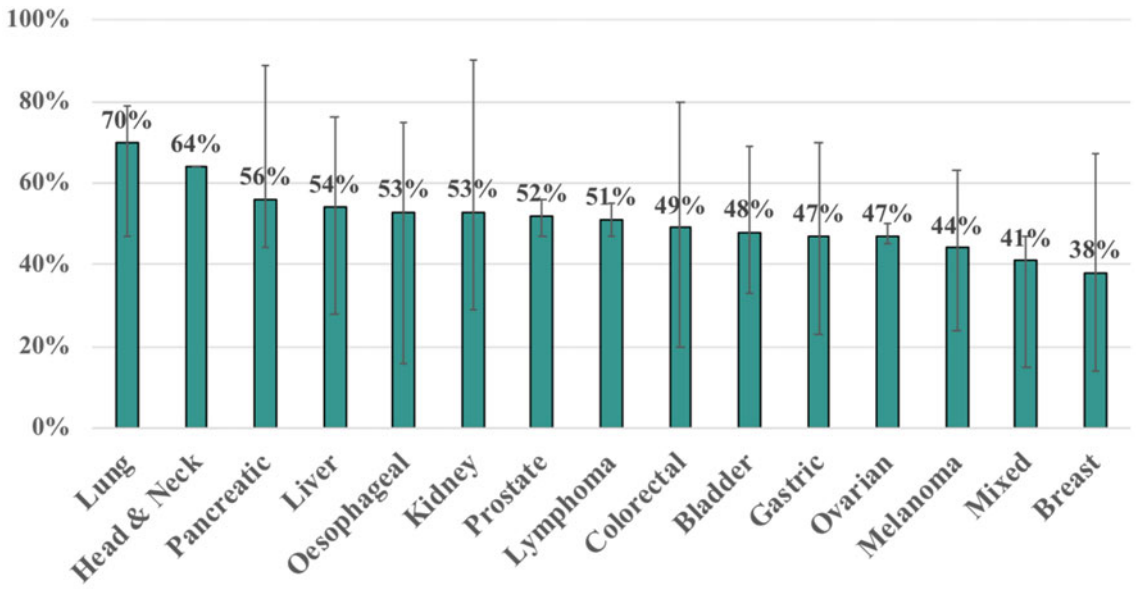

Fig. 1. Prevalence of sarcopenia in patients with cancer according to the primary tumour location in the literature (all stages).[63–68,136,41,61,69–73,111,180,256–260,90,94,261–264,12,113,265–270,95,271–275,52,60,149,150,276,277,185,260,278–280,86–88,281,282,283–287,91,288–293,11,47,57,58,92,162,164,268,294,295,7,93,96,100,165,296–299].

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].

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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

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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), $P = 0·007$ and HR 2·31 (95 % CI 1·30, 4·09), $P = 0·004$)[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), $P < 0·001$ and HR 1·61 95 % CI 1·20, 2·15, $P = 0·002$, 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].

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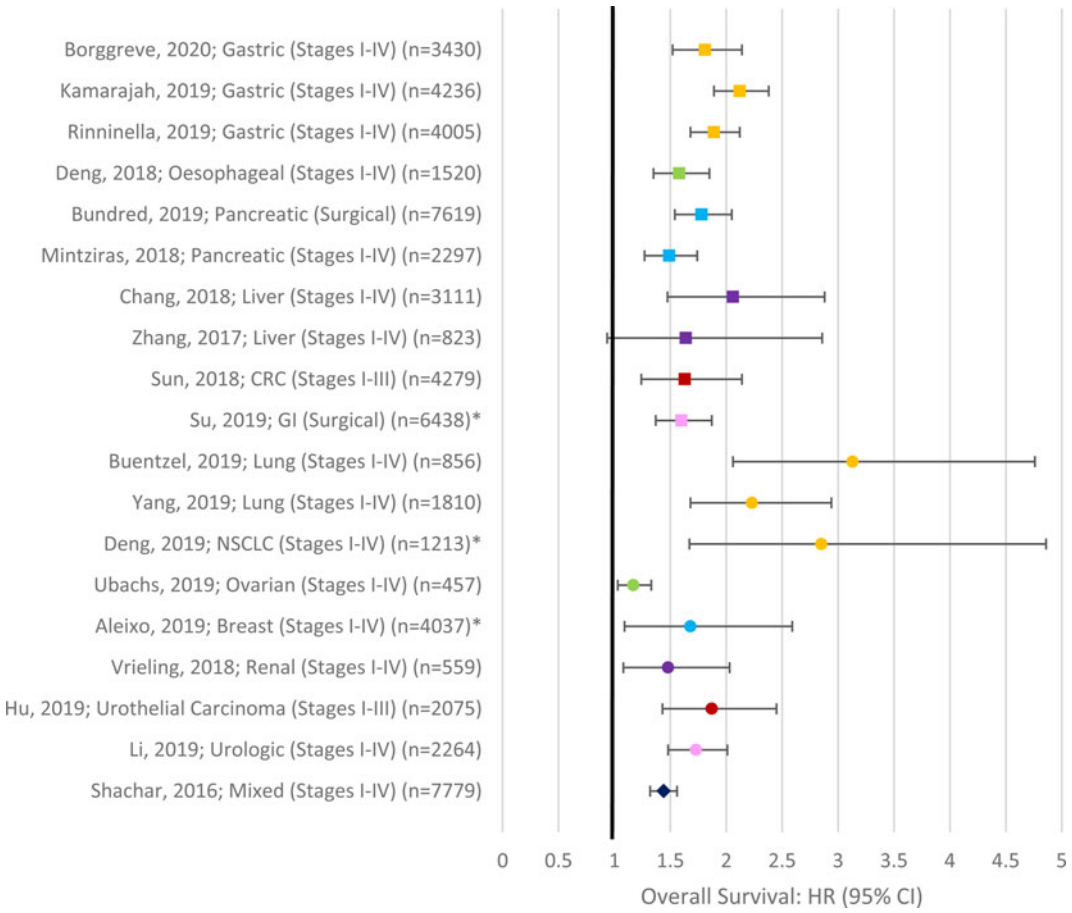

Fig. 2. (Colour online) Forest Plot depicting summary results of meta-analyses examining the role of sarcopenia in survival in cancer. Asterisks denote studies which did not confirm the inclusion of multivariate data in the meta-analysis[153,301–304,305–310,170,311–315].

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

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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].

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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

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

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Conflict of Interest

None

Authorship

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