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Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later

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An awareness of the importance of nutritional status in hospital settings began more than 40 years ago. Much has been learned since and has altered care. For the past 40 years several large studies have shown that cancer patients are amongst the most malnourished of all patient groups. Recently, the use of gold-standard methods of body composition assessment, including computed tomography, has facilitated the understanding of the true prevalence of cancer cachexia (CC). CC remains a devastating syndrome affecting 50–80 % of cancer patients and it is responsible for the death of at least 20 %. The aetiology is multifactorial and complex; driven by pro-inflammatory cytokines and specific tumour-derived factors, which initiate an energy-intensive acute phase protein response and drive the loss of skeletal muscle even in the presence of adequate food intake and insulin. The most clinically relevant phenotypic feature of CC is muscle loss (sarcopenia), as this relates to asthenia, fatigue, impaired physical function, reduced tolerance to treatments, impaired quality of life and reduced survival. Sarcopenia is present in 20–70 % depending on the tumour type. There is mounting evidence that sarcopenia increases the risk of toxicity to many chemotherapy drugs. However, identification of patients with muscle loss has become increasingly difficult as 40–60 % of cancer patients are overweight or obese, even in the setting of metastatic disease. Further challenges exist in trying to reverse CC and sarcopenia. Future clinical trials investigating dose reductions in sarcopenic patients and dose-escalating studies based on pre-treatment body composition assessment have the potential to alter cancer treatment paradigms.

Cancer: Cachexia: Sarcopenia: Quality of life: Malnutrition: Survival

Over 40 years ago Charles Butterworth penned the now infamous ‘Skeleton in the Hospital Closet’ paper which highlighted the ‘downright neglect of nutritional health’ in hospitals in the USA⁽¹⁾. He argued that ‘one of the largest pockets of unrecognised malnutrition in the USA and Canada was not in rural slums or urban ghettos, but in the private rooms of big city hospitals’. Furthermore, he adds that ‘when a sick person commits

himself to the total, unquestioning care of his doctor, his nutritional health at least should be assured...and it becomes imperative to ensure that preventable malnutrition does not contribute to mortality, morbidity and prolonged hospital stay’.

Shortly after this paper was published, articles began to appear in peer-reviewed journals highlighting the enormous problem of malnutrition in cancer patients. In a

Abbreviations: BSA, body surface area; CC, cancer cachexia; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; FFM, fat free mass; PAL, physical activity level; QoL, quality of life; REE, resting energy expenditure.

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classic study by Dewys *et al.*⁽²⁾ on 3047 patients with different tumour types, moderate-to-severe weight loss was reported in 30–70%. The greatest incidence of weight loss was seen in patients with solid tumours, e.g. gastric, pancreatic, lung, colorectal and head and neck. Within each tumour type, survival times were shorter for patients who had experienced weight loss and there was a trend towards decreased chemotherapy response rates⁽²⁾.

Almost 30 years later in 2009, Bozzetti *et al.*⁽³⁾ reported on the nutritional status of 1000 oncology outpatients reporting that 40% had lost more than 10% of their body weight and over 50% had anorexia. The mean weight loss in patients with solid tumours of the upper gut was 15%. When cancer patients are compared with other hospital patients they come out as amongst the most malnourished⁽³⁾. In a recent study by Tangvik *et al.*⁽⁴⁾ which screened 3279 hospital patients, 49% of cancer patients assessed were at nutritional risk, second only to those with acute infections. In this study, the highest number of patients at nutritional risk had a BMI in the normal or overweight category and were aged 60–80 years⁽⁴⁾. The largest study to date of 8160 cancer patients from Canada and Europe with locally advanced or metastatic disease reported that 73% experienced involuntary weight loss and that BMI and percentage weight loss predicted survival independent of disease site, stage or performance score⁽⁵⁾.

Aetiology

Nutritional deterioration has unfortunately become an accepted part of the pathogenesis of cancer and its treatment. The degree of malnutrition that occurs is affected by cancer type, stage and therapy modality; however, the aetiology of cancer-induced weight loss is multifactorial and complex. Changes in nutrition status can occur at any point in the timeline of cancer diagnosis, treatment or support⁽⁶⁾. These changes may occur as a result of metabolic changes, mechanical blockages or abnormalities, side effects of treatment or psychosocial issues.

Insufficient oral intake

Several factors may directly lead to diminished food intake and thereby insufficient energy intake, e.g. dysphagia, nausea, xerostomia and changes in taste and smell⁽⁷⁾. Other factors may have an indirect influence on energy intake by affecting appetite and the drive to eat, e.g. pain, fatigue and psychological problems⁽⁸⁾. Studies have suggested that a high prevalence of taste changes are associated with poor intakes in advanced cancer and that individuals reporting taste changes may ingest as little as 3765.6–4602.4 kJ/d (900–1100 kcal/d)⁽⁹⁾ with other studies reporting energy deficits of up to 230 120 kJ (55 000 calories) during chemoradiotherapy in head and neck cancers⁽¹⁰⁾. A wide variation in energy intake has been reported in cancer ranging from 16.74 to 221.75 kJ/kg per d (4 to 53 kcal/kg per d)⁽⁸⁾.

Tumour-related mechanisms

Tumour-related mechanisms include obstruction of the gastrointestinal tract causing dysphagia or odynophagia, as seen in oesophageal and head and neck cancers. Weight loss can be attributed to the physiologic abnormalities associated with the tumour, such as malabsorption, vomiting, diarrhoea, anorexia or the side effects of anti-cancer treatment, including chemotherapy, radiotherapy and surgery^(11–13). Oral and gastrointestinal symptoms have early effects on changes in weight without regard to nutrition status and treatment modalities. Patients with weight loss have also been shown to have more depression, abdominal fullness, taste changes, vomiting, dry mouth, dysphagia or loss of appetite⁽⁷⁾.

Host response to tumour

A variety of metabolic and endocrine changes, and activation of catabolic pathways also account for weight loss, which is typically greater than would be expected from the prevailing level of oral intake⁽⁷⁾. Pro-inflammatory cytokines (secreted by either immune cells or tumours) play a central role in mediating the metabolic, physiologic and behavioural features of cancer-induced weight loss. They are key signals for lipolysis and proteolysis. Cytokines have three major effects: (1) altering macronutrient metabolism, (2) depressing appetite and (3) initiation of an acute phase protein response. This acute phase protein response is energy-intensive with high requirements for essential amino acids. The need for amino acids drives the loss of muscle. Along with the acute phase protein response, changes in intermediary metabolism also occur, most notably, in protein metabolism. Anorexia results from pro-inflammatory cytokine activity and has both central and peripheral aspects. The central effect is at the level of the hypothalamic nuclei, which control feeding behaviours. Mediators such as corticotropin-releasing hormone, serotonin or leptin may be directly or indirectly involved in producing anorexia.

In addition, inflammatory cytokines directly induce signalling pathways that up-regulate enzymes inducing muscle protein turnover. The pathway most involved in muscle wasting is protein degradation that is mediated by the activation of the ubiquitin-dependent proteasome pathway. Additionally there are abnormalities in protein synthesis and degradation and amino acid metabolism along with increased apoptosis and an impaired capacity for regeneration⁽¹⁴⁾.

Skeletal muscle loss is accompanied by a profound loss of white adipose tissue due to a variety of factors. Lipid-mobilising factor is produced by cachexia-inducing tumours and is involved in the degradation of adipose tissue, with increased oxidation of the released fatty acids through an induction of uncoupling protein expression⁽¹⁵⁾. In addition, there is an increase in lipolytic activity through activation of hormone-sensitive lipase; a decreased anti-lipolytic effect of insulin on adipocytes; and an important decrease in lipoprotein lipase activity⁽¹⁴⁾. Consequently lipid uptake is severely hampered. Also *de novo* lipogenesis in adipose tissue is also



Table 1. Sarcopenia, weight loss and cachexia; predictors of reduced survival in cancer

Reference	Cancer type	Predictor of reduced survival	n	Follow up	Sarcopenia/cachexia defined as:	Outcome/hazard ratio (HR)	P value
Fearon <i>et al.</i> ⁽⁷⁸⁾	Locally advanced pancreatic	Cachexia	80	Minimum 6 months	Weight loss $\geq 10\%$, low food intake ≤ 6276 kJ/d (1500 kcal/d), and systemic inflammation (CRP ≥ 10 mg/l)	HR 4.9 (no CI reported)	<0.001
Bachmann <i>et al.</i> ⁽³⁶⁾	Ductal adenocarcinoma of pancreas	Weight loss	150	Median: 406 d	Weight loss was defined as any degree of weight loss	Weight loss (654 d v. 451 d)	0.001
Prado <i>et al.</i> ⁽³⁸⁾	Solid tumours of respiratory and GI tract	Sarcopenic obesity	250	Until death	SMI at L3, <55.4 cm ² /m ² for males and <38.9 cm ² /m ² females measured by CT	HR 4.2 (95 % CI 2.4, 7.2)	0.0001
Tan <i>et al.</i> ⁽¹⁰²⁾	Pancreatic	Sarcopenic overweight/obese	62	Until death or censored date	SMI at L3, ≤ 52.4 cm ² /m ² for men and ≤ 38.5 cm ² /m ² for women measured by CT	HR 2.07 (95 % CI 1.23, 3.50)	0.006
Van Vledder <i>et al.</i> ⁽⁵⁰⁾	Colorectal cancer with liver metastasis	Sarcopenic	196	Median: 29 months	SMI at L3, <43.75 cm ² /m ² for males and <41.1 cm ² /m ² for females measured by CT	HR 2.53 (95 % CI 1.60, 4.01)	<0.001
Villasenor <i>et al.</i> ⁽¹⁰³⁾	Breast	Sarcopenic	471	Median: 9.2 years	appendicular lean mass index <5.45 kg/m ² for females measured by DXA	HR 1.95 (95 % CI 0.87, 4.35)	NS
Peng <i>et al.</i> ⁽³⁷⁾	Pancreatic	Sarcopenia	557	3 years	Total psoas area <492 mm ² /m ² for men and <362 mm ² /m ² for females measured by CT	HR 1.63 (95 % CI 1.28, 2.07)	<0.001
Martin <i>et al.</i> ⁽⁴²⁾	Lung and GI	Weight loss, low muscle attenuation and low muscle index	1473	Median: 21.2 months	SMI at L3, <43 cm ² /m ² for men (BMI ≤ 24.9 kg/m ²) and <53 cm ² /m ² for overweight/obese men (BMI > 25 kg/m ²), <41 cm ² /m ² for women; muscle attenuation <41 HU for men and women (BMI ≤ 24.9 kg/m ²), <33 HU for overweight/obese men (BMI > 25 kg/m ²); weight loss $\geq 8\%$ measured by CT	Independent of BMI, patients with all three features (weight loss, low muscle attenuation and low muscle index) survived 8.4 months (95 % CI 6.5, 10.3) v. 28.4 months (95 % CI 24.2, 32.6) in patients with none of these features	<0.001
Langius <i>et al.</i> ⁽¹⁸⁾	Head and neck	Weight loss	1340	5 years	$>10\%$ weight loss before radiotherapy	HR 1.7 (95 % CI 1.2, 2.5)	0.002
Voron <i>et al.</i> ⁽¹⁰⁴⁾	Hepatocellular carcinoma	Sarcopenia	109	Median: 21.3 months	SMI at L3, ≤ 52.4 cm ² /m ² for men and ≤ 38.9 cm ² /m ² for women measured by CT	HR 3.19 (95 % CI 1.28, 7.96)	0.013
Psutka <i>et al.</i> ⁽¹⁰⁵⁾	Bladder	Sarcopenia	205	6.7 years	SMI at L3, < 55 cm ² /m ² for men and <39 cm ² /m ² for women measured by CT	HR 1.93 (95 % CI 1.23, 3.00)	0.004
Sharma <i>et al.</i> ⁽⁶⁹⁾	Metastatic renal cell carcinoma	Sarcopenia	93	13 months	SMI at L3, <43 cm ² /m ² for men (BMI < 25 cm ² /m ²), <53 cm ² /m ² for overweight/obese men & <41 cm ² /m ² for women measured by CT	HR 2.13 (95 % CI 1.15, 3.92)	0.016
Miyamoto <i>et al.</i> ⁽⁴⁹⁾	Colorectal	Sarcopenia	220	Median: 41.4 months	SMI at L3, those in the lowest quartiles for SMI at L3, for men: 32.6–49.5 cm ² /m ² ; for women 15.6–42.1 cm ² /m ²	HR 2.27 (95 % CI 1.14, 4.49)	0.019
Martin <i>et al.</i> ⁽⁵⁾	Variety of cancer types	Weight loss	8160	Median: 41.3 months	A robust grading system was developed incorporating the independent prognostic significance of both BMI and % weight loss	On average, there was a 4.9-fold difference in median survival between grade 0 (weight stable patients with BMI ≥ 25.0 kg/m ²) and grade 4 (lowest BMI and highest % weight loss) (20.9 months v. 4.3 months, respectively)	<0.001

Malnutrition in cancer

GI, gastrointestinal; CT, computed tomography; SMI, skeletal muscle index; L3, third lumbar vertebra; DXA, dual-energy X-ray absorptiometry; HU, Hounsfield units; Q4, fourth quartile.

reduced^(14,16). There are also recent data to suggest that white adipose tissue cells undergo a browning process and brown adipose tissue is associated with increased expression of uncoupling protein 1, which switches the use of mitochondrial electron transport from ATP synthesis to thermogenesis, resulting in increased lipid mobilisation and energy expenditure⁽¹⁴⁾. Adipose tissue also infiltrates muscle resulting in reduced muscle density⁽¹⁷⁾.

Energy expenditure and physical activity

The resting energy expenditure (REE) in cancer patients is determined by the type of tumour. REE can be unchanged, increased or decreased in relation to the predicted energy expenditure^(18–20). In about 25% of patients with active cancer, REE measured by the gold standard method, indirect calorimetry, is more than 10% higher, and in another 25% it is more than 10% lower than predicted energy expenditure⁽²¹⁾. REE has been shown to be significantly elevated in patients with an acute phase response⁽²²⁾.

Although REE may be elevated in cancer patients, the total energy expenditure is often decreased through reduction in the physical activity level (PAL) and it has been reported that that weight-losing cancer patients reduce the magnitude of their energy deficit by a reduction in PAL. Healthy sedentary adults have a PAL between 1.4 and 1.5⁽²³⁾. In a study of hypermetabolic, cachectic pancreatic cancer patients, it was shown that the measured mean PAL was much lower (mean 1.24) than that recorded in healthy adults of similar age (mean 1.62)⁽²⁴⁾. This level of physical activity is comparable with that observed in spinal cord injury patients living at home⁽²⁵⁾ or that observed in cerebral palsy (mean PAL 1.23)⁽²⁶⁾. Levels of physical activity as low as this may exacerbate muscle wasting^(27,28) and it is well understood in any individual, that a lack of physical activity will cause deconditioning and deterioration in muscle mass⁽²⁹⁾ which in turn impacts the ability to exercise. This vicious cycle leads to progressive decline in physical activity and of muscle mass.

Cancer cachexia

The wasting in cancer is often termed cancer cachexia (CC) and over the last few years several definitions of CC have emerged but they all share two common features: involuntary weight loss of muscle (and fat) and inflammation. Debate continues in the scientific literature surrounding its best definition and classification. Earlier papers described CC as 'a wasting syndrome involving loss of muscle and fat directly caused by tumour factors, or indirectly caused by an aberrant host response to tumour presence'⁽³⁰⁾ but more recent definitions describe it as 'a complex metabolic syndrome associated with underlying illness and characterised by loss of muscle with or without loss of fat mass'⁽³¹⁾. In addition to muscle and adipose tissue, other organs are affected by the cachectic process. Abnormalities in heart function, alterations in liver protein synthesis, changes in hypothalamic mediators and activation of brown adipose tissue are also involved in the cachectic syndrome⁽¹⁴⁾. Therefore tissues

and organs such as adipose tissue, brain, liver, gut and heart are all directly involved in the cachectic process.

In 2011, a consensus definition of CC was published by Fearon *et al.*⁽³²⁾ which proposed new criteria for diagnosing CC. Briefly this definition requires any one of the following criteria to be met: (1) involuntary weight loss >5% over the last 6 months in the absence of simple starvation; (2) weight loss >2% with a BMI < 20 kg/m²; (3) weight loss >2% with an appendicular skeletal muscle index consistent with sarcopenia as measured by dual-energy X-ray absorptiometry (DXA; males < 7.26 kg/m² and females < 5.45 kg/m²).

It is important to recognise that cachexia actually represents a spectrum of conditions. The first stage is 'precachexia'. Here, cancer cells release substances that initiate inflammatory actions, and the body's immune cells are mounting a response to the presence of cancer cells. Patients may first notice weight loss, sometimes even before the cancer diagnosis has been made. The 'cachexia syndrome' is characterised by weight loss in combination with evidence of systemic inflammation and reduced food intake. People with 'advanced/refractory cachexia' have depletion of fat reserves, severe muscle wasting and immunocompromise, and they are likely to die primarily as a result of these issues⁽³²⁾.

Whether or not a patient progresses down the pathway of worsening cachexia depends on the success of treating the primary disease and on addressing cachexia as well. Not all patients will progress down this spectrum to full cachexia. Some will die of their primary disease before they develop advanced cachexia, others will stabilise as a result of treatment of their primary disease. Such heterogeneity makes it difficult to target prophylactic therapy successfully. Prophylaxis would be best initiated in the precachexia phase yet there are few robust predictors to guide such a strategy.

Malnutrition, cancer cachexia and survival

If left untreated, tumour-related weight loss will progressively worsen. Such progression will negatively impact patient outcomes, particularly survival. There is a vast array of published studies showing reduced survival in weight-losing cancer patients and in those with cachexia. Studies have consistently demonstrated that the prognosis for cancer patients with weight loss is worse than that for weight-stable patients^(33–36). Table 1 summarises the available evidence for reduced survival in a variety of cancers which report hazard ratios of death ranging from 1.63 to 4.2^(37,38). A recent large paper by Martin *et al.*⁽⁵⁾ on 8160 cancer patients developed a robust grading system which could predict survival and was based on percentage weight loss and BMI. This research showed that weight-stable patients with BMI > 25 kg/m² had the longest survival and percentage weight loss values associated with lower BMI categories were related to shorter survival. This study demonstrated that the loss of the ability to maintain weight (even a weight loss of 2.4%) is significantly related to reduced survival and those cancer patients with the lowest BMI and highest level of weight loss experienced survival rates consistent

Table 2. Recent large studies highlighting the problem of increased BMI in cancer patients

Reference	Cancer site	n	% overweight or obese (BMI \geq 25 kg/m ²)
Ramos Chaves <i>et al.</i> ⁽⁴⁰⁾	Variety	450	63
Gioulbasanis <i>et al.</i> ⁽⁴¹⁾	Metastatic primaries	1469	42
Martin <i>et al.</i> ⁽⁴²⁾	GI & Lung	1473	52
Martin <i>et al.</i> ⁽⁵⁾	variety	8160	40

GI, gastrointestinal.

with Common Terminology Criteria for Adverse Events grade 4 which is consistent with a life-limiting toxic side effect from chemotherapy⁽⁵⁾.

Overweight and obesity in cancer

There is now convincing evidence that a substantial proportion of cancers are attributable to obesity. Indeed the World Cancer Research Fund⁽³⁹⁾ estimates that between 15 and 45 % of cancers are directly related to obesity. Despite the fact that the majority of cancer patients present with involuntary weight loss at the time of diagnosis⁽⁵⁾, in the era of obesity cancer patients may not look malnourished and many in fact are overweight or obese making the identification of ‘at risk’ patients harder for medical teams caring for them. Recent studies have reported that between 40 and 60 % of cancer patients are overweight or obese, even in the setting of metastatic disease^(5,40–42) (see Table 2). As the most clinically relevant phenotypic feature of CC is muscle loss, identifying those with muscle loss becomes a huge challenge in overweight and obese patients as the loss of muscle is masked by excessive adiposity.

Sarcopenia

Sarcopenia comes from the Greek ‘sarx’ for flesh, ‘penia’ for loss and was first defined by Evans *et al.* in 1993⁽⁴³⁾, as ‘the age-related loss in skeletal muscle mass, which results in decreased strength and aerobic capacity and thus functional capacity’. Today more commonly it is defined as having an appendicular skeletal muscle mass (kg/height (m)²) less than two standard deviations below the mean of a young reference group⁽⁴⁴⁾.

The best way to diagnose sarcopenia is by direct measurement of lean mass by either DXA or computed tomography (CT). Although DXA scans produce highly reproducible and accurate results, they lack the ability to discriminate among the lean tissue and adipose tissue sub-compartments. The third lumbar vertebra has been validated as the standard landmark for body composition analysis because in this region, skeletal muscle and adipose tissue correspond to whole body tissue quantities^(45,46). CT image analysis at third lumbar vertebra can distinguish adipose tissue (including visceral, subcutaneous and intramuscular) from skeletal tissue (including psoas, paraspinal muscles, transversus

abdominus, external and internal obliques, rectus abdominus)⁽⁴⁵⁾.

Specific tissues are identified based on their anatomical features and then demarcated and quantified based on pre-established thresholds of Hounsfield units using commercially available imaging analysis software. CT Hounsfield unit thresholds used are –29 to 150 for skeletal muscle⁽⁴⁷⁾, –190 to –30 for subcutaneous and intramuscular adipose tissue⁽⁴⁷⁾ and –150 to –50 for visceral adipose tissue⁽⁴⁸⁾. Individuals may be compared directly on this basis of total third lumbar vertebra skeletal muscle cross sectional area (cm²), skeletal muscle index (cm²/m²) or approximate whole-body tissue masses estimated from lumbar areas using predetermined regression equations⁽⁴⁵⁾. These regression equations were first developed for a cancer population using CT scans by Mourtzakis *et al.*⁽⁴⁵⁾ who converted the cut points developed in a healthy cohort by DXA⁽⁴⁴⁾ from kg/m² to cm²/m² using regression equations. Since then several cut points for sarcopenia have been published^(32,38) and more recently sex-specific and BMI-specific cut points for sarcopenia were defined by Martin *et al.* (<43 cm²/m² for men (BMI < 25 cm²/m²), <53 cm²/m² for overweight/obese men and <41 cm²/m² for women)⁽⁴²⁾.

Despite the presence of increasing prevalence of overweight and obesity in cancer patients, sarcopenia is present in between 20 and 70 % depending on the tumour type and sarcopenia definition used. There are over twenty-five studies in the literature reporting rates of sarcopenia in different cancer populations but studies are difficult to compare due to the variety of cut-off points for sarcopenia that were used. Of these twenty-five studies, ten used the cut points according to Prado *et al.*⁽³⁸⁾ (38.5 cm²/m² for females and 52.4 cm²/m² for males); five used the Baumgartner cut points⁽⁴⁴⁾ which were converted to cm²/m² using Mourtzakis regression equations⁽⁴⁵⁾ (38.9 cm²/m² for females and 55.4 cm²/m² for males); two used Martin *et al.*⁽⁴²⁾ (<43 cm²/m² for men (BMI < 25 cm²/m²), <53 cm²/m² for overweight/obese men and <41 cm²/m² for women), and the remainder used either Fearon *et al.*⁽³²⁾ (<55 cm²/m² for men and <39 cm²/m² for women) or were based on one muscle group⁽³⁷⁾, quartiles of muscle mass⁽³⁸⁾ or optimal stratification analysis⁽⁴⁹⁾. Thus, cross-comparison of rates of sarcopenia across different studies is hampered. Fig. 1 describes the rate of sarcopenia in fifteen different cancer populations using the most commonly used definitions^(38,45). Figures are compared with a reference healthy population of 378 adults who took part in the New Mexico Elder Health Survey between 1993 and 1999 and had their body composition measured by DXA⁽⁴⁴⁾. As can be seen in Fig. 1 the majority of the studies describing sarcopenia in oncology populations place cancer patients akin to those healthy elderly aged late 70s to early 80s.

As discussed previously, an additional challenge for cancer care providers is the fact that sarcopenia is a phenomenon that may be obscured within the bulk of body weight and body weight change and this is now recognised as a clinically important phenomenon. Fig. 2 depicts several CT scans at lumbar vertebra 3 in cancer

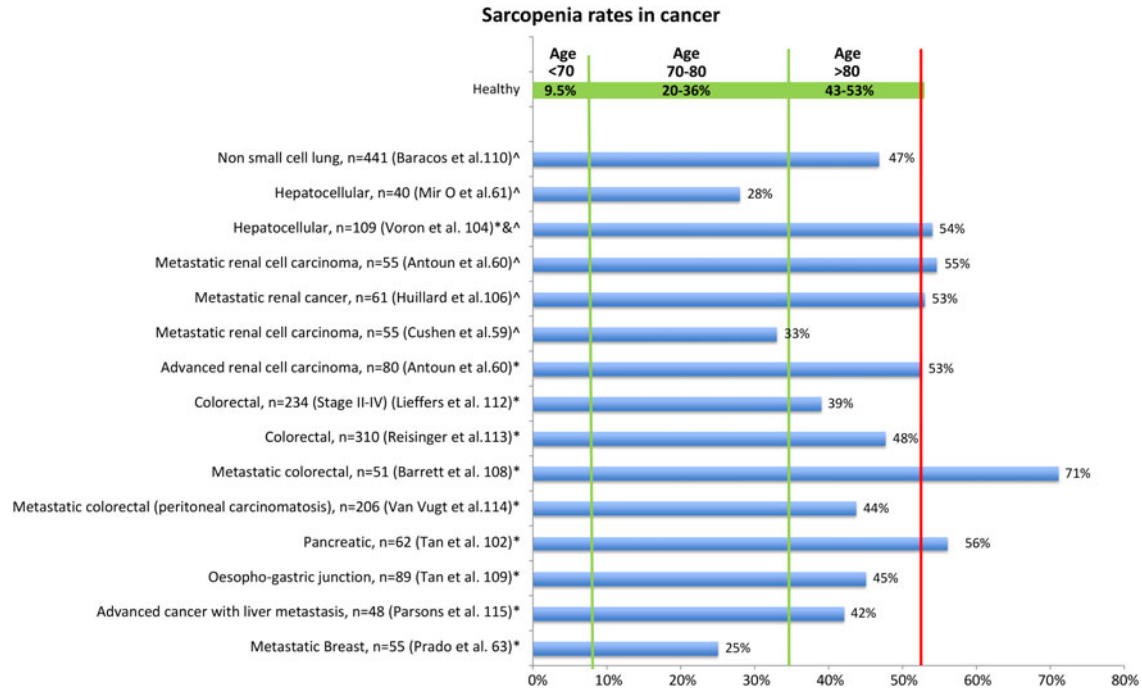


Fig. 1. (Colour online) Summary of studies reporting sarcopenia in a variety of cancers compared with healthy controls. For cancer populations sarcopenia defined by computed tomography scan using Prado *et al.*⁽³⁸⁾ values of 38.5 cm²/m² for females and 52.4 cm²/m² for males; Mourtzakis *et al.*⁽⁴⁵⁾ values of 38.9 cm²/m² for females and 55.4 cm²/m² for males. Reference ranges for healthy population based on appendicular lean mass as assessed by dual-energy X-ray absorptiometry of <5.45 kg/m² for females and <7.26 kg/m² for males.

patients. It shows the variation (Fig. 2(a)) for four males with identical amounts of skeletal muscle. Fig. 2(b) highlights skeletal muscle variation in three female patients with identical BMI.

Body composition, sarcopenia and dosing of chemotherapy

Body composition has emerged as an important predictor of anti-cancer drug efficacy and toxicity. Historically anti-cancer treatment is dosed using body surface area (BSA) which is calculated using the formula; $BSA = 0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$. This equation was published by du Bois and du Bois in 1916; however, the objective at this time was not to develop a formula to dose anticancer agents^(50,51). It was first introduced in oncology in order to derive a safe starting dose, and the use of BSA today as a means to individualise the dose of chemotherapy has been questioned⁽⁴²⁾. There is growing evidence that this approach is invalid⁽⁵²⁾ as there can be a 4–10-fold variation in drug clearance with medications like chemotherapy which have a narrow therapeutic index.

Many cytotoxic drugs are largely metabolised and excreted by the liver and kidney and BSA is not a good indicator of this function⁽⁵²⁾. Renal function, if based on serum creatinine concentration, may be overestimated in sarcopenic patients which may result in overdosing of renally excreted drugs, such as carboplatin⁽⁵³⁾. There is growing literature to suggest that lean body mass or fat

free mass (FFM), which is mainly composed of skeletal muscle and metabolic tissues such as liver and kidney⁽⁵⁴⁾, may be a better basis for normalising drug dosages in cancer patients, especially of hydrophilic drugs^(55,56). Likewise, increased adipose tissue may increase volume of distribution for highly lipophilic drugs prolonging their elimination half-lives.

The reason for the increased toxicity may be as a result of inappropriate dosing of chemotherapy drugs based on BSA, which has a weak correlation to whole body FFM. Prado *et al.*⁽³⁸⁾ reported that individual variation in FFM could account for up to three times variation in effective volume of distribution for chemotherapy administered per unit BSA in sarcopenic obese patients with solid tumours of the respiratory and gastrointestinal tracts. Thus, administering the same dose of chemotherapy drug in a patient with low FFM compared with a patient with normal FFM would increase the risk of chemotherapy toxicity⁽³⁸⁾.

The discrepancy between BSA and body composition has recently been investigated by Stobäus and co-workers⁽⁵⁷⁾ in a cross-sectional study of 630 cancer patients. They reported a significant discrepancy between BSA and body composition with more than 30% of patients differing considerably from the established mean of their respective BSA category⁽⁵⁷⁾. This implies that using the BSA in these patients under and over estimates body composition, which in theory leads to an over and under dose of chemotherapy. The extent of lean tissue loss in cancer patients varies from individual to individual and by basing chemotherapy dose on

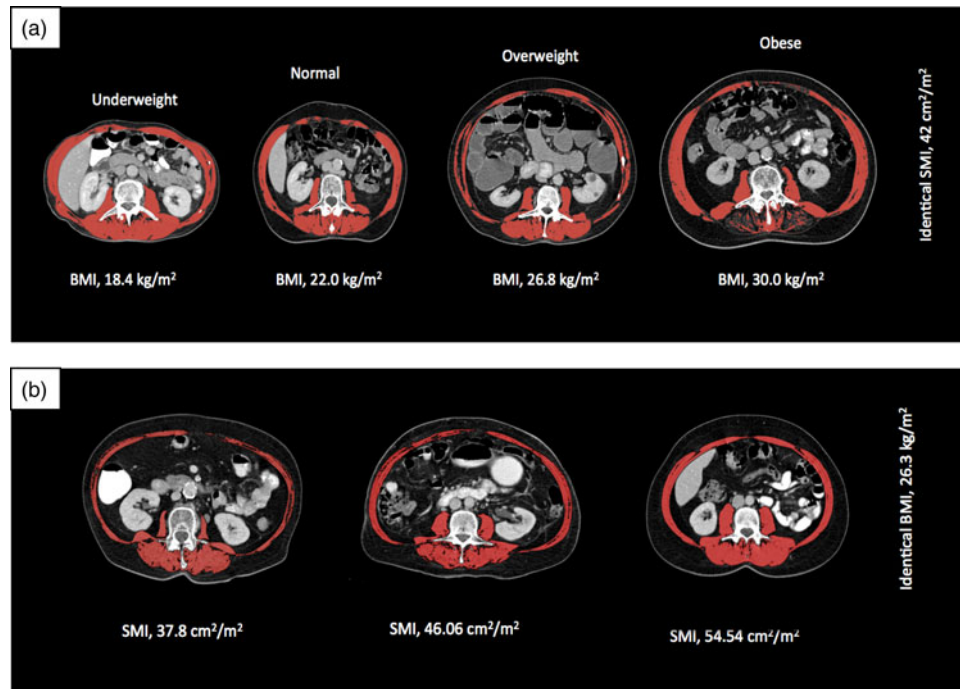


Fig. 2. (Colour online) (a, b) CT scans at lumbar vertebrae 3. Fig. 2(a) shows four male sarcopenic patients with identical skeletal muscle index (SMI) ranging across different BMI categories. Fig. 2(b) shows three female patients with identical BMI but varying SMI. Muscle depicted in red in all images.

BSA the patient may experience increased toxicity particularly with hydrophilic drugs.

Impact of sarcopenia on tolerance to cytotoxic chemotherapy

Variability in body composition of cancer patients may be a source of disparities in the metabolism of cytotoxic agents. Identification of those with sarcopenia is important because sarcopenia is associated with elevated toxicity to chemotherapy^(38,58–62). There is mounting evidence that sarcopenia increases the risk of toxicity to many drugs including Epirubicin⁽⁵⁸⁾, Capecitabine⁽⁶³⁾, Sunitinib⁽⁵⁹⁾, Sorafenib^(60,61), 5-FU and leucovorin⁽⁶²⁾. Table 3 summarises the available evidence for sarcopenia and dose-limiting toxicity in a variety of cancers and different chemotherapy drugs. Future clinical trials investigating dose reductions in patients with sarcopenia and dose-escalating studies based on pre-treatment body composition assessment have the potential to alter cancer treatment paradigms⁽⁶⁴⁾.

In addition to the argument that pharmacokinetic parameters can explain the higher risk of toxicity in sarcopenic patients it is also important to note that sarcopenic patients are excessively fragile and highly susceptible to acute medical events that exacerbate chemotherapy-related toxicity⁽⁶⁵⁾. Mechanisms outside the pharmacokinetic hypothesis linking sarcopenia to toxicity include metabolic alterations found in cancer or the role of systemic inflammation. The latter has been shown to decrease liver cytochrome activities and drug clearance and may modify drug exposure⁽⁶⁶⁾.

Inflammation can also increase the deposition of fat intramuscularly which then leads to reduced muscle density. Skeletal muscle density is assessed by analysing pixel values on CT images with lower density reflecting fatty muscle infiltration⁽⁶⁷⁾. This adds a qualitative dimension to the measurement of body composition.

In more recent years, the importance of muscle density has come to the forefront with much recent research highlighting its importance in progression-free survival, treatment response and overall survival. Higher skeletal muscle density has been associated with improved survival in renal cell carcinoma⁽³⁸⁾, melanoma⁽⁶⁸⁾ and in a number of others solid tumours⁽⁴²⁾. Skeletal muscle density could potentially be a more accurate measure of muscle function and therefore precede the development of sarcopenia. Low skeletal muscle density may be reflective of patients with a lower performance status.

Sarcopenia and survival

It has been reported that sarcopenia is independently prognostic of lower survival in obese patients with solid tumours of the lung and gastrointestinal tract. Prado *et al.*⁽³⁸⁾ reported that patients suffering from sarcopenic obesity had a shorter survival. The median survival was reduced in sarcopenic obese patients to 11.3 (95% CI 7.4, 15.2) months compared with 21.6 (95% CI 16.9, 26.3) months in non sarcopenic obese patients ($P < 0.0001$)⁽³⁸⁾. Sarcopenia has also been identified as a predictor of overall survival after cytoreductive nephrectomy for metastatic renal cell carcinoma, following pancreatic

Table 3. Summary of studies in various cancers showing toxicity in a variety of chemotherapy drugs according to sarcopenic status

Reference	Cancer type	<i>n</i>	Chemotherapy drug	% Sarcopenic exhibiting toxicity	% Non-sarcopenic exhibiting toxicity	<i>P</i> value
Prado <i>et al.</i> ⁽⁶²⁾	Stage II/III colon cancer	62	5-FU	93	52	0.001
Prado <i>et al.</i> ⁽⁶³⁾	Metastatic breast cancer	55	Capecitabine	50	20	0.039
Prado <i>et al.</i> ⁽⁵⁸⁾	Stage II/III breast cancer	24	Adjuvant 5-FU, Epirubicin, cyclophosphamide	55	19	0.03
Antoun <i>et al.</i> ⁽⁶⁰⁾	Metastatic renal cell carcinoma	55	Sorafenib	41	13	0.04
Mir <i>et al.</i> ⁽⁶¹⁾	Hepatocellular carcinoma	40	Sorafenib	82	31	0.005
Huillard <i>et al.</i> ⁽¹⁰⁶⁾	Renal cell carcinoma	61	Sunitinib	50	19.5	0.01
Massicotte <i>et al.</i> ⁽¹⁰⁷⁾	Advanced medullary thyroid cancer	33	Vandetanib	83	18	0.001
Cushen <i>et al.</i> ⁽⁵⁹⁾	Metastatic renal cell carcinoma	55	Sunitinib	77.7	70	NS
Barret <i>et al.</i> ⁽¹⁰⁸⁾	Metastatic colorectal cancer	51	1. Fluoropyrimidine (FP) + oxaliplatin 2. FP + irinotecan 3. FP alone 4. Irinotecan without FP	33.3	13.3	NS
Tan <i>et al.</i> ⁽¹⁰⁹⁾	Oesophago-gastric cancer	89	Cisplatin 80 mg/m ² , 5-FU 1000 mg/m ² Epirubicin 50 mg/m ² Cisplatin 60 mg/m ² Capecitabine 625 mg/m ²	54.5	28.8	0.015
Moryoussef <i>et al.</i> ⁽¹¹¹⁾	Gastrointestinal stromal tumours	31	Imatinib	100	73.7	NS

NS, non-significant; 5-FU, 5-fluorouracil; FP, fluoropyrimidine.

surgery and following curative resection of colorectal cancer^(37,60,69).

Martin *et al.*⁽⁴²⁾ showed similar results. This is a study with a larger sample size of cancer patients (*n* 1473). The most striking feature of this analysis is the shorter overall survival in patients with weight loss, sarcopenia and low muscle density 8.4 months (95 % CI 6.5, 10.3) compared with an overall survival of 28.4 months (95 % CI 24.2, 32.6, *P* < 0.001) in other patients regardless of body weight⁽⁴²⁾.

Quality of life

Cancer-associated malnutrition and CC have also been shown to have profound negative effects on patient's performance status, psychological well-being and overall quality of life (QoL)^(7,32,35,70). QoL for cancer patients is a subjective multidimensional construct that represents the patients psychosocial well-being, functional status, health perceptions and disease and treatment related symptoms^(71,72).

Due to the advances in oncological practice, which have resulted in improved morbidity and mortality rates for patients in recent years^(73,74), the relationship between nutritional status and QoL is becoming an important issue in oncology and almost all newly diagnosed cancer patients believe that nutrition has a role to play in their anticancer therapeutic strategy⁽⁷⁵⁾. Recent work has suggested that the complex interplay between metabolic disruption and pro-inflammatory cytokines in CC often leads to physical, biochemical and nutritional deterioration which subsequently leads to poor QoL⁽⁷⁶⁻⁷⁸⁾. A recent systematic

review reported a negative correlation between QoL and weight loss in 23/27 studies of patients with CC⁽⁷⁹⁾. Weight loss has been associated with poor QoL in head and neck cancer patients as well as in a large cohort of 907 mixed cancer patients⁽⁸⁰⁾. It is not surprising that weight loss has a negative impact on QoL, considering loss of muscle mass (sarcopenia) is a major cause of fatigue^(81,82) and weight loss is associated with reduced functional ability⁽⁷⁸⁾. Nutrition-related symptoms associated with chemotherapy such as nausea, vomiting, fatigue and constipation negatively impact the patients' wellbeing, thus reducing their QoL^(83,84). Appetite loss and fatigue, could be a cause or a consequence of malnutrition in cancer patients and lead to subsequent deterioration in global health status and functional scales, which might result in dose-limiting toxicities or suspension of chemotherapy treatment, and ultimately increased morbidity and mortality^(7,64,85,86).

Nutritional care of cancer patients

Unfortunately cachexia has perhaps suffered more from selective neglect and therapeutic nihilism than any other symptom requiring palliative care⁽⁸⁷⁾. While there are some new promising drugs undergoing phase III trials to treat CC at present these are as yet unavailable outside the research setting. There is currently no consensus on the optimal treatment for CC, yet there is an urgency for improving management. Several trials have examined single therapies for CC, including oral nutritional supplements, exercise or anti-inflammatory drugs; however, the results have been disappointing.

The fundamental difference between the weight loss observed in CC and that seen in simple starvation is the lack of reversibility with feeding alone. This seems to be caused by metabolic changes produced by the tumour, which have a profound effect on the prognosis of the disease, the symptoms experienced by patients, and ultimately their survival. Therefore, attempts to modify the metabolic response to cancer have the potential to improve both quality and length of life.

For dietitians, traditionally, body weight and BMI have been used as outcome measures, but these measures do not reflect the body composition changes that may occur during chronic diseases such as cancer. Weight loss alone does not identify the full effect of cachexia on physical function⁽⁷⁸⁾. It is the loss of FFM that is responsible for the reduced functional status, increased mortality and other negative outcomes associated with malnutrition. Body fat is easier to gain than FFM, so studies that show improved body weight may not translate into reductions in morbidity or improvements in functional status. To improve functional ability and hence QoL patients need not only to become weight stable but regain the lean tissue lost in the cachectic process.

Oral nutritional supplements

Unfortunately for those with established cachexia a meta-analysis of thirteen randomised controlled trials have concluded that weight, body composition and functional outcomes fail to improve with oral nutritional supplements alone⁽⁸⁸⁾. The clinical characteristic of cachexia is that it cannot be successfully treated with nutrition alone as there is partial block to the accretion of lean tissue in cancer patients. The use of anti-inflammatory agents (either drug agents or nutritional agents such as EPA) have therefore been advocated in the multi-pronged approach to care^(89,90).

Physical activity

Efforts should be made to encourage physical exercise (within the capacities of the patient) as a means of preserving and restoring muscle mass and to reduce systemic inflammation⁽⁷⁷⁾. The optimum means of achieving this is not yet clear but is the subject of major ongoing studies. Studies targeting cachectic patients have demonstrated that even in advanced disease peripheral muscle has the capacity to respond to exercise training⁽⁹¹⁾. Benefits of exercise include enhancing muscle protein synthesis, attenuating the catabolic effects of cachexia, and modulating levels of inflammation. However, there are challenges and limitations to cachectic patients engaging in exercise and many are not able or willing to undertake programmes.

Multimodal approaches

As multi-factors are responsible for the development of cachexia, it has recently been argued that optimal cachexia intervention should target all components; multimodal therapy for a multidimensional problem^(29,92,93). This multimodal approach would incorporate oral

nutritional supplements, exercise and anti-inflammatory medications and has been advocated in the prevention and treatment of CC. Underpinning this approach are meta-analyses suggesting that each of the interventions components, while not unequivocally associated with improved outcome, is more likely than not to be beneficial^(77,88,91,94,95).

The MENAC trial (a multimodal intervention of exercise, nutrition and anti-inflammatory medication plus standard care v. standard care alone) to prevent/attenuate cachexia will test the efficacy of a multi-dimensional approach during chemotherapy. Patients with advanced lung and inoperable pancreatic cancer about to start chemotherapy will be randomised to standard care or standard care plus oral nutritional supplements enriched with EPA, exercise and non-steroidal anti-inflammatory drugs. The primary objective is to determine whether the intervention achieves a difference in skeletal muscle index at 6 weeks.

Adequate protein alone only slows the loss of muscle mass. Exercise (both resistance and aerobic) in combination with adequate energy and protein intake is the key component of the prevention and management of sarcopenia. Preliminary results from the MENAC trials have shown that cancer patients can gain muscle mass by eating sufficient protein and engaging in 2 × 30 min walks per week and 3 × 20 min sessions of stair climbing in their own homes (resistance exercise (KC Fearon *et al.*, unpublished results).

Nutritional targets in cancer patients

We still know very little about the specific nutritional requirements of cancer patients. In general ranges are given; for example total daily energy expenditure in cancer patients is thought to range between 104.6 and 125.52 kJ/kg per d (25 and 30 kcal/kg per d)⁽⁹⁶⁾. The optimal nitrogen supply for cancer patients cannot be determined at present and current recommendations are based on expert opinion and range between a minimum of 1 g/kg per d and a target supply of 1.2–2 g/kg per d^(96–99). As we have argued, in another article on this subject⁽¹⁰⁰⁾ lean body mass drives protein requirements, and current recommended ranges for energy and protein do not take into account body composition and the likely important role that varying degrees of wasting or obesity (or both sarcopenic obesity) have on requirements^(100,101). Therefore targeted energy and protein recommendations should be used, so that protein intake is targeted to protect muscle mass and energy recommendations are calculated according to the overweight or obesity status⁽¹⁰⁰⁾. For those patients who are obese (between 17 and 19% of cancer patients) there are no specific guidelines as to the energy intake or the target body weight. It is unclear whether cancer patients experiencing obesity related morbidity benefit from maintenance of their heavy body weight or whether some (limited) degree of weight loss could in some way be desirable. However, separate from energy considerations it is reasonable to evaluate protein intake and increase it with the purpose of preventing erosion of lean body mass⁽⁴¹⁾.

Conclusions

Levels of malnutrition in 2015 are similar to those reported >30 years ago, but, today <7% of cancer patients have obvious malnutrition (BMI < 18.5 kg/m²). The majority look normal and 40–60% are overweight or obese. However, cachexia and sarcopenia are highly prevalent across all BMI categories with approximately one-third of obese cancer patients meeting the criteria for cachexia and 17–19% meeting criteria for sarcopenia. Cachexia and sarcopenia impact significantly on QoL, tolerance to chemotherapy and ultimately, survival.

Nutrition screening should be mandated in oncology but it is unclear what tool should be used. Further research is necessary to identify practical screening and assessment tools in oncology. At present not all cancer patients can avail of one-to-one dietetic care and all too often they are referred too late in the course of their disease/cachexia for a meaningful benefit to be achieved. In an ideal world, nutrition care should begin in parallel with medical care with weight stabilisation as an immediate priority, bearing in mind that this may not be achievable with nutrition alone and anti-inflammatory agents along with physical activity are critical in the multimodal approach. Irrespective of BMI protein intake is of fundamental importance to slow loss of lean body mass along with physical activity.

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Conflict of Interest

None.

Authorship

A. M. R. reviewed the literature and wrote the manuscript. L. D., D. G. P., S. C. and C. P. contributed text, tables and figures.

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