Proceedings of the Nutrition Society (2016), **75**, 188–198 doi:10.1017/S0029665115004279
 First published online 8 January 2016

The Nutrition Society Irish Section Meeting was held at the University College Cork, Cork on 16–19 June 2015

Conference on 'Nutrition at key life stages: new findings, new approaches' Symposium 4: Clinical nutrition: gold standards and practical demonstrations

Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact

C. M. Prado[1]*, S. J. Cushen[2], C. E. Orsso[1] and A. M. Ryan[2]
[1]*Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada*
[2]*School of Food and Nutritional Sciences, University College Cork, Cork, Republic of Ireland*

Our understanding of body composition (BC) variability in contemporary populations has significantly increased with the use of imaging techniques. Abnormal BC such as sarcopenia (low muscle mass) and obesity (excess adipose tissue) are predictors of poorer prognosis in a variety of conditions or clinical situations. As a catabolic illness, a defining feature of cancer is muscle loss. Although the conceptual model of wasting in cancer is typically conceived as involuntary weight loss leading to low body weight, recent studies have shown that both sarcopenia and cachexia can be present with obesity. The combination of low muscle and high adipose tissue (sarcopenic obesity) is an emerging abnormal BC phenotype prevalent across the body weight, and hence BMI spectra. Sarcopenia and sarcopenic obesity in cancer are in most instances occult conditions, which have been independently associated with higher incidence of chemotherapy toxicity, shorter time to tumour progression, poorer outcomes of surgery, physical impairment and shorter survival. Although the mechanisms are yet to be fully understood, the associations with poorer clinical outcomes emphasise the value of nutritional assessment as well as the need to develop appropriate interventions to countermeasure abnormal BC. Sarcopenia and sarcopenic obesity create diverse nutritional requirements, highlighting the compelling need for a more comprehensive and differentiated understanding of energy and protein requirements in this heterogeneous population.

Sarcopenia: Obesity: Sarcopenic obesity: Body composition: Nutritional assessment: Cancer: Nutritional status: Muscle: Lean body mass: Lean soft tissue

Body composition (BC) is a science that explores nutritional status in view of the different contributions of lean *v.* adipose tissue and its impact on health. The fast growing evidence of the importance of BC assessment may be attributed to the development of new *in vivo* technology and the resulting identification of abnormal BC phenotypes that can, in turn, negatively impact prognosis in any population. Here, we will briefly discuss recent advances in BC assessment, focusing on the prevalence and significance of these abnormal phenotypes in patients with cancer. Additionally, we will contextualise abnormal BC in view of the need for targeted nutrition interventions. Although the focus of this paper is oncology patients, we argue that issues hereby discussed are broadly relevant to other populations that, like cancer, have chronic diseases characterised by older age and inflammation and where concurrently obesity also occurs. These include, but are not limited to chronic obstructive pulmonary disease[1,2], insulin resistance/type II diabetes[3], cirrhosis[4,5], rheumatoid arthritis[6] and congestive heart failure[7].

Variability in body composition: a new face of an old problem

When one is asked to imagine how abnormal BC looks like in cancer, the idea of a cachectic looking, extremely

Abbreviations: BC, body composition; CT, computerised tomography; DLT, dose limiting toxicity; HR, hazard ratio.
***Corresponding author:** C. M. Prado, email carla.prado@ualberta.ca

emaciated person would likely be conceived by most people. As a public person, Steve Jobs' weight loss towards the end of his cancer disease trajectory was a classic example of how terminal illness is pictured. Weight loss (and muscle loss) is an important component of cancer, particularly advanced cancer and is observed as part of the conceptual model of cancer progression. This trajectory is characterised by involuntary weight loss that increases exponentially in incurable cancers with a notable acceleration in the last few months prior to death[8], a process also known as cancer cachexia.

Cancer cachexia can nonetheless manifest without the concurrent phenotype of emaciation. Medical oncologists nowadays face a new issue as 40–60 % of their patients present with excess body weight (overweight and obesity) at the time of cancer diagnosis[9]. Nonetheless, obesity does not preclude the presence of cancer cachexia and can indeed mask its appearance[10,11], a concept that has been changing paradigms in oncology research and practice. This new face of an old problem was first identified with the use of BC analysis, which looks beyond body weight and BMI and quantifies the different proportions of lean *v.* adipose tissue within a unit of body weight[11].

Computerised tomography: an opportunistic tool

Our understanding of BC research in cancer has substantially advanced due to the use of computerised tomography (CT) imaging scans. These images are readily available from electronic libraries of medical images taken for cancer diagnosis and prognostic follow up[12]. CT images can be retrieved for the additional purpose of BC analysis providing accurate and reliable information on muscle and different adipose tissue depots at the third lumbar vertebra cross-sectional area (Fig. 1), an area chosen as the best correlate to whole BC[13]. Using image specific analysis software (free-of-charge and paid): SliceOMatic, Tomovision; MeVislab, MeVis Medical Solutions AG; UltraVisual, UltraVisual Medical Systems Inc; ImageJ, National Institutes of Health; OsiriX, Pixmeo; analyzer Synapse Vincent 3D image analysis system, Fujifilm Medical, among others, tissue marking and automated computation can be accomplished. In addition to the availability of the image and the software for its analysis, trained personnel are also essential for accurate and reliable evaluation (note a radiologist is not required). These methods are highly reproducible, and have minimal additional cost. Importantly, automated software is currently being developed for rapid and practical imaging analysis[14]. Two brief videos containing an overview of the third lumbar vertebra CT analysis for BC using two different software are available at our UofANutrition YouTube Channel: https://www.youtube.com/watch?v=s1eJSK_CWco and https://www.youtube.com/watch?v=KJrsQ_dg5mM

The procedures for image analysis include finding the landmark of interest (third lumbar vertebra) and retrieving it for analysis (Digital Imaging and Communications in Medicine, DICOM format) by utilising the software of choice or a specific browser (e.g. iQ-VIEW, PACS, which are free DICOM viewers). Next, the image is uploaded in the software of choice for tissue analysis, where muscle and adipose tissue can be evaluated based on differences in pre-established measures of Hounsfield unit attenuations as follows: −29 to +150 for skeletal muscle[15], −190 to −30 for subcutaneous and intermuscular adipose tissue[15] and −150 to −50 for visceral adipose tissue[16].

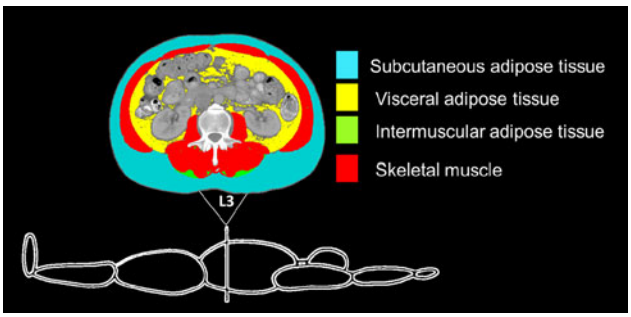

Fig. 1. (Colour online) Cross-sectional area at the third lumbar vertebra (L3) region analysed for body composition. Note muscle green area termed intermuscular adipose tissue represents both intra- and extra-myocellular lipid.

Defining divergent behaviour of muscle and adipose tissue in cancer

Using CT image analysis we, and others, were able to identify a great variability of BC in contemporary cancer patients[10,17–20], Fig. 2. As illustrated in this figure, patients with any given BMI can present with severe muscle depletion (sarcopenia) or with normal muscle mass. Alternatively, individuals may present with BMI of different (and extreme) categories, yet have exactly the same amount of muscle mass, Fig. 3.

As a catabolic illness, a defining feature of cancer is muscle loss. Low muscle mass, also termed sarcopenia is common in people with cancer regardless of stage (i.e. from curative to palliative). In fact, the overall prevalence of sarcopenia in the studies hereby reviewed is about 40–50 % in people with newly diagnosed cancer, considerably higher than about 15 % prevalence in healthy individuals of similar age (median 65 years)[21]. Since only about 10 % of cancer patients are clinically underweight[20], this widespread phenomenon of muscle depletion is independent of body weight or fat mass. Fig. 4 illustrates the widespread distribution of sarcopenia across the BMI spectrum using population cohort data of patients with colorectal cancer treated at a regional cancer centre in Alberta, Canada. Sarcopenia increased at all lower BMI strata, but was also substantially present at higher BMI. As discussed previously, sarcopenia can coexist with obesity (sarcopenic obesity), compounding health consequences for physical function and survival in cancer[11,22].

Sarcopenia is different from cancer-associated cachexia. In cancer cachexia diagnoses, sarcopenia needs to

https://doi.org/10.1017/S0029665115004279 Published online by Cambridge University Press

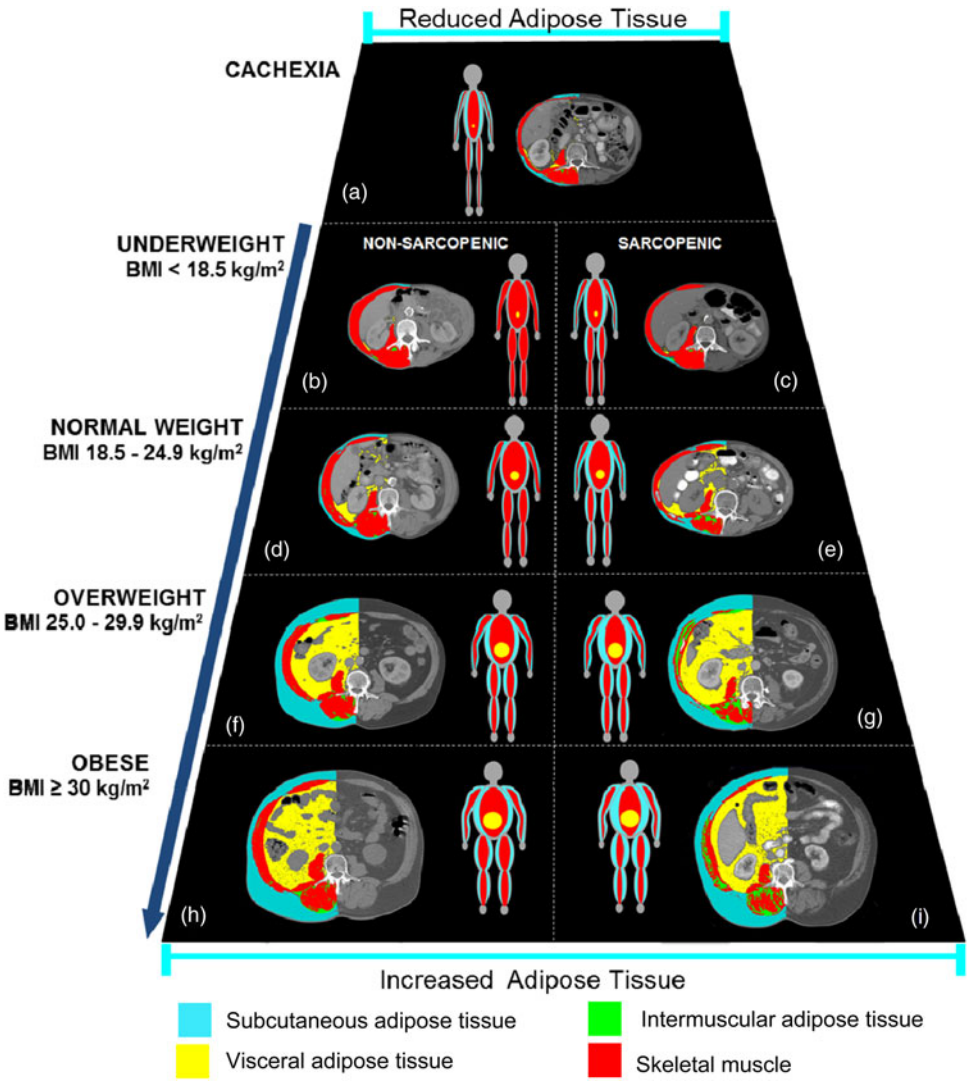

Fig. 2. (Colour online) Trapezium model of body composition in cancer illustrating the variability in body composition in patients with identical BMI. Male patients with lung or colorectal cancer. Muscle cross-sectional area (cm^2): (a) = 28·6, (b) = 51·5, (c) = 40·3, (d) = 52·8, (e) = 35·3, (f) = 51·3, (g) = 33·7, (h) = 70·7, (i) = 50·1 and for total adipose tissue cross-sectional area (cm^2/m^2): (a) = 2·7, (b) = 5·0, (c) = 3·5, (d) = 27·9, (e) = 27·9, (f) = 146·8, (g) = 161·2, (h) = 175·3, (i) = 218·3. Cancer patients of the same height, weight and hence BMI category can present with very distinct amount of skeletal muscle mass. Non-sarcopenic patients are depicted on the left side, while sarcopenic patients are shown on the right side. This figure also illustrates how overweight and obese cancer patients can present with severe muscle depletion, highlighting how sarcopenic obesity is a potential hidden condition to health care professionals.

be defined in conjunction with weight loss[23]. The understanding of abnormal BC in cancer has also impacted the definition of cancer cachexia. The international consensus group definition now recognises cancer cachexia as a:

> 'Multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (*with or without fat mass*) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment'(emphasis added)[23].

Therefore, sarcopenia, sarcopenic obesity and cancer cachexia can manifest at any given BMI and body weight, which may be undetected by use of these anthropometric tools alone, hence the importance of additional assessment using BC techniques. The most commonly used cutpoints to define sarcopenia have been developed in obese patients with lung or gastrointestinal cancer using optimal stratification analysis. The gender-specific values below which patients are categorised as sarcopenic are 52·4 cm^2/m^2 for men and 38·5 cm^2/m^2 for women[10]. These cutpoints have been used in many different cohorts of patients and clinical populations, consistently demonstrating an association with patient prognostication[2,4,24]. In the optimal stratification analysis approach, patients are stratified from least to most muscular and a gender-specific threshold for increased risk of a clinical outcome (in this case

https://doi.org/10.1017/S0029665115004279 Published online by Cambridge University Press

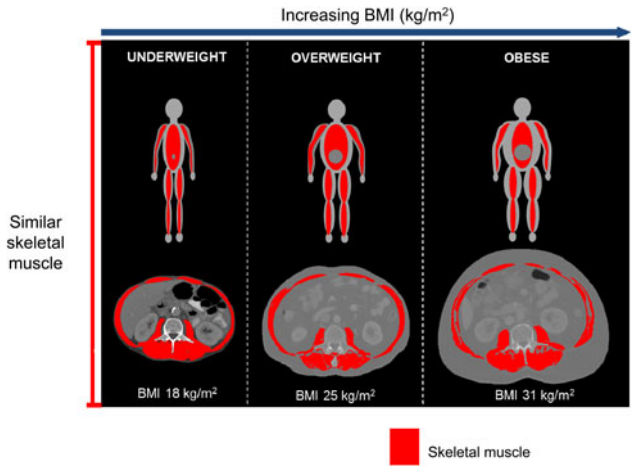

Fig. 3. (Colour online) Illustration of three male patients of different BMI presenting with similar amount of muscle cross-sectional area (skeletal muscle index = about 42·4 cm^2/m^2).

survival) identified. Using the same approach, Martin *et al.*[20] have more recently published BMI-specific cutpoints for sarcopenia diagnosis (underweight and normal weight: <43 cm^2/m^2 for men and <41 cm^2/m^2 for women; overweight and obese: <53 cm^2/m^2 for men and <41 cm^2/m^2 for women) Since these cutpoints are BMI-specific, they provide a better indication of the prevalence of sarcopenia in non-obese individuals (compared with Prado *et al.*[10] defined for obese individuals only). It is important to note that the cutpoints mentioned in this paragraph were developed in a North American population, which may limit its use in different ethnicities[25].

Although similar to the Prado *et al.* cutpoints[10], the ones proposed to diagnose sarcopenia by the cachexia consensus group[23] are not the same. The consensus group cutpoints[23] are the conversion from kg/m^2 to cm^2/m^2 of Baumgartner's dual-energy X-ray absorptiometry-assessed sarcopenia cutpoints defined for elderly individuals: <7·26 kg/m^2 for men and <5·45 kg/m^2 for women[26]. These are converted to <55 cm^2/m^2 for men and <39 cm^2/m^2 for women, as reported in Fearon *et al.*[23] using a regression equation previously published[27]. In addition to dual-energy X-ray absorptiometry and CT cutpoints, the international consensus group has also suggested cutpoints developed using bioelectrical impedance analysis, and for surrogate measurements of BC using the mid upper-arm muscle area[23]. Sarcopenic obesity has been most commonly identified using a combination of any sarcopenia cutpoints defined earlier in conjunction with BMI cutpoints (provided very muscular individuals can be identified by the CT image and are not incorrectly classified as obese)[10,20,24,28,29].

Implications of abnormal body composition

Despite the variability of available BC assessment tools and cutpoints, sarcopenia and sarcopenic obesity have been consistently associated as predictors of unfavourable outcomes in oncology patients. Selected examples will be discussed in this section.

Treatment toxicity

One of the very first research questions regarding the potential impact of abnormal BC on cancer prognosis was related to the issue of individualising chemotherapy treatment[30]. Most chemotherapy drugs are administered based on body surface area, which is a calculation that only accounts for height and weight. Therefore, individuals with identical height, weight and hence body surface area (as presented in each BMI category in Fig. 2) would consequently be receiving exactly the same amount of chemotherapy drug[31]. Such practice ignores the large individual variability in muscle mass and hence lean tissue compartment, where pharmacokinetics (drug metabolism) occurs[32–35]. This concept has been extensively reviewed previously and we refer the reader to other articles for a more detailed discussion[31,32]. Based on this concept, the original hypothesis was that a sarcopenic person would receive a large amount of drug for a small lean tissue compartment; increasing this person's risk for developing dose limiting toxicity (DLT)[31]. DLT is an unfavourable and undesirable outcome of chemotherapy, which leads to treatment termination, discontinuation, hospitalisation or death. The original hypothesis was investigated using several different studies with different chemotherapy drugs and in individuals with different cancer types[31,36]. In a recently published paper by Anandavadivelan *et al.*[28], DLT was investigated in seventy-two patients receiving neo-adjuvant therapy for oesophageal cancer. Unfortunately, absolute values of muscle mass were not stratified by gender when comparing those presenting *v.* not presenting with DLT. Nonetheless, using a gender-specific definition of sarcopenia, they showed that sarcopenic obese presented with higher DLT compared with their non-sarcopenic obese counterparts (OR 5·54; (95% CI 1·12, 27·44).

Collectively, these studies show that sarcopenia (withor without concurrent obesity) is an independent predictor of severe toxicity, affecting cancer treatment and its outcomes. The same hypothesis holds true for studies on targeted chemotherapy agents[19,37] (Fig. 5) and for hydrophobic agents, where both muscle and adipose tissue may play a role in predicting toxicity[34].

Therefore, there is enough evidence to suggest these patients behave as if they were overdosed. Future dose-escalating studies personalised by BC will illustrate the value of personalising chemotherapy treatment[38] using BC, and the respective impact on decreasing the risk of DLT consequently increasing the number of planned chemotherapy cycles in sarcopenic patients.

In addition to cancer being a catabolic condition leading to muscle loss, cancer-treatment itself can impact BC. Chemotherapy treatment can decrease muscle mass by 4·6 cm^2[39] which is about 0·8 kg at the whole body

https://doi.org/10.1017/S0029665115004279 Published online by Cambridge University Press

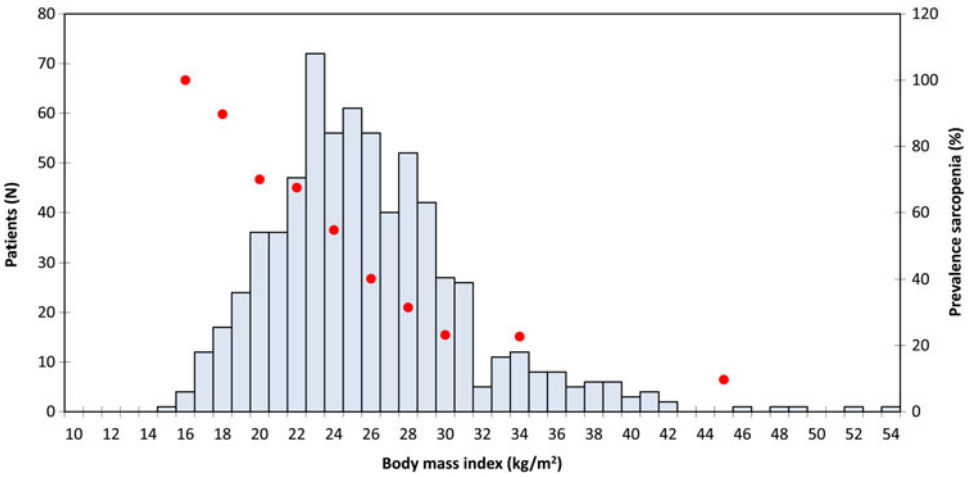

Fig. 4. (Colour online) Prevalence of sarcopenia (dots) in patients with stages I–IV colorectal cancer, *n* 684. Consecutive patients referred to a medical oncology service in a regional cancer centre in Alberta, Canada. Considering BMI categories, sarcopenia was prevalent in 74 % of underweight patients, 42 % of normal weight, 39 % overweight, 24·4 % obese (all classes). Among the obese individuals, sarcopenia was present in 28·8 % of class I, 18·2 % class II and 14·3 % of class III obese patients. Sarcopenia defined using BMI-specific cutpoints[20]. Data courtesy of Dr Vickie Baracos, University of Alberta.

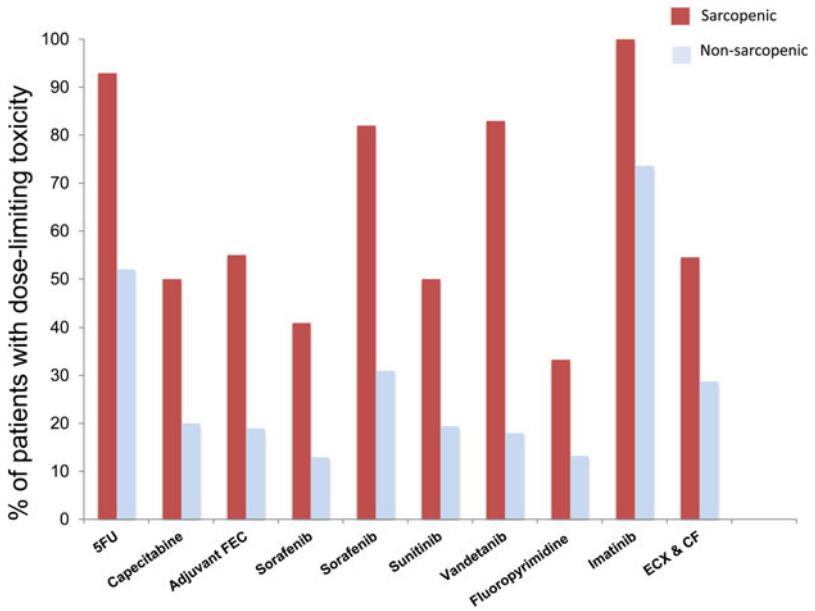

Fig. 5. (Colour online) Summary of individual study studies relating sarcopenia with dose-limiting toxicity; several antineoplastic therapies and cancer types represented. 5FU (5-fluorouracil), colorectal cancer[30]; Capecitabine, breast cancer[42]; Adjuvant FEC (%-fluorouracil, epirubicin, cyclophosphamide), breast cancer[33]; Sorafenib, renal cell cancer[37]; Sorafenib, renal cell cancer[77]; Sunitinib, renal cell cancer[78]; Vandetabin, advanced medullary thyroid carcinoma[79]; Fluoropyrimidine, colorectal cancer[80]; Imatinib, gastrointestinal stromal tumour (anaemia and fatigue)[81]; ECX and CF (Epirubicin, Cisplatin, Capecitabine) and CF (Cisplatin and 5-Fluorouracil), oesophagogastric cancer[82].

level using the regression equation in Shen *et al.*[13]: whole body muscle mass = 0·166 × (CT measured skeletal muscle (cm^2)) + 2·142, but using only the slope since the line has a non-zero intercept.

Survival

We have pioneered the findings of sarcopenic-obesity as an independent predictor of physical impairment (47 *v.* 26 % in non-sarcopenic obese, $P = 0{\cdot}005$) and survival

https://doi.org/10.1017/S0029665115004279 Published online by Cambridge University Press

in a population cohort of patients with lung or gastrointestinal cancer[10]. Survival was shorter for sarcopenic obese patients compared with non-sarcopenic obese (hazard ratio (HR) 4·2; 95% CI 2·4, 7·2)[10]. We have also reported similar findings in sarcopenic patients with hepatocellular carcinoma[40], and lung or colorectal cancer[41] and that sarcopenia is an independent predictor of shorter time to tumour progression[42].

More recently, 2-year overall survival was lower in sarcopenic patients with diffuse large B-cell lymphoma, compared with the non-sarcopenic counterparts (46 *v.* 84 %, respectively) with a HR 3·22; 95 % CI 1·73, 5·98[43]. Miyamoto *et al.*[44] investigated the prognostic effect of sarcopenia in patients with stages I–III colorectal cancer undergoing curative resection surgery. Sarcopenia was an independent predictor of shorter recurrence-free survival (HR 2·18; 95 % CI 1·20, 3·94) and overall survival (HR 2·27; 95 % CI 1·15, 4·5). In a separate study, the authors also showed that muscle loss was similarly associated with poor prognosis in patients with unresectable colorectal cancer[45]. Muscle loss >5 % after chemotherapy treatment was associated with shorter overall survival (HR 2·08; 95 % CI 1·19, 3·62). Sarcopenia was also a significant predictor of overall survival in patients with urothelial cancer (HR 3·36; 95 % CI 1·9, 6·1)[46], hepatocellular carcinoma (HR 3·2; 95 % CI 1·28, 8·0)[47], and metastatic renal cell carcinoma (HR 2·13; 95 % CI 1·15, 3·92)[48]. Additionally, several other recent studies have investigated the prognostic impact of sarcopenia on survival on cancer [39,49–51]; the growing body of literature on the topic is impressive.

Broader implications

Much broader implications can be attributed to abnormalities in BC. Sarcopenia has been associated with the development of postoperative infections, the need for inpatient rehabilitative care, incidence of hospitalisation and length of hospital stay as shown in Lieffers *et al.*[17] and Peng *et al.*[52]. More recently, Ida *et al.*[53] reported a higher incidence of postoperative respiratory complications among sarcopenic patients compared with non-sarcopenic (15·5 *v.* 6·5 %, respectively, $P = 0·01$) and showed sarcopenia (OR 5·82; $P = 0·0001$) was a risk factor for the occurrence of respiratory complication in patients with oesophageal cancer. In patients following pancreatectomy, sarcopenia was an independent predictor of major grade III complications, length of stay, intensive care unit admission, delayed gastric emptying, and infectious, gastrointestinal, pulmonary and cardiac complications[54]. Similar results were reported by van Vugt *et al.*[55] who demonstrated that sarcopenia was associated with severe postoperative complications in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal cancer.

Cancer therapy can also lead to abnormal BC. As an example, patients undergoing breast cancer therapy and androgen deprivation therapy for prostate cancer develop a pattern of fat gain with concurrent loss of lean mass (i.e. sarcopenic obesity)[56]. These patterns of change have been linked to decreased quality of life, decreased disease-free survival, increased risk of CVD, increase risk of insulin resistance/diabetes, reduced bone mass, increased risk of fractures at multiples sites and also, metabolic imbalances, consequences likely related to both sarcopenia and obesity[56–58]. Additionally, some drugs commonly used can also promote muscle loss such as corticosteroids, statins and tyrosine kinase inhibitors, as reviewed previously[36].

Impact of muscle radiodensity

Another metric associated with key health outcomes is muscle radiodensity. Prado *et al.* were the first to report an association between low muscle attenuation and sarcopenia in cancer patients[10]. Reduced muscle attenuation is reflective of intermuscular adipose tissue or poor 'quality' skeletal muscle. Aubrey *et al.*[59] introduced a radiation attenuation map of paraspinal/psoas muscles depicting the myoesteatosis phenomenon, a concept illustrated in Fig. 6. This concept highlights that skeletal muscle may contain areas of normal and reduced attenuation; and that these reduced attenuation areas are within radiodensity ranges of adipose tissue. Therefore the 'quality' of the muscle may be affected with individuals having less than half of muscle falling within normal muscle attenuation areas. Importantly, low muscle radiodensity is emerging as an important and in some cases stronger predictor of clinical outcomes (compared with muscle mass alone). In Sabel *et al.*[60] low (psoas) muscle radiodensity was associated with disease-free and distant disease-free survival ($P = 0·04$ and $P = 0·0002$, respectively). These results were supported by a Martin *et al.*[20] study, where low muscle attenuation was a powerful predictor of survival (HR 1·36, 95 % CI 1·2, 1·6), and more recently by Okumura *et al.*[50], who showed low muscle quality associated with poor overall (HR 2·5, $P < 0·001$) and recurrence free (HR 1·6; $P = 0·004$) survival.

The impact of abnormal body composition on nutritional therapy

All of the implications of sarcopenia and sarcopenic-obesity in cancer can be conceived as the potential clinical benefits of reversing these abnormalities by nutritional therapy. We now know cancer patients have anabolic potential[61]. Contrary to popular belief, sarcopenia in cancer is reversible even in people of older age, deconditioning, inflammation and concurrent comorbid conditions[62]. Evidence also shows that anabolic responsiveness is not suppressed by nutrition interventions[63–68]. In spite of this evidence, recent pharmacological studies on retention or gain of muscle mass in cancer have failed to provide (or account for) sufficient energy and protein to sustain muscle mass accretion[63,65]. While the importance of adequate nutrient intake is obvious, an important unanswered question relates to the optimal energy and protein intakes during cancer disease trajectory.

https://doi.org/10.1017/S0029665115004279 Published online by Cambridge University Press

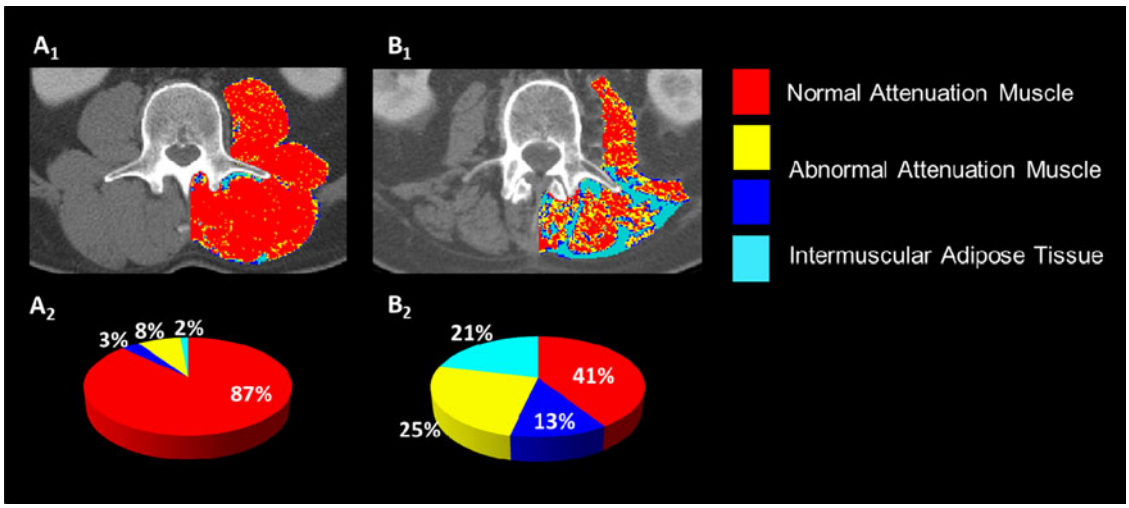

Fig. 6. (Colour online) Muscle radiodensity variability for psoas, erector spinae and quadratus lumborum at the third lumbar vertebra. A_1, B_1 represent contrast enhanced images of computerised tomography images analysed for body composition for two individual patients; A_2 and B_2 represent the pie chart of variability in muscle radiodensity attenuation showing the percentage total tissue area within the ranges of adipose tissue (light blue, −190 to −30 Hounsfield Units, HU), normal attenuation muscle (red, +30 to +150 HU) and abnormal (reduced) attenuation muscle in two ranges (dark blue, −29 to 0 HU; yellow, +1 to +29 HU). The patient on the right (B_1) presents with a significant amount of skeletal muscle lipid content and hence lower overall HU attenuation. This is indicative of muscle myosteatosis which more than 50 % of the tissue area following in HU range for the adipose tissue. Conversely, the patient on the left (A_1) has the majority of tissue area within normal muscle radiation attenuation values. This concept is presented in Aubrey *et al.*[59].

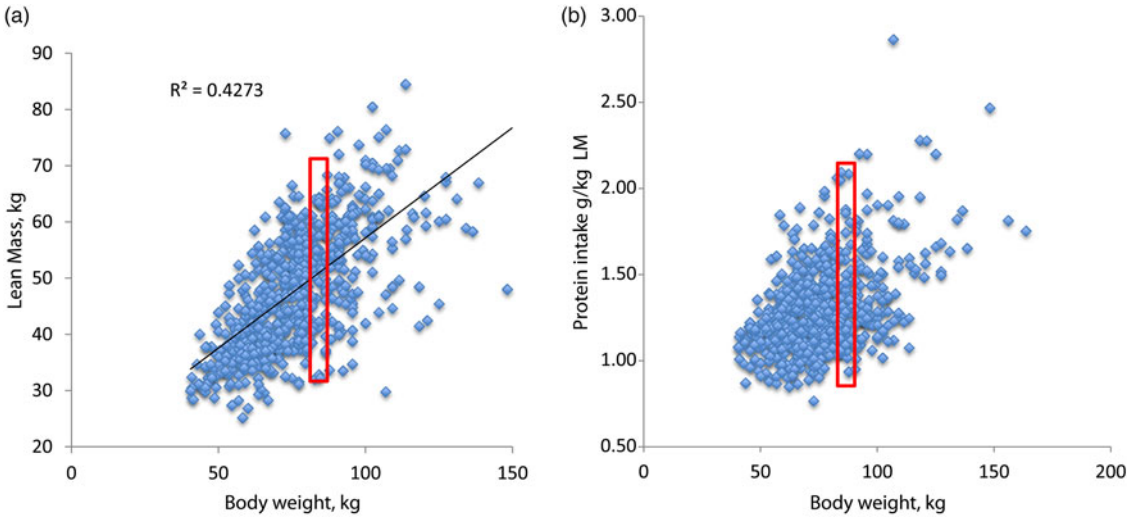

Fig. 7. (Colour online) (a) Correlation of lean mass (LM, which is primarily muscle mass) and body weight in patients (*n* 684) with colorectal cancer (stages I–IV cancer) receiving treatment at a regional cancer centre in Alberta, Canada and (b) variability in theoretical dose of protein per kg LM by body weight in the same cohort. The defect in defining a person by body weight: a person of 80 kg (highlighted in red box) can have anywhere between about 30 and 70 kg lean mass. This is a substantial difference. Example based on intake of 0·8 g protein/kg body weight/d, showing a wide range in dose of protein/kg of LM. In the highlighted example, people weighing 80 kg who are fed 0·8 g protein/kg/body weight would receive between 0·8 and 2·1 g protein/kg LM, depending on the amount of LM in their total BW. Data courtesy of Dr Vickie Baracos, University of Alberta.

Muscle loss in cancer is partially driven by increased muscle protein catabolism, when substrate availability (protein intake) is insufficient. Not only is a supply of protein essential, but an adequate dose and balance of calories and essential nutrients are required to support maintenance or gain of muscle. The optimal amounts of protein and calories are undefined for preventing or treating sarcopenia in people with cancer. Protein intake

https://doi.org/10.1017/S0029665115004279 Published online by Cambridge University Press

by cancer patients is variable (0·2–2·7 g/kg)[69] and many do not meet current dietary guidelines of 0·8 g/kg for healthy individuals[70] or 1·0–1·5 g/kg for those with cancer[71–73]. We previously reported that 35 % of cancer patients had protein intakes below 1·0 g/kg[74] and that protein intake correlated with muscle mass (r 0·4; P = 0·001) and lean mass (r 0·4; P = 0·003)[75].

Current protein and energy guidelines in cancer, and across a broad spectrum of other chronic conditions, recommend daily ranges of intake adjusted by body weight. This ignores the large variability of BC in contemporary population extensively discussed earlier and also shown in Fig. 7(a). As a theoretical example, patients who weigh the same and are provided protein at 0·8 g/kg body weight would receive anywhere between 0·8 and 2·1 g protein/kg lean mass, owing to differences in BC, Fig. 7(b). The proposition that lean mass drives protein requirements is widely accepted; thus adjusting dietary targets by BC is more appropriate. The same logic can be applied to energy recommendations, which estimate 25–35 kcal/kg per d for people with cancer[73] without considering BC. A sarcopenic obese patient thus would receive more calories than required, but less protein than needed[11], leading to gains in fat mass that are not associated with treatment success and longevity[10,76].

Current nutrition recommendations are inconsistent with findings of variable BC and do not meet the physiological needs of most cancer patients. At one end of the spectrum, underweight patients have elevated protein requirements due to their illness. They may receive adequate energy but inadequate amounts or quality of protein, placing them at risk for protein malnutrition and sarcopenia. In contrast, obese patients may have secondary pathologies related to their excess fat mass. They require tailored amounts and types of energy, targeted to prevent increases in fat mass and worsening of problems such as insulin resistance and lipid control. The obese patient may also have sarcopenia (sarcopenic obese), which would increase their protein needs. Thus, dietary prescriptions for energy and protein need to be disconnected. Their energy needs must relate to their obesity and other comorbidities, with protein intake targeted to protect muscle mass[11].

Conclusion

BC is variable within patients with identical body size. Sarcopenia and sarcopenic obesity are prevalent, can occur concurrently with cachexia and are prognostic for poorer quality of life, longer length of hospital stay, rehabilitation care, postoperative complication, survival, among others. Given the high and increasing prevalence of cancer and the high incidence of sarcopenia in people with cancer, sarcopenia and its attendant health risks and functional deficits are a significant problem potentially affecting hundreds of thousands of cancer patients.

The variability in BC in contemporary cancer population creates diverse nutritional requirements which have nonetheless been established as a range of intake, with no specific target for patients to achieve. Assuming that protein and energy feeding may be done by body weight ignores this variability in BC, promoting or enhancing the sarcopenic or sarcopenic obesity phenotype. Dietary guidelines for people with cancer are not optimal or evidence-based[11]. The need is compelling for a more comprehensive and differentiated understanding of energy and protein requirements in this heterogeneous population. Future research should integrate nutritional goals of energy retention and balance, for the development of guidelines and recommendations targeting individuals with different physiological needs to prevent or delay sarcopenia, and improve muscle mass while also optimising fat mass.

Acknowledgement

We thank Dr Vickie Baracos for kindly providing the data for the development of Figs. 4 and 7.

Financial Support

None.

Conflicts of Interest

None.

Authorship

C. M. P. was responsible for conception and draft of this review (presented at The Nutrition Society Irish Section Meeting, June, 2015); S. J. C., C. E. O. and R. M. O. are collaborators who contributed towards literature review and summary, the development of figures and online supplementary material, also providing scientific input in all content hereby presented. All authors reviewed and approved the manuscript prior to submission.

References

1. Schols AM (2015) Nutritional advances in patients with respiratory diseases. *Eur Respir Rev* **24**, 17–22.
2. Sheean PM, Peterson SJ, Gomez Perez S *et al.* (2014) The prevalence of sarcopenia in patients with respiratory failure classified as normally nourished using computed tomography and subjective global assessment. *JPEN J Parent Enteral Nutr* **38**, 873–879.
3. Staal-van den Brekel AJ, Schols AM & Dentener MA (1997) Metabolism in patients with small cell lung carcinoma compared with patients with non-small cell lung carcinoma and healthy controls. *Thorax* **52**, 338–341.
4. Montano-Loza AJ, Meza-Junco J, Prado CM *et al.* (2012) Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol* **10**, 166–173, 73e1.
5. Montano-Loza AJ, Angulo P, Meza-Junco J *et al.* (2015) Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. *J Cachexia, Sarcopenia Muscle* (epublication ahead of print version)

https://doi.org/10.1017/S0029665115004279 Published online by Cambridge University Press

6. Roubenoff R (2000) Sarcopenic obesity: does muscle loss cause fat gain? Lessons from rheumatoid arthritis and osteoarthritis. *Ann N Y Acad Sci* **904**, 553–557.
7. Wannamethee SG & Atkins JL (2015) Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. *Proc Nutr Soc* **74**, 405–412.
8. Baracos VE (2006) Cancer-associated cachexia and underlying biological mechanisms. *Annu Rev Nutr* **26**, 435–461.
9. Martin L, Senesse P, Gioulbasanis I *et al.* (2015) Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol* **33**, 90–99.
10. Prado CM, Lieffers JR, McCargar LJ *et al.* (2008) Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* **9**, 629–635.
11. Prado CM & Heymsfield SB (2014) Lean tissue imaging: a new era for nutritional assessment and intervention. *JPEN J Parent Enteral Nutr* **38**, 940–953.
12. Prado CM, Birdsell LA & Baracos VE (2009) The emerging role of computerized tomography in assessing cancer cachexia. *Curr Opin Support Palliat Care* **3**, 269–275.
13. Shen W, Punyanitya M, Wang Z *et al.* (2004) Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol* **97**, 2333–2338.
14. Chung H, Cobzas D, Lieffers JR *et al.* (2009) Muscle and adipose tissue segmentation in CT images. *Automated Segmentation of Muscle and Adipose Tissue on CT Images for Human Body Composition Analysis* 7261.
15. Mitsiopoulos N, Baumgartner RN, Heymsfield SB *et al.* (1998) Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol* **85**, 115–122.
16. Miller KD, Jones E, Yanovski JA *et al.* (1998) Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet* **351**, 871–875.
17. Lieffers JR, Bathe OF, Fassbender K *et al.* (2012) Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. *Br J Cancer* **107**, 931–936.
18. Baracos VE, Reiman T, Mourtzakis M *et al.* (2010) Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am J Clin Nutr* **91**, 1133S–1137S.
19. Cushen SJ, Power DG, Teo MY *et al.* (2014) Body composition by computed tomography as a predictor of toxicity in patients with renal cell carcinoma treated with sunitinib. *Am J Clin Oncol* (In the Press).
20. Martin L, Birdsell L, Macdonald N *et al.* (2013) Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* **31**, 1539–1547.
21. von Haehling S, Morley JE & Anker SD (2010) An overview of sarcopenia: facts and numbers on prevalence and clinical impact. *J Cachexia, Sarcopenia Muscle* **1**, 129–133.
22. Prado CM, Wells JC, Smith SR *et al.* (2012) Sarcopenic obesity: a critical appraisal of the current evidence. *Clin Nutr* **31**, 583–601.
23. Fearon K, Strasser F, Anker SD *et al.* (2011) Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* **12**, 489–495.
24. Tan BH, Birdsell LA & Martin L (2009) Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res* **15**, 6973–6979.
25. Silva AM, Shen W, Heo M *et al.* (2010) Ethnicity-related skeletal muscle differences across the lifespan. *Am J Hum Biol* **22**, 76–82.
26. Baumgartner RN, Koehler KM, Gallagher D *et al.* (1998) Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* **147**, 755–763.
27. Mourtzakis M, Prado CMM, Lieffers JR *et al.* (2008) A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* **33**, 997–1006.
28. Anandavadivelan P, Brismar TB, Nilsson M *et al.* (2015) Sarcopenic obesity: a probable risk factor for dose limiting toxicity during neo-adjuvant chemotherapy in oesophageal cancer patients. *Clin Nutr* (epublication ahead of print version).
29. Lodewick TM, van Nijnatten TJ, van Dam RM *et al.* (2015) Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases? *HPB* **17**, 438–446.
30. Prado CM, Baracos VE, McCargar LJ *et al.* (2007) Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin Cancer Res* **13**, 3264–3268.
31. Prado CM (2013) Body composition in chemotherapy: the promising role of CT scans. *Curr Opin Clin Nutr Metab Care* **16**, 525–533.
32. Prado CM, Maia YL, Ormsbee M *et al.* (2013) Assessment of nutritional status in cancer – the relationship between body composition and pharmacokinetics. *Anticancer Agents Med Chem* **13**, 1197–1203.
33. Prado CM, Lima IS, Baracos VE *et al.* (2011) An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity. *Cancer Chemother Pharmacol* **67**, 93–101.
34. Prado CM, Baracos VE, Xiao J *et al.* (2014) The association between body composition and toxicities from the combination of Doxil and trabectedin in patients with advanced relapsed ovarian cancer. *Appl Physiol Nutr Metab* **39**, 693–698.
35. Narjoz C, Cessot A, Thomas-Schoemann A *et al.* (2015) Role of the lean body mass and of pharmacogenetic variants on the pharmacokinetics and pharmacodynamics of sunitinib in cancer patients. *Invest New Drugs* **33**, 257–268.
36. Prado CM, Antoun S, Sawyer MB *et al.* (2011) Two faces of drug therapy in cancer: drug-related lean tissue loss and its adverse consequences to survival and toxicity. *Curr Opin Clin Nutr Metab Care* **14**, 250–254.
37. Antoun S, Birdsell L, Sawyer MB *et al.* (2010) Association of skeletal muscle wasting with treatment with sorafenib in patients with advanced renal cell carcinoma: results from a placebo-controlled study. *J Clin Oncol* **28**, 1054–1060.
38. Alberta Health Services. A Study Comparing Chemotherapy Dosing Based on Either Standard Body Surface Area or Lean Body Mass in Patients With Advanced Lung Cancer. *ClinicalTrialsgov [Internet] Bethesda (MD): National Library of Medicine (US)*
39. Stene GB, Helbostad JL, Amundsen T *et al.* (2015) Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. *Acta Oncol* **54**, 340–348.
40. Meza-Junco J, Montano-Loza AJ, Baracos VE *et al.* (2013) Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. *J Clin Gastroenterol* **47**, 861–870.
41. Prado CMM, Mourtzakis M, Baracos V *et al.* (2010) Overweight and obese patients with solid tumors may

https://doi.org/10.1017/S0029665115004279 Published online by Cambridge University Press

have sarcopenia, poor prognosis and early features of cachexia. *Int J Body Compos Res* **8**, 7–15.
42. Prado CM, Baracos VE, McCargar LJ *et al.* (2009) Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res* **15**, 2920–2926.
43. Lanic H, Kraut-Tauzia J, Modzelewski R *et al.* (2014) Sarcopenia is an independent prognostic factor in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Leuk Lymphoma* **55**, 817–823.
44. Miyamoto Y, Baba Y, Sakamoto Y *et al.* (2015) Sarcopenia is a negative prognostic factor after curative resection of colorectal cancer. *Ann Surg Oncol* **22**, 2663–2668.
45. Miyamoto Y, Baba Y, Sakamoto Y *et al.* (2015) Negative impact of skeletal muscle loss after systemic chemotherapy in patients with unresectable colorectal cancer. *PLoS ONE* **10**, e0129742.
46. Fukushima H, Yokoyama M, Nakanishi Y *et al.* (2015) Sarcopenia as a prognostic biomarker of advanced urothelial carcinoma. *PLoS ONE* **10**, e0115895.
47. Voron T, Tselikas L, Pietrasz D *et al.* (2014) Sarcopenia impacts on short- and long-term results of hepatectomy for hepatocellular carcinoma. *Ann Surg* **261**, 1173–1183.
48. Sharma P, Zargar-Shoshtari K, Caracciolo JT *et al.* (2015) Sarcopenia as a predictor of overall survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. *Urol Oncol* **33**, 339 e17–e23.
49. Reisinger KW, Bosmans JW, Uittenbogaart M *et al.* (2015) Loss of skeletal muscle mass during neoadjuvant chemoradiotherapy predicts postoperative mortality in esophageal cancer surgery. *Ann Surg Oncol* **22**, 4445–4452.
50. Okumura S, Kaido T, Hamaguchi Y *et al.* (2015) Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer. *Surgery* **157**, 1088–1098.
51. Reisinger KW, van Vugt JL, Tegels JJ *et al.* (2015) Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. *Ann Surg* **261**, 345–352.
52. Peng PD, van Vledder MG, Tsai S *et al.* (2011) Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB* **13**, 439–446.
53. Ida S, Watanabe M, Yoshida N *et al.* (2015) Sarcopenia is a predictor of postoperative respiratory complications in patients with esophageal cancer. *Ann Surg Oncol* **22**, 4432–4437.
54. Joglekar S, Asghar A, Mott SL *et al.* (2015) Sarcopenia is an independent predictor of complications following pancreatectomy for adenocarcinoma. *J Surg Oncol* **111**, 771–775.
55. van Vugt JL, Braam HJ, van Oudheusden TR *et al.* (2015) Skeletal muscle depletion is associated with severe postoperative complications in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* **22**, 3625–3631. doi: 10.1245/s10434-015-4429-z.
56. Di Sebastiano KM & Mourtzakis M (2012) A critical evaluation of body composition modalities used to assess adipose and skeletal muscle tissue in cancer. *Appl Physiol Nutr Metab* **37**, 811–821.
57. Tsai HK, D'Amico AV, Sadetsky N *et al.* (2007) Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst* **99**, 1516–1524.
58. Demark-Wahnefried W, Peterson BL, Winer EP *et al.* (2001) Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol* **19**, 2381–2389.
59. Aubrey J, Esfandiari N, Baracos VE *et al.* (2014) Measurement of skeletal muscle radiation attenuation and basis of its biological variation. *Acta Physiol* **210**, 489–497.
60. Sabel MS, Lee J, Cai S *et al.* (2011) Sarcopenia as a prognostic factor among patients with stage III melanoma. *Ann Surg Oncol* **18**, 3579–3585.
61. Prado CM, Sawyer MB, Ghosh S *et al.* (2013) Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? *Am J Clin Nutr* **98**, 1012–1019.
62. Baracos VE (2014) Skeletal muscle anabolism in patients with advanced cancer. *Lancet Oncol*. doi: 10.1016/S1470-2045(14)71185-4
63. Dobs AS, Boccia RV, Croot CC *et al.* (2013) Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. *Lancet Oncol* **14**, 335–345.
64. Garcia JM, Boccia RV, Graham CD *et al.* (2014) Anamorelin for patients with cancer cachexia: an integrated analysis of two phase 2, randomised, placebo-controlled, double-blind trials. *Lancet Oncol* **16**, 108–116.
65. Garcia JM, Boccia RV, Graham CD *et al.* (2015) Anamorelin for patients with cancer cachexia: an integrated analysis of two phase 2, randomised, placebo-controlled, double-blind trials. *Lancet Oncol* **16**, 108–116.
66. Deutz NE, Safar A, Schutzler S *et al.* (2011) Muscle protein synthesis in cancer patients can be stimulated with a specially formulated medical food. *Clin Nutr* (*Edinburgh, Scotland*) **30**, 759–768.
67. Winter A, MacAdams J & Chevalier S (2012) Normal protein anabolic response to hyperaminoacidemia in insulin-resistant patients with lung cancer cachexia. *Clin Nutr* **31**, 765–773.
68. MacDonald AJ, Johns N, Stephens NA *et al.* (2014) Habitual myofibrillar protein synthesis is normal in patients with upper GI cancer cachexia. *Clin Cancer Res* **21**, 1734–1740.
69. Hutton JL, Martin L, Field CJ *et al.* (2006) Dietary patterns in patients with advanced cancer: implications for anorexia-cachexia therapy. *Am J Clin Nutr* **84**, 1163–1170.
70. Institute of Medicine (2005) *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (Macronutrients)*. Washington: National Academies Press.
71. Martin C (2000) Calorie, protein, fluid, and micronutrient requirements. In *The Clinical Guide to Oncology Nutrition*, p. 270. [PD McCallum and CG Polisena, editors]. Chicago: American dietetic association.
72. Bozzetti F (2013) Nutritional support of the oncology patient. *Crit Rev Oncol Hematol* **87**, 172–200.
73. Arends J, Bodoky G, Bozzetti F *et al.* (2006) ESPEN guidelines on enteral nutrition: non-surgical oncology. *Clin Nutr* (*Edinburgh, Scotland*) **25**, 245–259.
74. Prado CM, Lieffers JR, Bergsten G *et al.* (2012) Dietary patterns of patients with advanced lung or colorectal cancer. *Can J Diet Pract Res* **73**, e298–e303.
75. Prado CMM, Lieffers JR, Bowthorpe L *et al.* (2013) Sarcopenia and physical function: in overweight patients with advanced cancer. *Can J Diet Pract Res* **74**, 69–74.

https://doi.org/10.1017/S0029665115004279 Published online by Cambridge University Press

76. Gonzalez MC, Pastore CA, Orlandi SP *et al.* (2014) Obesity paradox in cancer: new insights provided by body composition. *Am J Clin Nutr* **99**, 999–1005.
77. Mir O, Coriat R, Blanchet B *et al.* (2012) Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. *PLoS ONE* **7**, e37563.
78. Huillard O, Mir O, Peyromaure M *et al.* (2013) Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients. *Br J Cancer* **108**, 1034–1041.
79. Massicotte MH, Borget I, Broutin S *et al.* (2013) Body composition variation and impact of low skeletal muscle mass in patients with advanced medullary thyroid carcinoma treated with vandetanib: results from a placebo-controlled study. *J Clin Endocrinol Metab* **98**, 2401–2408.
80. Barret M, Antoun S, Dalban C *et al.* (2014) Sarcopenia is linked to treatment toxicity in patients with metastatic colorectal cancer. *Nutr Cancer* **66**, 583–589.
81. Moryoussef F, Dhooge M, Volet J *et al.* (2015) Reversible sarcopenia in patients with gastrointestinal stromal tumor treated with imatinib. *J Cachexia, Sarcopenia Muscle* **6**, 343–350.
82. Tan BH, Brammer K, Randhawa N *et al.* (2015) Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. *Eur J Surg Oncol: J Eur Soc Surg Oncol Br Assoc Surg Oncol* **41**, 333–338.

https://doi.org/10.1017/S0029665115004279 Published online by Cambridge University Press