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# Impact of weight loss and sarcopenia on response to chemotherapy, quality of life and survival.

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Abstract: The prevalence of malnutrition in patients with cancer has frequently been shown to be one of the highest of all hospital patient groups. Weight loss is a frequent manifestation of malnutrition in patients with cancer. Several large-scale studies over the last 35 years have reported that involuntary weight loss affects 50-80% of these patients with the degree of weight loss dependent on tumour site, type and stage of disease. This review will focus on the consequences of malnutrition, weight loss and muscle wasting in relation to chemotherapy tolerance, post-operative complications, quality of life and survival in oncology patients.

The prognostic impact of weight loss on overall survival has long been recognised with recent data suggesting losses as little as 2.4% predicts survival independent of disease, site, stage or performance score. Recently the use of gold-standard methods of body composition assessment, including computed tomography, have led to an increased understanding of the importance of muscle abnormalities, such as low muscle mass (sarcopenia), and more recently low muscle attenuation, as important prognostic indicators of unfavourable outcomes in patients with cancer. Muscle abnormalities are highly prevalent (ranging from 10-90%, depending on cancer site and the diagnostic criteria used). Both low muscle mass and low muscle attenuation have been associated with poorer tolerance to chemotherapy; increased risk of postoperative complications; significant deterioration in a patients' performance status, and poorer psychological well-being, overall quality of life, and survival.

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The prevalence of malnutrition in patients with cancer has frequently been shown to be one of the highest of all patient groups<sup>(1; 2; 3)</sup>. Weight loss is a frequent manifestation of malnutrition and is an important criterion included in several malnutrition screening tools commonly used in clinical settings. Several large scale studies over the last 35 years have reported that involuntary weight loss affects 50-80% of patients with cancer with the degree of weight loss dependent on tumour site, type and stage of disease<sup>(4; 5; 6)</sup>.

The prognostic impact of weight loss on overall survival has long been recognised with recent data suggesting ongoing weight loss of more than 2.4% predicts survival, independent of disease site, stage or performance score<sup>(6)</sup>. In addition to the adverse impact on survival, weight loss has been associated with severe chemotherapy-related toxicity<sup>(7; 8; 9)</sup>; and leads to a significant deterioration in a patients' performance status, psychological well-being and overall quality of life<sup>(10)</sup>.

#### *Causes of nutritional deterioration in cancer*

Nutritional deterioration has unfortunately become an accepted part of the pathogenesis of cancer and its treatment<sup>(11)</sup>. Changes in nutrition status can occur at any point in the timeline of a cancer diagnosis, treatment, or support. The degree of malnutrition that occurs is affected by cancer type, stage and therapy modality; however, the etiology of cancer-induced weight loss and malnutrition is both multifactorial and complex. The form of malnutrition that occurs in malignancy is particularly challenging to address as it is not driven by simple starvation but occurs secondary to a negative energy balance caused by the detrimental combination of reduced oral intake and metabolic derangements unique to cancer<sup>(12; 13)</sup>.

Cancer-associated malnutrition can occur as a result of poor oral intake, mechanical or physiological changes to the gut, side effects of treatment, or metabolic abnormalities caused by the tumour. Both the quantity and the quality of dietary intake can be significantly altered due any one of a number of factors including: dysphagia, nausea, changes in taste and smell, pain, early satiety or fatigue. In addition to this, the presence of cancer in the body causes a variety of metabolic and endocrine changes (such as inflammation, anabolic resistance, proteolysis, lipolysis and futile cycling) induced by the tumour and activated immune cells. Complex interactions between inflammation (pro-

inflammatory cytokines), neuro-hormonal changes, and potential proteolytic and lipolytic factors produced by the host and the tumour, fuel weight loss and loss of lean mass<sup>(13)</sup>.

#### *Weight loss and changes in body composition following a cancer diagnosis*

Involuntary weight loss is a hallmark feature of cancer-associated malnutrition and can lead to cancer cachexia; a multifactorial syndrome characterised by the ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutrition support<sup>(14)</sup>. It is a condition characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism<sup>(14)</sup>. Studies dating back over the past 35 years have reported that moderate-to-severe weight loss is present in 30-70% of cancer patients<sup>(2; 4; 5; 6; 11)</sup>. In the largest study to-date of 8,160 patients with locally advanced or metastatic disease, 73% experienced involuntary weight loss<sup>(6)</sup>. Table 1 summarises the prevalence of >5% weight loss in six months (a key component of the diagnostic criteria of cancer cachexia<sup>(14)</sup>) according to tumour site in the scientific literature. Weight loss has consistently been shown to be most frequent in patients with cancers in the upper gut and lung<sup>(15; 16; 17; 18; 19)</sup>.

**Table 1.** Prevalence of patients with >5% weight loss in less than 6 months according to primary tumor location in the scientific literature.

Primary Cancer	Percentage with >5% weight loss in 6 months.
Pancreatic <sup>(15; 16)</sup>	41-53%
Colorectal <sup>(20; 21; 22)</sup>	32-48%
Gastric <sup>(23; 24)</sup>	42-75%
Oesophageal <sup>(25)</sup>	33%
Lung <sup>(22; 26)</sup>	44-49%
Breast <sup>(22)</sup>	24%

Despite the fact that the majority of patients present with involuntary weight loss at the time of diagnosis<sup>(6)</sup>, in the era of obesity, patients may not appear malnourished and many in fact are well-nourished according to international standards<sup>(27)</sup>. Recent studies have reported that between 40-60% of patients with cancer are overweight or obese (BMI > 25kg/m<sup>2</sup>) even in the setting of metastatic disease<sup>(6; 28; 29; 30; 31)</sup>. In a recent pooled analysis of 22 randomised therapeutic treatment trials including 11,724 patients with cancer, 67%

were shown to be overweight or obese at the time of enrolment (i.e. cancer diagnosis)<sup>(32)</sup>. However, the simple measure of body mass index (BMI) or percentage weight loss does not capture abnormal body composition, including muscle mass<sup>(27)</sup>. The most clinically relevant phenotypic feature of cancer cachexia is muscle loss and identifying those with low muscle mass can become a huge challenge in patients with overweight or obesity<sup>(11)</sup>.

Although low muscle mass is a symptom commonly associated with cancer, it is important to note that cancer is a disease associated with aging, therefore the aetiology of muscle loss in these patients can be two-fold. First resulting from the age-related decline in muscle mass and second due to cytokine-mediated degradation of muscle and adipose depots, hypermetabolism and anorexia associated with cancer cachexia<sup>(13)</sup>. As such, distinguishing the exact cause of muscle loss can be difficult.

### *Muscle mass*

Advancements in image-based technologies including computed tomography (CT) that allows the precise quantification of both muscle and adipose tissue has led to a large volume of research which has increased our understanding of the importance of abnormal body composition phenotypes, such as low muscle mass (sarcopenia), and more recently low muscle attenuation (MA) as important prognostic indicators of unfavourable outcomes in patients with cancer<sup>(6; 33; 34; 35)</sup>. Reduced skeletal muscle attenuation (radiodensity) is indicative of intramuscular adipose tissue infiltration and therefore poor 'quality' skeletal muscle<sup>(36)</sup>.

Low muscle mass is now known to relate to asthenia, fatigue, impaired physical function, increased chemotherapy toxicity, impaired quality of life (QoL) and reduced survival<sup>(6; 10; 27; 37)</sup>. Recent studies have shown that cancer, and its treatment, exacerbate muscle loss and that patients continually lose muscle mass while on treatment<sup>(35; 38; 39)</sup>. While healthy adults over the age of forty have been shown to lose muscle at a rate of 1-1.4% per year,<sup>(40)</sup> patients with cancer have been shown to have a 24-fold higher rate of muscle loss than that observed in health aging adults<sup>(20; 38)</sup>. In studies examining the rate of muscle loss per 100 days, rates of 3.9% have been reported in foregut cancer<sup>(38)</sup>, 3.1% in pancreatic cancer<sup>(41)</sup>, 3.3% in metastatic melanoma<sup>(35)</sup> and 5.2% in ovarian cancer<sup>(39)</sup>.

### *Prevalence of cancer cachexia and sarcopenia in oncology*

The prevalence of cancer cachexia and low muscle mass can vary widely depending on the method of assessment and diagnostic criteria used<sup>(36)</sup>. From the literature, it can be estimated that the prevalence of cancer cachexia (based on past 6 months weight loss >5% as per latest consensus definition<sup>(14)</sup>) can vary between 24-75% depending on tumor site (table 1), and between 38-70% of patients are considered to have low muscle mass (i.e. sarcopenia, based on 3 of the most commonly used diagnostic criteria). The prevalence of low muscle mass is highest in lung (median 70%, range 47-79%)<sup>(42; 43; 44; 45)</sup> and pancreatic cancer (median 56%, range 44-89%)<sup>(16; 41; 46; 47; 48; 49; 50; 51; 52)</sup> however it is noteworthy that the majority of studies report a prevalence of above 40% at most other sites in the body (see table 2).

**Table 2.** Prevalence of sarcopenia in patients with cancer according to the primary tumor location in the literature (all stages)

Primary Cancer	Stage	% with sarcopenia, median (range)
Colorectal	Stage I-IV <sup>(20; 34; 53; 54; 55; 56; 57; 58; 59; 60; 61; 62; 63; 64; 65; 66; 67; 68; 69)</sup>	49% (20-80%)
Esophagus	Stage I-IV <sup>(70; 71; 72; 73; 74; 75; 76; 77; 78; 79; 80; 81)</sup>	53% (16-75%)
Gastric	Stage I-IV <sup>(82; 83; 84; 85; 86; 87)</sup>	47% (23-70%)
Lung	Stage I-IV <sup>(42; 43; 44; 45)</sup>	70% (47-79%)
Kidney	Stage I-IV <sup>(88; 89; 90; 91; 92; 93; 94; 95)</sup>	53% (29-90%)
Pancreatic	Stage I-IV <sup>(16; 41; 46; 47; 48; 49; 50; 51; 52)</sup>	56% (44-89%)
Liver	Stage I-IV <sup>(96; 97; 98; 99; 100)</sup>	54% (28-76%)
Breast	Stage I-IV <sup>(101; 102; 103; 104; 105; 106; 107)</sup>	38% (14-67%)
Ovarian	Stage I-IV <sup>(39; 108; 109)</sup>	47% (45-50%)
Melanoma	Stage I-IV <sup>(35; 110)</sup>	44% (24-63%)
Bladder	Stage I-IV <sup>(111; 112; 113; 114; 115)</sup>	48% (33-69%)
Prostate	Stage I-IV <sup>(116; 117)</sup>	52% (47-56%)
Head & Neck	Stage I-IV <sup>(118)</sup>	64%
Lymphoma	Stage I-IV <sup>(119; 120; 121)</sup>	51% (47-55%)
Mixed	Stage I-IV <sup>(29; 38; 122; 123; 124)</sup>	41% (15-47%)

Prevalence of sarcopenia defined using three of the most common definitions for defining low muscle mass is displayed in table 2. These definitions are as follows;

- Prado *et al.* (2008)<sup>(122)</sup>: Skeletal muscle index (SMI) <52.4 cm<sup>2</sup>/m<sup>2</sup> in men and <38.5 cm<sup>2</sup>/m<sup>2</sup> in women
- Martin *et al.* (2013)<sup>(29)</sup>: SMI <43.0 cm<sup>2</sup>/m<sup>2</sup> in men with a BMI <25 kg/m<sup>2</sup> and <53.0 cm<sup>2</sup>/m<sup>2</sup> in men with a BMI >25 kg/m<sup>2</sup> and SMI <41.0 cm<sup>2</sup>/m<sup>2</sup> in women.
- Baumgartner *et al.* (1998)<sup>(125)</sup> converted DXA cut points by Mourtzakis *et al.* (2008)<sup>(126)</sup> as SMI <55.4 cm<sup>2</sup>/m<sup>2</sup> in men and <38.9 cm<sup>2</sup>/m<sup>2</sup> in women



The rates of low muscle mass seen in cancer populations are of huge public health importance, given that cancer cachexia and sarcopenia have been reported to be unequivocally associated with negative clinical outcomes in patients with cancer including poorer tolerance to anti-cancer treatment, poorer overall quality of life, increased risk of post-operative complications and poorer overall survival<sup>(6; 10; 36; 37)</sup>.

#### *Impact of malnutrition on tolerance to systemic chemotherapy*

Chemotherapy can often be associated with severe toxicity that can result in dose delays, dose reductions and treatment termination, referred to as dose limiting toxicities (DLT). Severe toxic events can result in hospitalisations and can even be life threatening. Recent evidence suggests that variability in body composition of patients with cancer may be a source of disparities in the metabolism of cytotoxic agents resulting in increased toxicity<sup>(61; 62; 63)</sup>.

To date, in excess of 40 studies have examined the relationship between low lean mass (sarcopenia) and the prevalence of dose limiting toxicity in patients with cancer (see summary of studies in table 3). The relationship between low lean mass and increased toxicity to chemotherapy has been shown to be true even in both early and late stage disease irrespective of the cancer site and type of systemic chemotherapy (cytotoxic single agents, regimens, targeted agents and immunotherapies)<sup>(75; 82; 106; 122)</sup>. Although the relationship between low lean mass and poorer tolerance to treatment has been observed in the majority of studies, few smaller studies have reported no association<sup>(20; 50; 72; 95; 123; 127; 128; 129)</sup>.

Increased toxicity in patients with low lean mass may be attributed to alterations in the distribution, metabolism and clearance of systemic chemotherapy drugs<sup>(102)</sup>. Chemotherapy is traditionally dosed according to body surface area (BSA) but its use has been criticised in the dosage of medications with a narrow therapeutic index, such as chemotherapy. A four to ten-fold variation in drug clearance has been shown in individuals with similar BSA and there is growing concern that this approach to dosing is invalid<sup>(130; 131)</sup>. Its continued use relies on the lack of other more precise methods for dose individualisation<sup>(132)</sup>.

If body weight comprises two major components (lean and fat mass) then these are the two major sites of distribution of hydrophilic and lipophilic drugs<sup>(133; 134)</sup>. Therefore,

variability in individual lean mass or fat mass may lead to changes in the volume of distribution of drugs and therefore adversely affect the tolerance of cytotoxic drugs<sup>(36)</sup>. Tolerance is further compromised in individuals with sarcopenic obesity where the combination of excessive fat mass and diminished lean mass may significantly impact the tolerance of hydrophilic drugs by resulting in a disproportionately small volume of drug distribution in relation to their body weight or body surface area<sup>(102; 133)</sup>. Variations in lean and fat mass can therefore lead to considerable variation in the milligram of chemotherapy drug per kilogram lean mass with higher doses per kilogram lean mass shown to be associated with more frequent and severe toxic side effects<sup>(133; 135; 136)</sup>. Pharmacokinetic data have supported this hypothesis, with patients with low lean mass experiencing higher plasma concentrations of antineoplastic drugs and experiencing more toxicity<sup>(96; 137)</sup>. For lipophilic drugs such as doxorubicin or trabectedin, individuals with a low-fat mass may also present with toxicity due to a reduced volume of distribution<sup>(134)</sup>.

In addition to the argument that pharmacokinetic parameters can explain the higher risk of toxicity in patients with low lean mass it is also important to note that these patients are excessively fragile and highly susceptible to acute medical events that exacerbate chemotherapy-related toxicity<sup>(91)</sup>. Systemic inflammation has been shown to decrease liver cytochrome activities and drug clearance and may modify drug exposure. Low concentrations of circulation plasma proteins (e.g. albumin) may also affect the distribution of highly protein-bound drugs such as Vantetanib, sorafenib and epirubicin<sup>(96; 134; 137)</sup>. Future clinical trials investigating dosing chemotherapy drugs according to individual body composition are warranted and the outcome of these studies could inform future practice.

Table 3. Summary of studies examining the impact of computed tomography assessed skeletal muscle (at the third lumbar vertebrae) and treatment related toxicity in patients with cancer.

	Stage/n	Treatment	Summary of findings
<b>Breast Cancer</b>			
Prado <i>et al.</i> 2009 <sup>(102)</sup>	Metastatic/55	Capecitabine	DLT ↑ in sarcopenic pts (50% vs. 20%, $p=0.03$ )
Prado <i>et al.</i> 2011 <sup>(138)</sup>	Stage II-III/24	5-FU, Epirubicin, cyclophosphamide	LM was lower in pts with toxicity (41.6 kg vs. 56.2 kg, $p=0.002$ )
Shachar <i>et al.</i> 2016 <sup>(106)</sup>	Metastatic/40	Taxane based (paclitaxel, docetaxel, nab-paclitaxel)	Gr 3-4 toxicity ↑ in sarcopenic pts (57% vs. 18%, $p=0.02$ ) and ↑ in treatment related hospitalisations (39% vs. 0%, $p=0.005$ )
Shachar <i>et al.</i> 2016 <sup>(139)</sup>	Stage I-III/151	Anthracycline and taxanes	Every 5 unit decrease in SMI was associated with increased risk of gr 3-4 toxicity (RR 1.29 (95% CI 1.10-1.53), $p=0.002$ )
Mazzuca <i>et al.</i> 2018 <sup>(104)</sup>	Stage I-III/21	Anthracyclines	Lower baseline SMI was associated with Gr 3-4 vs. Gr 0-2 toxicities (33.4 cm <sup>2</sup> /m <sup>2</sup> (31.1–39.9) vs 40.5 cm <sup>2</sup> /m <sup>2</sup> (33.4–52.0), $p = 0.028$ ).
<b>Colorectal Cancer</b>			
Prado <i>et al.</i> 2007 <sup>(133)</sup>	Stage II-III/62	5-FU	Drug dose >20mg/kg LM associated with increased toxicity (93% vs. 52%, $p=0.005$ )
Barret <i>et al.</i> 2013 <sup>(68)</sup>	Metastatic/51	Fluoropyrimidine (FP)+Oxaliplatin; FP+ Irinotecan; FP Alone; Irinotecan without FP	Sarcopenia independently associated with ↑ risk of gr 3-4 toxicity (OR: 13.55, $p=0.043$ )
Ali <i>et al.</i> 2015 <sup>(140)</sup>	Stage I-IV/138	FOLFOX	Pts with the highest tertile of drug dose per kg LM experienced more DLT compared with those in the lowest tertile of drug dose (39.9% vs. 8.3%, $p<0.01$ )
Chemama <i>et al.</i> 2016 <sup>(58)</sup>	Advanced (liver mets)/97	Hyperthermic intraperitoneal chemotherapy	Toxicity ↑ in sarcopenic pts (57% vs, 26%, $p=0.004$ )
Blauwhoff-Buskermolen <i>et al.</i> 2016 <sup>(20)</sup>	Metastatic/67	CAPOX (±bevacizumab)	Sarcopenia was not associated with ↑ toxicity
Cespedes <i>et al.</i> 2017 <sup>(141)</sup>	Non-metastatic/533	FOLFOX	Lowest tertile of lean mass associated with early treatment discontinuation (OR 2.34, $p=0.03$ ), treatment delay (OR 2.24, $p=0.002$ ) and dose reduction (OR 2.28, $p=0.01$ )
<b>Lung Cancer</b>			
Arrieta <i>et al.</i> 2015 <sup>(43)</sup>	Metastatic/84	Afatinib	Patients with lower LM and BMI <25kg/m <sup>2</sup> developed more DLT than patients with higher LM and BMI >25 kg/m <sup>2</sup> (71.4% vs. 18.8%, $p=0.0017$ )
Sjblom <i>et al.</i> 2015 <sup>(136)</sup>	Stage IIIb-IV/153	Gemcitabine and vinorelbine or Carboplatin and vinorelbine	Higher doses of gemcitabine per kg LM were independently associated with gr 3-4 haematological toxicity in multivariate analyses (OR 1.15, 95% CI: 1.01-1.29, $p=0.018$ ), as were also higher doses of vinorelbine per kg LBM.
Srdic <i>et al.</i> 2016 <sup>(128)</sup>	Advanced/100	Platinum-doublet therapy	Cachexia and sarcopenia were not found to be predictors of chemotoxicity
Sjblom <i>et al.</i>	Stage IIIb-IV/424	Carboplatin-	Drug dose per kg/LM was associated with

	Stage/n	Treatment	Summary of findings
2016 <sup>(135)</sup>		Doublet (pemetrexed, gemcitabine or vinorelbine)	haematological toxicity. For doses >20% above or below the mean, the risk of gr 3-4 haematological toxicity was almost doubled (OR 1.93 (95% CI:1.21-3.10) and halved (OR 0.52 (95% CI: 0.32-0.83) respectively.
<b>Esophagogastric cancer</b>			
Yip <i>et al.</i> 2014 <sup>(72)</sup>	Stage I-III/35	5FU; Platinum/5-FU; ECX/ECF	Sarcopenia was not associated with ↑ toxicity or treatment dose reduction.
Tan <i>et al.</i> 2015 <sup>(75)</sup>	Stage I-III/89	Cisplatin, 5-FU, Epirubicin or Cisplatin, Capecitabine	Sarcopenia independently associated with DLT (OR 2.95, $p=0.015$ )
Anandavadivelan <i>et al.</i> 2016 <sup>(73)</sup>	Resectable/72	Cisplatin, 5-FU	Patients with a DLT had lower SMM than those without DLT (47 kg vs. 51 kg, $p=0.04$ ). Sarcopenic obesity associated with increased risk of DLT (OR 5.54, 95% CI: 1.12-27.44, $p=0.04$ )
Palmela <i>et al.</i> 2017 <sup>(82)</sup>	Stage II-III/48	Neoadjuvant chemotherapy	DLT ↑ in sarcopenic pts (65% vs. 39%, $p=0.181$ )
Dijksterhuis <i>et al.</i> 2019 <sup>(142)</sup>	Advanced/88	Capecitabine, Oxaliplatin	Gr 2-4 neuropathy ↑ in patients with sarcopenic obesity (OR 3.82, 95% CI: 1.20-12.18, $p=0.024$ )
<b>Pancreatic Cancer</b>			
Rollins <i>et al.</i> 2015 <sup>(50)</sup>	Advanced/228	Gemcitabine	Sarcopenia was not associated with rates of completion of palliative chemotherapy
Kurita <i>et al.</i> 2019 <sup>(143)</sup>	Advanced/82	FOLFIRINOX	Gr 3-4 hematologic toxicity was ↑ in sarcopenic obese patients ( $p=0.008$ )
<b>Renal Cell Carcinoma</b>			
Antoun <i>et al.</i> 2010 <sup>(144)</sup>	Metastatic/55	Sorafenib	DLT was most common (41%) in sarcopenic patients whose BMI was <25 kg/m <sup>2</sup> and least common (13%) in patients who were not sarcopenic and/or overweight or obese ( $p = 0.03$ ).
Huillard <i>et al.</i> 2013 <sup>(92)</sup>	Metastatic/61	Sunitinib	Sarcopenic pts with a BMI < 25 kg/m <sup>2</sup> experienced ↑ DLTs (OR 4.1, 95% CI: 1.3-13.3), ↑ cumulative gr 2 or 3 toxicities ( $p=0.008$ ), ↑ grade 3 toxicities ( $p=0.04$ ) and ↑ acute vascular toxicities ( $p=0.009$ ).
Cushen <i>et al.</i> 2017 <sup>(89)</sup>	Metastatic/55	Sunitinib	Pts with the lowest compared with the highest measurements of LM experienced more DLT (92% vs. 57%, $p=0.05$ )
Auclin <i>et al.</i> 2017 <sup>(95)</sup>	Metastatic/124	Everolimus	SMI was not associated with ↑ toxicity
<b>Melanoma</b>			
Heidelberger <i>et al.</i> 2017 <sup>(110)</sup>	Metastatic/68	Nivolumab/ Pembrolizumab	Sarcopenia and overweight (BMI >25kg/m <sup>2</sup> ) women had a 6.5 fold ↑ risk of toxicity.
Daly <i>et al.</i> 2017 <sup>(35)</sup>	Metastatic/84	Ipilimumab	Sarcopenic was associated with ↑ high grade adverse events (OR 5.34, $p=0.033$ )
<b>Hepatocellular carcinoma</b>			
Mir <i>et al.</i> 2012 <sup>(96)</sup>	Advanced/40	Sorafenib	DLT ↑ in sarcopenic pts (82% vs. 31%, $p=0.005$ )
Nault <i>et al.</i> 2015 <sup>(100)</sup>	Advanced/52	Sorafenib, Brivanib	Sarcopenia was associated with a greater rate of hand-foot syndrome ( $p=0.049$ )
<b>Other Cancer Sites</b>			
Parsons <i>et al.</i>	Mixed cancer	Hepatic arterial	Sarcopenia was not associated with ↑ toxicity

	Stage/n	Treatment	Summary of findings
2012 <sup>(127)</sup>	sites/Advanced/48	infusion	
Moryoussef <i>et al.</i> 2015 <sup>(145)</sup>	GI stromal tumours/advanced /31	Imatinib	Gr 1-2 toxicity ↑ in sarcopenic pts (100% vs. 73.7%)
Massicotte <i>et al.</i> 2013 <sup>(137)</sup>	Medullary thyroid /Advanced/33/	Vantetanib	SMI was lower in pts with DLT (37.2 vs. 44.3 cm <sup>2</sup> /m <sup>2</sup> , <i>p</i> =0.003)
Veasy-Rodrigues <i>et al.</i> 2013 <sup>(146)</sup>	Mixed solid tumours/ Advanced/16	Temsirolimus	Sarcopenia was not associated with ↑ toxicity
Cousin <i>et al.</i> 2014 <sup>(147)</sup>	Mixed cancer sites/ Stage I-IV/93	Phase 1 drugs	Severe toxic events were observed in 25.5% of the pts when the SMI was below the median value compared to 6.5% of patients with a high SMI ( <i>p</i> = 0.02)
Prado <i>et al.</i> 2014 <sup>(134)</sup>	Ovarian/Advanced/7 4	Doxil, trabectedin	LM alone was not predictive of DLT. A lower FM/LBM ratio was the most powerful variable associated with toxicity ( <i>p</i> =0.006)
Cushen <i>et al.</i> 2016 <sup>(116)</sup>	Prostate/Metastatic/ 63	Docetaxel	Sarcopenia and low MA associated with ↑DLT toxicity
Xiao <i>et al.</i> 2016 <sup>(121)</sup>	Lymphoma/stage I- IV/522	CHOP based chemotherapy	Sarcopenia was independently associated with ↑ risk of febrile neutropenia hospitalization (OR 1.64, 95% CI: 1.01-2.65) and ↓ completion of standard treatment cycles (OR 1.49, 95% CI: 1.02-2.16)
Wendrich <i>et al.</i> 2017 <sup>(148)</sup>	Head&neck/locally advanced/132	Platinum-based chemotherapy	Patients with low skeletal muscle mass experienced more DLT more frequently than patients with normal skeletal muscle mass (44.3% vs. 13.7%, <i>p</i> <0.001)
Versteeg <i>et al.</i> 2018 <sup>(129)</sup>	Mixed sites/Advanced/103	Not specified	Muscle parameters were not associated with ↑ toxicity

DLT, Dose limiting toxicity; Pts, patients; LM, lean mass; Gr, Grade; SMI, Skeletal muscle index; CI, confidence interval; OR, odds ratio; RR, relative risk; mg, milligrams; kg, kilograms; 5-FU, 5-Flurouracil; BMI, body mass index; HCC, hepatocellular carcinoma; GI, gastrointestinal.

### *Impact of malnutrition on performance status and quality of life*

Quality of life (QoL) in patients with cancer is a subjective multidimensional construct that represents the patient's psychological well-being, functional status, health perceptions, and disease- and treatment- related symptoms. It is now universally accepted that QoL is the central tenet in cancer care, especially in those patients with incurable disease.

Weight loss and malnutrition has been shown to have profound negative effects on QoL in patients with cancer. A recent systematic review examining the impact of weight loss on QoL in patients with cancer reported a negative correlation between weight loss and QoL in 23 out of 27 studies<sup>(10)</sup>. The negative impact on QoL is unsurprising, considering cancer-related malnutrition is a

major cause of fatigue<sup>(149; 150)</sup>, reduced functional ability<sup>(151)</sup> and a source of emotional distress<sup>(149; 152)</sup>.

Inconsistent reports on the relationship between muscle parameters and QoL have been published in the literature<sup>(127; 153; 154; 155)</sup>. Parsons and colleagues reported no significant associations between low muscle mass, and symptom burden or functional life domains assessed by the MD Anderson Symptom Inventory, in a cohort of 104 patients with advanced cancer<sup>(127)</sup>. However, in a study of 734 patients with advanced lung cancer, low muscle mass was non-linearly associated with lower global QoL, physical function and role function, and associated with more symptoms (fatigue and pain), while low MA was associated with poor physical function and more dyspnoea<sup>(155)</sup>. Low muscle mass has also been associated with greater depression symptoms and more fatigue in patients with advanced cancer<sup>(153; 154)</sup>.

The mode by which weight loss exerts its influence on QoL is not fully understood but may relate to muscle atrophy associated with cachexia and weight loss leading to fatigue or reduced functional capacity. Recent work has suggested that the complex interplay between metabolic disruption and pro-inflammatory cytokines (i.e. IL-6, IL-8 and TNF- $\alpha$ ) in cancer cachexia often leads to physical, biochemical and nutritional deterioration which subsequently leads to poor QoL<sup>(156)</sup>. Systemic inflammation and loss of muscle is also thought to drive cancer related fatigue, which is thought to affect up to 80% of patients<sup>(157)</sup> both during and after treatment cessation<sup>(157; 158; 159; 160)</sup>. Severe and persistent fatigue, along with muscle wasting has been shown to inhibit QoL by considerably reducing functional capacity to fully participate in daily living tasks<sup>(157)</sup>. Also, evidence from a variety of preclinical and clinical studies suggest that systemic inflammation has a direct role in the development of cancer associated symptom clusters including pain, fatigue, mood, anorexia and physical function<sup>(161)</sup>. Systemic inflammation has been shown to be associated with poorer QoL even in those with a good performance score<sup>(162)</sup>.

Importantly, interventions aimed at targeting nutritional status and attenuating weight loss have proven successful in improving aspects QoL in patients with cancer<sup>(163)</sup>. In addition, novel cachexia treatments, such as Anamorelin, an oral ghrelin-receptor agonist with appetite enhancing and anabolic activity have shown a favourable clinical response in alleviating anorexia-cachexia symptoms<sup>(26)</sup>. Research is warranted to determine if attenuating the systemic inflammatory response leads to clinically relevant improvements in symptoms, which may represent a new therapeutic approach to symptom management in patients with advanced cancer.

### Impact on survival

Over the past decade, an array of studies have examined the relationship between the presence of low muscle mass (sarcopenia) and its impact on survival in patients with cancer. Most studies report a significant decrease in overall survival in patients with low muscle mass compared with their counterparts, irrespective of the primary cancer site and stage (see Figure 1). Figure 1 displays the risk of mortality [adjusted HR (95% CI)] in sarcopenic patients compared with non-sarcopenic patients according to primary tumour location.

The relationship between low muscle mass and poor survival has been the topic of various systematic reviews and meta-analysis<sup>(164; 165; 166; 167)</sup>. In a recent systematic review and meta-analysis of 38 studies that included 7,843 patients with solid tumours, low muscle cross-sectional area was observed in 27.7% of patients with cancer and associated with poorer overall survival [HR: 1.44, 95% CI: 1.32–1.56], cancer-specific survival [HR: 1.93, 95% CI: 1.38–2.70], as well as disease-free survival [HR: 1.16, 95% CI: 1.00–1.30] but not with progression free survival (HR: 1.54, 95% CI: 0.90–2.64)<sup>(165)</sup>. This meta-analysis demonstrated that the adverse effects of low muscle mass on overall survival were similar in both metastatic [HR: 1.37, 95% CI: 1.21–1.56] and non-metastatic disease [HR: 1.54, 95% CI: 1.31–1.79], and this relationship was observed across different primary tumour sites. Recently, in two of the largest observational cohort studies to date, Caan and colleagues<sup>(168; 169)</sup> demonstrated the prognostic value of low muscle mass in non-metastatic breast ( $n=3,241$ ) and colorectal cancer ( $n=3,262$ ). Low lean mass was present in 34 and 42% of patients, respectively, and was independently associated with a 27–41% higher risk of overall mortality [colon: HR 1.24, (95% CI: 1.09–1.48); breast: HR 1.41 (95% CI: 1.18–1.69)]<sup>(168; 169)</sup>.

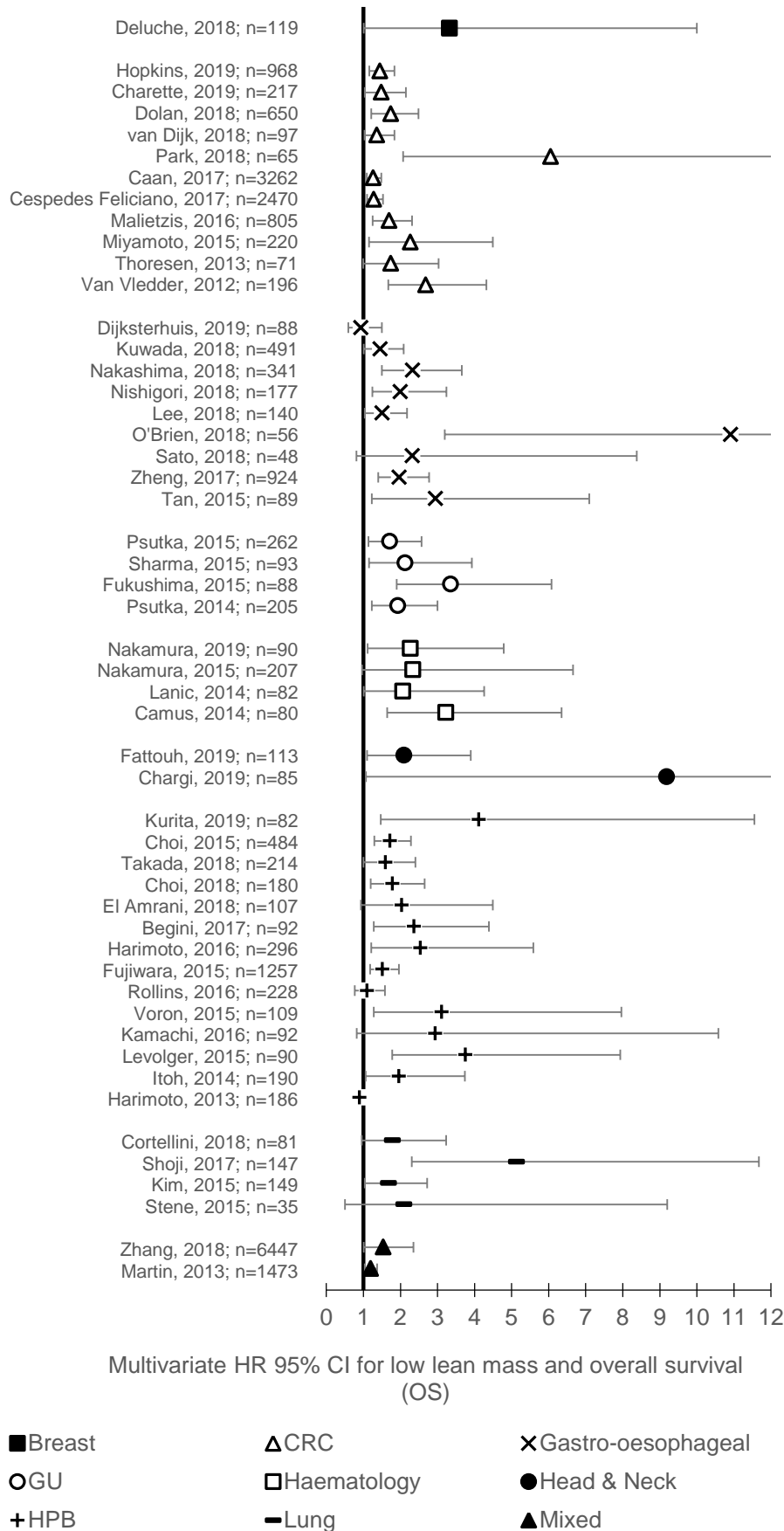
In addition to low muscle area (sarcopenia), low muscle attenuation (radiodensity) (indicative of fatty infiltration of muscle tissue) is also associated with poorer survival in a variety of tumours including non-small cell lung cancer, colorectal, endometrial, renal and ovarian cancer<sup>(170)</sup><sup>(171; 172; 173)</sup><sup>(174)</sup><sup>(109; 175)</sup><sup>(176)</sup>. Importantly, in some cases, low MA appears to superior in predicting mortality compared with low lean mass alone<sup>(87; 107; 170; 177; 178)</sup>. In a cohort of 1,681 early stage colorectal cancer (CRC) patients, low MA was associated with higher all-cause mortality [HR 1.91 (95% CI: 1.53–2.38)]<sup>(173)</sup>. Ataseven *et al.*<sup>(109)</sup> reported that in patients with advanced epithelial ovarian cancer receiving primary debulking surgery ( $n=323$ ), low MA (<32 HU) was associated with a significantly reduced overall survival compared with patients with a higher MA (median survival 28 months vs. 56 months,  $p<0.001$ ) and this relationship remained significant on multivariable

regression analysis (HR 1.79 (95% CI: 1.22-2.62). In another cohort of patients with early stage CRC ( $n=3,262$ ), low MA has also been described as an important predictor of mortality [HR 1.61 (95% CI: 1.36-1.90)] and CRC-specific mortality [HR 1.74 (95% CI: 1.38-2.21)]. Of note, in this study, patients with both low muscle mass and low MA were at the highest risk of overall [HR: 2.02 (95% CI: 1.65-2.47)] and cancer-specific mortality [HR: 2.54 (95% CI: 1.91-3.37)]<sup>(171)</sup>. It has also been demonstrated that the risk of mortality associated with low muscle mass and low MA can be independent of each other<sup>(179; 180; 181)</sup>.

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Figure 1: Forest plot of HR of death according to low muscle mass status



Deluche, 2018; n=119<sup>(105)</sup> Hopkins, 2019; n=968<sup>(182)</sup> Charette, 2019; n=217<sup>(179)</sup> Dolan, 2018; n=650<sup>(183)</sup> van Dijk, 2018; n=97<sup>(184)</sup> Park, 2018; n=65<sup>(185)</sup> Caan, 2017; n=3262<sup>(168)</sup> Cespedes Feliciano, 2017; n=2470<sup>(186)</sup> Malietzis, 2016; n=805<sup>(187)</sup> Miyamoto, 2015; n=220<sup>(188)</sup> Thoresen, 2013; n=71<sup>(67)</sup> Van Vledder, 2012; n=196<sup>(189)</sup> Dijksterhuis, 2019; n=88<sup>(142)</sup> Kuwada, 2018; n=491<sup>(190)</sup> Nakashima, 2018; n=341<sup>(191)</sup> Nishigori, 2018; n=177<sup>(192)</sup> Lee, 2018; n=140<sup>(193)</sup> O'Brien, 2018; n=56<sup>(194)</sup> Sato, 2018; n=48<sup>(80)</sup> Zheng, 2017; n=924<sup>(195)</sup> Tan, 2015; n=89<sup>(75)</sup> Psutka, 2015; n=262<sup>(196)</sup> Sharma, 2015; n=93<sup>(88)</sup> Fukushima, 2015; n=88<sup>(114)</sup> Psutka, 2014; n=205<sup>(115)</sup> Nakamura, 2019; n=90<sup>(197)</sup> Nakamura, 2015; n=207<sup>(198)</sup> Lanic, 2014; n=82<sup>(199)</sup> Camus, 2014; n=80<sup>(200)</sup> Fattouh, 2019; n=113<sup>(201)</sup> Chargi, 2019; n=85<sup>(202)</sup> Kurita, 2019; n=82<sup>(143)</sup> Choi, 2015; n=484<sup>(203)</sup> Takada, 2018; n=214<sup>(204)</sup> Choi, 2018; n=180<sup>(205)</sup> El Amrani, 2018; n=107<sup>(47)</sup> Begini, 2017; n=92<sup>(206)</sup> Harimoto, 2016; n=296<sup>(207)</sup> Fujiwara, 2015; n=1257<sup>(208)</sup> Rollins, 2016; n=228<sup>(209)</sup> Voron, 2015; n=109<sup>(98)</sup> Kamachi, 2016; n=92<sup>(99)</sup> Levolger, 2015; n=90<sup>(210)</sup> Itoh, 2014; n=190<sup>(211)</sup> Harimoto, 2013; n=186<sup>(97)</sup> Cortellini, 2018; n=81<sup>(212)</sup> Shoji, 2017; n=147<sup>(213)</sup> Kim, 2015; n=149<sup>(214)</sup> Stene, 2015; n=35<sup>(215)</sup> Zhang, 2018; n=6447<sup>(216)</sup> Martin, 2013; n=1473<sup>(29)</sup>

### *Loss of muscle during treatment & survival*

Notwithstanding the impact of low muscle mass on survival, several studies have emphasised that patients continually lose muscle while on treatment and that this is associated with an increased risk of mortality in a number of cancers. Patients with advanced pancreatic cancer ( $n=97$ ) who experienced early loss of skeletal muscle ( $>10\%$  within 3 months of diagnosis) were at increased risk of poorer overall survival and progression free survival compared to patients who did not experience muscle loss to the same degree [HR 2.16 (95% CI: 1.23-3.78),  $p=0.007$  and HR 2.31 (95% CI: 1.30-4.09),  $p=0.004$ ]<sup>(217)</sup>. In patients with surgically resected stage I-III CRC ( $n=1924$ ), those who experienced the largest decrease in muscle mass ( $\geq 2$  standard deviations or the equivalent to  $\geq 11.4\%$  loss) and the largest decline in mean MA ( $\geq 2$  SD;  $\geq 20.2\%$  loss) from baseline were at a significantly increased risk of mortality [HR 2.15 (95% CI: 1.59-2.92),  $p<0.001$  and HR 1.61 (95% CI: 1.20-2.15),  $p=0.002$ , respectively], and these findings were independent of changes in body mass or other body composition parameters<sup>(172)</sup>. To date, losses in muscle have been shown to be prognostic of reduced survival in pancreatic<sup>(51; 217)</sup>, oesophageal, gastric<sup>(218)</sup>, lung<sup>(219)</sup>, colorectal<sup>(20; 220; 221)</sup>, ovarian<sup>(39)</sup>, melanoma<sup>(35)</sup> and foregut cancers<sup>(38)</sup>.

### *Conclusions*

While weight loss and malnutrition have been frequently reported in cancer patients over the past 40 years, research over the past 15 years has unearthed the importance of low muscle mass as being the new face of malnutrition in oncology populations. The study of body composition in oncology has highlighted the importance of both low muscle mass and low muscle attenuation which are associated with poorer tolerance to chemotherapy; significant deterioration in a patients' performance status and quality of life, and poorer survival. Early screening to identify individuals with muscle loss and decreased muscle quality would allow for earlier multimodal interventions to attenuate adverse body composition changes. These include resistance exercise

training and optimal dietary intake and supplementation, combined with pharmacotherapy; these are currently the focus of randomised controlled trials<sup>(222)</sup>. It remains to be seen if multimodal therapies can provide a sufficient stimulus to prevent or slow the cascade of tissue wasting and if this then impacts on outcome in a positive manner. There also exists an equal need for routine, cost-efficient, and feasible methods to quantify muscle and adipose tissue in clinical practice. The study of body composition is one of the most provocative areas in oncology that offers tremendous promise to help patients with cancer live longer and healthier lives<sup>(223)</sup>.

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## References

1. Raja R, Lim AV, Lim YP *et al.* (2004) Malnutrition screening in hospitalised patients and its implication on reimbursement. *Intern Med J* **34**, 176-181.
2. Tangvik RJ, Tell GS, Guttormsen AB *et al.* (2015) Nutritional risk profile in a university hospital population. *Clin Nutr* **34**, 705-711.
3. Kruijenga H, van Keeken S, Weijs P *et al.* (2016) Undernutrition screening survey in 564,063 patients: patients with a positive undernutrition screening score stay in hospital 1.4 d longer. *Am J Clin Nutr* **103**, 1026-1032.
4. Bozzetti F, Group SW (2009) Screening the nutritional status in oncology: a preliminary report on 1,000 outpatients. *Support Care Cancer* **17**, 279-284.
5. Dewys WD, Begg C, Lavin PT *et al.* (1980) Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med* **69**, 491-497.
6. Martin L, Senesse P, Gioulbasanis I *et al.* (2015) Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol* **33**, 90-99.
7. Andreyev HJ, Norman AR, Oates J *et al.* (1998) Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer* **34**, 503-509.
8. Ross PJ, Ashley S, Norton A *et al.* (2004) Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? *Br J Cancer* **90**, 1905-1911.
9. Di Fiore F, Leclaire S, Pop D *et al.* (2007) Baseline nutritional status is predictive of response to treatment and survival in patients treated by definitive chemoradiotherapy for a locally advanced esophageal cancer. *Am J Gastroenterol* **102**, 2557-2563.
10. Wheelwright S, Darlington AS, Hopkinson JB *et al.* (2013) A systematic review of health-related quality of life instruments in patients with cancer cachexia. *Support Care Cancer* **21**, 2625-2636.
11. Ryan AM, Power DG, Daly L *et al.* (2016) Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. *Proc Nutr Soc*, 1-13.
12. Arends J, Bachmann P, Baracos V *et al.* (2017) ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* **36**, 11-48.
13. Argilés JM, Busquets S, Stemmler B *et al.* (2015) Cachexia and sarcopenia: mechanisms and potential targets for intervention. *Curr Opin Pharmacol* **22**, 100-106.
14. Fearon K, Strasser F, Anker SD *et al.* (2011) Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* **12**, 489-495.
15. Bachmann J, Heiligensetzer M, Krakowski-Roosen H *et al.* (2008) Cachexia worsens prognosis in patients with resectable pancreatic cancer. *J Gastrointest Surg* **12**, 1193-1201.
16. Wesseltoft-Rao N, Hjerstad MJ, Ikdaahl T *et al.* (2015) Comparing two classifications of cancer cachexia and their association with survival in patients with unresected pancreatic cancer. *Nutr Cancer* **67**, 472-480.
17. Krishnan S, Rana V, Janjan NA *et al.* (2006) Prognostic factors in patients with unresectable locally advanced pancreatic adenocarcinoma treated with chemoradiation. *Cancer* **107**, 2589-2596.
18. Olson SH, Xu Y, Herzog K *et al.* (2016) Weight Loss, Diabetes, Fatigue, and Depression Preceding Pancreatic Cancer. *Pancreas* **45**, 986-991.
19. Nemer L, Krishna SG, Shah ZK *et al.* (2017) Predictors of Pancreatic Cancer-Associated Weight Loss and Nutritional Interventions. *Pancreas* **46**, 1152-1157.
20. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA *et al.* (2016) Loss of Muscle Mass During Chemotherapy Is Predictive for Poor Survival of Patients With Metastatic Colorectal Cancer. *J Clin Oncol* **34**, 1339-1344.
21. van der Werf A, van Bokhorst QNE, de van der Schueren MAE *et al.* (2018) Cancer Cachexia: Identification by Clinical Assessment versus International Consensus Criteria in Patients with Metastatic Colorectal Cancer. *Nutr Cancer*, 1-8.
22. Pressoir M, Desné S, Berchery D *et al.* (2010) Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. *Br J Cancer* **102**, 966-971.
23. Pacelli F, Bossola M, Rosa F *et al.* (2008) Is malnutrition still a risk factor of postoperative complications in gastric cancer surgery? *Clin Nutr* **27**, 398-407.
24. Correia M, Cravo M, Marques-Vidal P *et al.* (2007) Serum concentrations of TNF-alpha as a surrogate marker for malnutrition and worse quality of life in patients with gastric cancer. *Clin Nutr* **26**, 728-735.
25. Lakenman P, Ottens-Oussoren K, Witvliet-van Nierop J *et al.* (2017) Handgrip Strength Is Associated With Treatment Modifications During Neoadjuvant Chemoradiation in Patients With Esophageal Cancer. *Nutr Clin Pract* **32**, 652-657.
26. Temel JS, Abernethy AP, Currow DC *et al.* (2016) Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *Lancet Oncol* **17**, 519-531.
27. Bozzetti F (2017) Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. *Ann Oncol* **28**, 2107-2118.

28. Gioulbasanis I, Martin L, Baracos VE *et al.* (2015) Nutritional assessment in overweight and obese patients with metastatic cancer: does it make sense? *Ann Oncol* **26**, 217-221.
29. 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.
30. Ramos Chaves M, Boléo-Tomé C, Monteiro-Grillo I *et al.* (2010) The diversity of nutritional status in cancer: new insights. *Oncologist* **15**, 523-530.
31. Ní Bhuachalla É, Daly LE, Power DG *et al.* (2018) Computed tomography diagnosed cachexia and sarcopenia in 725 oncology patients: is nutritional screening capturing hidden malnutrition? *J Cachexia Sarcopenia Muscle* **9**, 295-305.
32. Greenlee H, Unger JM, LeBlanc M *et al.* (2017) Association between Body Mass Index and Cancer Survival in a Pooled Analysis of 22 Clinical Trials. *Cancer Epidemiol Biomarkers Prev* **26**, 21-29.
33. Cespedes Feliciano EM, Kroenke CH, Bradshaw PT *et al.* (2017) Postdiagnosis Weight Change and Survival Following a Diagnosis of Early-Stage Breast Cancer. *Cancer Epidemiol Biomarkers Prev* **26**, 44-50.
34. 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.
35. Daly LE, Power DG, O'Reilly Á *et al.* (2017) The impact of body composition parameters on ipilimumab toxicity and survival in patients with metastatic melanoma. *Br J Cancer* **116**, 310-317.
36. Daly LE, Prado CM, Ryan AM (2018) A window beneath the skin: how computed tomography assessment of body composition can assist in the identification of hidden wasting conditions in oncology that profoundly impact outcomes. *Proc Nutr Soc* **77**, 135-151.
37. Prado CM, Cushen SJ, Orsso CE *et al.* (2016) Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. *Proc Nutr Soc* **75**, 188-198.
38. Daly LE, Ní Bhuachalla É, Power DG *et al.* (2018) Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer. *J Cachexia Sarcopenia Muscle*.
39. Rutten IJ, van Dijk DP, Kruitwagen RF *et al.* (2016) Loss of skeletal muscle during neoadjuvant chemotherapy is related to decreased survival in ovarian cancer patients. *J Cachexia Sarcopenia Muscle* **7**, 458-466.
40. Frontera WR, Zayas AR, Rodriguez N (2012) Aging of human muscle: understanding sarcopenia at the single muscle cell level. *Phys Med Rehabil Clin N Am* **23**, 201-207, xiii.
41. Tan BH, Birdsell LA, Martin L *et al.* (2009) Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res* **15**, 6973-6979.
42. 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.
43. Arrieta O, De la Torre-Vallejo M, López-Macías D *et al.* (2015) Nutritional Status, Body Surface, and Low Lean Body Mass/Body Mass Index Are Related to Dose Reduction and Severe Gastrointestinal Toxicity Induced by Afatinib in Patients With Non-Small Cell Lung Cancer. *Oncologist* **20**, 967-974.
44. Stene GB, Helbostad JL, Amundsen T *et al.* (2014) Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. *Acta Oncol* **54**, 340-348.
45. Kim EY, Kim YS, Park I *et al.* (2015) Prognostic Significance of CT-Determined Sarcopenia in Patients with Small-Cell Lung Cancer. *J Thorac Oncol* **10**, 1795-1799.
46. Sandini M, Patino M, Ferrone CR *et al.* (2018) Association Between Changes in Body Composition and Neoadjuvant Treatment for Pancreatic Cancer. *JAMA Surg* **153**, 809-815.
47. El Amrani M, Vermersch M, Fulbert M *et al.* (2018) Impact of sarcopenia on outcomes of patients undergoing pancreatotomy: A retrospective analysis of 107 patients. *Medicine (Baltimore)* **97**, e12076.
48. Di Sebastiano KM, Yang L, Zbuk K *et al.* (2013) Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia. *Br J Nutr* **109**, 302-312.
49. Cooper AB, Slack R, Fogelman D *et al.* (2015) Characterization of Anthropometric Changes that Occur During Neoadjuvant Therapy for Potentially Resectable Pancreatic Cancer. *Ann Surg Oncol* **22**, 2416-2423.
50. Rollins KE, Tewari N, Ackner A *et al.* (2015) The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. *Clin Nutr* **35**, 1103-1109.
51. Dalal S, Hui D, Bidaut L *et al.* (2012) Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: a pilot study. *J Pain Symptom Manage* **44**, 181-191.
52. Carrara G, Pecorelli N, De Cobelli F *et al.* (2017) Preoperative sarcopenia determinants in pancreatic cancer patients. *Clin Nutr* **36**, 1649-1653.
53. Thoresen L, Frykholm G, Lydersen S *et al.* (2012) The association of nutritional assessment criteria with health-related quality of life in patients with advanced colorectal carcinoma. *Eur J Cancer Care (Engl)* **21**, 505-516.

54. Black D, Mackay C, Ramsay G *et al.* (2017) Prognostic Value of Computed Tomography: Measured Parameters of Body Composition in Primary Operable Gastrointestinal Cancers. *Ann Surg Oncol* **24**, 2241-2251.
55. van Roekel EH, Bours MJL, Te Molder MEM *et al.* (2017) Associations of adipose and muscle tissue parameters at colorectal cancer diagnosis with long-term health-related quality of life. *Qual Life Res* **26**, 1745-1759.
56. Liefvers 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.
57. Thoresen L, Frykholm G, Lydersen S *et al.* (2013) Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal results. *Clin Nutr* **32**, 65-72.
58. Chemama S, Bayar MA, Lanoy E *et al.* (2016) Sarcopenia is Associated with Chemotherapy Toxicity in Patients Undergoing Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis from Colorectal Cancer. *Ann Surg Oncol* **23**, 3891-3898.
59. McSorley ST, Black DH, Horgan PG *et al.* (2017) The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer. *Clin Nutr*.
60. 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.
61. Kurk SA, Peeters PHM, Dorresteijn B *et al.* (2018) Impact of different palliative systemic treatments on skeletal muscle mass in metastatic colorectal cancer patients. *J Cachexia Sarcopenia Muscle*.
62. van Vugt JLA, Coebergh van den Braak RRJ, Lalmahomed ZS *et al.* (2018) Impact of low skeletal muscle mass and density on short and long-term outcome after resection of stage I-III colorectal cancer. *Eur J Surg Oncol* **44**, 1354-1360.
63. van der Kroft G, Bours DMJL, Janssen-Heijnen DM *et al.* (2018) Value of sarcopenia assessed by computed tomography for the prediction of postoperative morbidity following oncological colorectal resection: A comparison with the malnutrition screening tool. *Clin Nutr ESPEN* **24**, 114-119.
64. Broughman JR, Williams GR, Deal AM *et al.* (2015) Prevalence of sarcopenia in older patients with colorectal cancer. *J Geriatr Oncol*.
65. Nakanishi R, Oki E, Sasaki S *et al.* (2018) Sarcopenia is an independent predictor of complications after colorectal cancer surgery. *Surg Today* **48**, 151-157.
66. Malietzis G, Johns N, Al-Hassi HO *et al.* (2016) Low Muscularity and Myosteatosis Is Related to the Host Systemic Inflammatory Response in Patients Undergoing Surgery for Colorectal Cancer. *Ann Surg* **263**, 320-325.
67. Eriksson S, Nilsson JH, Strandberg Holka P *et al.* (2017) The impact of neoadjuvant chemotherapy on skeletal muscle depletion and preoperative sarcopenia in patients with resectable colorectal liver metastases. *HPB (Oxford)* **19**, 331-337.
68. 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.
69. Järvinen T, Ilonen I, Kauppi J *et al.* (2018) Loss of skeletal muscle mass during neoadjuvant treatments correlates with worse prognosis in esophageal cancer: a retrospective cohort study. *World J Surg Oncol* **16**, 27.
70. Elliott JA, Doyle SL, Murphy CF *et al.* (2017) Sarcopenia: Prevalence, and Impact on Operative and Oncologic Outcomes in the Multimodal Management of Locally Advanced Esophageal Cancer. *Ann Surg* **266**, 822-830.
71. Black D, Mackay C, Ramsay G *et al.* (2017) Prognostic Value of Computed Tomography: Measured Parameters of Body Composition in Primary Operable Gastrointestinal Cancers. *Ann Surg Oncol* **24**, 2241-2251.
72. Yip C, Goh V, Davies A *et al.* (2014) Assessment of sarcopenia and changes in body composition after neoadjuvant chemotherapy and associations with clinical outcomes in oesophageal cancer. *Eur Radiol* **24**, 998-1005.
73. Anandavadivelan P, Brismar TB, Nilsson M *et al.* (2016) Sarcopenic obesity: A probable risk factor for dose limiting toxicity during neo-adjuvant chemotherapy in oesophageal cancer patients. *Clin Nutr* **35**, 724-730.
74. Grotenhuis B, Shapiro J, van Adrichem S *et al.* (2016) Sarcopenia/Muscle Mass is not a Prognostic Factor for Short- and Long-Term Outcome After Esophagectomy for Cancer. *World J Surg* **40**, 2698-2704.
75. Tan BH, Brammer K, Randhawa N *et al.* (2015) Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. *Eur J Surg Oncol* **41**, 333-338.
76. 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.
77. Awad S, Tan BH, Cui H *et al.* (2012) Marked changes in body composition following neoadjuvant chemotherapy for oesophagogastric cancer. *Clin Nutr* **31**, 74-77.
78. Paireder M, Asari R, Kristo I *et al.* (2017) Impact of sarcopenia on outcome in patients with esophageal resection following neoadjuvant chemotherapy for esophageal cancer. *Eur J Surg Oncol* **43**, 478-484.
79. Tamandl D, Paireder M, Asari R *et al.* (2016) Markers of sarcopenia quantified by computed tomography predict adverse long-term outcome in patients with resected oesophageal or gastro-oesophageal junction cancer. *Eur Radiol* **26**, 1359-1367.

80. Sato S, Kunisaki C, Suematsu H *et al.* (2018) Impact of Sarcopenia in Patients with Unresectable Locally Advanced Esophageal Cancer Receiving Chemoradiotherapy. *In Vivo* **32**, 603-610.
81. Nishigori T, Okabe H, Tanaka E *et al.* (2016) Sarcopenia as a predictor of pulmonary complications after esophagectomy for thoracic esophageal cancer. *J Surg Oncol* **113**, 678-684.
82. Palmela C, Velho S, Agostinho L *et al.* (2017) Body Composition as a Prognostic Factor of Neoadjuvant Chemotherapy Toxicity and Outcome in Patients with Locally Advanced Gastric Cancer. *J Gastric Cancer* **17**, 74-87.
83. Kudou K, Saeki H, Nakashima Y *et al.* (2017) Prognostic Significance of Sarcopenia in Patients with Esophagogastric Junction Cancer or Upper Gastric Cancer. *Ann Surg Oncol* **24**, 1804-1810.
84. O'Brien S, Twomey M, Moloney F *et al.* (2018) Sarcopenia and Post-Operative Morbidity and Mortality in Patients with Gastric Cancer. *J Gastric Cancer* **18**, 242-252.
85. Tegels JJ, van Vugt JL, Reisinger KW *et al.* (2015) Sarcopenia is highly prevalent in patients undergoing surgery for gastric cancer but not associated with worse outcomes. *J Surg Oncol* **112**, 403-407.
86. Nishigori T, Tsunoda S, Okabe H *et al.* (2016) Impact of Sarcopenic Obesity on Surgical Site Infection after Laparoscopic Total Gastrectomy. *Ann Surg Oncol* **23**, 524-531.
87. Hayashi N, Ando Y, Gyawali B *et al.* (2016) Low skeletal muscle density is associated with poor survival in patients who receive chemotherapy for metastatic gastric cancer. *Oncol Rep* **35**, 1727-1731.
88. Sharma P, Zargar-Shoshtari K, Caracciolo JT *et al.* (2015) Sarcopenia as a predictor of overall survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. *Urol Oncol* **33**, 339.e317-323.
89. Cushen SJ, Power DG, Teo MY *et al.* (2017) Body Composition by Computed Tomography as a Predictor of Toxicity in Patients With Renal Cell Carcinoma Treated With Sunitinib. *Am J Clin Oncol* **40**, 47-52.
90. Psutka SP, Boorjian SA, Moynagh MR *et al.* (2016) Decreased Skeletal Muscle Mass is Associated with an Increased Risk of Mortality after Radical Nephrectomy for Localized Renal Cell Cancer. *J Urol* **195**, 270-276.
91. Antoun S, Lanoy E, Albiges-Sauvin L *et al.* (2014) Clinical implications of body composition assessment by computed tomography in metastatic renal cell carcinoma. *Expert Rev Anticancer Ther* **14**, 279-288.
92. 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.
93. 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.
94. Fukushima H, Nakanishi Y, Kataoka M *et al.* (2016) Prognostic Significance of Sarcopenia in Patients with Metastatic Renal Cell Carcinoma. *J Urol* **195**, 26-32.
95. Auclin E, Bourillon C, De Maio E *et al.* (2017) Prediction of Everolimus Toxicity and Prognostic Value of Skeletal Muscle Index in Patients With Metastatic Renal Cell Carcinoma. *Clin Genitourin Cancer* **15**, 350-355.
96. 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.
97. Harimoto N, Shirabe K, Yamashita Y *et al.* (2013) Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. *Br J Surg* **100**, 1523-1530.
98. Voron T, Tselikas L, Pietrasz D *et al.* (2015) Sarcopenia Impacts on Short- and Long-term Results of Hepatectomy for Hepatocellular Carcinoma. *Ann Surg* **261**, 1173-1183.
99. Kamachi S, Mizuta T, Otsuka T *et al.* (2016) Sarcopenia is a risk factor for the recurrence of hepatocellular carcinoma after curative treatment. *Hepatol Res* **46**, 201-208.
100. Nault JC, Pigneur F, Nelson AC *et al.* (2015) Visceral fat area predicts survival in patients with advanced hepatocellular carcinoma treated with tyrosine kinase inhibitors. *Dig Liver Dis* **47**, 869-876.
101. Del Fabbro E, Parsons H, Warneke CL *et al.* (2012) The relationship between body composition and response to neoadjuvant chemotherapy in women with operable breast cancer. *Oncologist* **17**, 1240-1245.
102. 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.
103. Weinberg MS, Shachar SS, Muss HB *et al.* (2018) Beyond sarcopenia: Characterization and integration of skeletal muscle quantity and radiodensity in a curable breast cancer population. *Breast J* **24**, 278-284.
104. Mazzuca F, Onesti CE, Roberto M *et al.* (2018) Lean body mass wasting and toxicity in early breast cancer patients receiving anthracyclines. *Oncotarget* **9**, 25714-25722.
105. Deluche E, Leobon S, Desport JC *et al.* (2018) Impact of body composition on outcome in patients with early breast cancer. *Support Care Cancer* **26**, 861-868.
106. Shachar SS, Deal AM, Weinberg M *et al.* (2017) Skeletal Muscle Measures as Predictors of Toxicity, Hospitalization, and Survival in Patients with Metastatic Breast Cancer Receiving Taxane-Based Chemotherapy. *Clin Cancer Res* **23**, 658-665.

107. Rier HN, Jager A, Sleijfer S *et al.* (2017) Low muscle attenuation is a prognostic factor for survival in metastatic breast cancer patients treated with first line palliative chemotherapy. *Breast* **31**, 9-15.
108. Kumar A, Moynagh MR, Multinu F *et al.* (2016) Muscle composition measured by CT scan is a measurable predictor of overall survival in advanced ovarian cancer. *Gynecol Oncol* **142**, 311-316.
109. Ataseven B, Luengo TG, du Bois A *et al.* (2018) Skeletal Muscle Attenuation (Sarcopenia) Predicts Reduced Overall Survival in Patients with Advanced Epithelial Ovarian Cancer Undergoing Primary Debulking Surgery. *Ann Surg Oncol* **25**, 3372-3379.
110. Valentine H, François G, Nora K *et al.* (2017) Sarcopenic overweight is associated with early acute limiting toxicity of anti-PD1 checkpoint inhibitors in melanoma patients. *Invest New Drugs* **35**, 436-441.
111. Mayr R, Fritsche HM, Zeman F *et al.* (2018) Sarcopenia predicts 90-day mortality and postoperative complications after radical cystectomy for bladder cancer. *World J Urol* **36**, 1201-1207.
112. Kocher NJ, Jafri S, Balabhadra S *et al.* (2018) Is sarcopenia and sarcopenic obesity associated with clinical and pathological outcomes in patients undergoing radical nephroureterectomy? *Urol Oncol* **36**, 156.e117-156.e122.
113. Hirasawa Y, Nakashima J, Yunaiyama D *et al.* (2016) Sarcopenia as a Novel Preoperative Prognostic Predictor for Survival in Patients with Bladder Cancer Undergoing Radical Cystectomy. *Ann Surg Oncol* **23**, 1048-1054.
114. Fukushima H, Yokoyama M, Nakanishi Y *et al.* (2015) Sarcopenia as a prognostic biomarker of advanced urothelial carcinoma. *PLoS One* **10**, e0115895.
115. Psutka SP, Carrasco A, Schmit GD *et al.* (2014) Sarcopenia in patients with bladder cancer undergoing radical cystectomy: impact on cancer-specific and all-cause mortality. *Cancer* **120**, 2910-2918.
116. Cushen SJ, Power DG, Murphy KP *et al.* (2016) Impact of body composition parameters on clinical outcomes in patients with metastatic castrate-resistant prostate cancer treated with docetaxel. *Clinical Nutrition* **13**, e39-e45.
117. Mason RJ, Boorjian SA, Bhindi B *et al.* (2018) The Association Between Sarcopenia and Oncologic Outcomes After Radical Prostatectomy. *Clin Genitourin Cancer* **16**, e629-e636.
118. Fattouh M, Chang GY, Ow TJ *et al.* (2018) Association between pretreatment obesity, sarcopenia, and survival in patients with head and neck cancer. *Head Neck*.
119. Camus V, Lanic H, Kraut J *et al.* (2014) Prognostic impact of fat tissue loss and cachexia assessed by computed tomography scan in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Eur J Haematol* **93**, 9-18.
120. 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.
121. Xiao DY, Luo S, O'Brian K *et al.* (2016) Impact of sarcopenia on treatment tolerance in United States veterans with diffuse large B-cell lymphoma treated with CHOP-based chemotherapy. *Am J Hematol* **91**, 1002-1007.
122. 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.
123. Veasey Rodrigues H, Baracos VE, Wheler JJ *et al.* (2013) Body composition and survival in the early clinical trials setting. *Eur J Cancer* **49**, 3068-3075.
124. Ní Bhuachalla É, Daly LE, Power DG *et al.* (2017) Computed tomography diagnosed cachexia and sarcopenia in 725 oncology patients: is nutritional screening capturing hidden malnutrition? *J Cachexia Sarcopenia Muscle*.
125. Baumgartner RN, Koehler KM, Gallagher D *et al.* (1998) Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* **147**, 755-763.
126. Mourtzakis M, Prado CM, Lieffers JR *et al.* (2008) A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* **33**, 997-1006.
127. Parsons HA, Tsimberidou AM, Pontikos M *et al.* (2012) Evaluation of the clinical relevance of body composition parameters in patients with cancer metastatic to the liver treated with hepatic arterial infusion chemotherapy. *Nutr Cancer* **64**, 206-217.
128. Srdic D, Plestina S, Sverko-Peternac A *et al.* (2016) Cancer cachexia, sarcopenia and biochemical markers in patients with advanced non-small cell lung cancer-chemotherapy toxicity and prognostic value. *Support Care Cancer* **24**, 4495-4502.
129. Versteeg KS, Blauwhoff-Buskermolen S, Buffart LM *et al.* (2018) Higher Muscle Strength Is Associated with Prolonged Survival in Older Patients with Advanced Cancer. *Oncologist* **23**, 580-585.
130. Takimoto CH (2009) Maximum tolerated dose: clinical endpoint for a bygone era? *Target Oncol* **4**, 143-147.
131. Baker SD, Verweij J, Rowinsky EK *et al.* (2002) Role of body surface area in dosing of investigational anticancer agents in adults, 1991-2001. *J Natl Cancer Inst* **94**, 1883-1888.
132. Felici A, Verweij J, Sparreboom A (2002) Dosing strategies for anticancer drugs: the good, the bad and body-surface area. *Eur J Cancer* **38**, 1677-1684.



133. 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.
134. 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.
135. Sjøblom B, Benth J, Grønberg BH *et al.* (2017) Drug Dose Per Kilogram Lean Body Mass Predicts Hematologic Toxicity From Carboplatin-Doublet Chemotherapy in Advanced Non-Small-Cell Lung Cancer. *Clin Lung Cancer* **18**, e129-e136.
136. Sjøblom B, Grønberg BH, Benth J *et al.* (2015) Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. *Lung Cancer* **90**, 85-91.
137. 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.
138. 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.
139. Shachar SS, Deal AM, Weinberg M *et al.* (2017) Body Composition as a Predictor of Toxicity in Patients Receiving Anthracycline and Taxane-Based Chemotherapy for Early-Stage Breast Cancer. *Clin Cancer Res* **23**, 3537-3543.
140. Ali R, Baracos VE, Sawyer MB *et al.* (2016) Lean body mass as an independent determinant of dose-limiting toxicity and neuropathy in patients with colon cancer treated with FOLFOX regimens. *Cancer Med* **5**, 607-616.
141. Cespedes Feliciano EM, Lee VS, Prado CM *et al.* (2017) Muscle mass at the time of diagnosis of nonmetastatic colon cancer and early discontinuation of chemotherapy, delays, and dose reductions on adjuvant FOLFOX: The C-SCANS study. *Cancer* **123**, 4868-4877.
142. Dijksterhuis WPM, Pruijt MJ, van der Woude SO *et al.* (2019) Association between body composition, survival, and toxicity in advanced esophagogastric cancer patients receiving palliative chemotherapy. *J Cachexia Sarcopenia Muscle*.
143. Kurita Y, Kobayashi N, Tokuhisa M *et al.* (2019) Sarcopenia is a reliable prognostic factor in patients with advanced pancreatic cancer receiving FOLFIRINOX chemotherapy. *Pancreatology* **19**, 127-135.
144. Antoun S, Baracos VE, Birdsell L *et al.* (2010) Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. *Ann Oncol* **21**, 1594-1598.
145. 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.
146. Veasey-Rodrigues H, Parsons HA, Janku F *et al.* (2013) A pilot study of temsirolimus and body composition. *J Cachexia Sarcopenia Muscle* **4**, 259-265.
147. Cousin S, Hollebecque A, Koscielny S *et al.* (2014) Low skeletal muscle is associated with toxicity in patients included in phase I trials. *Invest New Drugs* **32**, 382-387.
148. Wendrich AW, Swartz JE, Bril SI *et al.* (2017) Low skeletal muscle mass is a predictive factor for chemotherapy dose-limiting toxicity in patients with locally advanced head and neck cancer. *Oral Oncol* **71**, 26-33.
149. Evans WJ, Lambert CP (2007) Physiological basis of fatigue. *Am J Phys Med Rehabil* **86**, S29-46.
150. Ryan JL, Carroll JK, Ryan EP *et al.* (2007) Mechanisms of cancer-related fatigue. *Oncologist* **12 Suppl 1**, 22-34.
151. Fearon KC, Voss AC, Husted DS *et al.* (2006) Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *Am J Clin Nutr* **83**, 1345-1350.
152. Hopkinson JB, Brown JC, Okamoto I *et al.* (2012) The effectiveness of patient-family carer (couple) intervention for the management of symptoms and other health-related problems in people affected by cancer: a systematic literature search and narrative review. *J Pain Symptom Manage* **43**, 111-142.
153. Neefjes ECW, van den Hurk RM, Blauwhoff-Buskermolen S *et al.* (2017) Muscle mass as a target to reduce fatigue in patients with advanced cancer. *J Cachexia Sarcopenia Muscle* **8**, 623-629.
154. Nipp RD, Fuchs G, El-Jawahri A *et al.* (2017) Sarcopenia Is Associated with Quality of Life and Depression in Patients with Advanced Cancer. *Oncologist*.
155. Bye A, Sjøblom B, Wentzel-Larsen T *et al.* (2017) Muscle mass and association to quality of life in non-small cell lung cancer patients. *J Cachexia Sarcopenia Muscle* **8**, 759-767.
156. Aapro M, Arends J, Bozzetti F *et al.* (2014) Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. *Ann Oncol* **25**, 1492-1499.
157. Baguley BJ, Skinner TL, Wright ORL (2018) Nutrition therapy for the management of cancer-related fatigue and quality of life: a systematic review and meta-analysis. *Br J Nutr*, 1-48.
158. Bower JE, Ganz PA, Tao ML *et al.* (2009) Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. *Clin Cancer Res* **15**, 5534-5540.
159. Bower JE, Lamkin DM (2013) Inflammation and cancer-related fatigue: mechanisms, contributing factors, and treatment implications. *Brain Behav Immun* **30 Suppl**, S48-57.

160. Wang XS, Zhao F, Fisch MJ *et al.* (2014) Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors. *Cancer* **120**, 425-432.
161. McSorley S, Dolan R, Roxburgh C *et al.* (2017) How and why systemic inflammation worsens quality of life in patients with advanced cancer. *Expert review of quality of life in cancer care* **2**, 167-175.
162. Laird BJ, Fallon M, Hjermstad MJ *et al.* (2016) Quality of Life in Patients With Advanced Cancer: Differential Association With Performance Status and Systemic Inflammatory Response. *J Clin Oncol* **34**, 2769-2775.
163. Baldwin C, Spiro A, Ahern R *et al.* (2012) Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* **104**, 371-385.
164. Pamoukdjian F, Bouillet T, Lévy V *et al.* (2018) Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: A systematic review. *Clin Nutr* **37**, 1101-1113.
165. Shachar SS, Williams GR, Muss HB *et al.* (2016) Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. *Eur J Cancer* **57**, 58-67.
166. Kazemi-Bajestani SM, Mazurak VC, Baracos V (2016) Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. *Semin Cell Dev Biol* **54**, 2-10.
167. Gibson DJ, Burden ST, Strauss BJ *et al.* (2015) The role of computed tomography in evaluating body composition and the influence of reduced muscle mass on clinical outcome in abdominal malignancy: a systematic review. *Eur J Clin Nutr* **69**, 1079-1086.
168. Caan BJ, Meyerhardt JA, Kroenke CH *et al.* (2017) Explaining the Obesity Paradox: The Association between Body Composition and Colorectal Cancer Survival (C-SCANS Study). *Cancer Epidemiol Biomarkers Prev* **26**, 1008-1015.
169. Caan BJ, Cespedes Feliciano EM, Prado CM *et al.* (2018) Association of Muscle and Adiposity Measured by Computed Tomography With Survival in Patients With Nonmetastatic Breast Cancer. *JAMA Oncol* **4**, 798-804.
170. Sjöblom B, Grønberg BH, Wentzel-Larsen T *et al.* (2016) Skeletal muscle radiodensity is prognostic for survival in patients with advanced non-small cell lung cancer. *Clin Nutr* **35**, 1386-1393.
171. Kroenke CH, Prado CM, Meyerhardt JA *et al.* (2018) Muscle radiodensity and mortality in patients with colorectal cancer. *Cancer* **124**, 3008-3015.
172. Brown JC, Caan BJ, Meyerhardt JA *et al.* (2018) The deterioration of muscle mass and radiodensity is prognostic of poor survival in stage I-III colorectal cancer: a population-based cohort study (C-SCANS). *J Cachexia Sarcopenia Muscle* **9**, 664-672.
173. van Baar H, Beijer S, Bours MJL *et al.* (2018) Low radiographic muscle density is associated with lower overall and disease-free survival in early-stage colorectal cancer patients. *J Cancer Res Clin Oncol* **144**, 2139-2147.
174. de Paula NS, Rodrigues CS, Chaves GV (2018) Comparison of the prognostic value of different skeletal muscle radiodensity parameters in endometrial cancer. *Eur J Clin Nutr*.
175. 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.
176. Antoun S, Lanoy E, Iacovelli R *et al.* (2013) Skeletal muscle density predicts prognosis in patients with metastatic renal cell carcinoma treated with targeted therapies. *Cancer* **119**, 3377-3384.
177. Chu MP, Lieffers J, Ghosh S *et al.* (2017) Skeletal muscle density is an independent predictor of diffuse large B-cell lymphoma outcomes treated with rituximab-based chemoimmunotherapy. *J Cachexia Sarcopenia Muscle* **8**, 298-304.
178. Van Rijssen LB, van Huijgevoort NC, Coelen RJ *et al.* (2017) Skeletal Muscle Quality is Associated with Worse Survival After Pancreatoduodenectomy for Periapillary, Nonpancreatic Cancer. *Ann Surg Oncol* **24**, 272-280.
179. Charette N, Vandeputte C, Ameye L *et al.* (2019) Prognostic value of adipose tissue and muscle mass in advanced colorectal cancer: a post hoc analysis of two non-randomized phase II trials. *BMC Cancer* **19**, 134.
180. Sueda T, Takahashi H, Nishimura J *et al.* (2018) Impact of Low Muscularity and Myosteatosis on Long-term Outcome After Curative Colorectal Cancer Surgery: A Propensity Score-Matched Analysis. *Dis Colon Rectum* **61**, 364-374.
181. Okumura S, Kaido T, Hamaguchi Y *et al.* (2017) Impact of Skeletal Muscle Mass, Muscle Quality, and Visceral Adiposity on Outcomes Following Resection of Intrahepatic Cholangiocarcinoma. *Ann Surg Oncol* **24**, 1037-1045.
182. Hopkins JJ, Reif RL, Bigam DL *et al.* (2019) The Impact of Muscle and Adipose Tissue on Long-Term Survival in Patients With Stage I to III Colorectal Cancer. *Dis Colon Rectum*.
183. Dolan RD, Almasaudi AS, Dieu LB *et al.* (2018) The relationship between computed tomography-derived body composition, systemic inflammatory response, and survival in patients undergoing surgery for colorectal cancer. *J Cachexia Sarcopenia Muscle*.
184. van Dijk DPJ, Krill M, Farshidfar F *et al.* (2018) Host phenotype is associated with reduced survival independent of tumour biology in patients with colorectal liver metastases. *Journal of Cachexia, Sarcopenia and Muscle*.
185. Park SE, Hwang IG, Choi CH *et al.* (2018) Sarcopenia is poor prognostic factor in older patients with locally advanced rectal cancer who received preoperative or postoperative chemoradiotherapy. *Medicine* **97**, e13363.
186. Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA *et al.* (2017) Association of Systemic Inflammation and Sarcopenia With Survival in Nonmetastatic Colorectal Cancer. *JAMA Oncology* **3**.

187. Malietzis G, Currie AC, Athanasiou T *et al.* (2016) Influence of body composition profile on outcomes following colorectal cancer surgery. *Br J Surg* **103**, 572-580.
188. 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.
189. van Vledder MG, Levolger S, Ayez N *et al.* (2012) Body composition and outcome in patients undergoing resection of colorectal liver metastases. *Br J Surg* **99**, 550-557.
190. Kuwada K, Kuroda S, Kikuchi S *et al.* (2018) Sarcopenia and Comorbidity in Gastric Cancer Surgery as a Useful Combined Factor to Predict Eventual Death from Other Causes. *Annals of Surgical Oncology* **25**, 1160-1166.
191. Nakashima Y, Saeki H, Nakanishi R *et al.* (2018) Assessment of Sarcopenia as a Predictor of Poor Outcomes after Esophagectomy in Elderly Patients with Esophageal Cancer. *Annals of surgery* **267**, 1100-1104.
192. Nishigori T, Tsunoda S, Obama K *et al.* (2018) Optimal Cutoff Values of Skeletal Muscle Index to Define Sarcopenia for Prediction of Survival in Patients with Advanced Gastric Cancer. *Annals of Surgical Oncology* **25**, 3596-3603.
193. Lee JS, Kim YS, Kim EY *et al.* (2018) Prognostic significance of CT-determined sarcopenia in patients with advanced gastric cancer. *PLoS one* **13**, e0202700.
194. O'Brien S, Twomey M, Moloney F *et al.* (2018) Sarcopenia and Post-Operative Morbidity and Mortality in Patients with Gastric Cancer. *J Gastric Cancer* **18**, 242-252.
195. Zheng ZF, Lu J, Zheng CH *et al.* (2017) A Novel Prognostic Scoring System Based on Preoperative Sarcopenia Predicts the Long-Term Outcome for Patients After R0 Resection for Gastric Cancer: Experiences of a High-Volume Center. *Ann Surg Oncol* **24**, 1795-1803.
196. Psutka SP, Boorjian SA, Moynagh MR *et al.* (2015) Mortality after radical cystectomy: impact of obesity versus adiposity after adjusting for skeletal muscle wasting. *J Urol* **193**, 1507-1513.
197. Nakamura N, Ninomiya S, Matsumoto T *et al.* (2019) Prognostic impact of skeletal muscle assessed by computed tomography in patients with acute myeloid leukemia. *Ann Hematol* **98**, 351-359.
198. Nakamura N, Hara T, Shibata Y *et al.* (2015) Sarcopenia is an independent prognostic factor in male patients with diffuse large B-cell lymphoma. *Ann Hematol* **94**, 2043-2053.
199. 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.
200. Camus V, Lanic H, Kraut J *et al.* (2014) Prognostic impact of fat tissue loss and cachexia assessed by computed tomography scan in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Eur J Haematol* **93**, 9-18.
201. Fattouh M, Chang GY, Ow TJ *et al.* (2019) Association between pretreatment obesity, sarcopenia, and survival in patients with head and neck cancer. *Head Neck* **41**, 707-714.
202. Chergi N, Bril SI, Emmelot-Vonk MH *et al.* (2019) Sarcopenia is a prognostic factor for overall survival in elderly patients with head-and-neck cancer. *Eur Arch Otorhinolaryngol.*
203. Choi Y, Oh DY, Kim TY *et al.* (2015) Skeletal Muscle Depletion Predicts the Prognosis of Patients with Advanced Pancreatic Cancer Undergoing Palliative Chemotherapy, Independent of Body Mass Index. *PLoS one* **10**, e0139749.
204. Takada H, Kurosaki M, Nakanishi H *et al.* (2018) Impact of pre-sarcopenia in sorafenib treatment for advanced hepatocellular carcinoma. *PLoS one* **13**.
205. Choi MH, Yoon SB, Lee K *et al.* (2018) Preoperative sarcopenia and post-operative accelerated muscle loss negatively impact survival after resection of pancreatic cancer. *J Cachexia Sarcopenia Muscle* **9**, 326-334.
206. Begini P, Gigante E, Antonelli G *et al.* (2017) Sarcopenia predicts reduced survival in patients with hepatocellular carcinoma at first diagnosis. *Annals of hepatology* **16**, 107-114.
207. Harimoto N, Yoshizumi T, Shimokawa M *et al.* (2016) Sarcopenia is a poor prognostic factor following hepatic resection in patients aged 70 years and older with hepatocellular carcinoma. *Hepatol Res* **46**, 1247-1255.
208. Fujiwara N, Nakagawa H, Kudo Y *et al.* (2015) Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. *J Hepatol* **63**, 131-140.
209. Rollins KE, Tewari N, Ackner A *et al.* (2016) The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. *Clin Nutr* **35**, 1103-1109.
210. Levolger S, van Vledder MG, Muslem R *et al.* (2015) Sarcopenia impairs survival in patients with potentially curable hepatocellular carcinoma. *J Surg Oncol* **112**, 208-213.
211. Itoh S, Shirabe K, Matsumoto Y *et al.* (2014) Effect of body composition on outcomes after hepatic resection for hepatocellular carcinoma. *Ann Surg Oncol* **21**, 3063-3068.
212. Cortellini A, Palumbo P, Porzio G *et al.* (2018) Single-institution study of correlations between skeletal muscle mass, its density, and clinical outcomes in non-small cell lung cancer patients treated with first-line chemotherapy. *Thorac Cancer* **9**, 1623-1630.
213. Shoji F, Matsubara T, Kozuma Y *et al.* (2017) Relationship Between Preoperative Sarcopenia Status and Immunonutritional Parameters in Patients with Early-stage Non-small Cell Lung Cancer. *Anticancer research* **37**, 6997-7003.

214. Kim EY, Kim YS, Park I *et al.* (2015) Prognostic Significance of CT-Determined Sarcopenia in Patients with Small-Cell Lung Cancer. *J Thorac Oncol* **10**, 1795-1799.
215. 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.
216. Zhang S, Tan S, Jiang Y *et al.* (2018) Sarcopenia as a predictor of poor surgical and oncologic outcomes after abdominal surgery for digestive tract cancer: A prospective cohort study. *Clin Nutr.*
217. Basile D, Parnofiello A, Vitale MG *et al.* (2019) The IMPACT study: early loss of skeletal muscle mass in advanced pancreatic cancer patients. *J Cachexia Sarcopenia Muscle.*
218. Park HS, Kim HS, Beom SH *et al.* (2018) Marked Loss of Muscle, Visceral Fat, or Subcutaneous Fat After Gastrectomy Predicts Poor Survival in Advanced Gastric Cancer: Single-Center Study from the CLASSIC Trial. *Ann Surg Oncol* **25**, 3222-3230.
219. Nattenmüller J, Wochner R, Muley T *et al.* (2017) Prognostic Impact of CT-Quantified Muscle and Fat Distribution before and after First-Line-Chemotherapy in Lung Cancer Patients. *PLoS One* **12**, e0169136.
220. Takeda Y, Akiyoshi T, Matsueda K *et al.* (2018) Skeletal muscle loss is an independent negative prognostic factor in patients with advanced lower rectal cancer treated with neoadjuvant chemoradiotherapy. *PLoS One* **13**, e0195406.
221. 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.
222. Solheim TS, Laird BJA, Balstad TR *et al.* (2018) Cancer cachexia: rationale for the MENAC (Multimodal-Exercise, Nutrition and Anti-inflammatory medication for Cachexia) trial. *BMJ Support Palliat Care* **8**, 258-265.
223. Brown JC, Cespedes Feliciano EM, Caan BJ (2018) The evolution of body composition in oncology-epidemiology, clinical trials, and the future of patient care: facts and numbers. *J Cachexia Sarcopenia Muscle* **9**, 1200-1208.