

VU Research Portal

Diagnosis and clinical consequences of cachexia in patients with advanced cancer

Buskermolen, S.

2016

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Buskermolen, S. (2016). *Diagnosis and clinical consequences of cachexia in patients with advanced cancer*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

Chapter 8

Loss of muscle mass during chemotherapy
is predictive for poor survival of patients
with metastatic colorectal cancer

Susanne Blauwhoff-Buskermolen

Kathelijn S.Versteeg

Marian A.E. de van der Schueren

Nicole R. den Braver

Johannes Berkhof

Jacqueline A.E. Langius

Henk M.W.Verheul

Journal of Clinical Oncology 2016; 34(12):1339-1344

Abstract

Purpose: Low muscle mass is present in approximately 40% of patients with metastatic colorectal cancer (mCRC) and may be associated with poor outcome. We studied change in skeletal muscle during palliative chemotherapy in patients with mCRC and its association with treatment modifications and overall survival.

Methods: In 67 patients with mCRC (mean age 66.4 ± 10.6 years, 63% male), muscle area (cm^2) was assessed using L3 CT scans before and during palliative chemotherapy. Treatment modifications due to toxicity were evaluated including delay, dose reduction or termination of chemotherapy. Multiple regression analyses were performed for the association between change in muscle area and treatment modifications and secondly overall survival.

Results: Muscle area of patients with mCRC decreased significantly during 3 months of chemotherapy by 6.1% (95% CI -8.4 to -3.8, $p < 0.001$). Change in muscle area was not associated with treatment modifications. However, patients with a $\geq 9\%$ muscle loss during treatment (lowest tertile) had significantly lower survival rates than patients with muscle loss of less than 9% (at 6 months 33% v 69% of patients alive and at 1 year 17% v 49% of patients alive; log-rank $p = 0.001$). Muscle loss of $\geq 9\%$ remained independently associated with survival when adjusted for sex, age, baseline LDH concentration, comorbidity, mono- or multi-organ metastases, treatment line and tumor progression at first evaluation by CT scan (HR 4.47, 95% CI 2.21-9.05, $p < 0.001$).

Conclusion: Muscle area decreased significantly during chemotherapy and was independently associated with survival in patients with mCRC. Further clinical evaluation is required to determine whether nutritional interventions and exercise training may preserve muscle area and thereby improve outcome.

Introduction

Colorectal cancer is the third most common cancer in the world, with nearly 1.4 million new cases diagnosed in 2012 (1). Approximately one-fifth of patients are being diagnosed with synchronic metastatic disease (mCRC), while almost 50% of patients will eventually develop metastatic disease after their primary diagnosis. A large number of patients with mCRC is overweight or obese with prevalence ranging between 45-53% (2-4). By way of contrast, a low muscle mass is present in approximately 40% of patients, and not only in underweight patients (3). A low muscle mass in combination with a body mass index (BMI) above 30 kg/m² is referred to as 'sarcopenic obesity' and was a prognostic indicator of worse overall survival in patients with pancreatic cancer (5) and patients with solid tumours of the respiratory or gastrointestinal tract (6).

Causes of low muscle mass may be found in a combination of reduced food intake, low physical activity and abnormal metabolism (7). Abnormal metabolism was found to be the most important contributor to low muscle mass in progressive end-stage disease (8-10) and is referred to as 'cachexia'. Reversing muscle loss in patients with cancer is difficult, because cachexia is caused by tumor activity and released cytokines. Nevertheless, during active anticancer treatment, there might be a window of opportunity for nutritional support and exercise programs.

Cross-sectional studies have shown that low muscle mass is associated with poor survival and increased treatment toxicity in patients with colorectal cancer undergoing treatment with chemotherapy (2;3;11-13). However, longitudinal studies on changes in muscle mass during chemotherapy for mCRC are lacking. The aim of this prospective study was to evaluate muscle mass changes using single Computed Tomography (CT) images of the abdominal region (L3) in relation to chemotherapy toxicity and survival in patients with mCRC. Secondly, baseline muscle measurements in relation to clinical benefit and toxicities from chemotherapy were evaluated.

Materials and Methods

Data were prospectively collected in a study on (pre)cachexia, in which nutritional and biochemical features from patients with advanced cancer were evaluated before start of chemotherapy at the VU University Medical Center, Amsterdam, The Netherlands. A first interim analysis of these data was published in 2014 (14).

Patients were invited to enter the study before start of chemotherapy. Inclusion criteria were: adult patients with stage III/IV lung cancer; stage IV breast cancer; stage IV prostate cancer or stage IV colorectal cancer who are planned to receive chemotherapy. Exclusion criteria were: systemic treatment in the past month and clinically overt ascites or serious pitting edema.

Measurements of nutritional and biochemical features were performed at one time point: before start of chemotherapy treatment. For the current subgroup analyses, all consecutive patients with mCRC, recruited between October 2011 and January 2014, were selected. CT scans made for diagnostic purposes, at baseline and during treatment with chemotherapy (according to standard evaluation schemes) were used to evaluate change in muscle mass during treatment.

The research protocol was approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants.

Measurements

Skeletal muscle measurement

Skeletal muscle area (cm^2) was measured with SliceOmatic Software V 5.0 (Tomovision, Magog, Canada) using routine CT scans conducted for diagnostic purposes. We used 2 CT scans: one at baseline (before start of chemotherapy) and one during treatment, according to standard evaluation schemes. Median time between the two scans was 78 (IQR 67-92) days. The third lumbar vertebra (L3) was used as a standard landmark as this correlates best with whole body muscle mass (15;16); the first image extending from L3 to the iliac crest was chosen to measure total muscle cross-sectional area. The L3 region contains psoas, paraspinal muscles, and the abdominal wall muscles. These muscles were identified based on their anatomic features by two trained researchers (SB and NdB). The structures of those specific muscles were quantified based on pre-established thresholds of Hounsfield Units (HU) (-29 to + 150) of skeletal muscle tissue (17). Cross-sectional areas (cm^2) of the sum of all these muscles were computed by summing tissue pixels and multiplying by the pixel surface area for each patient at each time point. We found a mean coefficient of variation between observers of 0.6% for skeletal muscle area in a random sample of 20 patients, which is regarded to be low (18). To estimate total body skeletal muscle mass, the regression equation of Shen et al (15) was used. Changes between the first and second scan were calculated as

a rate of change per 3 months, meaning change per first evaluation, to be able to compare with available literature (19;20). Relative muscle change per three months was categorized into tertiles of muscle change; tertile 1: Highest muscle loss until 9%, 2: Muscle loss of 9% to 1.5% and 3: muscle loss of 1.5% until highest gain in muscle. Muscle density (MD) was measured using the muscle radiation attenuation rate (in HU) because of its prognostic value in patients with cancer (21;22).

Skeletal Muscle Index (SMI) was calculated as the ratio of skeletal muscle area (cm^2)/height (m)². Body height was measured using a stadiometer; the patient was standing barefoot and height was determined to the nearest cm. Sex- and BMI-specific cut-off values of low SMI and low MD according to Martin et al (23) were used to define patients with normal and low values.

Body weight

Baseline body weight was measured within 0.2 kg on a calibrated scale (Seca type 888) and self-reported weight loss in the past 6 months was noted. Body weight during chemotherapy was obtained from the medical records within 2 weeks of the date of the second CT scan. A correction factor for clothes or clothes and shoes was made by deducting weight with respectively 1.6 and 2.0 kilograms for men and 1.0 and 1.3 kilograms for women (24). To compare with change in muscle mass, we calculated the rate of change (%) standardized to three months. BMI was calculated as the ratio of body weight (kg)/height (m)².

Treatment modifications

Treatment modifications that were taken into account consisted of delay, dose reduction or discontinuation of chemotherapy due to reported toxicity in the period between the two CT scans. Other modifications, such as delay because of patient's preference or vacation were not taken into consideration. Also, the number of treatment modifications was not taken into account, as treatment modifications were measured on a dichotomous scale (present or absent). Information on treatment modifications was obtained from medical records.

Survival

Total follow-up time was 3.5 years. Survival time was defined as time from inclusion in the study until death or last consultation in the hospital.

Covariates

The following variables were obtained from the medical record and used in statistical analyses as covariates, as they carry prognostic value: sex, age, treatment line ($\geq 2^{\text{nd}}$ versus 1^{st} , counted as consecutive chemotherapy line based on the fact that a new type of chemotherapy was introduced), start dose of chemotherapy (normal/decreased), WHO performance status (≥ 2 versus 0/1), Charlson Comorbidity Index (25) (CCI ≥ 1 versus 0), serum lactate dehydrogenase (LDH, measured within four weeks before start of chemotherapy), severity of disease (multi-organ vs. mono-organ metastases) and outcome of first evaluation CT scan ('progression' vs. 'stable disease/regression of the tumor').

Statistics

Statistical analyses were performed using SPSS for Windows v. 20.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics (count (%), means \pm SD, or median and interquartile ranges, as appropriate) were used to describe the study sample.

Paired samples t-tests were conducted to assess changes in skeletal muscle area, MD and body weight. Spearman's correlation coefficient was used to assess correlation between body weight change and muscle area change.

Logistic regression analyses were used to test associations between treatment modifications and muscle measurements (baseline SMI: low vs. normal (reference), baseline MD: low versus normal (reference) and change in muscle area per percent). In multiple regression analyses, adjustments were made for age, sex, comorbidity score, start dose, treatment line and WHO performance status.

Kaplan-Meier curves for overall survival were constructed separately for patients in the first, second and third tertile of relative muscle change. Differences between the curves were evaluated by log-rank tests. Six months and 1 year survival proportions were also calculated.

Cox proportional hazards analyses were performed to test associations between overall survival and muscle measurements (baseline SMI: low vs. normal (reference), baseline MD: low versus normal (reference) and change in muscle area per percent). In multiple regression analyses, adjustments were made for age, sex, baseline serum LDH level, comorbidity score, severity of disease and treatment line. For analyses including change in muscle mass during chemotherapy, an extra adjustment was performed for tumor progression at 1st evaluation by CT scan (progression vs response/stable disease (reference)) as a potential confounder for rate of muscle

loss and survival. Furthermore, overall survival times were calculated with the second CT scan as starting point for these analyses.

A p-value of ≤ 0.05 was considered significant for all analyses.

Results

Sixty-seven with mCRC and evaluable CT scans at baseline were included. For longitudinal analyses, four patients were excluded because they had died (n=2) or because they had no CT scan for other reasons (n=2) at the time of evaluation.

Table 1. Baseline patient characteristics (n=67)

	n (%)
Age (years)*	66.4 (10.6)
Sex (male)	42 (63)
Metastases	
Liver only	12 (18)
Multi-organ	55 (82)
Treatment line	
1st line	52 (78)
2nd line or higher	15 (23)
Start dose of chemotherapy	
Full dose	52 (78)
Reduced	15 (22)
Chemotherapy type	
Capecitabine + oxaliplatin (\pm bevacizumab)	44 (66)
5FU + oxaliplatin (\pm bevacizumab)	5 (7)
Capecitabine + Irinotecan	2 (3)
Capecitabine + Bevacizumab	1 (1)
Capecitabine monotherapy	5 (7)
Irinotecan monotherapy	10 (15)
WHO performance status	
0	27 (40)
I	35 (52)
≥ 2	5 (8)
Charlson Comorbidity Index	
0	45 (67)
1-2	19 (28)
≥ 3	3 (5)

* mean (SD)

Baseline patient and treatment characteristics

The mean age of patients was 66.4 ± 10.6 years and 63% was male. Eighty-two percent of patients had multi-organ metastases and 78 percent received first line chemotherapy. Patients received standard systemic treatment for colorectal cancer; the majority of them ($n=44$, 66%) received a combination of capecitabine plus oxaliplatin with or without bevacizumab (CAPOX B or CAPOX, respectively, table 1).

Critical weight loss of $>5\%$ in 6 months before start of chemotherapy was prevalent in 33% of patients. At baseline, more than half of the patients were overweight (55%) or obese (8%) while 57% suffered from a low SMI. Sarcopenic obesity was present in one patient (table 2).

Table 2. Nutritional status at baseline ($n=67$)

	n (%)
Weight change in 6 months prior to baseline	
Weight gain $> 5\%$	6 (9)
Stable weight	39 (58)
Weight loss 5-10%	15 (22)
Weight loss $>10\%$	7 (10)
Body mass index	
$<20 \text{ kg/m}^2$	4 (6)
$20\text{-}24.9 \text{ kg/m}^2$	21 (31)
$25\text{-}29.9 \text{ kg/m}^2$	37 (55)
$>30 \text{ kg/m}^2$	5 (8)
Skeletal muscle index $<$ reference value*	38 (57)
Skeletal muscle density $<$ reference value*	43 (64)
Sarcopenic obesity†	1 (2)

*Sex- and BMI specific cut-off values: Martin et al (23)

†BMI $\geq 30 \text{ kg/m}^2$ and low skeletal muscle index according to Martin et al (23)

Changes in muscle mass and body weight

Skeletal muscle area decreased, both in males and females, by 6.1% (95% CI -8.4 to -3.8, $p<0.001$) in three months, corresponding to 1.7 kg in males and 1.1 kg in females. The proportion of patients with low SMI increased from 57% at baseline to 70% at the second CT scan (table 3).

Table 3. Muscle area and density during chemotherapy (n=63)

	First CT scan		Second CT scan		Change		Change /3 months		Relative change/3 months (%)	
	Mean	SD	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI
Muscle area (cm ²)	138.6	32.1	131.9	31.7	-6.6		-8.6	-11.8 to -5.3	-6.1	-8.4 to -3.8
Males	156.8	24.4	149.2	25.3	-7.6		-9.7	-14.6 to -4.9	-6.2	-9.3 to -3.1
Females	108.9	17.5	103.9	17.9	-5.0		-6.6	-10.5 to -2.7	-6.0	-9.5 to -2.5
Muscle density (HU)	33.8	8.1	32.8	8.8	-1.1		-1.6	-3.2 to 0.0	-3.7	-9.2 to 1.8
Males	35.2	7.5	33.6	9.0	-1.6		-2.0	-3.9 to -0.2	-5.8	-11.5 to -0.03
Females	31.6	8.8	31.5	8.4	-0.1		-0.9*	-4.0 to 2.1	-0.3	-11.7 to 11.1

Abbreviations: HU: Hounsfield Units

*Skewed data, median - 0.3, IQR -3.8 to 4.1

Body weight decreased significantly in females by 4.4% (95%CI -8.5 to -0.4, $p=0.031$), corresponding with -2.9 kg ($n=18$) but not in males (change -3.3%, 95% CI -8.1 to 1.5, $p=0.167$). Change in muscle area correlated significantly with change in body weight for males, but not for females (Spearman's rho for males: 0.34, $p=0.050$, for females: 0.36, $p=0.140$).

MD decreased in males by 5.8% (95% CI -11.5 to -0.03 $p=0.049$) but remained stable in females (-0.3%, 95% CI -11.7 to 11.1, $p=0.957$, table 3).

Treatment modifications

Treatment modifications due to toxicity occurred in 29 patients (43%), including delay of treatment in 13 patients (19%), dose reduction in 18 patients (27%) and discontinuation of treatment in 6 patients (9%).

SMI and MD at baseline were not associated with treatment modifications (SMI OR: 1.01, 95% CI 0.35-2.91, $p=0.99$; MD OR: 1.43, 95% CI 0.44-4.63, $p=0.555$). In the more homogenous group of patients undergoing first line treatment with CAPOX, also no association was found ($n=35$, SMI OR: 0.64 (95% CI: 0.07-5.71), $p=0.692$; MD OR 1.21 (95% CI 0.15-9.96), $p=0.857$). A change in skeletal muscle area during treatment was not associated with treatment modifications, neither in the total cohort (OR per 1% decrease: 1.03 (95% CI 0.95-1.12) $p=0.441$), nor in a homogenous group of patients undergoing first line treatment with CAPOX ($n=34$, OR 1.07 (95% CI 0.95-1.22), $p=0.274$).

Survival

Median OS was 17.5 (95% CI 13.3-21.7) months for patients receiving first line chemotherapy and 8.5 (95% CI 4.4-12.6) months for patients receiving second line chemotherapy or higher. Survival curves were significantly different for the tertiles of muscle change (log-rank: $p=0.005$, figure 1).

In pairwise comparison, the survival curve of tertile 1 ($\geq 9\%$ muscle loss) was significantly different from the survival curve of tertile 2 (muscle loss of 9 to 1.5%, log-rank: $p=0.007$) and also from the survival curve of tertile 3 (-1.5% until highest gain in muscle, log-rank: $p=0.009$). However, the survival curve of tertile 2 was not significantly different from the survival curve of tertile 3 (log-rank: $p=0.961$) therefore tertile 2 and 3 were pooled (cut-off: 9% muscle loss).

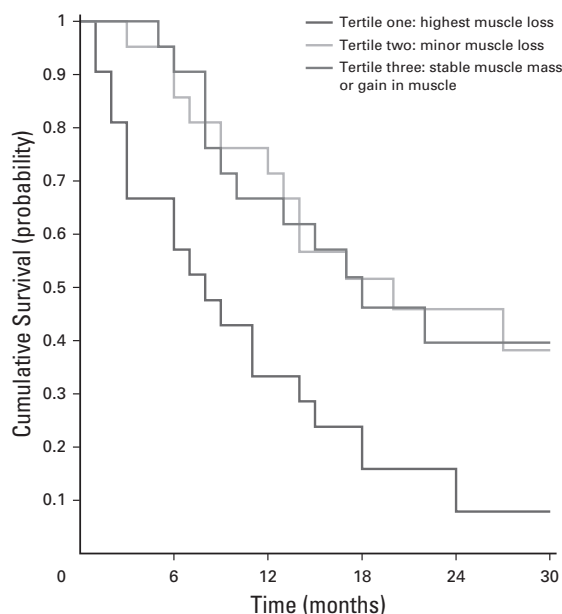


Figure 1. Kaplan Meier curve for tertiles of muscle change

Patients with muscle loss of $\geq 9\%$ (tertile 1) during chemotherapy had significantly lower overall survival rates than patients with $<9\%$ muscle loss (tertile 2 and 3): at 6 months 33% vs. 69% of patients were alive and at 1 year 17% vs. 49% of patients were alive; log-rank $p=0.001$. Muscle loss of $\geq 9\%$ remained independently associated with shorter survival when adjusted for sex, age, baseline LDH concentration, comorbidity, mono- or multi-organ metastases, treatment line and tumor progression at 1st evaluation by CT scan (HR 4.47, 95%CI 2.21-9.05, $p<0.01$). Low MD at baseline was associated with shorter survival after adjustment for covariates, (HR 2.38, 95% CI 1.16-4.87, $p=0.018$). Low SMI at baseline was not associated with survival (table 4).

Table 4. Associations between muscle area and muscle density with overall survival

	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Low SMI baseline (n=67)	1.30 (0.72-2.35)	0.390	1.65 (0.85-3.18)*	0.138
Low MD baseline (n=67)	1.36 (0.74-2.50)	0.321	2.38 (1.16-4.87)*	0.018
$\geq 9\%$ decrease in muscle (n=63)	2.69 (1.45-5.01)	0.002	4.47 (2.21-9.05)**	<0.001

Abbreviation: SMI: skeletal muscle index; MD: muscle density

* adjusted for sex, age, LDH concentration, comorbidity, metastases & chemotherapy line

** adjusted for sex, age, LDH concentration, comorbidity, metastases, chemotherapy line and tumor progression at 1st evaluation by CT scan

Discussion

This is the first study to present a change in muscle area during palliative chemotherapy for patients with mCRC. Patients with 9% or more decrease in muscle area during chemotherapy, the lowest tertile of patients, had significantly lower overall survival rates than patients with less than 9% decrease, independent of known prognostic covariates.

Previously, a rapid decrease in skeletal muscle mass has been shown in patients with colorectal cancer in the last year of their life (8;9). In the current study, patients lost skeletal muscle during active anticancer treatment. The rate of muscle loss was comparable to that of patients with cholangiocarcinoma and esophageal cancer during treatment (19;20). Compared to muscle loss in normal aging, patients with cancer suffer from a twenty-four-fold more rapid loss of muscle mass than normal: 6% muscle loss in 3 months (table 2) versus 1% per year (26). Overall consequences of muscle atrophy in humans are found to be devastating; increased risk of falling (27), diminished self-reliance (28), decreased quality of life, increased risk of treatment-related complications and shorter survival (29).

Although previous studies described an association between reduced muscle mass before treatment and treatment modifications (2;11), we did not observe this association. A possible explanation for this may be found in the heterogeneity regarding treatment regimens and follow-up time: six different treatment regimens were recorded and follow-up time depended on the timing of the second CT scan. Prado (11) and Barrett (2) looked at homogeneous groups of patients with mCRC with one type of chemotherapy and specific follow-up time (e.g. number of cycles). Nevertheless, in post-hoc analyses no associations between skeletal muscle and treatment toxicity in a homogeneous group of patients who were treated with Capecitabine and Oxaliplatin in first line treatment were found either. We hypothesize that muscle mass may not be related to bone marrow toxicity, one of the most important types of toxicity of this treatment regimen (30). Furthermore, peripheral neuropathy is a type of toxicity which might be related to muscle loss but has been regarded as a more long-term type of toxicity and therefore, may not yet be present in the first three months of treatment.

Although there was an association with low MD at baseline (in multiple regression analysis only), low SMI at baseline was not associated with survival in the evaluated group of patients with mCRC. This is in contrast with some (5;6;12;31;32), but not all previous findings. Stene and colleagues described comparable results in non small

cell lung cancer (33) and Antoun and colleagues have also found comparable results in patients with melanoma (22). One possible explanation might be found in the phenomenon of 'sarcopenic obesity': patients with sarcopenic obesity had worse prognosis compared to patients without sarcopenic obesity in earlier studies (5;6). Although the number of obese patients in our study was too small for subgroup analyses, we found that the prevalence of low muscle mass in obese patients in our study was comparable to the prevalence found in the study of Prado and colleagues (6); 20% (1/5) versus 15% (38/250), respectively. Muscle loss during chemotherapy was associated with worse overall survival, independent of important prognostic covariates. This is a new finding and raises the question whether interventions aimed at preservation of muscle mass during treatment are effective to improve outcome. One example of a promising intervention might be increasing physical activity during treatment, as this has been proven to improve muscle strength in cancer survivors (34) and during chemotherapy (35). Another promising intervention might be nutritional counselling with use of high amounts of proteins during the day (36) with high enough thresholds per meal (37) as this also has been proven to increase protein synthesis in healthy elderly. Potentially, the two interventions may be optimal when combined (38). The use of ghrelin agonists for the treatment of cancer-associated anorexia could also be considered (39). Furthermore, future studies should consider recruiting not only patients with severe weight loss or cachexia, as we have shown that muscle loss during treatment was a predictor of poor survival independent of the amount of muscle mass at baseline.

Alternatively, causes of muscle loss could be studied more in depth to find rational intervention possibilities. For example, the intervention strategy will be different when anorexia is the most important cause of muscle loss than when cachexia is the most important cause of muscle loss. In order to study this, a higher number of patients is required to also evaluate food intake and energy expenditure before and during chemotherapy.

In conclusion, significant muscle loss occurred in patients with mCRC during chemotherapy. Muscle loss of 9% or more during chemotherapy was independently associated with a poorer survival. Future studies should investigate causes of muscle loss and whether interventions may attenuate or improve muscle mass during treatment and may lead to improvement in clinical outcomes such as survival.

References

1. World Health Organisation International Agency for Research on cancer: GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. 2014. 27-6-2014.
2. Barret M, Antoun S, Dalban C, Malka D, Mansoubakht T, Zaanani A, Latko E, Taieb J. Sarcopenia is linked to treatment toxicity in patients with metastatic colorectal cancer. *Nutr Cancer* 2014;66:583-9.
3. Thoresen L, Frykholm G, Lydersen S, Ulveland H, Baracos V, Prado C, Birdsall L, Falkmer U. Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal results. *Clin Nutr* 2013;32:65-72.
4. Barret M, Malka D, Aparicio T, Dalban C, Locher C, Sabate JM, Louafi S, Mansoubakht T, Bonnetain F, Attar A et al. Nutritional status affects treatment tolerability and survival in metastatic colorectal cancer patients: results of an AGEO prospective multicenter study. *Oncology* 2011;81:395-402.
5. Tan BHL, Birdsall LA, Martin L, Baracos VE, Fearon KCH. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res* 2009;15:6973-9.
6. Prado CMM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008;9:629-35.
7. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;12:489-95.
8. Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CMM, Baracos VE. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. *Am J Clin Nutr* 2009;89:1173-9.
9. Prado CM, Sawyer MB, Ghosh S, Lieffers JR, Esfandiari N, Antoun S, Baracos VE. Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? *Am J Clin Nutr* 2013;98:1012-9.
10. Wallengren O, Iresjö B, Lundholm K, Bosaeus I. Loss of muscle mass in the end of life in patients with advanced cancer. *Support Care Cancer* 2014.
11. Prado CMM, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T, Butts CA, Scarfe AG, Sawyer MB. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin Cancer Res* 2007;13:3264-8.
12. van Vledder MG, Levogler S, Ayez N, Verhoef C, Tran TCK, Ijzermans JNM. Body composition and outcome in patients undergoing resection of colorectal liver metastases. *Br J Surg* 2012;99:550-7.
13. Malietzis G, Aziz O, Bagnall NM, Johns N, Fearon KC, Jenkins JT. The role of body composition evaluation by computerized tomography in determining colorectal cancer treatment outcomes: a systematic review. *Eur J Surg Oncol* 2015;41:186-96.
14. Blauwhoff-Buskermolen S, de van der Schueren MAE, Verheul HMW, Langius JAE. 'Pre-cachexia': a non-existing phenomenon in cancer? *Ann Oncol* 2014;25:1668-9.
15. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, Heymsfield SB, Heshka S. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol* 2004;97:2333-8.
16. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. 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* 2008;33:997-1006.
17. Mitsopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol* (1985) 1998;85:115-22.
18. MacDonald AJ, Greig CA, Baracos V. The advantages and limitations of cross-sectional body composition analysis. *Curr Opin Support Palliat Care* 2011;5:342-9.
19. Awad S, Tan BH, Cui H, Halla A, Fearon KCH, Parsons SL, Catton JA, Lobo DN. Marked changes in body composition following neoadjuvant chemotherapy for oesophagogastric cancer. *Clin Nutr* 2012;31:74-7.

20. Prado CMM, Bekaii-Saab T, Doyle LA, Shrestha S, Ghosh S, Baracos VE, Sawyer MB. Skeletal muscle anabolism is a side effect of therapy with the MEK inhibitor: selumetinib in patients with cholangiocarcinoma. *Br J Cancer* 2012;106:1583-6.
21. Sabel MS, Lee J, Cai S, Englesbe MJ, Holcombe S, Wang S. Sarcopenia as a prognostic factor among patients with stage III melanoma. *Ann Surg Oncol* 2011;18:3579-85.
22. Antoun S, Lanoy E, Iacovelli R, biges-Sauvin L, Lorient Y, Merad-Taoufik M, Fizazi K, di Palma M, Baracos VE, Escudier B. Skeletal muscle density predicts prognosis in patients with metastatic renal cell carcinoma treated with targeted therapies. *Cancer* 2013;119:3377-84.
23. Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, McCargar LJ, Murphy R, Ghosh S, Sawyer MB, Baracos VE. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor; independent of body mass index. *J Clin Oncol* 2013;31:1539-47.
24. Frank E, Dunlop AL. What does a patient's outfit weight? *Fam Med* 2000;32:595-6.
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
26. Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. *J Appl Physiol* (1985) 2000;88:1321-6.
27. Landi F, Liperoti R, Russo A, Giovannini S, Tosato M, Capoluongo E, Bernabei R, Onder G. Sarcopenia as a risk factor for falls in elderly individuals: results from the iSIRENTE study. *Clin Nutr* 2012;31:652-8.
28. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 2002;50:889-96.
29. Rolland Y, Czerwinski S, bellan Van Kan G, Morley JE, Cesari M, Onder G, Woo J, Baumgartner R, Pillard F, Boirie Y et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. *J Nutr Health Aging* 2008;12:433-50.
30. Cassidy J, Clarke S, az-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Rittweger K, Gilberg F, Saltz L. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. *Br J Cancer* 2011;105:58-64.
31. Prado CMM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, Mackey JR, Koski S, Pituskin E, Sawyer MB. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res* 2009;15:2920-6.
32. Sjoblom B, Gronberg BH, Benth JS, Baracos VE, Flotten O, Hjermsstad MJ, Aass N, Jordhoy M. Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. *Lung Cancer* 2015;90:85-91.
33. Stene G, Helbostad J, Amundsen T, Sorhaug S, Hjelde H, Kaasa S, Gronberg B. Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. *Acta Oncol* 2014;1-9.
34. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv* 2010;4:87-100.
35. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, Ladha AB, Proulx C, Vallance JKH, Lane K et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol* 2007;25:4396-404.
36. Paddon-Jones D, Leidy H. Dietary protein and muscle in older persons. *Curr Opin Clin Nutr Metab Care* 2014;17:5-11.
37. Paddon-Jones D, Rasmussen BB. Dietary protein recommendations and the prevention of sarcopenia. *Curr Opin Clin Nutr Metab Care* 2009;12:86-90.
38. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. *Nat Rev Clin Oncol* 2013;10:90-9.
39. Zhang H, Garcia JM. Anamorelin hydrochloride for the treatment of cancer-anorexia-cachexia in NSCLC. *Expert Opin Pharmacother* 2015;16:1245-53.

Letter to the Editor

To the editor,

The article by Blauwhoff-Buskermolen et al (1) highlights changes in body composition that occur during chemotherapy in patients with metastatic colorectal cancer. Literature on the impact of body composition, as defined by specific computed tomography criteria, in cancer management is evolving and, in our view, has the potential to become a valuable clinical biomarker across an array of cancers, with the ability to predict toxicity from systemic therapy as well as overall outcome. Altered body composition is common in many cancers. Studies that have evaluated body composition changes during anticancer treatment by using single-slice computed tomography images of the abdominal region (L3) are becoming more frequent and have focused primarily on the prognostic significance of changes in muscle mass (2,3). The current study by Blauwhoff-Buskermolen et al (1) focuses on the prognostic role of loss of muscle mass during chemotherapy in patients with metastatic colorectal cancer. The authors report that patients who experienced a loss of muscle mass $> 9\%$ (lowest tertile) had significantly lower survival rates than did those who experienced a loss of $< 9\%$, which remained significant after controlling for important prognostic covariates (hazard ratio, 4.47; 95% CI, 2.21 to 9.05; $P < 0.001$). In the current study, low skeletal muscle index (SMI; skeletal muscle area at L3/height [m^2]) at baseline was not associated with reduced survival, which contrasts with some (4), but not all, research findings (2,5,6). In the literature today, the most commonly used cut points for the definition of low SMI (or sarcopenia) using body composition from computed tomography scanning are those published by both Martin et al (4), who defined low SMI of $< 43 \text{ cm}^2/\text{m}^2$ for men with body mass index $< 25 \text{ cm}^2/\text{m}^2$, $< 53 \text{ cm}^2/\text{m}^2$ for men with body mass index $\geq 25 \text{ cm}^2/\text{m}^2$, and $< 41 \text{ cm}^2/\text{m}^2$ for women to be prognostic of reduced survival in a large cohort of 1,473 patients with lung and GI cancer; and by Prado et al (7), who defined low SMI of $< 52.4 \text{ cm}^2/\text{m}^2$ for men and $< 38.5 \text{ cm}^2/\text{m}^2$ for women as a predictor of poor overall survival in a cohort of 250 obese patients with lung and GI cancer. Both sets of cut points have been derived by using optimal stratification analysis in a North American population, and their use in other ethnicities has been questioned (8). This is largely in response to significant differences in skeletal muscle mass and in the rates of muscle loss with age that have been observed among different ethnic groups—African Americans, Whites, Hispanics, and Asians (8). Ethnic variation in cancer survival is not new, for example, East meets West in gastric cancer (9), and

toxicity from chemotherapy can also vary depending on the population studied, for example, regional differences for the tolerability of fluoropyrimidines (10). Within their study, Blauwhoff-Buskermolen et al (1) defined low SMI by using the cut points established by Martin et al (4). Extrapolating such cut points to a cohort of Dutch patients may have been a suboptimal approach to identify the true prevalence of low SMI and the relationship between low SMI and survival within this cohort. This may identify why changes in skeletal muscle area in this study was predictive of reduced survival, whereas low SMI at a specific time point was not. Although these North American–derived cut points have been widely applied in studies that have examined the clinical implications of low SMI, the validity of these cut points in a large European cohort has not been examined. Several of the published studies, which have reported nonsignificant relationships between low baseline SMI and reduced survival have been from European studies (2,5) that have used the North American–derived cut points. Further large-scale investigations are warranted in European populations, where cut points for low SMI are devised by using optimal stratification to determine its prognostic value within this population. This would provide cut points that have been validated to predict survival in large cohorts of European patients with cancer; and would not rely on cut points previously established in populations that are not representative of those being studied. In our view, the utility of body composition analysis could be even greater if ethnic variation is accounted for.

Louise E. Daly and Aoife M. Ryan University College Cork, Cork, Ireland Derek G. Power Cork University Hospital, Cork, Ireland A

References

1. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, et al: Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. *J Clin Oncol* 34:1339-1344, 2016
2. Stene GB, Helbostad JL, Amundsen T, et al: Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. *Acta Oncol* 54:340-348, 2015
3. Rutten IJ, van Dijk DP, Kruitwagen RF, et al: Loss of skeletal muscle during neoadjuvant chemotherapy is related to decreased survival in ovarian cancer patients. *J Cachexia Sarcopenia Muscle* 10.1002/jcsm.12107 [epub ahead of print on March 7, 2016]
4. Martin L, Birdsell L, Macdonald N, et al: 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, 2013
5. Rollins KE, Tewari N, Ackner A, et al: The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. *Clin Nutr* 10.1016/j.clnu.2015.08.005 [epub ahead of print on September 1, 2015]
6. Awad S, Tan BH, Cui H, et al: Marked changes in body composition following neoadjuvant chemotherapy for oesophagogastric cancer. *Clin Nutr* 31:74-77, 2012
7. Prado CM, Lieffers JR, McCargar LJ, et al: 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, 2008
8. Silva AM, Shen W, Heo M, et al: Ethnicity-related skeletal muscle differences across the lifespan. *Am J Hum Biol* 22:76-82, 2010
9. Cunningham D, Chua YJ: East meets west in the treatment of gastric cancer. *N Engl J Med* 357:1863-1865, 2007
10. Haller DG, Cassidy J, Clarke SJ, et al: Potential regional differences for the tolerability profiles of fluoropyrimidines. *J Clin Oncol* 26:2118-2123, 2008

Response from the authors

We thank Daly et al (1) for providing valuable comments regarding our recent paper on the prognostic role of muscle loss during anticancer treatment in patients with metastatic colorectal cancer.² We have found that muscle mass decreased significantly during chemotherapy and a decrease in muscle mass was independently associated with poor survival in patients with metastatic colorectal cancer. Daly et al correctly note that we observed no associations between a low skeletal muscle index at baseline and reduced survival, in contrast to some but not all previous studies. In our article, we provide some explanations for this discrepancy, for example, the heterogeneity regarding treatment regimens and follow-up time (2). Daly et al add a possible explanation as there may be a possible difference in body composition reference values between a North American (Canadian) and European population. Daly et al suggest that extrapolating cutoff points from a Canadian population to a cohort of Dutch patients may have been a suboptimal approach to identify the true prevalence of low SMI and the relationship between low SMI and survival within this cohort. We acknowledge the importance of differences in body composition between countries. For example, the Dutch population, on average, is taller and the prevalence of overweight and obesity is lower compared with the Canadian population (3,4). Although a large percentage of the Canadian population consists of (European) immigrants (5), we agree that it would be better to compare our study data with normative values derived from a European, or even a Dutch, population. Although we did find a new publication with cutoff values for an Asian population (6), normative data for a European population are not available yet. There are several options to consider to overcome the question of ethnic variation in body composition in the near future. Data on body composition measured with computed tomography scans from recent European studies (7-10) could be pooled to build a database with reference values for the European population. Another approach is to derive normative values from a healthy population, which is what our group is working on at the moment. It would then be interesting to repeat the statistical analyses of our study and to investigate whether our population truly displayed a low skeletal muscle index compared with European reference values. Only then we will be able to understand why skeletal muscle index was not associated with survival in our cohort and whether this may have been caused by choosing the wrong reference group. In the meantime, while we await reference values for different countries and/or ethnic groups, we recommend that future

studies on body composition display patient characteristics with regard to ethnicity, especially when cutoff values or reference values are being used. This does not apply to Europe alone, but also to other regions across the world.

Susanne Blauwhoff-Buskermolen

VU University Medical Center, Amsterdam, the Netherlands

Marian A.E. de van der Schueren

VU University Medical Center, Amsterdam, and HAN University of Applied Sciences, Nijmegen, the Netherlands

Jacqueline A.E. Langius

VU University Medical Center, Amsterdam, and The Hague University of Applied Sciences, The Hague, the Netherlands

Henk M.W. Verheul

VU University Medical Center, Amsterdam, the Netherlands

References

1. Daly LE, Ryan AM, Power DG: Re: Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. *J Clin Oncol* doi:10.1200/JCO.2016.68.8010
2. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, et al: Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. *J Clin Oncol* 34:1339-1344, 2016
3. National Institute for Health and the Environment: Prevalence of overweight and obesity in the Netherlands in 2015. <https://www.volksgezondheidenzorg.info/onderwerp/english/introduction>
4. Shields M, Connor Gorber S, Janssen I, et al: Bias in self-reported estimates of obesity in Canadian health surveys: An update on correction equations for adults. *Health Rep* 22:35-45, 2011
5. Citizenship and Immigration Canada: Statistics. <http://www.cic.gc.ca/english/resources/statistics/>
6. Hamaguchi Y, Kaido T, Okumura S, et al: Proposal for new diagnostic criteria for low skeletal muscle mass based on computed tomography imaging in Asian adults. *Nutrition* 10.1016/j.nut.2016.04.003 [epub ahead of print on May 4, 2016]
7. Stene GB, Helbostad JL, Amundsen T, et al: Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. *Acta Oncol* 54:340-348, 2015
8. Weijs PJM, Looijaard WGPM, Dekker IM, et al: Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. *Crit Care* 18:R12, 2014
9. van Vledder MG, Levolger S, Ayez N, et al: Body composition and outcome in patients undergoing resection of colorectal liver metastases. *Br J Surg* 99:550-557, 2012
10. Thoresen L, Frykholm G, Lydersen S, et al: 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, 2012