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Original article

Sarcopenia as an independent prognostic factor in patients with metastatic colorectal cancer: A retrospective evaluation



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SUMMARY

Background & aims: Sarcopenia has been associated with poor prognosis in a number of malignancies. However, whether sarcopenia is associated with colorectal cancer (CRC) prognosis in a metastatic setting remains unclear. The aim of the study presented was to evaluate the impact of sarcopenia on progression-free survival (PFS) and overall survival (OS) in patients with metastatic CRC.

Methods: We retrospectively studied 72 patients with stage IV CRC treated at the University of Campinas between 2009 and 2015. Computed tomography images were analyzed to assess body composition. The Kaplan–Meier and multivariate Cox proportional hazards regression were used for survival analysis and to evaluate the influence of sarcopenia on PFS and OS.

Results: Median PFS for sarcopenic patients ($n = 32$) was 7.2 months, which was significantly different from non-sarcopenic patients ($n = 40$), which was 15.2 months (hazard ratio [HR]: 1.78; 95% confidence interval [CI], 1.00–3.14; $P = 0.048$). Sarcopenia was also a significant predictor of OS. Median OS for sarcopenic patients was 12.5 months versus 36.7 months for non-sarcopenic patients (HR: 1.86; 95% CI, 1.02–3.38; $P = 0.043$), after adjustment for number of metastatic lesions, metastasectomy, and performance status.

Conclusions: Sarcopenia was associated with worse CRC PFS and OS. These findings require prospective trials to validate this association.

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1. Introduction

The establishment of more effective chemotherapy regimens for the treatment of metastatic colorectal cancer (mCRC) has launched an intensive search for predictive and prognostic factors [1]. Although colorectal cancer (CRC) patients should be tested for the oncogenes *RAS* and *BRAF* mutational analysis and mismatch repair status [1], stratifying patients based on overall clinical characteristics remains unclear. Thus, identifying clinical aspects that are

associated with a high risk of progression and mortality are of utmost importance.

Sarcopenia, a syndrome defined by loss of muscle mass, and reduction of strength and physical performance [2], is a key criterion for the diagnosis of cancer cachexia [3]. Sarcopenia prevalence is highly variable according to the underlying neoplasm; for instance, 46% of non-mCRC patients present with sarcopenia [4], while sarcopenia is observed in only 27% of patients with advanced hepatocellular carcinoma [5]. Interestingly, the incidence of sarcopenia in CRC is observed in 11% of patients with non-advanced adenomas [6] and in 46.8% of patients with mCRC [7], suggesting that both risk factors involved in CRC carcinogenesis, as well as tumor-secreting factors, are involved in the genesis of muscle wasting. Importantly, sarcopenia has recently emerged as a predictor of poorer overall survival in non-mCRC [4], increased toxicity to chemotherapy [8], and increased cancer recurrence after metastasectomy in patients with stage IV CRC [9]. Interestingly, not only

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Abbreviations			
ARCAD	<i>Aide et Recherche en Cancerologie Digestive</i>	HU	Hounsfield units
AJCC	American Joint Committee on Cancer	IMAT	intramuscular adipose tissue
BMI	body mass index	IQR	interquartile ranges
BRAF	<i>v-raf murine sarcoma viral oncogene homolog B1</i>	L3	third lumbar vertebra
CAIRO	Capecitabine, Irinotecan, and Oxaliplatin in advanced colorectal cancer	MA	mean muscle attenuation
CEA	carcinoembryonic antigen	mCRC	metastatic colorectal cancer
CRC	colorectal cancer	OS	overall survival
CTCAE	Common Terminology Criteria for Adverse Events	PACS	Picture Archiving and Communication System
CI	confidence interval	PFS	progression-free survival
CT	computed tomography	RAS	retrovirus-associated DNA sequences
ECOG	Eastern Cooperative Oncology Group	SM	skeletal muscle
EWGSOP	European Working Group on Sarcopenia in Older People	SMI	skeletal muscle index
HR	hazard ratio	SFI	subcutaneous fat index
		SAT	subcutaneous adipose tissue
		VAT	visceral adipose tissue
		VFI	visceral fat index

the amount of muscle mass loss have been associated with the prognosis of oncologic patients, but also a condition known as myosteosis [10], that represents muscle fat infiltration, and is inversely related to muscle radiodensity, strength and performance [11]. However, studies assessing the effects of body composition as a prognostic factor of survival in mCRC are still scarce.

When treating mCRC, the ability of clinicians to prognosticate response based upon the characteristics of patients is of great interest to customize the treatment of patients and anthropometric parameters might be decisive. Interestingly, analysis of the *Aide et Recherche en Cancerologie Digestive* (ARCAD) database demonstrated a strong association between low body mass index (BMI) and worse prognosis for mCRC patients [12]. On the other hand, analysis of Capecitabine, Irinotecan, and Oxaliplatin in advanced colorectal cancer (CAIRO) and CAIRO 2 studies showed that being overweight and obese was associated with increased overall survival [13]. Thus, there is a great interest in evaluating parameters that refine body composition prediction ability such as sarcopenia, which better defines metastatic patient functionality and quality of life in the palliative care setting. Although not routinely analyzed in clinical practice, the measurement of fat and muscle mass by a cross-sectional computed tomography (CT) image at the level of the third lumbar vertebra (L3) is easily assessed and strongly correlates with total body composition [14]. In the present analysis, we investigated whether CT-defined sarcopenia at the L3 level could predict efficacy outcomes in stage IV CRC.

2. Material and methods

2.1. Patients and procedures

In this retrospective study, the database from Fundação Oncocentro de São Paulo (an authoritative organ of São Paulo State that registers data from Hospitals, which treat cancer) was used to identify patients with stage IV CRC treated at Campinas State University Hospital between December 2009 and December 2015 ($n = 110$). We analyzed 72 patients who met the following inclusion criteria: 1. Histologically confirmed colon or rectum adenocarcinoma; 2. Stage IV CRC according to 7th edition of the American Joint Committee on Cancer (AJCC) cancer staging manual [15]; 3. Had abdominal CT scans stored electronically in the Picture Archiving and Communication System (PACS) that were performed within 6 months of diagnosis; and 4. Availability of clinical, anthropometric, and demographic data of interest. Patients with primary cancer

elsewhere and the ones who died in 30 days or had follow-up less than 12 months were excluded.

Follow-up for progression-free survival (PFS) was performed routinely and consisted of clinical evaluation, measurement of carcinoembryonic antigen (CEA), and evaluation of abdominal and thoracic CTs. Functional status, height, and weight were measured by hospital staff and used to determine Eastern Cooperative Oncology Group (ECOG) performance status and body mass index (BMI), respectively. Medical records were reviewed for data collection from the diagnosis date until the last date of follow-up or death.

The Campinas State University Institutional Review board approved the study with a waiver of informed consent (2577599).

2.2. Body composition

CT scans, routinely obtained for diagnostic and staging purposes, were evaluated using Slice-OMatic Software, version 5.0 (Tomovision™, Canada) [16,17] by a single trained observer who was blinded to outcome assessment. On average, scans were performed 1.6 months after diagnosis (range, -2.6 – 5.8 months).

Total skeletal muscle (SM), visceral (VAT), subcutaneous (SAT) and intramuscular adipose tissue (IMAT) cross-sectional areas, and mean muscle attenuation (MA) were averaged from two consecutive axial images at the level of L3. The different tissues were identified by their anatomic features and quantified using pre-established tissue-specific Hounsfield units (HU) ranges: -29 to 150 HU for SM; -190 to -30 HU for subcutaneous and IMAT; and -150 to -50 HU for VAT [18] (Supplementary Fig. 1).

Adipose tissue areas and the sum of SM areas were normalized for stature (cm^2/m^2) to calculate the subcutaneous fat index (SFI), visceral fat index (VFI), and skeletal muscle index (SMI). The MA in HU was also reported for the whole muscle area at L3. Predefined cutoffs previously reported by Martin and colleagues were used to define sarcopenia ($\text{SMI} < 41 \text{ cm}^2/\text{m}^2$ for women; $\text{SMI} < 43 \text{ cm}^2/\text{m}^2$ if $\text{BMI} < 25 \text{ kg}/\text{m}^2$ and $\text{SMI} < 53 \text{ cm}^2/\text{m}^2$ if $\text{BMI} \geq 25 \text{ kg}/\text{m}^2$ for men) and myosteosis ($\text{MA} < 41 \text{ HU}$ if $\text{BMI} < 25 \text{ kg}/\text{m}^2$ and $\text{MA} < 33 \text{ HU}$ if $\text{BMI} \geq 25 \text{ kg}/\text{m}^2$) [16]. Visceral obesity was defined as $\text{VAT} > 163.8 \text{ cm}^2$ in males and $\text{VAT} > 80.1 \text{ cm}^2$ for females [19].

2.3. Treatment toxicity

Data on treatment toxicity was collected from medical records for every patient. The severity of each adverse event reported (e.g.,

nausea, vomit, diarrhea, mucositis, hematologic disorders, etc) was classified based on a scale that uses standardized definitions for chemotherapy related adverse events - Common Terminology Criteria for Adverse Events [CTCAE v4.03] [20]. Treatment toxicity was considered present if any type of grade III or IV toxicity on first-line chemotherapy was reported. Treatment toxicity was dichotomized into present or absent. Doublets of 5-fluorouracil associated with oxaliplatin or irinotecan were selected at the discretion of the attendant physician as the first-line chemotherapy regimen.

2.4. Endpoints

The primary endpoint was overall survival (OS) (time between CRC diagnosis and death from any cause). The secondary outcome was PFS (time between the date of disease progression or death). Patients who were still alive were censored on the date of the last follow-up registered in the medical record.

2.5. Statistical analysis

Baseline characteristics are presented as mean and standard deviation (SD) or median and interquartile ranges (IQR) for continuous variables and proportions for categorical variables. These characteristics were analyzed using Student's t-test or Mann–Whitney and χ^2 or Fisher's exact tests when appropriate, respectively. The impact of sarcopenia on survival was analyzed using Kaplan–Meier curves, log-rank tests, and univariate Cox proportional hazards. A model of Cox multivariate regression was constructed using the variables that interfere with the outcomes in univariate analysis ($P < 0.10$). The non-parametric Kaplan–Meier method was applied to evaluate OS and PFS. Analyses were performed using *Stata* software, version 12.0 (*StataCorp LP*[®]), and a P value < 0.05 was considered significant.

3. Results

3.1. Patient and body composition characteristics

From December 2009 to December 2015, 110 patients received treatment for mCRC, among them, 72 patients met the inclusion criteria. The median follow-up at the time of evaluation was 23.6 months (interquartile range [IQR]: 3.1–39.6 months).

As shown in Table 1, we detected sarcopenia in 32 patients (44.4%). Sarcopenic patients tended to be older, female, and ECOG 2–3 compared to non-sarcopenic individuals. We observed that myosteatosis was more frequent in sarcopenic individuals (Table 2). Interestingly, there was a trend toward sarcopenic individuals presenting with more visceral obesity.

3.2. Survival analysis

In the sarcopenia group, there were 30 events (94%) compared with 32 (80%) for the non-sarcopenic group. Kaplan–Meier curves showed that sarcopenic patients presented with reduced PFS compared to those without sarcopenia (log-rank $P < 0.001$) (Fig. 1A). Adjusted Cox regression analysis demonstrated that the hazard ratio (HR) for PFS was 1.78 (95% confidence interval [CI]: 1.00–3.14, $P = 0.048$), showing a significantly worse PFS related to sarcopenia. Median PFS was 7.2 months in the sarcopenia group and 15.9 months for non-sarcopenic individuals (Table 3). Six-month PFS rates were 37.5% and 20% in the sarcopenia and non-sarcopenia groups, respectively. Similar results were obtained calculating PFS using as reference the date of performed CT instead of diagnosis date (Supplementary Table 1).

Analysis of OS also showed statistically significant differences between the sarcopenia and non-sarcopenia groups. Kaplan–Meier curves showed that sarcopenic individuals presented with reduced

Table 1
Selected characteristics according to sarcopenia of colorectal cancer patients.

Characteristic	All-patients (n = 72)	Non-sarcopenic (n = 40)	Sarcopenic (n = 32)	P value
Age, mean (SD), y	59.4 (13.2)	56.7 (12.0)	62.7 (14.1)	0.05
Sex, N^o (%)				0.02
Male	40 (55.6)	27 (67.5)	13 (40.6)	
Female	32 (44.4)	13 (33.5)	19 (59.4)	
Body mass index (kg/m²), N^o (%)				0.18
<18.5	5 (6.9)	1 (2.5)	4 (12.5)	
18.5–24.9	43 (59.7)	26 (65.0)	17 (53.1)	
25–30	22 (30.6)	11 (27.5)	11 (34.4)	
>30	2 (2.8)	2 (5.0)	0 (0.0)	
Metastasis, N^o (%)				0.61
Peritoneum	16 (22.2)	8 (20.0)	8 (25.0)	
Other organs	56 (77.8)	32 (80.0)	24 (75.0)	
Metastasis, N^o (%)				0.26
One organ	52 (72.2)	31 (77.5)	21 (65.6)	
Two or more organs	20 (27.8)	9 (22.5)	11 (34.4)	
Metastectomy, N^o (%)				0.22
Yes	21 (29.2)	14 (35.0)	7 (21.9)	
No	51 (70.8)	26 (65.0)	25 (78.1)	
Chemotherapy, N^o (%)				0.17
Yes	55 (76.4)	33 (82.5)	22 (68.8)	
No	17 (23.6)	7 (17.5)	10 (31.2)	
Toxicity grade III-IV, N^o (%)				0.06
Yes	38 (69.1)	26 (78.8)	12 (54.6)	
No	17 (30.9)	7 (21.2)	10 (45.4)	
Cancer site, N^o (%)				0.75
Colon	42 (58.3)	24 (60.0)	18 (56.2)	
Rectum	30 (41.7)	16 (40.0)	14 (43.8)	
ECOG, N^o (%)				<0.01
0–1	54 (75.0)	35 (87.5)	19 (59.4)	
2–3	18 (25.0)	5 (12.5)	13 (40.6)	

Abbreviations: ECOG: Eastern Cooperative Oncology Group Performance; SD: Standard deviation.

Table 2
Body composition according to sarcopenia of colorectal cancer patients.

Parameter	All-patients (n = 72)	Non-sarcopenic (n = 40)	Sarcopenic (n = 32)	P value
Skeletal Muscle, median (IQR)				
Area (cm ²)	118.8 (94.6–143.2)	136.4 (118.8–159.0)	95.5 (87.4–109.3)	<0.01
Mean MA (HU)	33.0 (22.9–39.2)	37.8 (32.7–41.5)	27.3 (23.2–31.1)	<0.01
SMI (cm ² /m ²)	45.3 (39.6–51.6)	50.2 (45.8–57.8)	38.7 (34.8–40.6)	<0.01
Adipose Tissue, median (IQR)				
Visceral, area (cm ²)	76.4 (40.5–132.2)	66.4 (40.9–132.6)	82.4 (39.3–123.2)	0.79
VFI (cm ² /m ²)	30.9 (16.1–51.3)	26.8 (17.7–50.7)	34.5 (14.6–51.7)	0.89
Subcutaneous, area (cm ²)	100.6 (66.2–158.7)	97.2 (68.0–137.5)	107.8 (61.1–211.6)	0.50
SFI (cm ² /m ²)	40.0 (24.1–63.2)	38.3 (24.9–52.5)	40.9 (21.9–75.5)	0.55
Intramuscular, area (cm ²)	7.9 (5.2–12.2)	6.9 (4.1–9.3)	10.7 (5.3–15.3)	0.02
Myosteotosis, N^o (%)				
Yes	51 (70.8)	17 (42.5)	28 (87.5)	<0.01
No	21 (29.2)	23 (57.5)	4 (12.5)	
Visceral obesity, N^o (%)				
Sim	19 (26.4)	7 (17.5)	20 (62.5)	0.06
No	53 (73.6)	33 (82.5)	12 (37.5)	

Abbreviations: HU: Hounsfield Units; IQR: Interquartile range; MA: Muscle attenuation; SFI: Subcutaneous Fat Index; SMI: Skeletal Muscle Index; VFI: Visceral Fat Index.

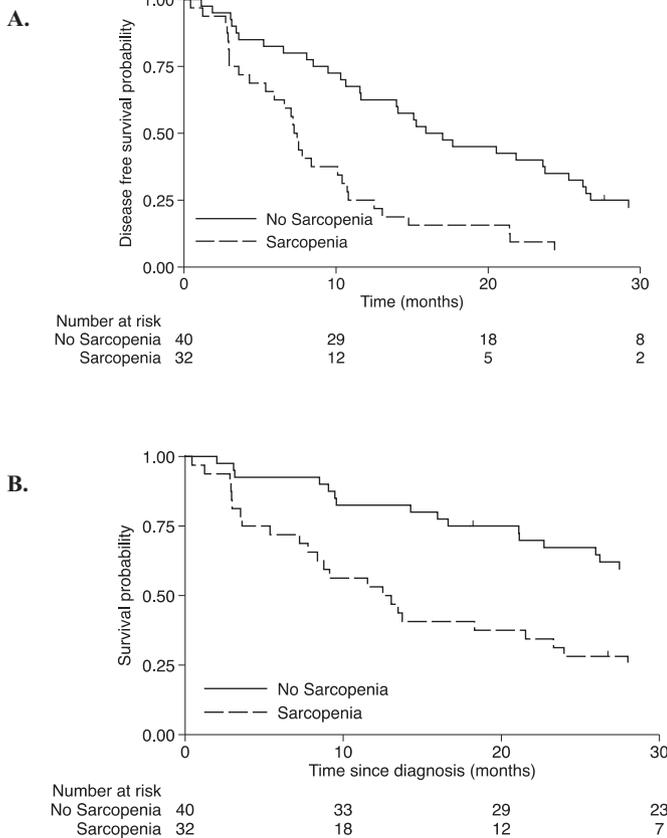


Fig. 1. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) according to sarcopenia status.

OS compared to those without sarcopenia (log-rank $P < 0.001$) (Fig. 1B). As shown in Table 3, adjusted Cox regression analysis of OS revealed a HR of 1.86 (95% CI, 1.02–3.38; $P = 0.043$). Median OS was 12.5 months in the sarcopenia group and 36.7 months for non-sarcopenic individuals (Table 3). Similar results were obtained calculating OS using as reference the date of performed CT (Supplementary Table 1).

Kaplan–Meier curves also revealed that although individuals with myosteotosis had similar PFS (Fig. 2A), they presented significantly worse OS than the non-myosteotosis group (log-rank

Table 3
Sarcopenia and survival from date of diagnosis.

Parameter	Non-sarcopenic (n = 40)	Sarcopenic (n = 32)	P value
Progression free survival			
# Events/at risk	32/40	30/32	
Median (months)	15.9	7.2	
Unadjusted	Referent	2.34 (1.40–3.93)	0.001
Adjusted ^a	Referent	1.78 (1.00–3.14)	0.048
Overall survival			
# Events/at risk	24/40	27/32	
Median (months)	36.7	12.5	
Unadjusted	Referent	2.57 (1.46–2.53)	0.001
Adjusted ^b	Referent	1.86 (1.02–3.38)	0.043

^a Cox model adjusted for sex (male versus female), metastasectomy (yes or no) and ECOG (0–1 versus 2–3).

^b Cox model adjusted for metastasis number (one versus two or more organs), metastasectomy (yes or no) and ECOG (0–1 versus 2–3).

$P < 0.001$) (Fig. 2B). After adjusting for metastasis number, metastasectomy, and ECOG, Cox regression analysis of OS demonstrated an HR of 2.77 (95% CI: 1.30–5.87, $P = 0.008$). Median OS was 18.3 months in the myosteotosis group and 46.8 months for non-myosteotosis patients.

4. Discussion

A number of studies suggest an association between sarcopenia and reduced OS in different treatment settings of certain cancers [21,22]. Our study extends these series demonstrating that sarcopenia is associated with decreased PFS and OS in patients with mCRC.

Few studies have examined the effects of sarcopenia on survival outcomes in mCRC patients. For instance, the effects of sarcopenia on CRC patients with liver metastasis submitted to metastasectomy is controversial. One study observed that sarcopenia was associated with increased disease recurrence and mortality [9]. In contrast, other studies did not detect an impact of sarcopenia on prognosis, but observed that sarcopenia was associated with reduced functional liver volume [23], higher rates of liver surgery complications [24], and with readmission rates when associated with obesity [7].

Outside of the liver metastasectomy setting, much less is known. We found three previous studies that investigated this association. Similar to our results, a Norwegian/Canadian study demonstrated a trend ($P = 0.053$) toward worse OS in sarcopenic patients [25]. On the other hand, a cohort from Japan and another from the Netherlands did not detect an effect of baseline sarcopenia on

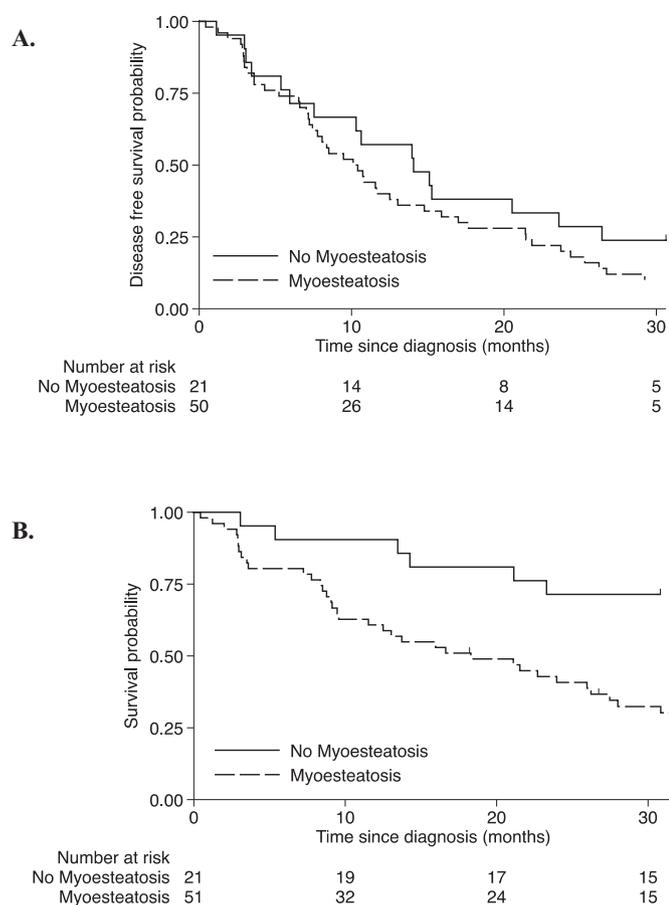


Fig. 2. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) according to myosteatosi status.

prognosis, although there was a negative influence of SM wasting on OS [26,27]. Discrepancies on prognosis between our and these studies might be linked to the methods used to determine sarcopenia and to the different patterns of body composition of the studied populations. Consistent with a previous Brazilian report [28], our results showed that 44% of the cohort was sarcopenic; while Thoresen et al. [25] and Blauwhoff-Buskermol et al. [27] found that 39% and 57% of their mCRC population was sarcopenic, respectively. Moreover, we identified that 33.6% of our population was overweight or obese compared to 63% in the Netherlands and 53.2% in the Canadian/Norwegian population. In contrast, the Japanese study did not use pre-established cutoff points to report their data, instead it used quartiles distribution and the lower quartile was defined as sarcopenia [26], making a direct comparison inappropriate. Moreover, the cutoffs to determine sarcopenia in Asiatic populations was recently validated for gastric cancer [21], and it is different than that established by Martin et al. [16]. Altogether, these studies suggest that defining sarcopenia cutoffs criteria for different populations is crucial to the development of the field.

The pathophysiological mechanisms that underpin the worst prognosis in sarcopenia are not clear. Consistent with previous reports [16,29], our data shows an increased content of fat in muscle ($P = 0.02$) that was mirrored by a higher number of patients with myosteatosi in the sarcopenic group ($P < 0.01$). Importantly, intramyocellular fat deposits are commonly observed in different insulin resistance states, and it is involved in the pathogenesis of this condition [30]. Accordingly, we also detected a trend toward a higher number of patients with visceral obesity in the sarcopenic

group ($P = 0.06$). Although these insulin resistance-induced phenotypes may be epiphenomena of the chronic inflammation background involved in sarcopenia development, another possibility is that these anomalous deposits of fat have a role in the amplification of the inflammatory state and, thus, have contributed to the worse prognosis observed in our study. Interestingly, in our cohort, myosteatosi was independently associated with reduced OS. In line with this hypothesis and similarly to insulin resistance states, the adipose tissue of patients with cachexia present with infiltration of immune cells as crown-like structures [31]. These aspects are crucial for the understanding of sarcopenia's influence on prognosis and response to treatment and deserve further investigation.

The present study demonstrated that conditions generally neglected during the oncologic treatment, such as body composition, might contribute on stratifying prognosis. The use of CT as a convenient method for evaluation of body composition is practical, low cost and contributes for better understanding of the disease as well as contributes to refine the clinical and nutritional performance of the patient. Overall, identifying sarcopenic individuals with the potential for increased mortality may be a useful tool to guide clinical decision process. Of note, our study is the first to evaluate the impact of sarcopenia on a Latin American population with mCRC. In addition, the study was confined to a well-defined tumor group (CRC stage IV).

On the other hand, this study has several limitations. First, we defined sarcopenia without the measurement of muscle function as recommended by the European Working Group on Sarcopenia in Older People (EWGSOP) [2]. Second, the low number of patients included in our study did not allow for the performance of sensitivity test to exclude patients with early death. Moreover, given that the sarcopenic patients were generally elderly and ECOG 2–3 as well presented a trend to have more adverse events, the possibility of low treatment intensity in sarcopenic group and reverse causality should be considered. It is important to consider that changes related to treatment over the period of this study also could have impacted on our results. Finally, the study's retrospective and single-centered nature as well as the large number of patients excluded because they do not have a CT stored in our PACS within 6 months of the date of diagnosis may have introduced selection bias.

In conclusion, sarcopenia was associated with significantly worse prognosis in patients with mCRC. Understanding the pathophysiological mechanisms that underpin this association is crucial for improving CRC prognosis. Given how easily it is to evaluate sarcopenia in routine CTs and its implementation in clinical practice, it is imperative that prospective trials be designed to further explore this association.

Conflict of interest and funding sources

The authors declare that they have no conflict of interest.

Statement of authorship

LPC and MNS collected the data, these authors contributed equally for this paper. LPC, MNS, MCSM, FOC, LTM, NSS, and JBCC discussed and interpreted the results from the study. LPC, MNS, MCSM, and JBCC conceived and wrote the manuscript. All authors critically reviewed and approved the manuscript for submission.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnesp.2019.04.004>.

References

- [1] Sepulveda AR, Hamilton SR, Allegra CJ, Grody W, Cushman-Vokoun AM, Funkhouser WK, et al. Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American society for clinical pathology, college of American pathologists, association for molecular pathology, and the American society of clinical oncology. *J Clin Oncol* 2017;35(13):1453–86.
- [2] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. *Age Ageing* 2010;39(4):412–23.
- [3] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;12(5):489–95.
- [4] Feliciano EMC, Kroenke CH, Meyerhardt JA, Prado CM, Bradshaw PT, Kwan ML, et al. Association of systemic inflammation and sarcopenia with survival in nonmetastatic colorectal cancer: results from the C SCANS study. *JAMA Oncol* 2017;3(12):e172319.
- [5] Mir O, Coriat R, Blanchet B, Durand JP, Boudou-Rouquette P, Michels J, et al. Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. *PLoS One* 2012;7(5):e37563.
- [6] Park YS, Kim JW, Kim BG, Lee KL, Lee JK, Kim JS, et al. Sarcopenia is associated with an increased risk of advanced colorectal neoplasia. *Int J Colorectal Dis* 2017;32(4):557–65.
- [7] Lodewick TM, van Nijnatten TJ, van Dam RM, van Mierlo K, Dello SA, Neumann UP, et al. Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases? *HPB (Oxf)* 2015;17(5):438–46.
- [8] Ali R, Baracos VE, Sawyer MB, Bianchi L, Roberts S, Assenat E, et al. Lean body mass as an independent determinant of dose-limiting toxicity and neuropathy in patients with colon cancer treated with FOLFOX regimens. *Cancer Med* 2016;5(4):607–16.
- [9] Van Vledder MG, Levolger 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(4):550–7.
- [10] Kroenke CH, Prado CM, Meyerhardt JA, Weltzien EK, Xiao J, Cespedes Feliciano EM, et al. Muscle radiodensity and mortality in patients with colorectal cancer. *Cancer* 2018;124(14):3008–15.
- [11] Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. *Acta Physiol (Oxf)* 2014;210(3):489–97.
- [12] Renfro LA, Loupakis F, Adams RA, Seymour MT, Heinemann V, Schmoll HJ, et al. Body mass index is prognostic in metastatic colorectal cancer: pooled analysis of patients from first-line clinical trials in the ARCAD database. *J Clin Oncol* 2016;34(2):144–50.
- [13] Simkens LH, Koopman M, Mol L, Veldhuis GJ, Ten Bokkel Huinink D, Muller EW, et al. Influence of body mass index on outcome in advanced colorectal cancer patients receiving chemotherapy with or without targeted therapy. *Eur J Cancer* 2011;47(17):2560–7.
- [14] Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. *Semin Cell Dev Biol* 2016;54:2–10.
- [15] Sobin LH, Gospodarowicz M, Wittekind C. *Colon and rectum. TNM classification of malignant tumours (UICC)*. 7th ed. Oxford Wiley-Blackwell; 2009. p. 100–5.
- [16] Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, McCargar LJ, 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* 2013;31(12):1539–47.
- [17] Mourtzakis M, Prado CM, 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(5):997–1006.
- [18] Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: advances in models and methods. *Annu Rev Nutr* 1997;17:527–58.
- [19] Doyle SL, Bennett AM, Donohoe CL, Mongan AM, Howard JM, Lithander FE, et al. Establishing computed tomography-defined visceral fat area thresholds for use in obesity-related cancer research. *Nutr Res* 2013;33(3):171–9.
- [20] SERVICES USDOHAH. Common Terminology criteria for adverse events (CTCAE). National Institutes of Health, National Cancer Institute; 2009.
- [21] Zhuang CL, Huang DD, Pang WY, Zhou CJ, Wang SL, Lou N, et al. Sarcopenia is an independent predictor of severe postoperative complications and long-term survival after radical gastrectomy for gastric cancer: analysis from a large-scale cohort. *Medicine (Baltim)* 2016;95(13):e3164.
- [22] Iritani S, Imai K, Takai K, Hanai T, Ideta T, Miyazaki T, et al. Skeletal muscle depletion is an independent prognostic factor for hepatocellular carcinoma. *J Gastroenterol* 2015;50(3):323–32.
- [23] Dello SA, Lodewick TM, van Dam RM, Reisinger KW, van den Broek MA, von Meyenfeldt MF, et al. Sarcopenia negatively affects preoperative total functional liver volume in patients undergoing liver resection. *HPB (Oxf)* 2013;15(3):165–9.
- [24] Peng PD, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB (Oxf)* 2011;13(7):439–46.
- [25] Thoresen L, Frykholm G, Lydersen S, Ulveland H, Baracos V, Prado CM, et al. Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal results. *Clin Nutr* 2013;32(1):65–72.
- [26] Miyamoto Y, Baba Y, Sakamoto Y, Ohuchi M, Tokunaga R, Kurashige J, et al. Negative impact of skeletal muscle loss after systemic chemotherapy in patients with unresectable colorectal cancer. *PLoS One* 2015;10(6):e0129742.
- [27] Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, den Braver NR, Berkhof J, Langius JA, et al. Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. *J Clin Oncol* 2016;34(12):1339–44.
- [28] Souza BU, Souza NCS, Martucci RB, Rodrigues VD, Pinho NB, Gonzalez MC, et al. Factors associated with sarcopenia in patients with colorectal cancer. *Nutr Cancer* 2018;70(2):176–83.
- [29] McSorley ST, Black DH, Horgan PG, McMillan DC. The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer. *Clin Nutr* 2018;37(4):1279–85.
- [30] Perseghin G, Scifo P, De Cobelli F, Pagliato E, Battezzati A, Arcelloni C, et al. Intramyocellular triglyceride content is a determinant of in vivo insulin resistance in humans: a ¹H-¹³C nuclear magnetic resonance spectroscopy assessment in offspring of type 2 diabetic parents. *Diabetes* 1999;48(8):1600–6.
- [31] Batista Jr ML, Henriques FS, Neves RX, Olivan MR, Matos-Neto EM, Alcantara PS, et al. Cachexia-associated adipose tissue morphological rearrangement in gastrointestinal cancer patients. *J Cachexia Sarcopenia Muscle* 2016;7(1):37–47.