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ORIGINAL ARTICLE

Skeletal muscle loss during chemotherapy and its association with survival and systemic treatment toxicity in metastatic colorectal cancer: An AGEO prospective multicenter study

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KEYWORDS
Metastatic colorectal cancer;

Abstract
Purpose: We showed in a previous study that the PG-SGA score is associated with survival and chemotherapy-related toxicities in metastatic colorectal cancer (mCRC) patients. The objective

Abbreviations: ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; CI, confidence interval; CT, computerized tomography; D0, day 0; D60, day 60; HR, hazard ratio; LDH, lactate dehydrogenase; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; PG-SGA, Patient-Generated Subjective Global Assessment; PS, performance status; SMI, skeletal muscle index.

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Skeletal muscle index;
Sarcopenia;
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Chemotherapy toxicity

was to evaluate the association between pretherapeutic sarcopenia and variation in skeletal muscle index (SMI) during treatment with these outcomes in the same population.
Methods: This prospective, multicenter, observational study enrolled non-pretreated mCRC patients. SMI was measured on routine CT scan at day 0 (D0) and day 60 (D60). Nutritional factors were collected at D0. Progression-free survival (PFS) and overall survival (OS) were calculated from treatment start.
Results: 149 patients were included from 7/2013 to 11/2016. Pretherapeutic sarcopenia was not significantly associated with survival or chemotherapy-related toxicities. The decrease in SMI > 14% was significantly associated with shorter PFS (6 vs 9 mo; HR 1.8, 95% CI 1.1—3.1, p = 0.02) and OS (8.5 vs 26 mo; HR 2.6, 95% CI 1.4—4.8, p = 0.002), independently of hypoalbuminemia and malnutrition defined by PG-SGA. Patients with a SMI decrease > 14% had a higher rate of grade ≥ 2 clinical toxicities (40% vs 22%, OR 3.0, 95% CI 1.2—7.7, p = 0.02), but the difference was not statistically significant in multivariable analysis.
Conclusion: To our knowledge, this is the first study to assess prospectively the association of skeletal muscle loss with survival and treatment toxicities in non-pretreated patients with mCRC. Pretherapeutic sarcopenia was not associated with poor outcomes, but the loss of skeletal muscle mass within 60 days from treatment start was highly prognostic, independently of other prognostic and nutritional factors.

Introduction

Sarcopenia has been shown to be associated with the risk of postoperative complications [1], chemotherapy-related toxicities and survival in many cancers [2—5]. The evaluation of muscle mass by measurement of the skeletal muscle index (SMI) can easily be done on computerized tomography (CT) scans that are routinely performed in the management of cancer patients [2].

In patients with metastatic colorectal cancer (mCRC), the prevalence of sarcopenia ranges from 16 to 76% in the literature [3,6—9] probably due to different definitions and thresholds, but sarcopenia seems to be associated with poorer survival in several reports [3,8]. In the adjuvant setting, it has been shown that sarcopenia was associated with chemotherapy-related toxicities [10,11]. In metastatic setting, a previous study [6] showed that sarcopenia was significantly associated with the occurrence of grade 3—4 chemotherapy toxicities, but this study was retrospective and included patients with mCRC at different stages of their therapeutic management, and the recently published study by Kurk et al. showed from the phase 3 CAIRO3 trial, that SMI loss > 2% during the first-line maintenance treatment with capecitabine plus bevacizumab was associated with dose-limiting toxicities, whereas sarcopenia at the start of this treatment was not [9].

Among the variety of nutritional scores, the ''Patient-Generated Subjective Global Assessment'' (PG-SGA) has become a standard in oncology for nutritional assessment [12,13]. We showed in another recently published study of chemotherapy-naïve patients with mCRC, that PG-SGA was independently associated with survival and chemotherapy-related toxicities [14].

The main objective of the present work was to evaluate the association of baseline sarcopenia and variation in SMI during treatment with survival and treatment-related toxicities in our population of non-pretreated mCRC patients [14].

Patients and methods

Patients

This prospective, multicenter, observational study involved eight French medical centers. Inclusion criteria included age > 18 years, histologically proven metastatic colon or rectum adenocarcinoma, prior adjuvant chemotherapy allowed if ended at least 6 months before patient enrolment, and no previous chemotherapy for metastatic disease. Patients with non-adenocarcinomatous tumors, surgery within two months, a history of previously treated mCRC, and another cancer considered as not cured, were not included.

Data collection

Clinical and laboratory data

Data collection was done on a computer platform at the beginning of first-line chemotherapy (D0). The nutritional data collected on D0 were: body weight at D0 and 6 months before, body mass index (BMI), a potential nutritional intervention (type and calories), blood albumin and PG-SGA.

PG-SGA included an overall assessment by the physician classifying the patient as category A (no malnutrition), B (moderate malnutrition) or C (severe malnutrition) and a numerical score, the values of each section (questionnaire completed by the patient and physical examination) being summed. Malnutrition was defined by a grade B—C of PG-SGA and/or a PG-SGA score ≥ 9 and severe malnutrition was defined by a grade C of PG-SGA, as previously described [13].

Oncological data collected on D0 were: date of diagnosis of CRC and metastatic disease, number of metastatic sites, WHO performance status (PS), chemotherapy protocol, and the plasma levels of lymphocytes, hemoglobin, platelets, carcinoembryonic antigen (CEA), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH).

Chemotherapy tolerability was collected every two weeks from D0 to day 60 (D60) and was evaluated by the

National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0 [15].

RECIST criteria were assessed on the first evaluation CT scan on D60 (progressive disease, stable disease or partial response). PFS and OS were evaluated from treatment start.

The study was approved by our institutional ethics committee.

Measurement of skeletal muscle index (SMI)

SMI was measured on D0 and D60 centrally by a radiologist with more than ten years of experience of routine CT scans. Two consecutive cross-sections at the level of the third lumbar vertebra (L3), preferably with a cutting thickness of 2.5 mm, otherwise 1.25 mm or 5 mm, were transferred to the DICOM format on the Slice-O-Matic software version 5.0 (Tomovision, Yves Martel, Magog, Canada). The cross-sectional area of skeletal muscle (in cm^2) was measured with a window width of -10 to 150 HU. The cross-sectional area of muscle (cm^2) at the L3 level computed from the two cross-sections was adjusted for height squared (m^2) to obtain the SMI (cm^2/m^2). We decided to define sarcopenia as the lowest sex-specific quartile of SMI [16]. The variation of SMI (in percentage) was evaluated from D0 to D60.

Statistical analyses

The qualitative variables were compared using the Chi2 test or Fisher test. The best cut-point value of SMI variation (between D0 and D60) for OS prediction was obtained by a log-rank maximization method [17] and was used as a variable in univariate and multivariable analyses for PFS, OS and chemotherapy-related toxicities. The factors associated with PFS and OS were investigated using univariate and multivariable Cox models. PFS and OS were described using the Kaplan—Meier method and compared using log-rank tests. Log-rank p-values were not corrected for multitests.

Univariate and multivariable logistic regressions were performed to investigate factors independently associated with the clinically significant toxicities of chemotherapy (grade $\geq$ 2). The adjustment factors used in the multivariable analyses for toxicities and survival were the variables with a p value < 0.05 and/or relevant variables, in the univariate analyses.

Results

Patient characteristics

Among our initial population of 168 patients with newly diagnosed mCRC, enrolled between July 2013 and November 2016 [14], the baseline CT-scan could be analyzed for SMI assessment in 149 patients (88.7%), 137 of them with an analyzable CT-scan on D60 (81.5%), CT-scan images were not available for other patients. The median age of our population was 70 years, with 45% of women and 45% of patients with more than two metastatic sites (Table 1).

The mean SMI was 45.4 cm^2/m^2 in men and 35.5 cm^2/m^2 in women at D0, and 43.1 cm^2/m^2 and 34.1 cm^2/m^2 at D60, respectively. The threshold value for defining sarcopenia (lowest quartile) was 40.3 cm^2/m^2 in men and 32.0 cm^2/m^2 in women at D0. The mean variation of SMI between D0 and D60 was -4% in men and women (Table 2).

BMI < 18.5 kg/m^2 was significantly more frequent in sarcopenic patients at baseline compared to non-sarcopenic patients (23.4% versus 6.3%, p = 0.002) and there was a trend to more malnourished patients according to PG-SGA ($\geq$ 9) in sarcopenic patients at baseline (55.3% versus 39.4%, p = 0.09). Table 1 shows the different clinical and laboratory characteristics of patients with or without sarcopenia at baseline.

SMI assessment and survival

In the overall population, after a median follow-up of 23 months (95% confidence interval [CI] [21—27]), median PFS was 8 months (95%CI [7—9]) and median OS was 22 months (95%CI [20—31]). At the end of follow-up, 126 patients (84.6%) progressed and 78 patients (52.3%) died. Patients with pretherapeutic sarcopenia and those without sarcopenia had a median PFS of 6 months (95% CI [5—9]) and 8 months (95% CI [8—12]), respectively (p = 0.055), and a median OS of 20 months (95% CI [9-not reached]) and 26 months (95% CI [21—31]), respectively (p = 0.29) (Fig. 1).

The best cut-point value of SMI variation (between D0 and D60) for OS prediction obtained with a log-rank maximization method was —14%. For the 115 patients (84%) with an increase or stability or decrease in SMI < 14% between D0 and D60, the median PFS was 9 months (95% CI [8—11]) and the median OS was 26 months (95% CI [21—31]), whereas the 22 patients (16%) with a decrease in SMI > 14% had a median PFS of 6 months (95% CI [3—12]) and a median OS of 8.5 months (95% CI [5-not reached]) (p = 0.005 and p = 0.008 for PFS and OS, respectively) (Fig. 1).

For other nutritional factors in univariate analyses, weight loss > 10% before treatment was significantly associated with OS, blood albumin < 35 g/L, malnutrition defined by the PG-SGA score ($\geq$ 9), the category letter of PG-SGA (B—C) and the variation of SMI as a continuous variable between D0 and D60 were associated with both PFS and OS (Table 3).

In multivariable analysis, SMI decrease > 14% was still significantly associated with a decrease in PFS (HR 1.8, 95% CI 1.1—3.1, p = 0.02) and OS (HR 2.6, 95% CI 1.4—4.8, p = 0.002), independently of hypoalbuminemia and malnutrition defined by the PG-SGA score ($\geq$ 9), and in addition for OS, independently of the progression of the disease on D60 according to RECIST criteria. Blood albumin < 35 g/L was also associated with a decrease in PFS (HR 1.8, 95% CI 1.1—2.9, p = 0.02) and OS (HR 2.0, 95% CI 1.1—3.5, p = 0.03), whereas malnutrition defined by the PG-SGA score was associated with a trend to a decreased PFS (HR 1.1, 95%CI 0.7—1.8, p = 0.7) and OS (HR 1.5, 95% CI 0.9—2.5, p = 0.2) in the two multivariable models (Table 3). Though prognostic in univariate analyses, the plasma LDH level was not included in the two multivariable models for PFS and OS, because of too many missing data (25%), and weight loss > 10% was also not included in the multivariable model for OS due to its inherent correlation with the PG-SGA score [13].

The factors significantly associated with the decrease in SMI > 14% between D0 and D60

Table 1 Baseline patient characteristics in the whole population and according to sarcopenia.

			All patients (n = 149)	Patients without sarcopenia* on D0 (n = 111)	Patients with sarcopenia* on D0 (n = 38)	p	
		Missing data, n					
Age < 65 years			58 (38.9%)	0	48 (43.2%)	10 (26.3%)	0.06
Female gender			67 (45.0%)	0	50 (45.0%)	17 (44.7)	1.0
Number of metastatic sites >2			67 (45.0%)	0	21 (19.0%)	5 (13.2%)	0.4
PS 2—3			28 (18.8%)	0	16 (14.4%)	12 (31.6%)	**0.019****
Chemotherapy protocol	5-FU-based		143 (96.0%)	0	107 (96.4%)	36 (94.7%)	0.6
	Capecitabine-based		6 (4.0%)		4 (3.6%)	2 (5.3%)	0.5
	Oxaliplatin-based		99 (66.4%)		75 (67.6%)	24 (63.2%)	0.6
	Irinotecan-based		59 (39.6%)		46 (41.4%)	13 (34.2%)	0.4
	Single agent		10 (6.7%)		5 (4.5%)	5 (13.2%)	0.2
	Doublet		120 (80.5%)		91 (82.0%)	29 (76.3%)	
	Triplet		19 (12.7%)		15 (13.5%)	4 (10.5%)	
	Bevacizumab		68 (45.6%)		49 (44.1%)	19 (50.0%)	0.5
	Anti-EGFR therapy		11 (7.4%)		10 (9.0%)	1 (2.6%)	0.3
	BMI (kg/m^2)	<18.5	16 (10.7%)	0	7 (6.3%)	9 (23.7%)	**0.002****
	18.5—25	83 (55.7%)	59 (53.1%)		24 (63.2%)		
	25—30	39 (26.2%)	35 (31.5%)		4 (10.5%)		
	>30	11 (7.4%)	10 (9.0%)		1 (2.6%)		
Weight loss >10%			43 (29.0%)	1	28 (25.4%)	15 (39.5%)	0.1
	Nutritional intervention	All	21 (15.7%)	15	14 (14.3%)	7 (19.4%)	0.5
	ONS	20 (13.4%)		13 (11.7%)	7 (19.4%)		
	Parenteral nutrition	1 (0.7%)		1 (0.9%)			
	caloric value: median (range)	600 kcal (300—1200)	7	600 kcal (300—900)	700 kcal (300—1200)		
CEA > 200 ng/mL			37 (25.7%)	4	29 (26.8%)	8 (22.2%)	0.6
LDH > 250 IU/L			52 (46.8%)	38	43 (49.4%)	9 (37.5%)	0.3
Platelets > 400,000/mm^3			46 (30.9%)	0	35 (31.5%)	11 (28.9%)	0.8
ALP > 300 IU/L			29 (20.1%)	5	23 (21.5%)	6 (16.2%)	0.5
Lymphocytes < 1000/mm3			12 (8.2%)	3	9 (8.33%)	3 (7.89%)	1.0
Blood albumin < 35 g/L			50 (33.6%)	0	37 (33.3%)	13 (34.2%)	0.9
	Malnutrition	PG-SGA ≥ 9	64 (43.5%)	2	43 (39.4%)	21 (55.3%)	0.09
	PG-SGA B—C	66 (44.6%)	1	47 (42.7%)	19 (50.0%)	0.4	
Severe malnutrition		PG-SGA C		18 (12.1%)	13 (11.8%)	5 (13.2%)	0.7

D0: day 0; 5-FU: 5-fluorouracil; EGFR: epidermal growth factor receptor; BMI: body mass index; CEA: carcinoembryonic antigen; ONS: oral nutritional supplements; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; Hg: hemoglobin; PG-SGA: Patient-Generated Subjective Global Assessment; SD: standard deviation.

* Sarcopenia defined by the lowest sex-specific quartile of SMI.

** p < 0.05.

were: platelets > 400,000/mm3 (OR: 2.6, p = 0.04), CEA > 200 ng/mL (OR: 3.0, p = 0.02), LDH > 250 IU/L (OR: 5.2, p = 0.008), ALP > 300 IU/L (OR: 3.5, p = 0.01), BMI > 25 kg/m^2 (OR: 2.8, p = 0.03) and treatment by anti-EGFR therapy (OR 4.0, p = 0.04). Initial weight loss > 10% over the last 6 months was not significantly associated with the decrease in SMI > 14% (p = 0.7).

SMI assessment and chemotherapy-related toxicities

The proportion of patients with grade ≥ 2 clinical toxicities in the first two months of treatment was 27.0% with: 15.0% for nausea/vomiting, 8.8% for diarrhea, 4.0% for mucositis, 0.7% for hand-foot skin reactions and 4.0% for alopecia.

Table 2 Assessment of skeletal muscle index (SMI) in the whole population and according to gender on day 0 and day 60.

SMI on D0 (cm^2/m^2)			
	All patients (n = 149)	Men (n = 82)	Women (n = 67)
Mean (SD)	41 (8.8)	45.4 (8.41)	35.5 (5.62)
Median (min; max)	40.5 (18.5; 70.3)	45.3 (22.4; 70.3)	35.6 (18.5; 46.6)
Q1 (sarcopenia)	18.5—34.9 (n = 38)	22.4—40.3 (n = 21)	18.5—31.4 (n = 17)
Q2	35—40.5 (n = 37)	40.6—45.2 (n = 19)	32.7—35.6 (n = 17)
Q3	40.6—45.9 (n = 37)	45.3—49.8 (n = 21)	35.7—39.2 (n = 16)
Q4	46—70.3 (n = 37)	51—70.3 (n = 21)	39.4—46.6 (n = 17)
SMI on D60 (cm^2/m^2)			
	All patients (n = 137)	Men (n = 77)	Women (n = 60)
Mean (SD)	39.2 (8.09)	43.1 (7.46)	34.1 (5.76)
Median (min; max)	38.9 (18.5—58.3)	42.7 (22.8—58.3)	35.0 (18.5—49)
Q1 (sarcopenia)	18.5—32.7 (n = 34)	22.8—38.6 (n = 19)	18.5—29.3 (n = 15)
Q2	32.7—38.9 (n = 34)	38.6—42.7 (n = 20)	30.0—34.9 (n = 15)
Q3	38.9—44.7 (n = 35)	42.9—48.2 (n = 19)	35.0—38.2 (n = 15)
Q4	44.9—58.3 (n = 34)	48.2—58.3 (n = 19)	38.5—49 (n = 15)
SMI variation D0—D60			
Mean (SD)	−4% (9%)	−4% (9%)	−4% (10%)
Median (min; max)	−4% (−27%;+17%)	−5% (−24%;+17%)	−3% (−27%;+15%)

SMI: skeletal muscle index; D0: day 0; D60: day 60; Q: quartile; SD standard deviation.

Twenty-six percent of non-sarcopenic patients and 29.0% of sarcopenic patients at baseline developed grade ≥ 2 clinical toxicities (p = 0.2). Forty percent of patients with a SMI decrease > 14% between D0 and D60, and 22% of patients with a SMI increase or stability or decrease < 14% developed grade ≥ 2 clinical toxicities (p = 0.02; Table 4).

In univariate analyses, the variables associated with the occurrence of grade ≥ 2 clinical toxicities were: age < 65 years (OR 3.8, 95% CI 1.9—7.9, $p < 10^{-4}$), female gender (OR 2.1, 95% CI 1.0—4.1, p = 0.04), irinotecan-based chemotherapy (OR 2.1, 95% CI 1.05—4.2, p = 0.04), the variation of SMI as a continuous variable between D0 and D60 (OR 1.1, 95% CI 1.0—1.2, p = 0.04), the decrease in SMI > 14% (OR 3.0, 95% CI 1.2—7.7, p = 0.02) and malnutrition defined by the PG-SGA score (OR 2.8, 95% CI 1.4—5.7, p = 0.04). Blood albumin < 35 g/L and weight loss > 10% were not associated with the occurrence of grade ≥ 2 clinical toxicities (Table 4). In multivariable analysis, age < 65 years, female gender and malnutrition defined by the PG-SGA score were still significantly associated with grade ≥ 2 clinical toxicities, whereas SMI decrease > 14% was not (OR 2.3, 95% CI 0.8—6.7, p = 0.1) (Table 4). Twenty-one percent of patients developed grade ≥ 2 hematological toxicities with: 13% of neutropenia, 1.3% of febrile neutropenia, 11% of anemia and 1.3% of thrombocytopenia. In univariate analyses, no variable was associated with the occurrence of these toxicities in the first two months of treatment (Table 4).

The decrease in SMI > 14% was not significantly associated with dose reduction of the chemotherapy drugs during the first two months of treatment (data not shown).

Discussion

To our knowledge, this is the first study to assess prospectively the association of skeletal muscle loss with survival and treatment toxicities in patients with mCRC. In our population of non-pretreated mCRC patients, pretherapeutic sarcopenia was not associated with a decrease in PFS or OS, but the early loss of skeletal muscle mass during treatment was highly prognostic. Indeed, the decrease in SMI > 14% from the start of treatment to 2 months later was significantly associated with decreased PFS and OS, independently of other prognostic factors (WHO-PS, platelets and plasma ALP levels, progression of the disease according to RECIST criteria on D60) and other nutritional factors as malnutrition defined by PG-SGA score and blood albumin <35 g/L. This cut-point value of SMI variation was obtained by a log-rank maximization method for OS prediction and seemed clinically relevant.

One of the limits of the results on sarcopenia is the lack of standardization of its definition in the literature. Thus, the threshold value of SMI by gender for the diagnosis of sarcopenia was determined according to the risk of mortality, the two most frequently used definitions being that of Prado et al. (52.4 cm^2/m^2 in males and 38.9 cm^2/m^2 in female) [3] and that of Martin et al. (SMI < 43 cm^2/m^2 in males with a BMI < 25 kg/m^2, <53 cm^2/m^2 in males with a BMI > 25 kg/m^2 and <41 cm^2/m^2 in females independently of BMI) [4], but including heterogeneous populations with solid tumors of the respiratory or gastrointestinal tract and specifically in obese patients for the study of Prado et al. For this reason, we decided to define sarcopenia in our specific population

Table 3 Factors associated with progression-free survival (PFS) and overall survival (OS) in univariate and multivariable analyses.

		PFS						OS					
		Univariate analyses			Multivariable analysis			Univariate analyses			Multivariable analysis		
		HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p
Age > 65 years		1.0	1.0—1.02	0.7				0.9	0.6—1.5	0.8			
Female gender		0.9	0.7—1.4	0.8				0.9	0.6—1.4	0.6			
Number of metastatic sites >2		1.6	1.0—2.6	**0.03***	1.2	0.7—2.1	0.4	1.5	0.9—2.6	0.1			
PS 2—3		1.7	1.1—2.7	**0.02***	1.0	0.5—1.8	0.9	2.4	1.4—3.9	**0.001***	1.3	0.7—2.5	0.4
Oxaliplatin		1.1	0.7—1.5	0.7				1.1	0.7—1.8	0.6			
Irinotecan		0.9	0.6—1.3	0.5				0.7	0.4—1.1	0.09			
Single agent		2.1	1.1—4.2	0.1				2.6	1.2—5.4	0.08			
Triplet		1.2	0.7—2.0					1.0	0.5—2.0				
Bevacizumab		1.2	0.8—1.7	0.4				1.2	0.8—1.9	0.4			
Anti-EGFR therapy		0.8	0.4—1.6	0.6				0.6	0.2—1.7	0.4			
BMI < 18.5 kg/m^2		0.8	0.4—1.4	0.5				1.0	0.4—2.0	0.9			
Weight loss >10%		1.2	0.8—1.7	0.4				1.9	1.2—3.1	**0.008***			
CEA > 200 ng/mL		1.3	0.9—2.0	0.1				1.3	0.8—2.1	0.3			
LDH > 250 IU/L		2.0	1.3—3.0	**0.001***				2.5	1.4—4.2	**0.001***			
Platelets > 400,000/mm^3		2.1	1.4—3.1	**<10^{-4}***	1.4	0.9—2.3	0.1	2.3	1.4—3.7	**<10^{-4}***	1.1	0.6—2.0	0.7
ALP > 300 IU/L		2.5	1.6—3.9	**<10^{-4}***	2.0	1.1—3.4	**0.01***	2.4	1.4—4.0	**0.001***	2.0	1.1—3.7	**0.03***
Hg < median (12.1 g/dL)		1.21	0.8—1.7	0.3				1.4	0.9—2.2	0.1			
Lymphocytes < 1000/mm^3		2.0	1.1—3.7	**0.02***	2.1	1.0—4.3	**0.04***	1.5	0.7—3.3	0.3			
Blood albumin < 35 g/L		1.9	1.2—2.8	**<10^{-4}***	1.8	1.1—2.9	**0.02***	2.6	1.6—4.2	**<10^{-4}***	2.0	1.1—3.5	**0.03***
Malnutrition	PG-SGA ≥ 9	1.6	1.1—2.3	**0.009***	1.1	0.7—1.8	0.7	2.1	1.3—3.3	**0.001***	1.5	0.9—2.5	0.2
	PG-SGA B—C	1.5	1.0—2.1	**0.03***				2.2	1.4—3.5	**0.001***			
Severe malnutrition	PG-SGA C	1.5	0.9—2.7	0.12				3.0	1.6—5.6	**0.001***			
Sarcopenia		1.5	1.0—2.2	0.06				1.3	0.8—2.2	0.3			
SMI decrease >14% between D0 and D60		1.9	1.2—3.1	**0.006***	1.8	1.1—3.1	**0.02***	2.1	1.2—3.8	**0.01***	2.6	1.4—4.8	**0.002***
SMI variation between D0 and D60		1.05	1.0—1.1	**0.049***				1.06	1.0—1.1	**0.05***			
Tumor response according to RECIST criteria at D60	PD							1			1		
	SD							0.3	0.2—0.5	**<10^{-4}***	0.2	0.1—0.4	**<10^{-4}***
	PR							0.3	0.2—0.6	**<10^{-4}***	0.3	0.1—0.6	**<10^{-4}***

PFS: progression-free survival; OS: overall survival; HR: hazard ratio; 95% CI: 95% Confidence Interval; EGFR: epidermal growth factor receptor; BMI: body mass index; CEA: carcinoembryonic antigen; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; Hg: hemoglobin; PG-SGA: Patient-Generated Subjective Global Assessment; SMI: skeletal muscle index; D0: day 0; D60: day 60; PD: progressive disease; SD: stable disease; PR: partial response.

* $p < 0.05$.

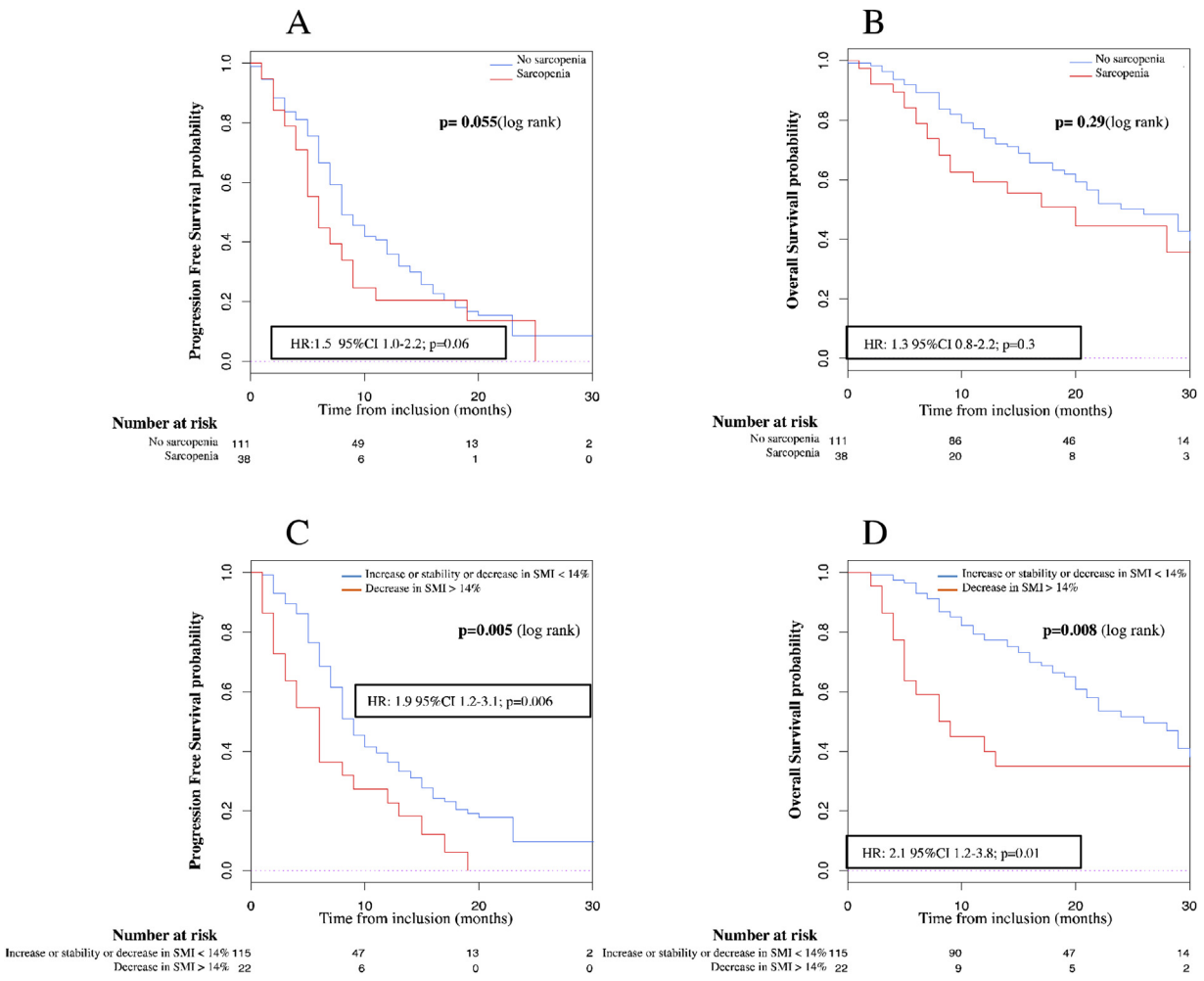

Figure 1 Kaplan–Meier curves of progression-free survival (PFS) and overall survival (OS) according to sarcopenia and the variation of SMI between day 0 and day 60.
(A) PFS and (B) OS according to sarcopenia (C) PFS and (D) OS according to the variation of SMI between D0 and D60.
D0: day 0; D60: day 60; HR: hazard ratio; 95% CI: 95% confidence interval; SMI: skeletal muscle index; PFS: progression-free survival; OS: overall survival.

as the lowest sex-specific quartile of SMI, as in the Japanese study by Miyamoto et al. [16].

The prognostic effect of sarcopenia in patients was demonstrated in various cancers such as pancreatic cancer [5], gastrointestinal and respiratory tract cancers [3,4], and renal cancer [18], while in colorectal cancer the prognostic value of sarcopenia remains controversial [3,8,16,19]. More than baseline sarcopenia before treatment start, it seems that muscle mass change during treatment has the best prognostic value.

In the same way, concerning chemotherapy-naïve patients, in the study of Miyamoto et al. [19] including mCRC patients and in the recently published study of Basile et al. including advanced pancreatic cancer patients [20], baseline sarcopenia was also not significantly associated with PFS or OS, while patients with an early decrease in SMI > 5% and >10%, respectively, had a significantly shorter OS compared to those without skeletal muscle loss, in multivariable analysis. Conversely, in patients with advanced lung cancer, the study by Stene et al. [21] showed that around 50% of patients had stable or increased muscle mass during chemotherapy and almost all of these patients responded to chemotherapy; the increase in muscle mass was a significant prognostic factor, unlike the presence of sarcopenia at the beginning of treatment. Skeletal muscle loss may reflect the increased catabolic activity of a more aggressive tumor, which may explain its association with prognosis. Therefore, controlling tumors with effective chemotherapy would be likely to reverse this process.

Blood albumin < 35 g/L was also an independent prognostic factor in multivariable analysis and is known to be an important prognostic factor in oncology [22].

As for survival outcomes, baseline sarcopenia was not associated with grade ≥ 2 clinical toxicities in the first two months of treatment, while the decrease in SMI > 14% was associated with the occurrence of grade ≥ 2 toxicities (40% versus 22%), but this result was not confirmed in multivariable analysis, probably partly due to a small sample size (n = 25) limiting the statistical power of the analysis.

Table 4 Factors associated with grade ≥ 2 chemotherapy-induced toxicities in the first two months of treatment.

	Clinical toxicities grade ≥ 2						Hematological toxicities grade ≥ 2		
	Univariate analyses			Multivariable analysis			Univariate analyses		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Age > 65 years	0.3	0.1—0.5	**<10^{-4}***	0.2	0.1—0.6	**0.002***	0.6	0.3—1.2	0.1
Female gender	2.1	1.0—4.1	**0.04***	2.7	1.1—6.5	**0.03***	1.5	0.7—3.1	0.3
Irinotecan-based chemotherapy	2.1	1.1—4.2	**0.04***	2.3	0.9—5.8	0.07	0.8	0.4—1.7	0.6
BMI < 18.5 kg/m^2	2.1	0.7—6.4	0.2				0.2	0.02—1.5	0.1
Weight loss > 10%	1.0	0.9—1.0	0.7				1.0	0.9—1.1	0.8
Blood albumin < 35 g/L	0.9	0.4—1.9	0.8				1.8	0.8—3.7	0.1
Baseline sarcopenia	1.1	0.5—2.6	0.7				1.7	0.7—4.0	0.2
SMI variation	1.1	1.0—1.2	**0.04***				1.1	0.9—1.2	0.2
PG-SGA ≥ 9	2.8	1.4—5.7	**0.004***	4.2	1.6—10.6	**0.003***	1.1	0.5—2.4	0.7
SMI variation	1.1	1.0—1.2	**0.04***				1.1	1.0—1.2	0.2
SMI decrease > 14%	3	1.2—7.7	**0.02***	2.3	0.8—6.7	0.1	2.1	0.7—5.8	0.1

OR: odds ratio; 95% CI: 95% Confidence Interval; BMI: body mass index; PG-SGA: Patient-Generated Subjective Global Assessment; SMI: skeletal muscle index.
* $p < 0.05$.

Skeletal muscle loss associated with chemotherapy-related toxicities could be explained by a direct effect of lean body mass loss on the appearance of side effects because of a smaller volume of distribution of cytotoxic drugs leading to more toxicity [9], but also by the fact that toxicities (especially gastrointestinal) could lead to a decrease in weight and therefore in muscle mass.

The most high risk patients of having a significant loss of muscle mass at the beginning of treatment for metastatic disease are those with initial biological factors of poor prognosis (high levels of platelets, CEA, ALP and LDH), overweight/obesity and anti EGFR therapy. Maybe physicians would be less aware of sarcopenia in overweight or obese patients. We have no pathophysiological hypothesis on the association of muscle loss with anti EGFR therapy.

Thus, vigilance should be increased for patients who combine these risk factors at the diagnosis of the disease in order to start nutritional management earlier.

The strengths of our work are its multicenter and prospective nature, focusing on a homogeneous population of chemotherapy-naive mCRC patients with a comprehensive nutritional assessment in addition to the change in skeletal muscle mass during treatment.

However, this work also has some limitations, in particular the limited number of events that occurred regarding the evaluation of OS (51% of patients) and the relatively low rate of reported chemotherapy-related toxicities during the first two months of treatment (27% of grade ≥ 2 clinical toxicities in the whole population). In addition, compared to the study that we recently published on nutritional evaluation by PG-SGA [14], we found in this work that malnutrition defined by PG-SGA was also associated in multivariable analysis with grade ≥2 clinical chemotherapy-related toxicities, but not anymore with OS with only a trend (HR 1.4, 95% CI 0.8—2.4, p = 0.2). A possible hypothesis is that by selecting the patients who had an SMI evaluation on D0 and D60, the sample was smaller (n = 137 patients), limiting the statistical power when we integrated the change in SMI in the multivariable model. Finally, we did not find a significant association between sarcopenia and chemotherapy-related toxicities, as shown by Barret et al. [6], but the latter study concerned patients with mCRC at any stage of care with a greater number of events for grade 3—4 toxicities (28%) using a different definition of sarcopenia [3].

To conclude, in our population of non-pretreated mCRC patients, pretherapeutic sarcopenia was not associated with poor survival outcomes, but skeletal muscle loss within 60 days from treatment start was highly prognostic. Indeed, a decrease in SMI > 14% during the first two months of treatment was significantly associated with decreased PFS and OS, independently of other prognostic and nutritional factors. An interventional study assessing the efficacy of early physical exercise associated with nutritional management in mCRC patients would be of interest.

Authors' contributions

CG, MB and JT contributed to the study concept and design. CG, CB, EA, PA, AL, TL, CL, LM, RF, SP, MB and JT contributed to data collection and critical revision of the manuscript for important intellectual content. CG, EA and JT contributed to data analysis and interpretation, and manuscript writing.

The final version of the manuscript has been approved by all authors.

Conflicts of interest

CG has participated in consulting and/or advisory boards for Servier and Sanofi, and has received support for travel to meetings from Amgen. AL has participated in consulting and/or advisory boards for Merck, Amgen, Shire, Bayer, and Ipsen, has received honoraria for lectures from Merck, Amgen, Roche, Servier, BMS, Novartis, and Ipsen and has received support for travel to meetings from Novartis and Ipsen. CL has received personal fees from Merck and sup-

port for travel to meetings from Novartis and Roche. SP has participated in consulting and/or advisory boards for Amgen, has received support for travel to meetings from Amgen, Bayer, and Servier, and has received research grants from Roche. MB has received consulting fees from Nutricia Medical (2011-2012). JT has participated in consulting and/or advisory boards for Lilly, Celgene, Shire, Servier, Merck KGaA, Sanofi, Roche Genentech, Pfizer, and Amgen. The other authors declare no conflict of interest.

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