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Skeletal muscle loss during systemic chemotherapy for colorectal cancer indicates treatment response: a pooled analysis of a multicenter clinical trial (KSCC 1605-A)

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Abstract

Background Sarcopenia or degenerative loss of skeletal muscle mass is related to poor prognosis in patients with cancer. This study aimed to clarify the clinical significance of skeletal muscle loss (SML) during chemotherapy for metastatic colorectal cancer (mCRC).

Methods A total of 249 patients who were secondarily registered in a pooled database of mCRC patients with the first-line systemic chemotherapy and prospectively enrolled in six clinical trials of Kyushu Study Group of Clinical Cancer were included in this study. Skeletal muscle area was calculated from computed tomography images before and 3 and 6 months after treatment. Baseline sarcopenia and SML (cut-off value = 9%) were evaluated.

Results Baseline sarcopenia was observed in 135 of 219 patients who were evaluated before treatment. They tended to be male; older; and have lower body mass index, lower visceral and subcutaneous fat contents, and a lower waist circumference ($P < 0.01$); however, baseline sarcopenia was not associated with prognosis. SML at 3 months was associated with an incidence of adverse events ($P = 0.01$), poor objective response rate (ORR) ($P < 0.01$), and poor progression-free survival (PFS) ($P = 0.03$), and it was an independent predictive factor for poor ORR ($P < 0.01$) and PFS ($P = 0.04$).

Conclusion SML at 3 months after systemic chemotherapy for mCRC was associated with poor treatment response. Thus, clarifying the importance of SML prevention guarantees a more effective chemotherapy.

Keywords Cachexia · Chemotherapy response · Metastatic colorectal cancer · Sarcopenia · Skeletal muscle loss

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Introduction

In Japan, colorectal cancer (CRC)-related mortality increased substantially to > 49,000 in 2015 [1]. However, great advances in surgery and chemotherapy have been made for the treatment of CRC. For patients with metastatic CRC (mCRC), the efficacy of systemic chemotherapy has been demonstrated in pivotal clinical trials [2–5], with conversion surgery being one of the standard treatments for patients showing good response to chemotherapy [6]. Thus, systemic chemotherapy has become an essential treatment strategy for mCRC.

Sarcopenia, which is a progressive and systemic loss of skeletal muscle mass associated with aging or atrophy, was reported by Rosenberg et al. [7, 8]. It is commonly diagnosed by measuring the skeletal muscle area (SMA) from computed tomography (CT) images [9]. Sarcopenia is associated with increased postoperative complications and poor survival rate in esophageal cancer, gastric cancer, CRC, hepatocellular carcinoma, and non-small cell lung carcinoma (NSCLC) [10–14].

Moreover, skeletal muscle loss (SML) is associated with the prognosis of patients with cancer not only after surgery but also during chemotherapy. Two studies reported that SML during chemotherapy for mCRC is associated with poor progression-free survival (PFS) and overall survival (OS) rates [15, 16]. SML of more than 5% and 9% were determined as independent factors for poor prognosis by Miyamoto et al. and Blauwhoff et al., respectively. However, the former was a single-institution retrospective study and had several biases, and the latter had no detailed analysis of the relationship between chemotherapy response and the incidence of adverse events (AEs), although it was a subset analysis of a prospective study.

Hence, the aim of this study was to investigate in detail the relevance of SML during systemic chemotherapy for mCRC to treatment outcome, including the incidence of AEs, objective response rates (ORR), PFS, and OS. This study was conducted using the pooled data of patients in phase II clinical trials of Kyushu Study Group of Clinical Cancer (KSCC).

Patients and methods

This study used a pooled database of mCRC patients prospectively enrolled in six phase II clinical trials (KSCC0701 [17], KSCC0801 [18], KSCC0802 [19], KSCC0902 [20], KSCC1002 [21], and KSCC1101 [22]). Patients' clinical data, laboratory data, and CT images were obtained from the database of the KSCC data center. This study was registered to a national review board: University Hospital Medical Information (UMIN; UMIN000027558).

The six trials evaluated the efficacy of first-line chemotherapy for mCRC patients. The study protocol was approved by the institutional review boards of Kyushu University and conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Studies. Furthermore, the ethical, medical, and scientific aspects of the trial was reviewed and approved by the ethics committees of each participating institution. The patients in KSCC1002 and 1101 provided written informed consent for the use of clinical data prior to enrollment. Some of the trials (KSCC0701, 0801, 0802, and 0902) used the opt-out method, which allowed the enrolled patients to decline joining the study if they did not agree with the participation agreement published on the homepage.

Eligibility criteria

Eligibility criteria in all clinical trials included in this study were as follows: histologically confirmed CRC and metastatic disease, which were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST); no previous exposure to systemic chemotherapy for metastatic disease; age 20–75 years; Eastern Cooperative Oncology Group performance status (PS) 0–2; and adequate bone marrow and renal functions. In KSCC0802 and 1002, liver-limited mCRC patients who had ≥ 5 metastases, with the largest diameter being > 5 cm, were enrolled and evaluated for liver resectability after the first-line treatment.

Trial treatment plans

The treatment plans for each clinical trial are shown in Table S1 [17–22]. In KSCC0701, 0801, 0902, and 1101, treatment with chemotherapy was continued until disease progression or prohibitive toxicity. In KSCC0802 and 1002, patients who were amenable to curative resection after systemic chemotherapy underwent liver resection.

Study design

This is a retrospective pooled analysis of several clinical studies. The main objective was to investigate the relationship between OS and sarcopenia; the secondary objectives were to investigate the effect of sarcopenia on PFS and ORR, according to RECIST version 1.0, and on the incidence of AEs. SMA was measured using follow-up CT images at pretreatment and around 3 months (range 60–120 days) and 6 months (range 150–210 days) after the first chemotherapy session. Sarcopenia before chemotherapy (baseline sarcopenia) and SML after the first chemotherapy was evaluated for correlation with primary and secondary endpoints to clarify the clinical significance of sarcopenia. In cases where the prior tumor response, according to RECIST version 1.0, was stable disease (SD) or progressive disease (PD), subsequent CT images were not obtained.

Measurement of SMA, visceral fat area (VFA), and subcutaneous fat area (SFA)

SMA, VFA, SFA, and waist circumference (WST) were measured retrospectively on CT images. The third lumbar vertebra was used as a standard landmark, because this correlated best with whole-body muscle mass [23, 24]. VFA, SFA, and WST were measured on the same CT images. The SliceOmatic software (version 5.0; Tomovision, Magog, Quebec, Canada) was used to distinguish and measure the SMA, VFA, and SFA. The structures of the muscle and fats were quantified (in Hounsfield units) based on pre-established thresholds (SMA − 29 to 150, VFA − 190 to − 30, and SFA − 150 to 50) [25, 26] Skeletal muscle index (SMI) was calculated as the ratio of SMA (cm^2) divided by the square of the height (m^2). The cut-off value of SMI was 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women, which was previously reported by Prado et al. [27]. Patients with lower SMI at pretreatment than the cut-off values were categorized as having baseline sarcopenia. The cut-off value of SML during systemic chemotherapy for mCRC patients was set to 9%, as previously reported [16]. The cut-off value of VFA was determined according to the diagnostic criteria of metabolic syndrome in the Japanese population; high VFA was > 130 cm^2 for men and > 90 cm^2 for women [28]. The values of SFA and WST were divided into two groups using the median as follows: for SFA, < 86.2 cm^2 and ≥ 86.2 cm^2, and for WST, < 80.6 cm^2 and ≥ 80.6 cm^2.

Response and survival analysis

Tumor response was evaluated at 3 and 6 months after chemotherapy using CT images and classified according to RECIST version 1.0, as follows: complete response (CR), partial response (PR), SD, or PD. Patients with either CR or PR were classified as responders and those with SD or PD as non-responders. OS was defined as the time from the day of registration to death (all causes). Survivors were censored at the last follow-up. PFS was defined as the time from the day of registration to the first recorded evidence of progression or death (all causes). Survivors without evidence of disease progression or who had received curative resection of metastatic sites were censored at the last follow-up. The incidence of AEs was evaluated according to the Common Terminology Criteria for Adverse Events (version 4.0). Grade 3 and 4 AEs were taken into account for determining the rate of AEs in this study.

Statistical analysis

Statistical analyses were performed using SAS software ver9.3 (SAS Institute Inc., Cary NC). Survival functions of PFS and OS were estimated by the Kaplan–Meier method. The influence of factors on OS and PFS was evaluated using the stratified log-rank test and the Cox proportional hazards model, with each study as a stratum. ORR and rate of AEs were analyzed by stratified logistic regression, with each study as a stratum. In multiple regression analyses, the covariates analyzed were age (< 64.0 vs. ≥ 64.0 years), sex (male vs. female), PS (0 vs. 1–2), body mass index (BMI; < 25.0 vs. ≥ 25.0 kg/m^2), and primary tumor resection (not performed vs. performed), which are clinically associated with the prognosis of CRC, baseline sarcopenia, or SML during chemotherapy. A two-sided $P < 0.05$ was considered statistically significant.

Results

Trial profiles and patient background

The KSCC trials used in the pooled analysis of CT images are shown in Fig. 1. In total, 249 patients were registered from the six trials. Among them, 219 patients with available CT images before chemotherapy were included in the analyses. Baseline sarcopenia was evaluated in these patients. A total of 30 patients were excluded, because CT images were unavailable or magnetic resonance images for routine examinations were used. The number of patients with CT images 60–120 days and 150–210 days after systemic chemotherapy administration was 142 and 87, respectively; SML at 3 and 6 months from the first chemotherapy administration was evaluated in these patients. A total of 77 patients (35.2%) at 3 months or 132 patients (60.3%) at 6 months were excluded, because the CT images were unavailable or not within the applicable period, and the tumor response was previously classified as SD or PD by the previous effect judgement. Table 1 shows the background of the registered patients. A total of 135 patients (61.6%) were categorized as having baseline sarcopenia. The median OS of the per-protocol set was 30.0 months (95% CI 26.6–36.2 months), and the median PFS was 10.7 months (95% CI 9.7–11.9 months). The median length of follow-up among the surviving patients was 29.2 months.

Associated baseline characteristics and clinical significance of baseline sarcopenia

Table S2 shows the baseline characteristics of patients with baseline sarcopenia. They tended to be male and older, and have low BMI, VFA, SFA, and WST ($P < 0.001$). No

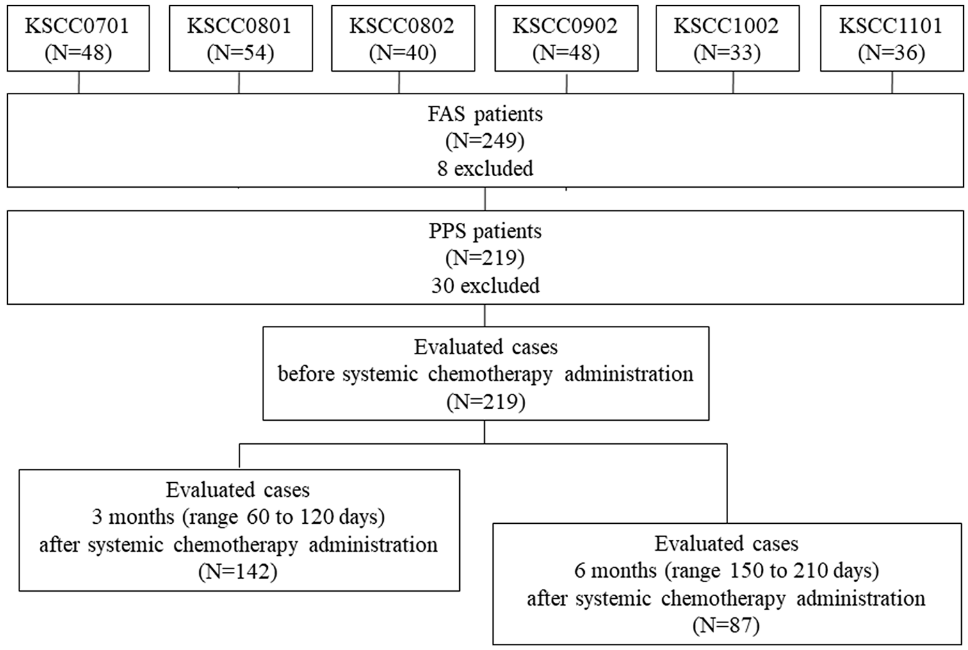

Fig. 1 Study design of KSCC 1605-A. Full analysis set (FAS) of all original studies that included 249 patients in total. With 30 patients excluded because of the absence of computed tomography (CT) images in our data center, the per-protocol set (PPS) included 219 patients, who were evaluated for baseline sarcopenia. Skeletal muscle loss at 3 and 6 months after systemic chemotherapy administration was measured in 142 and 87 patients, respectively

Table 1 Background of registered patients

Variables	*N* (219)	(%)
Sex		
Male	143	(65.3)
Female	76	(34.7)
Median age (range), years	64.0	(37.0–83.0)
Median BW (range), kg	56.0	(32.0–98.0)
BMI		
< 25.0 (kg/m^2)	187	(85.4)
≥ 25.0 (kg/m^2)	32	(14.6)
PS		
0	190	(86.8)
1	27	(12.3)
2	2	(0.9)
Primary tumour resection		
Not performed	110	(50.2)
Performed	109	(49.8)
Median SMI (range), cm^2	44.7	(27.6–75.2)
Sarcopenia before chemotherapy		
No sarcopenia	84	(38.4)
Sarcopenia	135	(61.6)
Median VFA (range), cm^2	55.1	(1.2–313.7)
Median SFA (range), cm^2	86.2	(4.8–434.2)
Median WST (range), cm^2	80.6	(58.4–116.8)

BMI body mass index, *BW* body weight, *PS* performance status, *SFA* subcutaneous fat area, *SMI* skeletal muscle index, *VFA* visceral fat area, *WST* waist circumference

association with PS was found. The patients with baseline sarcopenia were not inferior in terms of ORR to those without baseline sarcopenia [odds ratio (OR) 0.89, $P = 0.67$) (Table S3). The rate of AEs was not different between those with and those without baseline sarcopenia (OR 0.96, $P = 0.88$) (Table S3). No significant difference in PFS [hazard ratio (HR) 1.1, $P = 0.49$) (Fig. S1a) and in OS (HR 1.0, $P = 0.87$) (Fig. S1b) between the two groups was found.

Baseline characteristics of patients with SML after the first chemotherapy

Table 2 shows the baseline characteristics of patients with SML at 3 and 6 months after the first chemotherapy. Significantly more skeletal muscle reduction was observed in patients older than 64 years (OR 4.7, $P < 0.01$). However, no other factors at baseline were correlated with SML.

Relationship between SML after the first chemotherapy and the incidence of AEs

Figure 2 shows the rate of AEs in patients with SML after the first chemotherapy. As shown in Fig. 2a, the incidence of AEs was significantly higher in patients with SML than in those without SML at 3 months (58.1% vs. 29.7%, OR 3.0, $P = 0.01$). Each AE tended to increase in patients with SML at 3 months; however, no significant difference was found (Table S4). As shown in Fig. 2b, the incidence of AEs in patients with SML was similar to that in those without SML at 6 months.

Table 2 Baseline characteristics of patients with > 9% skeletal muscle loss after the first chemotherapy

Variables	CT analysis at 3 months					CT analysis at 6 months				
	No SML		SML		*P* value	No SML		SML		*P* value
	N	%	*N*	%		*N*	%	*N*	%	
Sex										
Male	64	74.4	22	25.6	0.22	37	72.5	14	27.5	0.59
Female	47	83.9	9	16.1		29	80.6	7	19.4	
Age										
< Median (64.0 years)	61	84.7	11	15.3	0.06	41	87.2	6	12.8	< 0.01
≥ Median	50	71.4	20	28.6		25	62.5	15	37.5	
BW										
< Median (56.0 kg)	55	75.3	18	24.7	0.29	36	78.3	10	21.7	0.91
≥ Median	56	81.2	13	18.8		30	73.2	11	26.8	
BMI										
< 25.0 (kg/m^2)	52	74.3	18	25.7	0.50	58	77.3	17	22.7	0.67
≥ 25.0 (kg/m^2)	59	81.9	13	18.1		8	66.7	4	33.3	
PS										
0	100	79.4	26	20.6	0.63	59	78.7	16	21.3	0.22
1–2	11	68.8	5	31.3		7	58.3	5	41.7	
Primary tumour resection										
Not performed	54	84.4	10	15.6	0.36	30	76.9	9	23.1	0.66
Performed	57	73.1	21	26.9		36	75.0	12	25.0	
Baseline sarcopenia										
Non-sarcopenia	43	74.1	15	25.9	0.26	26	70.3	11	29.7	0.26
Sarcopenia	68	81.0	16	19.0		40	80.0	10	20.0	
VFA										
Male < 130, female < 90 (cm^2)	89	78.8	24	21.2	0.80	55	78.6	15	21.4	0.31
Others	22	75.9	7	24.1		11	64.7	6	35.3	
SFA										
< Median (86.24 cm^2)	53	77.9	15	22.1	0.92	30	75.0	10	25.0	0.96
≥ Median	58	78.4	16	21.6		36	76.6	11	23.4	
WST										
< Median (80.62 cm)	55	76.4	17	23.6	0.53	34	77.3	10	22.7	0.88
≥ Median	56	80.0	14	20.0		32	74.4	11	25.6	
Chemotherapy regimens										
Combination of mFOLFOX6 and FOLFIRI	6	54.5	5	45.5	0.11	9	60.0	6	40.0	0.53
Combination of mFOLFOX6 + Bev and FOLFIRI + Bev	25	78.1	7	21.9		21	72.4	8	27.6	
mFOLFOX6 + Bev	22	95.7	1	4.3		2	100.0	0	0.0	
XELOX + Bev	21	87.5	3	12.5		14	93.3	1	6.7	
SOX + Cet	18	75.0	6	25.0		5	71.4	2	28.6	
XELIRI + Bev	19	67.9	9	32.1		15	78.9	4	21.1	

Bev bevacizumab, *BMI* body mass index, *BW* body weight, *Cet* cetuximab, *CT* computed tomography, *FOLFIRI* irinotecan, leucovorin, and 5-fluorouracil, *mFOLFOX6* modified oxaliplatin, leucovorin, and 5-fluorouracil, *PS* performance status, *SOX* S-1 and oxaliplatin, *SFA* subcutaneous fat area, *SML* skeletal muscle loss, *VFA* visceral fat area, *WST* waist circumference, *XELIRI* capecitabine and irinotecan, *XELOX* capecitabine and oxaliplatin

ORR, PFS, and OS associated with SML after the first chemotherapy

Table 3 shows the unadjusted and adjusted analyses for ORR, PFS, and OS according to SML after the first chemotherapy. In the unadjusted analysis, ORR was significantly lower in those with SML at 3 months (48.4% vs. 68.4%, OR 0.3, $P < 0.01$). In the analysis adjusted for covariates

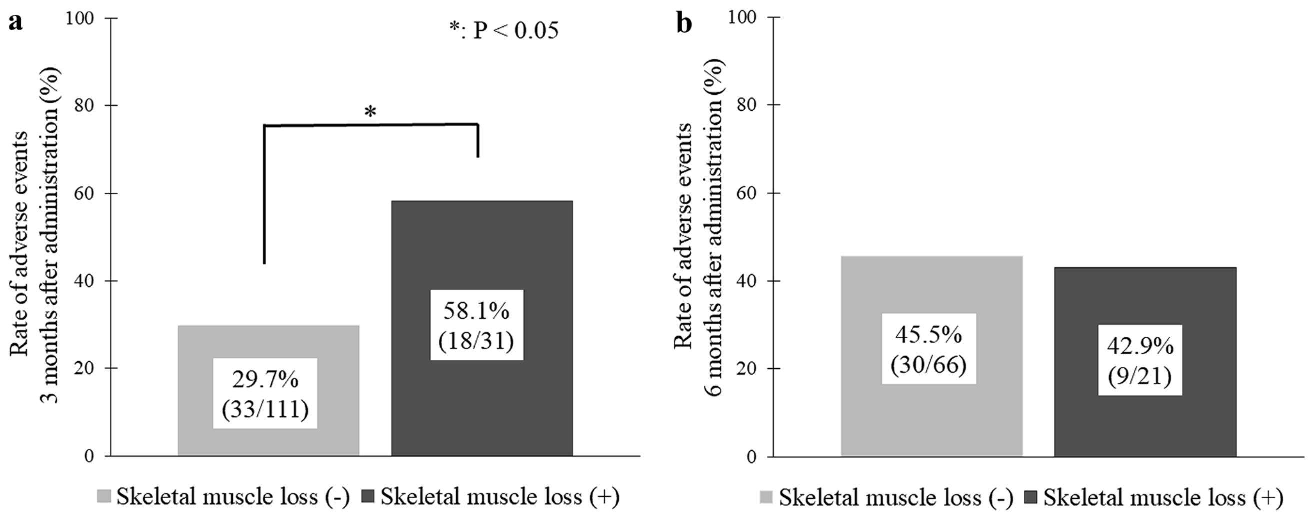

Fig. 2 Rate of adverse events (grade 3 or 4) according to skeletal muscle loss (SML) at 3 months (**a**) or 6 months (**b**) after chemotherapy. **a** A higher rate of adverse events (AEs) was noted in patients with SML at 3 months (58.1% vs. 29.7%, $P=0.01$). **b** No significant difference in the rate of AEs was noted between SML at 6 months and without SML ($P>0.05$)

Table 3 Univariate and multivariate analyses of survival outcome and objective response rate according to > 9% skeletal muscle loss after the first chemotherapy

Variables (SML vs. no SML)	CT analysis at 3 months (*N* = 142)				CT analysis at 6 months (*N* = 87)			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
	HR (OR[b]) (95% CI)	*P* value	HR (OR[b]) (95% CI)	*P* value	HR (OR[b]) (95% CI)	*P* value	HR (OR[b]) (95% CI)	*P* value
ORR	0.3 (0.1–0.7)	< 0.01	0.2 (0.1–0.6)	< 0.01	0.4 (0.1–1.2)	0.11	0.4 (0.1–1.2)	0.10
PFS	1.6 (1.0–2.6)	0.03	1.6 (1.0–2.7)	0.04	1.0 (0.6–1.8)	0.90	1.1 (0.6–2.0)	0.79
OS	1.2 (0.7–2.0)	0.55	1.0 (0.6–1.8)	1.00	1.0 (0.5–1.9)	0.99	0.8 (0.4–1.6)	0.51

CI confidence interval, *CT* computed tomography, *HR* hazard ratio, *OR* odds ratio, *ORR* objective response rate, *PFS* progression-free survival, *OS* overall survival, *SML* skeletal muscle loss

[a]Adjusted for sex, age at treatment, performance status (PS), body mass index (BMI), and primary tumour resection

[b]Odds ratio (OR) is shown in the analysis of ORR

(age, sex, BMI, PS, and primary tumor resection), SML at 3 months was independently associated with ORR (OR 0.2, $P<0.01$).

Figure 3 shows the Kaplan–Meier analyses of PFS and OS according to SML at 3 or 6 months. PFS was shorter in patients with SML at 3 months (Fig. 3a) [median PFS (mPFS) 10.3 vs. 11.8 months, HR 1.6, $P=0.03$). Patients with SML at 3 months showed a tendency to decrease in OS, but there was no significant difference in OS between patients with SML at 3 months and those without, but a tendency to decrease for patients with SML was observed (Fig. 3b) [median OS (mOS) 35.7 vs. 36.6 months, HR 1.2, $P=0.55$]. To determine whether SML during chemotherapy was independently associated with PFS and OS, a multivariate Cox regression analysis with covariates (age, sex, BMI, PS, primary tumor resection) was performed. As shown in Table 3, SML at 3 months was identified as an independent predictive factor for poor PFS (HR 1.6, $P=0.04$). However, no significant correlation with poor OS was observed in the multivariate analysis.

In the unadjusted analysis with CT images at 6 months, no difference in ORR (HR 0.4, $P=0.11$) (Table 3), PFS (HR 1.0, $P=0.90$) (Fig. 3c), and OS (HR 1.0, $P=0.99$) between patients with SML and those without SML was found (Fig. 3d).

Discussion

In our study, baseline sarcopenia was not associated with chemotherapy response in patients with mCRC who received the first-line chemotherapy. SML at 3 months from the start

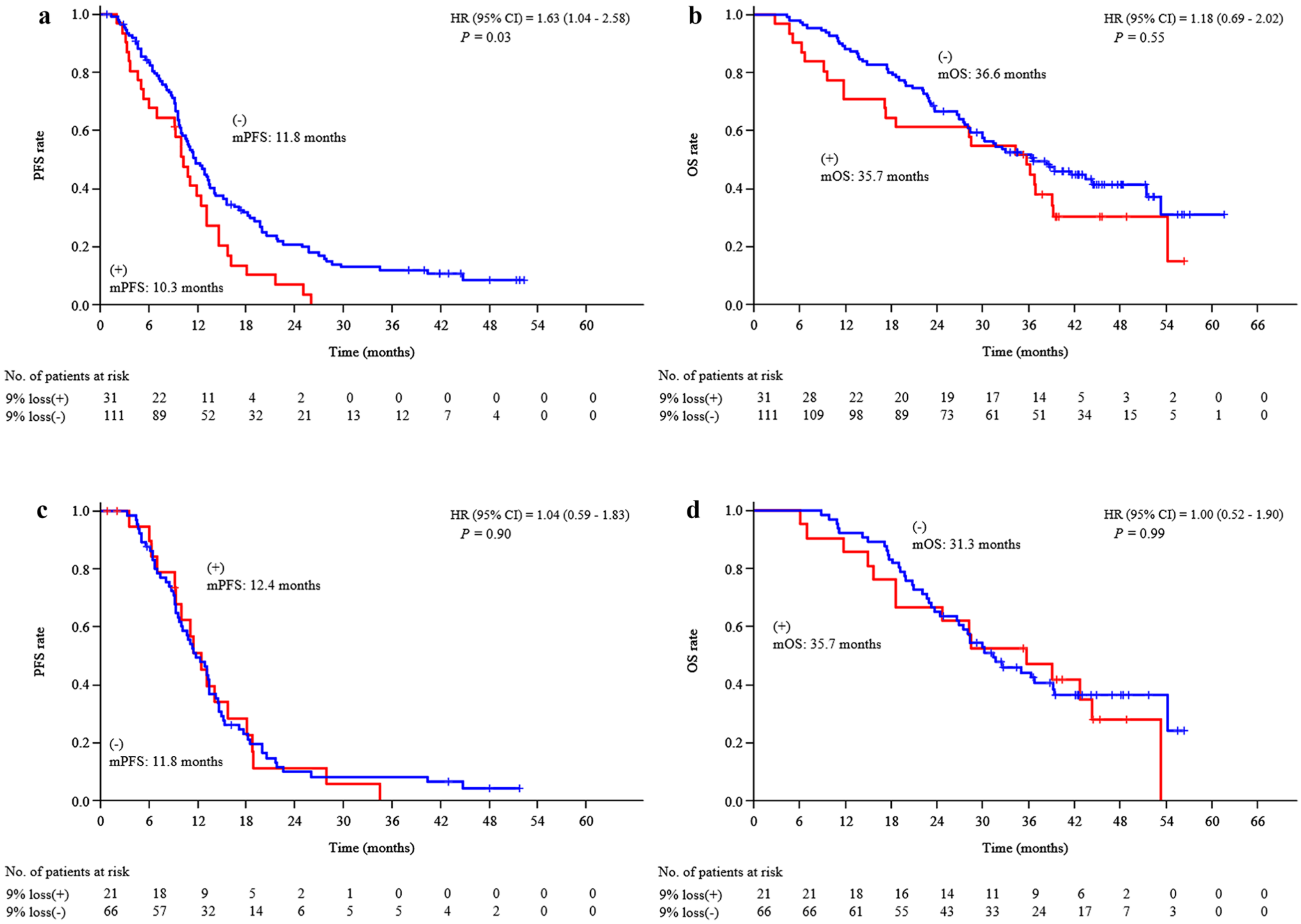

Fig. 3 Kaplan–Meier analyses of progression-free survival (PFS) and overall survival (OS) according to skeletal muscle loss (SML) at 3 months (Fig. 3a, b) and 6 months (Fig. 3c, d) after the first chemotherapy. **a** The PFS of patients with SML at 3 months was significantly shorter ($P = 0.03$). **b** No significant difference in OS between SML and no SML patients at 3 months was noted ($P = 0.55$). **c** No significant difference in PFS between SML and no SML patients at 6 months was observed ($P = 0.90$). **d** No significant difference in OS between SML and no SML patients at 6 months ($P = 0.99$)

of chemotherapy was independently associated with a high incidence of AEs and low ORR and PFS. Therefore, SML at the early phase of chemotherapy may have an effect on the time to treatment failure and the chemotherapy response itself.

Cancer-induced sarcopenia could be recognized as an indicator of cancer cachexia progression [29]. Cancer cachexia is characterized by progressive SML that cannot be completely recovered by the conventional nutritional support and is the cause of approximately 20% of cancer-related deaths [30]. Cancer cachexia progression is categorized into three stages according to severity, pre-cachexia, cachexia, and refractory cachexia [29], which was associated with sarcopenia in a prospective study [31]. Thus, sarcopenia evaluation could be helpful in preventing SML occurrence before patients reach refractory cachexia, which is irreversible. However, our study did not clarify the efficacy of SML prevention in cancer cachexia.

The AEs associated with chemotherapy include malnutrition, fatigue, and malaise due to insufficient oral intake. They also include physical dysfunction related to peripheral sensory neuropathy and degenerative diseases with febrile neutropenia [32, 33]. These AEs could cause SML. This study showed that most patients with AEs at 3 months also had SML. Thus, SML was often accompanied by AEs at the early phase of chemotherapy. In addition, a high incidence of AEs results in dose reduction, discontinuation, and delay of chemotherapy, and inadequate chemotherapy could induce tumor progression. Inflammation is continuously activated during the course of tumor progression [34]. Thus, inflammatory cytokines, such as interleukin-6 or tumor necrosis factor-α, are elevated, which could further induce SML [35, 36]. Hence, a high incidence of AEs and tumor progression could be the cause of SML.

Whether prophylactic support for SML is effective for cancer treatment remains to be clearly established, because whether SML is a result of or a risk factor for tumor progression is not clear. Thus, if SML were only a result of tumor progression, the effort to prevent SML would be useless in improving the efficacy of chemotherapy. However, a previous study on advanced NSCLC showed that SML at 6 weeks from the start of chemotherapy is greater than that at 10 weeks and is significantly associated with poor chemotherapy response [37]. In our study, we showed that SML at 6 months is not related to a high incidence of AEs and poor chemotherapy response. Briefly, SML itself could be a risk factor for poor treatment outcome as SML occurs during the early phase of chemotherapy. The myokines secreted by the skeletal muscle are key to elucidating how SML could worsen cancer-related mortality [38, 39]. Some myokines induced by exercise, such as irisin and secreted protein acidic and rich in cysteine (SPARC), are thought to play important roles in tumor suppression and improve cancer-related mortality for several types of tumors, including CRC [40–43]. Thus, it could be assumed that preventing SML could activate the myokines and improve chemotherapy response. To clarify the clinical efficacy of prophylactic support for SML, a therapeutic intervention for muscle wasting should be investigated prospectively.

Furthermore, in our study, baseline sarcopenia was not associated with a high incidence of AEs and poor RR, PFS, and OS, which is consistent with the results of previous reports on mCRC or urothelial cancer [15, 16, 44]. Most patients with advanced cancer have cancer cachexia to some extent [29]. Therefore, baseline sarcopenia has less effect on treatment outcomes. Nevertheless, a common cut-off value needs to be determined for baseline sarcopenia, and the cut-off value should be different depending on sex, race, and cancer type [45]. Currently, no cut-off value for sarcopenia has been established; thus, baseline sarcopenia could not be evaluated precisely. Moreover, baseline sarcopenia might not be related to chemotherapy response for mCRC.

Our study has some limitations. This was a pooled study of several phase II trials. Data on clinicopathological factors that could affect treatment prognosis (metastatic sites and numbers, resection of metastases, tumor location, and molecular pathological biomarkers, such as KRAS and BRAF) and blood data indicating nutritional status (serum albumin, total protein, and cholesterol) were not sufficiently obtained. Furthermore, the number of analyzed patients decreased, especially at 6 months after the first chemotherapy. Moreover, the chemotherapy regimens were not uniform across all trials. Thus, further prospective studies are necessary to confirm our results.

In conclusion, our results indicated a positive relationship between SML at 3 months after the start of chemotherapy and a high incidence of AEs and poor ORR and PFS. The efficacy of SML prevention during the early phase of chemotherapy may have some influence on the treatment outcome of mCRC and, thus, should be prospectively investigated in the future.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

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