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ORIGINAL RESEARCH ARTICLE

Effect of Changes in Skeletal Muscle Mass on Oncological Outcomes During First-Line Sunitinib Therapy for Metastatic Renal Cell Carcinoma

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Abstract

Background Sarcopenia is a state of degenerative skeletal muscle wasting induced by cancer cachexia.

Objective To evaluate the prognostic impact of changes in skeletal muscle mass (SMM) during first-line sunitinib therapy on oncological outcomes in metastatic renal cell carcinoma (mRCC).

Patients and Methods Sixty-nine patients were evaluated retrospectively. The skeletal muscle index (SMI) was calculated based on computed tomography images obtained before the initiation (pre-treatment SMI) and after two cycles of sunitinib treatment (post-treatment SMI). The change in SMM was evaluated based on the value of ΔSMI, which was calculated as [(posttreatment SMI – pretreatment SMI)/ pretreatment SMI] × 100. Oncological outcomes were compared between patients with ΔSMI <0 (SMM decrease) and ΔSMI ≥0 (SMM maintenance).

Results A decrease in SMM was observed in 38 patients (55.1%). Progression-free survival (PFS) and overall survival (OS) after sunitinib therapy initiation were significantly shorter in patients with ΔSMI <0 than in those with ΔSMI ≥0 (median PFS: 9.53 vs. 28.4 months, $p < 0.0001$; OS: 19.8 vs. 52.6 months, $p = 0.0001$). ΔSMI was an independent predictive factor for PFS (HR 3.25, 95% CI 1.74–6.29, $p = 0.0002$) and OS (HR 4.53, 95% CI 2.15–10.5, $p < 0.0001$). The objective response rate was significantly lower in patients with ΔSMI <0 than in those with ΔSMI ≥0 (23.7% vs. 51.6%, $p = 0.0164$).

Conclusion Decreased SMM during first-line sunitinib therapy can be an effective marker of outcome prediction for mRCC.

Key Points

Sarcopenic change predicted oncological outcomes in patients receiving first-line sunitinib therapy for metastatic renal cell carcinoma

Sarcopenic change was associated with patient survival and objective response rate, and with poor tolerability of sunitinib therapy

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1 Introduction

Cancer cachexia is a multifactorial syndrome characterized by the loss of skeletal muscle, which leads to functional impairment [1]. The syndrome encompasses involuntary weight loss, systematic inflammatory status, metabolic changes, or decreased skeletal muscle mass (SMM). The condition of low muscle mass is also termed sarcopenia [2]. In various types of cancers, loss of SMM is closely associated with oncological outcomes. For example, in curative surgery for localized cancers, preoperative sarcopenia is significantly associated with poor survival in gastrointestinal or hepatocellular carcinoma [3–5], lung cancer [6, 7], urothelial carcinoma [8–10], and renal cell carcinoma (RCC) [11]. In addition, an influence of pretreatment sarcopenia on poor prognosis or tolerability after systematic therapy for advanced or metastatic cancer has been reported in various cancers such as melanoma [12], breast cancer [13, 14], head and neck cancer [15], ovarian cancer [16], urothelial carcinoma [17], and RCC [18, 19].

In this context, we previously reported a significant association between sarcopenia and survival in metastatic RCC

(mRCC) patients who received sunitinib therapy [20]. In this study, shorter progression-free survival (PFS) and overall survival (OS) after first-line sunitinib therapy initiation was significantly associated with pretreatment sarcopenia, which was evaluated using the SMM calculation on imaging examination and a well-established systematic inflammatory marker, namely, the modified Glasgow Prognostic Score (mGPS). Sunitinib, a multi-targeted tyrosine kinase inhibitor, is one of several recommended first-line agents for mRCC used in the current consensus guideline [21].

Additionally, several studies reported that decreased SMM during systematic therapies such as cytotoxic chemotherapy and immune checkpoint inhibitor therapy was negatively associated with prognosis in patients with advanced or metastatic disease [22–26]. For targeted therapy, in a previous randomized phase III clinical trial, Antoun et al. revealed that SMM loss was specifically exacerbated during sorafenib therapy, which is another multi-targeted tyrosine kinase inhibitor and used for mRCC therapy [27]. However, the prognostic impact of the SMM loss on oncological outcome was not evaluated in that study.

In this current retrospective study, we investigated the prognostic impact of SMM change during first-line sunitinib therapy for mRCC.

2 Materials and Methods

2.1 Study Design and Patient Selection

The Internal Ethics Review Board of the Tokyo Women's Medical University approved this retrospective study (ID: 4850), which was performed in accordance with the principals outlined in the Declaration of Helsinki. Because this is a retrospective study, no formal consent is required.

In our department, 139 patients received first-line sunitinib therapy for mRCC between January 2007 and April 2018. Patients were excluded from this analysis if they discontinued the therapy within the initial two cycles because of intolerability or rapid disease progression, had received cytokine therapy previously, had received the therapy as neoadjuvant or adjuvant therapy, or had no pre-treatment imaging data or post-treatment imaging performed after two cycles.

All clinical and laboratory data were obtained from the electronic database and patient medical records.

2.2 Imaging Evaluation of Skeletal Muscle Mass Change and Sarcopenia

As previously described [28], baseline imaging examinations, including plain or contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis, were performed within 1 month before the start of therapy. During the treatment, regular scans were performed every 2–3 months of therapy, according to the patient's condition.

The skeletal muscle index (SMI) was calculated from the CT images obtained within 1 month before the initiation of and immediately after two cycles of sunitinib therapy. The calculation of SMI was based on the definition of previous studies [29, 30]. Briefly, the cross-sectional area of the lumbar skeletal muscles (including the rectus abdominus; internal, external, and lateral obliques on both sides; psoas; quadratus lumborum; and erector spinae) was identified using attenuation thresholds of −29 Hounsfield units (HU) to +150 HU on a Toshiba Aquilion 64 multidetector scanner (Toshiba, Tochigi, Japan). The areas of interest were defined manually at each 1-mm level, and the values for each level were added together. To calculate the SMI, the third lumber vertebra (L3) was set as the landmark, and the mean value of two consecutive images was computed for each patient and normalized for stature as follows: SMI (cm^2/m^2) = (skeletal muscle cross-sectional area at L3)/ $height^2$ [29]. The SMI was assessed as a continuous variable and used as an indicator of whole-body muscle mass, based on the finding of a previous study that the total lumbar-skeletal muscle cross-sectional area was linearly correlated with whole-body muscle mass [30].

To evaluate the SMM change, we calculated ΔSMI, the relative SMI change during the initial two cycles of sunitinib therapy, as follows: [(posttreatment SMI – pretreatment SMI)/ pretreatment SMI] × 100. ΔSMI <0 reflects decreased SMM, whereas ΔSMI ≥0 reflects maintained SMM. As the aim of this study was to clarify the prognostic impact of SMM change on oncological outcomes, we divided the patients into two groups according to ΔSMI (i.e., patients with ΔSMI <0 and those with ΔSMI ≥0).

Sarcopenia was defined based on a previous definition [31]. Briefly, sarcopenic status was stratified using thresholds of SMI: < 43 cm^2/m^2 among male patients with a body mass index (BMI) < 25 kg/m^2, < 53 cm^2/m^2 among male patients with a BMI > 25 kg/m^2, and < 41 cm^2/m^2 among female patients.

All imaging analyses were performed by a single investigator (H.I.) who was blinded to the other clinical parameters and patient outcomes.

2.3 Protocol for Sunitinib Therapy

The protocol for sunitinib therapy used in our department was previously described [32]. Briefly, we administered sunitinib using a 2-week-on/1-week-off treatment schedule to maintain patient tolerability for drug-induced toxicity, which was based on our previous study [33]. The standard initial dose was 50 mg/day. We considered dose reduction if patients met the following criteria: age > 65 years, serum creatinine level > 2.0 mg/dL, and body weight < 50 kg. If one of the three factors was present, the initial dose was reduced to 37.5 mg/day. If

two factors were present, we decreased the dose to 25 mg/day. The dose was increased by 12.5 mg/day until we determined the highest dose a given patient could tolerate, although the dose never exceeded 50 mg/day.

2.4 Evaluation of the Objective Response to Sunitinib Therapy

The target lesions were selected based on the results of baseline imaging and evaluated according to the standard Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [34].

2.5 Evaluation of Adverse Events with Sunitinib Therapy

Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.0, and dose modifications, including reduction or interruption (i.e., dose-limiting toxicities [DLTs]), were subsequently performed as necessary. When a patient experienced multiple AEs, the highest grade of AE was evaluated for each patient. Additionally, when a patient underwent both dose reduction and treatment interruption, the interruption was evaluated as the dose modification in the patient.

2.6 Statistical Analysis

Continuous variables were analyzed using the Mann-Whitney U test because data were non-normally distributed in this study. Categorical variables were analyzed using the χ^2 test or Fisher exact test. PFS and OS were defined as the time from therapy initiation to the date of progression and/or to the date of death from any cause, respectively. Survival was calculated using the Kaplan-Meier survival curve method and compared using the log-rank test. Univariate and multivariate analyses using Cox proportional hazard regression models were used to identify factors for survival. The survival risk is expressed as a hazard ratio (HR) and 95% confidence interval (CI). All analyses were performed using JMP software (version 14; SAS Institute Inc., Cary, NC, USA), and $p < 0.05$ was considered statistically significant.

3 Results

3.1 Patient Characteristics According to ΔSMI

Among the 139 patients, we excluded 24 who discontinued the therapy within the initial two cycles because of intolerability or rapid disease progression, seven who had received cytokine therapy previously, 16 who had received the therapy as neoadjuvant or adjuvant therapy, 14 without pre-treatment imaging data, and six without post-treatment imaging performed after two cycles. After the final exclusion of three patients without detailed clinical data, the remaining 69 patients were evaluated in this retrospective study (Fig. 1).

Decreased SMM during sunitinib therapy was observed in 38 patients (55.1%) (Table 1). A lower rate of histopathological diagnosis of clear cell carcinoma (CCC) (68.4% vs. 90.3%, $p = 0.0282$) and a higher rate of sarcopenia before therapy (73.7% vs. 45.2%, $p = 0.0157$) was observed in patients with ΔSMI <0 than in those with ΔSMI ≥0. Moreover, the rate of diabetes mellitus tended to be lower in patients with ΔSMI <0 than in those with ΔSMI ≥0 (10.5% vs. 29.0%, $p = 0.0505$). There were no statistically significant differences in other clinical factors between the two groups. The follow-up period was significantly shorter in patients with ΔSMI <0 than in those with ΔSMI ≥0 (median: 17.2 vs. 31.5 months, $p < 0.0001$).

3.2 Progression-Free Survival and Overall Survival According to ΔSMI

During the follow-up period, 51 (73.9%) and 38 patients (55.1%) had disease progression and died of any cause after sunitinib therapy initiation, respectively. Figure 2 shows that patients with ΔSMI <0 had significantly shorter PFS and OS than those with ΔSMI >0 (median PFS: 9.53 [95% CI 5.49–11.1] vs. 28.4 [95% CI 13.6–48.6] months, $p < 0.0001$; OS: 19.8 [95% CI 11.2–29.1] vs. 52.6 [95% CI 33.9–not reached (N.R.)] months, $p = 0.0001$).

Given that a significant difference in survival between CCC and non-CCC patients has been reported in mRCC [35, 36], the prognostic influence of ΔSMI on survival was further evaluated in 54 CCC patients. Consequently, Fig. 3 shows that CCC patients with ΔSMI <0 had significantly shorter PFS and OS than those with ΔSMI ≥0 (PFS: 10.6 [95% CI 5.19 – 14.7] vs. 28.4 [95% CI 10.0 – 49.4] months, $p = 0.0012$; OS: 26.6 [95% CI 16.6 – 30.8] vs. 51.7 [95% CI 30.0 – N.R.] months, $p = 0.0056$).

Moreover, we evaluated the impact of pretreatment sarcopenia on survival during sunitinib therapy. Consequently, pretreatment sarcopenic patients had significantly shorter PFS and OS than non-sarcopenic patients (PFS: 9.27 [95% CI 6.18–11.1] vs. 30.8 [95% CI 11.3–49.4] months, $p < 0.0001$; OS: 19.8 [95% CI 11.5–30.0] vs. N.R. [95% CI 42.8–N.R.] months, $p < 0.0001$). In addition, we evaluated the prognostic impact of a combination of ΔSMI and pretreatment sarcopenic status. Figure 4 shows that PFS and OS were significantly shorter in those with ΔSMI <0, among both pretreatment sarcopenic and non-sarcopenic patients. This finding showed that ΔSMI had a significant impact on prognosis regardless of the patient's pretreatment sarcopenic status.

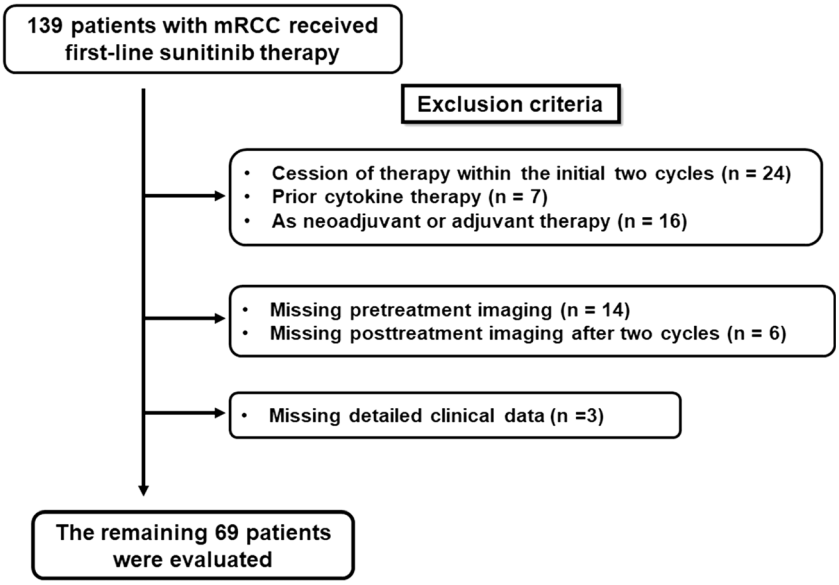

Fig. 1 Flow chart of patient selection

3.3 Univariate and Multivariate Analyses of Progression-Free Survival and Overall Survival

Univariate analysis of PFS showed that ΔSMI <0, the presence of non-clear cell carcinoma, and intermediate/poor Memorial Sloan-Kettering Cancer Center (MSKCC) risk were significant factors (all, $p < 0.05$) (Table 2). Multivariate analysis of PFS showed that ΔSMI <0 was an independent factor (HR 3.25, 95% CI 1.74–6.29, $p = 0.0002$) after adjustment for the other two factors.

Univariate analysis of OS showed that ΔSMI <0 and intermediate/poor risk were significant factors (both, $p < 0.05$) and that multiple metastases tended to be a significant factor ($p = 0.0536$) (Table 3). Multivariate analysis of OS showed that ΔSMI <0 was an independent factor (HR 3.82, 95% CI 1.86–8.42, $p = 0.0002$), together with the intermediate/poor risk (HR 3.59, 95% CI 1.50–10.7, $p = 0.0028$) and presence of multiple metastases (HR 2.80, 95% CI 1.41–5.72, $p = 0.0033$).

Furthermore, to manage larger statistical effects for categorical classification based on dichotomous values in ΔSMI, we also performed analyses using a continuous variable (model 2 in Tables 2 and 3). Consequently, ΔSMI as a continuous variable was also an independent factor for PFS (HR 0.95, 95% CI 0.93–0.98, $p = 0.0017$) and OS (HR 0.94, 95% CI 0.91–0.98, $p = 0.0007$).

In addition, because the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model is also an established tool of risk classification for survival [37, 38], we further performed the analysis by incorporating the IMDC risk. Of the 69 patients, the IMDC risk was evaluated in 58 patients (Table 1). In the patient cohort, univariate analysis for PFS and OS showed no significant association of the IMDC risk with PFS or OS in our analysis (PFS: $p = 0.223$; OS: $p = 0.184$), whereas ΔSMI <0 was an independent factor for PFS and OS (both: $p < 0.0001$).

3.4 Objective Response Rate According to ΔSMI

Figure 5 shows the comparison of the best overall response according to ΔSMI. According to the RECIST classification, complete response, partial response, stable disease, and progressive disease were found in one (2.63%), eight (21.1%), 22 (57.9%), and seven (18.4%) patients with ΔSMI <0 and in four (12.9%), 12 (38.7%), 15 (48.4%), and 0 patients with ΔSMI ≥0, respectively. The objective response rate was significantly lower in patients with ΔSMI <0 than in those with ΔSMI ≥0 (23.7% vs. 51.6%, $p = 0.00164$).

3.5 Association of Dose-Limiting Toxicities with ΔSMI

Table 4 shows the association of DLTs with ΔSMI. The incidence rate of DLTs was similar between the patients with ΔSMI <0 and those with ΔSMI ≥0 (57.9% vs. 54.8%, $p = 0.799$). The incidence rate of AEs with grade ≥ 3 was similar (31.6% vs. 22.6%, $p = 0.408$) between them. However, treatment discontinuation was observed more often in patients with ΔSMI <0 than in those with ΔSMI ≥0 (39.5% vs. 16.1%, $p = 0.0163$).

4 Discussion

This retrospective single-center analysis showed that decreased SMM was observed in more than half of patients during first-line sunitinib therapy for mRCC. Decreased SMM was significantly associated with PFS and OS, and it had a prognostic effect for both pretreatment sarcopenic and non-

Table 1 Patient characteristics according to ΔSMI

	ΔSMI < 0 ($n = 38$)	ΔSMI ≥ 0 ($n = 31$)	p value
Age, years			0.218
≥ 65	14 (36.8%)	16 (51.6%)	
Sex			0.290
Male	25 (65.8%)	24 (77.4%)	
Height, m*	1.64 (1.58 – 1.71)	1.64 (1.58 – 1.70)	0.668
Weight, kg*	61.3 (52.8 – 70.6)	60.3 (52.7 – 70.7)	0.795
BMI, kg/m^{2}*	22.7 (20.2 – 24.3)	23.1 (20.7 – 25.2)	0.492
SMM, cm^{2}*	111.4 (92.6 – 130.9)	116.9 (87.8 – 131.6)	0.691
SMI, cm^{2}/m^{2}*	41.1 (35.6 – 45.4)	43.7 (34.3 – 47.7)	0.554
Pretreatment sarcopenic status			0.0157
Presence of sarcopenia	28 (73.7%)	14 (45.2%)	
Posttreatment SMM, cm^{2}*	107.8 (81.5 – 123.5)	124.6 (95.7 – 135.3)	0.0348
Posttreatment SMI, cm^{2}/m^{2}*	38.7 (33.2 – 44.4)	46.3 (36.1 – 51.8)	0.0066
ΔSMI*	−5.00 (−7.26 − 1.39)	5.06 (1.97 – 9.07)	< 0.0001
Histopathology			0.0282
Clear cell carcinoma	26 (68.4%)	28 (90.3%)	
MSKCC risk			0.0867
Favorable	6 (15.8%)	8 (25.8%)	
Intermediate	28 (73.7%)	15 (48.4%)	
Poor	4 (10.5%)	8 (25.8%)	
IMDC risk**			0.777
Favorable	4 (13.8%)	6 (20.7%)	
Intermediate	20 (69.0%)	18 (62.1%)	
Poor	5 (17.2%)	5 (17.2%)	
Number of metastatic sites			0.570
Multiple	17 (44.7%)	16 (51.6%)	
Sunitinib treatment schedule			0.819
4-week-on/2-week-off	12 (31.6%)	9 (29.0%)	
2c-RDI, %			0.348
≥75	19 (50.0%)	19 (61.3%)	
Diabetes mellitus			0.0505
Presence	4 (10.5%)	9 (29.0%)	
Hypertension			0.732
Presence	12 (31.6%)	11 (35.5%)	
Follow-up period, months*	17.2 (9.71 – 27.8)	31.5 (20.4 – 51.4)	< 0.0001

* Data are presented as median (interquartile range)

**IMDC risk was evaluated in 58 patients

BMI, body mass index; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan-Kettering Cancer Center; SMI, skeletal muscle index; SMM, skeletal muscle mass; 2c-RDI, two initial cycles-relative dose intensity; ΔSMI, change in skeletal muscle index

sarcopenic patients. Moreover, the prognostic impact of decreased SMM was confirmed when the histological type of cancer was limited to CCC. Additionally, the objective response rate was negatively correlated with decreased SMM. Furthermore, treatment discontinuation was more frequent in patients with decreased SMM than in those without. Collectively, decreased SMM was significantly associated with poor oncological outcomes. To the best of our knowledge, the present study is the first to indicate the significance of decreased SMM during first-line sunitinib therapy for mRCC.

A prognostic impact of decreased SMM during cancer treatment has been previously reported [22–26]. In this context, a unique point of our findings was demonstrating its prognostic impact in molecular-targeted therapy. Furthermore, we found that decreased SMM affected survival regardless of patients' pretreatment sarcopenic status, and this point was a novel

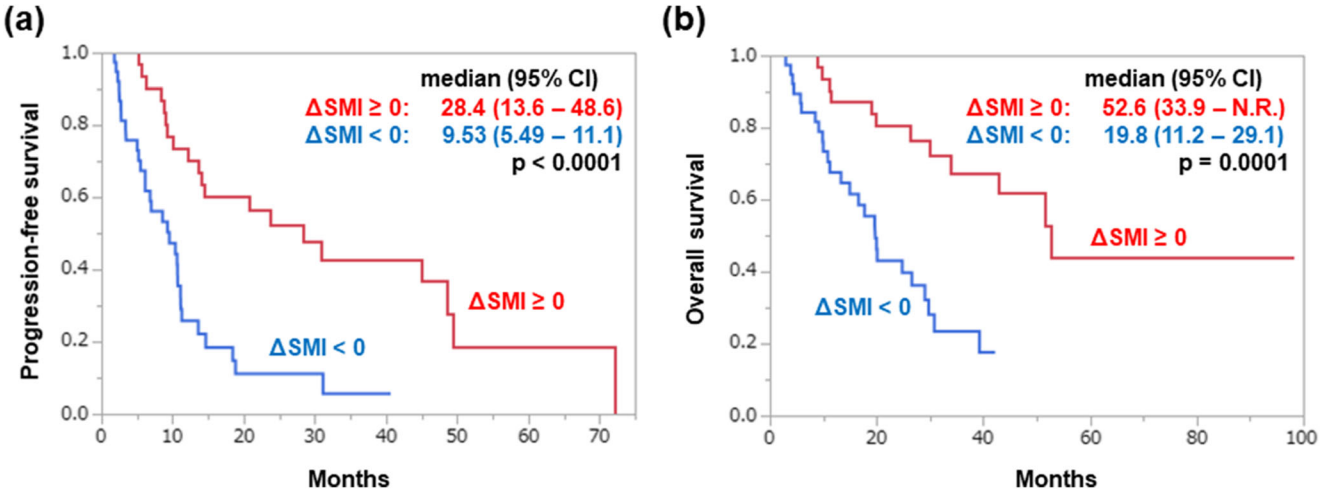

Fig. 2 Progression-free survival and overall survival after first-line sunitinib therapy initiation according to ΔSMI. **a** Progression-free survival and **b** overall survival after first-line sunitinib therapy initiation according to ΔSMI. ΔSMI, change in skeletal muscle index; CI, confidence interval

finding in sarcopenia research. As we previously reported, pretreatment non-sarcopenic patients had favorable survival after the initiation of first-line sunitinib therapy for mRCC [20]. Even in these patients, the prognosis could be deteriorated when SMM decreased during the therapy. Therefore, SMM change could be an effective prognostic biomarker reflecting the host's metabolism under the systematic inflammation induced by cancer.

The SMM change has several advantages for the survival prediction in real-world clinical practice for mRCC. Some systematic inflammation markers, such as serum C-reactive protein level or neutrophil count (including neutrophil-to-lymphocyte ratio), are already identified as effective and easy-to-use prognosticators in molecular-targeted therapy [37, 39–42]. However, the value of these markers can be influenced by infections or myelosuppression due to the drug-induced toxicity. Thus, it is sometimes difficult to accurately evaluate them as predictive markers in clinical practice. In contrast, the SMM is an objective and reproducible marker because the evaluation basically depends on imaging examination. Furthermore, the imaging examination, which is routinely performed in patient follow-up, can be used for SMM evaluation. Therefore, neither additional invasion nor cost for patients is needed. Furthermore, when the SMM decreased in a patient, we can shift to other treatments with different modes of action within the early phase of treatment because the SMM change can be evaluated after the initial two cycles.

It remains unexplored through which molecular mechanisms decreased SMM is associated with oncological outcome. Ma et al. suggested that the STAT3 pathway, triggered by interleukin-6 [43–45], promotes cytokine-induced muscle wasting [46]. Rapid tumor growth induces highly inflammatory

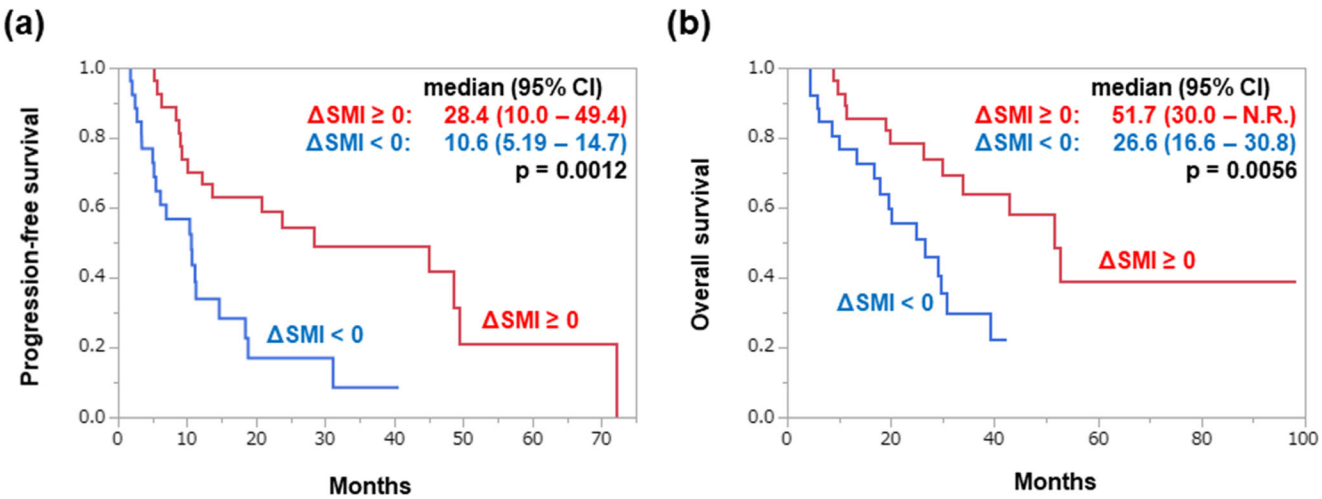

Fig. 3 Progression-free survival and overall survival after first-line sunitinib therapy initiation according to ΔSMI in patients diagnosed with clear-cell carcinoma. **a** Progression-free survival and **b** overall survival after first-line sunitinib therapy initiation according to ΔSMI in patients with clear-cell renal cell carcinoma. ΔSMI, change in skeletal muscle index; CI, confidence interval

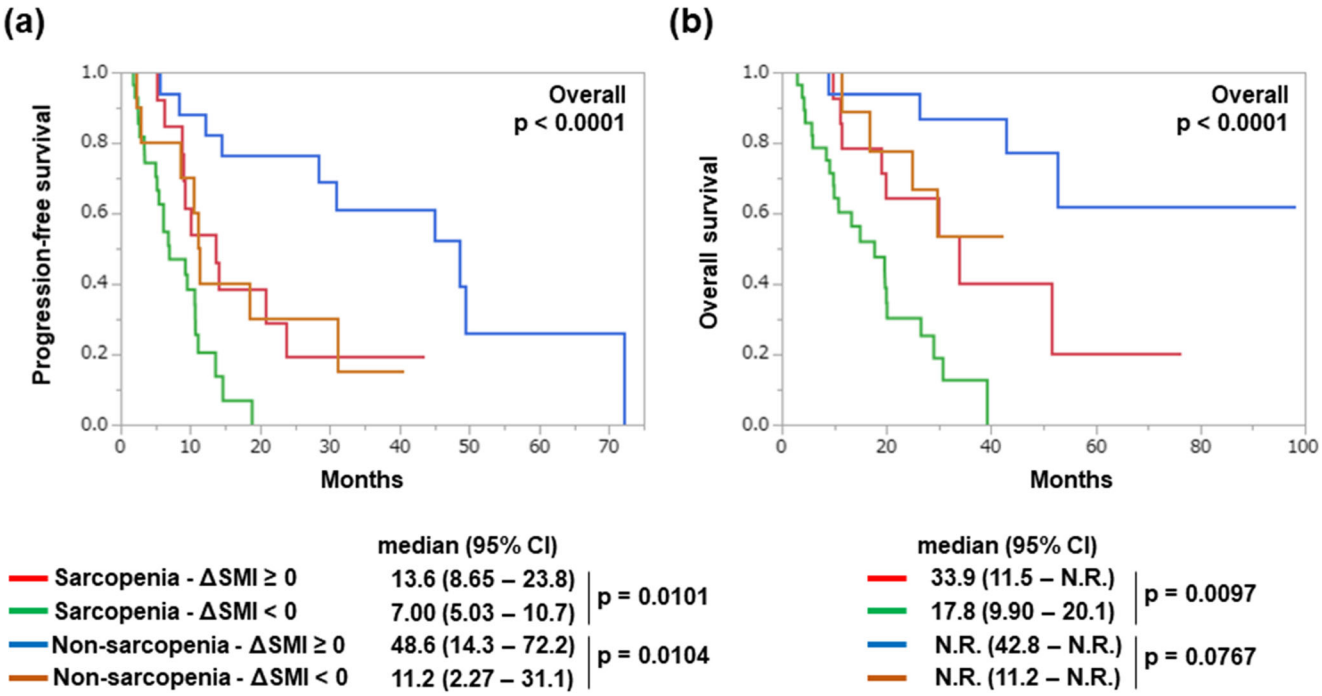

Fig. 4 Progression-free survival and overall survival after first-line sunitinib therapy initiation according to pretreatment sarcopenic status and ΔSMI. **a** Progression-free survival and **b** overall survival after first-line sunitinib therapy initiation according to pre-treatment sarcopenic status and ΔSMI. N.R., not reached; ΔSMI, change in skeletal muscle index

cytokines through this pathway, resulting in decreased SMM. Exercise decreases tumor growth through the regulation of natural killer (NK) cell infiltration and mobilization [47]. Thus, decreased SMM, which reflects low activity, may inactivate NK

Table 2 Univariate and multivariate analyses of progression-free survival

	Univariate analysis HR (95% CI)	*p* value	Multivariate model 1 HR (95% CI)	*p* value	Multivariate model 2 HR (95% CI)	*p* value
Age, years		0.874				
≥65 (ref. < 65)	0.96 (0.54 – 1.67)					
Sex		0.246				
Male (ref. female)	0.69 (0.38 – 1.31)					
BMI as a continuous variable, kg/m^2	0.97 (0.90 – 1.03)	0.302				
ΔSMI		< 0.0001		0.0002		
< 0 (ref. ≥ 0)	3.49 (1.89 – 6.69)		3.25 (1.74 – 6.29)			
ΔSMI as a continuous variable	0.95 (0.92 – 0.98)	0.0009			0.95 (0.93 – 0.98)	0.0017
Histopathology		0.0130		0.143		0.175
Presence of non-CCC (ref. CCC)	2.37 (1.21 – 4.41)		1.68 (0.83 – 3.26)		1.63 (0.80 – 3.20)	
MSKCC risk		0.0276		0.108		0.0558
Intermediate/poor (ref. favorable)	2.27 (1.09 – 5.55)		1.90 (0.88 – 4.74)		2.14 (0.98 – 5.35)	
Number of metastatic sites		0.600				
Multiple (ref. single)	1.16 (0.66 – 2.05)					
Sunitinib treatment schedule		0.400				
4-week-on/2-week-off (ref. 2-week-on/1-week-off)	1.29 (0.70 – 2.30)					
2c-RDI, %		0.441				
≥ 75 (ref. < 75)	0.80 (0.46 – 1.41)					
Diabetes mellitus		0.943				
Presence	1.03 (0.48 – 1.99)					
Hypertension		0.974				
Presence	0.99 (0.54 – 1.76)					

CI, confidence interval; CCC, clear cell carcinoma; HR, hazard ratio; MSKCC, Memorial Sloan-Kettering Cancer Center; 2c-RDI, two initial cycles-relative dose intensity; ΔSMI, change in skeletal muscle index

Table 3 Univariate and multivariate analyses of overall survival

	Univariate analysis HR (95% CI)	*p* value	Multivariate model 1 HR (95% CI)	*p* value	Multivariate model 2 HR (95% CI)	*p* value
Age, years		0.995				
≥ 65 (ref. < 65)	1.00 (0.52 – 1.90)					
Sex		0.244				
Male (ref. female)	0.66 (0.35 – 1.34)					
BMI as a continuous variable, kg/m^2	0.94 (0.86 – 1.02)	0.144				
ΔSMI		0.0001		< 0.0001		
< 0 (ref. ≥ 0)	4.08 (1.96 – 9.32)		4.53 (2.15 – 10.5)			
ΔSMI as a continuous variable	0.96 (0.93 – 0.99)	0.0047			0.94 (0.91 – 0.98)	0.0007
Histopathology		0.143				
Presence of non-CCC (ref. CCC)	1.82 (0.80 – 3.72)					
MSKCC risk		0.0178		0.0033		0.0007
Intermediate/poor (ref. favorable)	2.78 (1.18 – 8.16)		3.65 (1.49 – 11.0)		4.63 (1.83 – 14.4)	
Number of metastatic sites		0.0536		0.0033		0.0018
Multiple (ref. single)	1.89 (0.99 – 3.68)		2.80 (1.41 – 5.72)		3.12 (1.52 – 6.61)	
Sunitinib treatment schedule		0.742				
4-week-on/2-week-off (ref. 2-week-on/1-week-off)	1.12 (0.54 – 2.19)					
2c-RDI, %		0.310				
≥ 75 (ref. < 75)	0.72 (0.38 – 1.37)					
Diabetes mellitus		0.710				
Presence	1.16 (0.51 – 2.35)					
Hypertension		0.792				
Presence	1.09 (0.55 – 2.10)					

CCC clear cell carcinoma, *CI* confidence interval, *HR* hazard ratio, *MSKCC* Memorial Sloan-Kettering Cancer Center, *2c-RDI* two initial cycles-relative dose intensity, *ΔSMI* change in skeletal muscle index

cells, resulting in the acceleration of disease progression. Fukushima et al. reported that SMM recovery (defined as SMM ≥ 0) was associated with favorable survival and higher tumor shrinkage during platinum-based chemotherapy for urothelial carcinoma [25]. They explained that chemotherapy might attenuate cancer-associated inflammation and subsequently improve the host metabolism, resulting in SMM recovery.

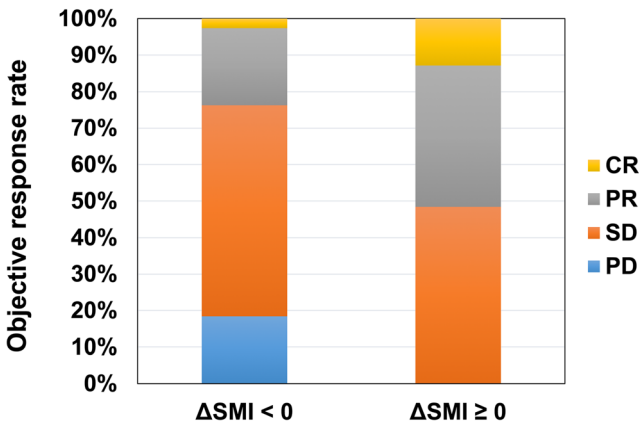

Fig. 5 Objective response rate according to ΔSMI. Objective response rate during first-line sunitinib therapy according to ΔSMI. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; ΔSMI, change in skeletal muscle index

Finally, we found a possible association of SMM change with tolerability during sunitinib therapy. Although the overall incidence rates of DLTs and severe AEs (i.e., grade ≥ 3) were not different according to the change in SMM, the incidence of treatment discontinuation was higher in patients with decreased SMM than in those without. Thus, sarcopenic change had a possible association with poor tolerability of sunitinib therapy. This finding was also a unique point of this study because the relationship between SMM change and tolerability of sunitinib therapy remains unclear. Interestingly, the treatment schedule was not associated with SMM change as shown in Table 1. Moreover, the treatment schedule was neither associated with the incidence of DLTs ($p = 0.261$) nor treatment discontinuation ($p = 0.584$). Collectively, these findings showed that the possible association of decreased SMM with treatment discontinuation development was independent of the treatment schedule.

This study had several limitations. First, this study was a single-center retrospective analysis with a small number of patients. Thus, the findings were affected by unavoidable selection bias. Second, the definitions of SMI and sarcopenia

Table 4 Dose-limiting toxicity according to ΔSMI

	ΔSMI < 0 (n = 38)	ΔSMI ≥ 0 (n = 31)	p value
DLTs			0.799
Yes (ref. no)	22 (57.9%)	17 (54.8%)	
Treatment modification for DLTs			0.0163
Discontinuation	15 (39.5%)	5 (16.1%)	
Dose reduction	7 (18.4%)	12 (38.7%)	
Grade of adverse events for DLTs			0.408
Grade ≥ 3 (ref. < 3)	12 (31.6%)	7 (22.6%)	

DLT dose-limiting toxicity

were established in Western population studies [29–31]. Therefore, it should be clarified whether these criteria appropriately reflect Japanese patients' sarcopenic condition. Third, the majority of patients (69.6%) received an alternative 2-weeks-on/1-week-off treatment schedule, which can improve the tolerability and survival as previously reported [48, 49]. Bjarnason et al. suggested that the maximum tolerated dose and individualized schedule based on sunitinib-induced toxicity could improve patient survival [50]. In our analysis, no significant association was observed between the treatment schedule and the incidence rate of DLTs ($p = 0.261$), relative dose intensity ($p = 0.177$), or survival (Tables 2 and 3). Moreover, decreased SMM was not associated with the treatment schedule (Table 1). Based on these findings, the influence of alternative schedule on survival is considered to be minimal, but a possible bias caused by the modified schedule pattern adopted in our department should be recognized as a limitation of this study.

5 Conclusions

Decreased SMM during first-line sunitinib therapy for mRCC was significantly associated with patient survival and closely correlated with the objective response rate. Thus, decreased SMM can be an effective prognosticator, and the understanding of SMM change has the potential to improve outcome prediction and the treatment strategy of sunitinib.

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Compliance with Ethical Standards

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Conflict of Interest Tsunenori Kondo received honoraria from Pfizer, Bayer, and Novartis. All other authors including Hiroki Ishihara, Toshio Takagi, Hironori Fukuda, Kazuhiko Yoshida, Junpei Iizuka, and Kazunari Tanabe declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

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