Sarcopenia and the Modified Glasgow Prognostic Score are Significant Predictors of Survival Among Patients with Metastatic Renal Cell Carcinoma Who are Receiving First-Line Sunitinib Treatment.

Sarcopenia and modified Glasgow prognostic score are significant predictors of survival among patients with metastatic renal cell carcinoma who are receiving first-line sunitinib treatment

Hiroki Ishihara, Tsunenori Kondo*, Kenji Omae, Toshio Takagi, Jumpei Iizuka, Hirohito Kobayashi, Kazunari Tanabe

Department of Urology, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan, 162-8666

*Address correspondence to:

Dr. Tsunenori Kondo

Tokyo Women's Medical University

Department of Urology, Kidney Center, Tokyo Women's Medical University

8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan, 162-8666

Tel: +81-3-3353-8111

FAX: +81-3-3356-0293

E-mail address: tkondo@kc.twmu.ac.jp

Abstract

Background: Cancer cachexia is associated with patient outcomes. *Objective*: To evaluate the effect of cachexia on survival among patients with metastatic renal cell carcinoma (mRCC) who received first-line sunitinib treatment. *Patients and methods*: Seventy-one patients were retrospectively evaluated. Sarcopenia was diagnosed using sex-specific cut-offs for skeletal muscle index (measured using pre-treatment computed tomography) that were adjusted for body mass index. The modified Glasgow prognostic score (mGPS) was measured using C-reactive protein (CRP) and albumin levels (mGPS 2: CRP >1.0 mg/dL and albumin <3.5 g/dL; mGPS 1: CRP >1.0 mg/dL; mGPS 0: CRP ≤1.0 mg/dL). Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method and Cox proportional hazard models. *Results*: Forty-five patients (63.4%) had sarcopenia, with 53 (74.6%), 10 (14.1%), and 8 (11.3%) patients having an mGPS of 0, 1, and 2, respectively. Sarcopenia was associated with significantly inferior PFS and OS, compared to non-sarcopenic patients (PFS: 7.6 vs. 18.2 months, $p = 0.0004$; OS: 22.3 months vs. not reached, $p = 0.0019$). Higher mGPS was associated with inferior PFS and OS (mGPS 0, 1, and 2: PFS = 11.5, 10.9, and 4.12 months, $p < 0.0001$; OS = 47.2, not reached, and 5.28 months, $p < 0.0001$; respectively). Sarcopenia was an independent predictor of shorter PFS ($p = 0.0163$), and mGPS was an independent predictor of shorter OS ($p = 0.0012$). *Conclusion*: Sarcopenia and mGPS can predict outcomes among patients with mRCC who are receiving first-line sunitinib treatment.

Key points

1) Cachexia has a significant effect on the survival of metastatic renal cell carcinoma patients who are receiving sunitinib treatment

2) Sarcopenia and the modified Glasgow prognostic score predict the survival of metastatic renal cell carcinoma patients, regardless of dose-limiting toxicities

1. Introduction

Frailty among cancer patients is associated with poor patient survival [1], which is likely related to frailty being a state of increased vulnerability to stressors, which leads to an increased risk of developing adverse health outcomes [2]. Although the precise definition and biological characteristics of frailty are not clear, severe weight loss and skeletal muscle wasting (i.e., sarcopenia) are considered prominent features of frailty. Sarcopenia is an emerging index of nutritional status that has been studied in patients with cancer [3, 4]. As cancer cachexia might affect therapy response and survival, sarcopenia has recently been suggested as a significant predicator of outcomes for various cancers [5-8]. For example, sarcopenia can predict survival among patients with metastatic renal cell carcinoma (mRCC), with Sharma et al. [9] describing its value among patients with mRCC who underwent cytoreductive nephrectomy, and Fukushima et al. [10] describing its value for predicting overall survival (OS) among patients with mRCC. Furthermore, Antoun et al. [11], Huillard et al. [12], and Mir et al. [13] have reported that the dose-limiting toxicities (DLTs) of tyrosine kinase inhibitors are significantly associated with sarcopenia. In this context, sarcopenia is typically defined using the cross-sectional areas of the lumbar skeletal muscle, and this definition was established using pre-treatment imaging in a Canadian cohort study [14].

Another marker of the malignancy-induced systematic inflammatory response is the modified Glasgow prognostic score (mGPS), which is calculated using levels of C-reactive protein (CRP) and

albumin. The mGPS is an independent predictor of patient outcomes [15, 16], and several studies have also reported that a similar inflammation-based score is effective in predicting outcomes from renal cancers [16-18] . Unfortunately, these tumor and host responses can lead to involuntary progressive weight loss or nutritional impairment, which may affect the patient's performance status and quality of life. Although sarcopenia or mGPS, as indexes of cancer cachexia, are useful for predicting patient survival in renal cancers, few studies have evaluated whether cachexia affects outcomes among patients with mRCC who are receiving first-line sunitinib (SU), which is a first-line molecular targeted agent [19-21]. Therefore, this study aimed to examine whether cachexia (as measured using sarcopenia and mGPS) could predict survival, as well as SU safety and tolerability among patients with mRCC who were receiving first-line SU treatment.

2. **Patients and Methods**

The Internal Ethics Review Board of Tokyo Women's Medical University approved this retrospective study (ID: 3654), which was performed in accordance with the tenets of the Declaration of Helsinki. All patients provided their written informed consent for treatment and the collection of their data. A total of 156 patients received first-line tyrosine kinase inhibitor treatment without prior cytokine therapy at our department between 2007 and 2014. However, we excluded the patients who received sorafenib (n=50), pazopanib (n=7), and axitinib (n=2). Among the remaining 97 patients who received

first-line SU, we excluded patients who received abbreviated SU administration during a single cycle (n = 3), patients who received hemodialysis or transplant therapy (n = 2), and patients for whom detailed pre-treatment information and computed tomography (CT) data were missing (n = 21). As the current treatment strategy for mRCC consists of molecular targeted agents [19, 21], we excluded patients who had received prior cytokine therapy. Finally, we included 71 patients in this study, and extracted their clinical and laboratory data from an electronic database and the patients' medical records (Table 1).

2.1. Imaging methods and evaluation of sarcopenia

The cross-sectional area of the lumbar skeletal muscles (including the rectus abdominus; bilateral internal, external, and lateral obliques; psoas; quadratus lumborum; and erector spinae) was identified using attenuation thresholds of -29 Hounsfield units (HU) to +150 HU via 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 skeletal muscle index (SMI), L3 was set as the landmark and the mean value of two consecutive images was computed for each patient and normalized for stature: SMI (cm^2/m^2) = (skeletal muscle cross-sectional area at L3)/ $height^2$ [7, 22]. 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 lumber-skeletal muscle cross-

sectional area was linearly correlated with whole-body muscle mass [23]. To classify the patients as sarcopenic and non-sarcopenic, we used sex-specific SMI cut-offs that were stratified according to body mass index (BMI): for men with a BMI of <25 kg/m^2, the SMI cut-off was < 43 cm^2/m^2; for men with a BMI of > 25 kg/m^2, the SMI cut-off was < 53 cm^2/m^2; and for women, the SMI cut-off was < 41 cm^2/m^2 [14]. Martin et al. [14] have also reported BMI-adjusted cut-off values for skeletal muscle density (SMD), which we defined as low or high muscle attenuation (MA) : low MA was defined as < 41 HU for BMIs of < 25 kg/m^2, and as < 33 HU for BMIs of ≥ 25 kg/m^2 (no sex-specific differences). The CT scans were performed for diagnostic or follow-up purposes within 30 days before the initiation of SU treatment. All image analyses were performed by a single investigator (H.I.) who was blinded to the other clinical parameters and patient outcomes.

2.2. Defining mGPS

We calculated mGPS as previously described [15]: patients with high CRP levels (> 1.0 mg/ dL) and low albumin levels (< 3.5 g/ dL) were assigned a score of 2. Patients with high CRP levels (> 1.0 mg/ dL) were assigned a score of 1, and patients with CRP levels of ≤1.0 mg/ dL were assigned a score of 0; albumin levels do not affect a score of 1 or 0. The mGPS for all patients was determined at the time of their SU treatment initiation.

2.3 Sunitinib treatment and toxicity assessment

To evaluate SU safety and tolerability, we investigated the associations between sarcopenia and mGPS with SU-related adverse events and relative dose intensity (RDI), respectively. At our department, we treat our mRCC patients using a 4-week-on/2-week-off (4/2) schedule or a 2-week-on/1-week-off (2/1) schedule, as described by Kondo et al. [24]. SU treatment was initiated at a dosage of 50 mg/day, and was modified based on patient factors. Three factors were considered for reduction of the initial dose: (1) age of > 65 years, (2) serum creatinine levels of > 2 mg/dL, and (3) a body weight of < 50 kg. If one of these three factors was observed, the initial dose was reduced to 37.5 mg. If two of these three factors were observed, the initial dose was reduced to 25 mg. We never reduced the initial dose to < 25 mg. The dose was subsequently increased by 12.5 mg until we found the highest dose that these patients could tolerate, although this dose never exceeded 50 mg. Toxicity was assessed at each visit (every 1-2 weeks during the first cycle), and then monthly according to the patient's condition. Adverse events were graded using the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.0. Dose reduction or interruption was performed based on the guidelines for SU therapy [25]. The RDI was determined during first cycle and during six cycles as the ratio of the cumulative dose that was received during the cycle to 1,400 mg. When SU treatment was withdrawn before reaching the sixth cycle due to any cause, the RDI was calculated until the last treatment cycle. DLTs were defined as any toxicity leading to a dose reduction, temporary or

permanent discontinuation of SU treatment. According to a previous study [12], only DLTs occurring during the first cycle were considered in our study. Moreover, we compared the cumulative incidences of DLTs according to sarcopenic status and mGPS severity. A cycle of treatment was determined as a period of 6 weeks.

2.4. Statistical analysis

Continuous variables were analyzed using the Mann-Whitney *U*-test and categorical variables were analyzed using the χ^2 test or Fisher's exact test. Progression-free survival (PFS) and OS after first-line SU therapy initiation, and cumulative incidence of experiencing DLTs, were calculated using the Kaplan-Meier method, and compared using the log-rank test between sarcopenic and non-sarcopenic patients, according to mGPS. PFS was defined as the time from first-line SU therapy initiation to the date of progression or death from any cause, whichever came first. OS was defined as the time from first-line SU therapy initiation to death from any cause. Univariate and multivariate analyses were used to identify factors that were associated with PFS and OS, via Cox proportional hazards regression models. Risk was expressed as hazard ratios (HR) and 95% confidence intervals (CI). All analyses were performed using JMP software (version 11; SAS Institute Inc., Cary, NC, USA), and differences were considered statistically significant at a *p*-value of <0.05.

3. Results

3.1. Patient characteristics

The patients' characteristics are shown in Table 1. Sarcopenia was diagnosed in 45 patients (63.4%), and the sarcopenic patients were significantly older (mean age: 65.5 years vs. 61.0 years, $p = 0.0194$) and significantly more likely to be female (42.2% vs. 7.69%, $p = 0.0025$). Furthermore, sarcopenic patients exhibited a significantly higher rate of having multiple metastases (64.4% vs. 38.5%, $p = 0.048$), and a higher rate of hypoalbuminemia (3.90 g/dL vs. 4.38 g/dL, $p < 0.0001$). Moreover, sarcopenic patients exhibited significantly lower BMI (mean BMI: 22.9 kg/m^2 vs. 24.9 kg/m^2, $p = 0.0431$), skeletal muscle area (96.2 cm^2 vs. 139.7 cm^2, $p < 0.0001$), and SMI (36.6 cm^2/m^2 vs. 50.7 cm^2/m^2, $p < 0.0001$). However, there were no significant differences in the remaining characteristics (pathology, radical nephrectomy, Karnofsly perforemance status, time from diagnosis to treatment, MSKCC risk, pT stage, eGFR, or serum CRP level at SU treatment initiation; all, $p > 0.05$). There was no significant difference in the two groups' SMD values ($p = 0.197$), although a marginal difference was observed in their mGPS ($p = 0.0534$). Sarcopenic patients had a significantly shorter mean follow-up period (16.0 months vs. 27.4 months, $p = 0.0012$).

3.2. Patient survival according to sarcopenia status

During this follow-up period, progression disease (PD) was observed in 50 patients (70.4%), and

27 patients (38.0%) died due to cancer, including one patient who died due to a raptured aortic aneurysm. Because many patients in this study died due to cancer, we evaluated OS rather than cancer-specific survival. Figures 2 and 3 show the Kaplan-Meier survival curves for PFS and OS after SU treatment initiation according to sarcopenia status. Sarcopenia was associated with a significantly shorter median PFS (7.6 months vs. 18.2 months, $p = 0.0004$) and median OS (22.3 months vs. not reached, $p = 0.0019$).

3.3. Patient survival according to mGPS

Figures 4 and 5 show the Kaplan-Meier survival curves for PFS and OS after SU treatment initiation according to mGPS. The magnitude of the mGPS was significantly associated with median PFS (score 0: 11.5 months, score 1: 10.9 months, score 2: 4.12 months; $p < 0.0001$) and median OS (score 0: 47.2, score 1: not reached, score 2: 5.28 months, $p < 0.0001$).

3.4. Prognostic indicators for patient survival

In the univariate analysis, the significant predictors of PFS and OS were sarcopenia, mGPS, pathological diagnosis, Karnofsky performance status, time to diagnosis to treatment, MSKCC risk, metastatic sites, and pT stage (Table 2). In the multivariate analysis, sarcopenia was an independent predictor of shorter PFS (HR: 2.54, p=0.0163), and mGPS was an independent predictor of shorter OS

(p=0.0012), altogether with pathological findings (HR: 4.27, p=0.0173).

3.5. Sunitinib safety and tolerability according to sarcopenia and mGPS

The comparisons between sarcopenic patients and non-sarcopenic patients, and between patients with mGPS 0 and those with mGPS 1 and 2 are summarized in Tables 4 and 5. No significant differences were found regarding the initial dose, RDI during first cycle, DLTs, or prevalence of toxicities according to both sarcopenic status, and mGPS (all $p > 0.05$). After experiencing DLTs (n=36), we observed 31 cases of dose reduction (86.1%), 4 cases of discontinued treatment (11.1%), and 1 case of switching to other targeted agents (2.78%). We did not observe any significant differences when we performed subanalyses of these outcomes according to sarcopenic status or mGPS severity (sarcopenia: $p = 0.194$, mGPS: $p = 0.763$). SU treatment was withdrawn before the 2^{nd}, 3^{rd}, 4^{th}, 5^{th}, and 6^{th} cycles for 4, 6, 7, 11, and 2 patients, respectively. Sarcpenic status or mGPS severity exhibited no significant influence in the long-term RDI (sarcopenia: $p = 0.302$, mGPS: $p = 0.774$). Moreover, there were no significant differences in the cumulative incidences of experiencing DLTs according to sarcopenic status ($p = 0.741$) or mGPS severity ($p = 0.164$) (Figure 6, 7).

4. **Discussion**

To our best knowledge, this retrospective study is the first to evaluate the associations of sarcopenia

and mGPS (as indicators of cancer cachexia) with survival among patients with mRCC who were receiving first-line SU treatment without prior cytokine therapy. Our data indicate that sarcopenia was an independent predictor of PFS, whereas mGPS was an independent predictor of OS. Moreover, there were no significant differences in SU safety or tolerability between sarcopenic patients and non-sarcopenic patients, and between patients with mGPS 0 and those with mGPS 1 and 2.

Our analysis revealed that mGPS significantly predicted OS, which confirms a large cohort study's findings that higher mGPS scores were associated with shorter OS and cancer-specific survival (independent of the tumor site) [16]. Furthermore, Lamb et al. [17] have reported that mGPS was at least equivalent to, and independent of, other validated prognostic models for predicting survival among patients with RCC who were undergoing curative nephrectomy. Thus, mGPS is an independent and strong predictor of patient outcomes. Ramsey et al. [18] have suggested that GPS (the inflammation-based prognostic score that preceded mGPS) compared favorably with, and was independent of, the MSKCC scoring system. In contrast, our findings indicate that the MSKCC risk was not an independent predictor of OS, although this discrepancy might be related to differences in the patients' characteristics. Meanwhile, non-CCC was a significant predictor of OS, altogether with mGPS in our analysis. This finding confirms a previous study's hypothesis that non-CCC is a risk factor for inferior patient survival [26].

SMD is closely related to muscle lipid content and muscle function, and it is also linked to

inflammatory processes [27]. Interestingly, a Canadian study has revealed that SMD was a significant predicator of cancer patients' outcomes [14], and Antoun et al. [22] have also reported that low SMD was associated with inferior PFS and OS among patients with mRCC who were receiving several kinds of targeted agents. However, we did not observe any significant association between SMD and patient outcomes, and another Japanese group has also reported no significant association between SMD and OS among patients with mRCC [10]. This discrepancy might be related to the patients' ethnicity or the studies' sizes, and further large-scale studies are needed to confirm the value of SMD for predicting outcomes among patients with mRCC.

The mechanism by which a systematic inflammatory response may influence survival among cancer patients remains unclear. However, CRP is produced in the liver and is strongly induced by cytokines, and especially by interleukin-6 (IL-6). Experimental studies have demonstrated that RCC cells can produce IL-6, and that IL-6 itself is recognized as a growth promoter in RCC cells [28-31]. Furthermore, the increased protein degradation during sarcopenia is induced by catabolic drivers, such as systematic inflammation, and sarcopenia itself is considered to be driven by a decrease in protein synthesis and an increase in protein degradation [32]. Schaap et al.[33] have suggested that higher levels of CRP and IL-6 are significantly associated with the loss of muscle strength, and both the systematic inflammatory response and related nutritional decline may influence treatment tolerance and compliance [34]. For example, previous studies have demonstrated that sarcopenia is a significant

predictor of DLT among patients with mRCC who are receiving SU treatment [12, 35]. Huillard et al. [12] described that patients with sarcopenia and a BMI of < 25kg/m^2 experienced significantly more DLTs during the first cycle of SU treatment, although there was no difference in PFS or OS between sarcopenic patients and non-sarcopenic patients. We speculate that these discrepancies were caused by differences in the SU treatment regimens. A 2/1 schedule of SU provided a lower incidence of dose interruption in our previous study [24], and other studies also reported similar suggestions [36, 37]. Moreover, there were more patients receiving 50 mg as an initial dose in Huillard's study [12] than in the present study (49/60 vs. 21/71); our relative lower initial dose might explain the lower rate of early DLTs. Moreover, we found that the long-term tolerability of SU treatment was not affected by cachexic status, as there were no significant differences in RDI during the six cycles, or in the cumulative incidences of DLTs according to sarcopenic status or mGPS severity. Therefore, the results suggest that sarcopenia and mGPS were independent predictors of patient survival, regardless of DLTs.

In this study, no significant differences in DLT or RDI were observed between cachexic and non-cachexic patients. Moreover, there were no significant differences in the changing of the treatment strategy after DLTs, and SU administration was reduced, rather than discontinued, in most patients. These results might also be explained by our choice of treatment regimen; the adoption of a 2/1 schedule might be effective and safe, even for cachexic patients. Meanwhile, other tyrosine kinase, such as pazopanib, are suggested as a targeted agent with better safety and quality-of-life profiles,

compared to SU [38, 39]. Therefore, when a cachexic patient who is receiving SU experiences a DLT, switching to pazopanib may be an effective strategy. Further studies are needed to demonstrate this possibility.

The pharmacokinetics of SU in patients with cachexia remain unknown. Mir et al. [13] report that sarcopenia had a significant effect on early DLTs among patients with hepatocellular carcinoma who received sorafenib treatment, based on pharmacokinetic measurements. A previous study also reported that systematic inflammation has a negative effect on the activity of CYP3A4 [40], which is one of the enzymes that is involved in the metabolism of SU. Therefore, it is possible that an unknown mechanism could affect survival among patients who are receiving SU, and the effect of cachexia on CYP3A4 activity deserves further investigation, which should include phenotype and genotypic testing.

The present study revealed one difference between sarcopenia and mGPS: sarcopenia was only associated with PFS, whereas mGPS was only associated with OS. This result is interesting, as both sarcopenia and mGPS are similar indicators of cachexia, and we observed a marginal correlation between sarcopenia and mGPS (p = 0.0534). Unfortunately, we cannot explain this phenomenon, although we speculate that it may be influenced by some interactions between the factors that drive sarcopenia and mGPS in the cachexia-induced systematic inflammatory environment. Moreover, we found that albumin levels, but not CRP levels, were correlated with sarcopenic status (Table 1). This

result is also interesting, as it might mean that sarcopenic status represents a low nutrient condition that is induced by systematic inflammation, rather than an inflammatory response.

There are several limitations in the present study. First, we used a retrospective single-center design with a relative small sample size, which may have biased our survival analyses. Second, we were unable to retrospectively evaluate weight loss (due to no available data), which is an important symptom of cachexia [14, 18]. A further prospective study is needed to evaluate the effect of weight loss on survival among patients who are receiving SU treatment. Third, the definitions of sarcopenia in this study were based on sex-specific BMI-adjusted Canadian cut-off values for SMI [14], although it is possible that these cut-off values may not be appropriate for the Japanese population, due to race-related differences in physical attributes and muscle mass. Therefore, it may be relevant to identify more appropriate cut-off values that are specific to the Japanese population. Fourth, we analyzed the cumulative incidence of DLTs using the Kaplan-Meier method, although this method might have provided a misleading estimation, based on treatment discontinuation being a possible competing risk.

In summary, the present study demonstrated that sarcopenia and mGPS were independent predicators of survival after initiating first-line SU treatment in patients with mRCC and no prior cytokine therapy, regardless of the absence of DLTs, under our alternative treatment regimens. The advantage of these parameters is that both sarcopenia and mGPS can be easily evaluated without extra cost or effort, as both are quantified using routine CT and blood test findings. Therefore, these parameters might be

useful for improving the management of patients with mRCC, although further studies are needed to validate our findings.

Acknowledgements

We thank Editage (www.editage.jp) for English language editing.

Compliance with Ethical Standards

Funding none.

Conflicts of interest

TK received remuneration for a lecture from Pfizer Japan (Tokyo, Japan). HI, KO, TT, JI, HK & KT declare no conflict of interest.

References

1. Reisinger KW, van Vugt JL, Tegels JJ, Snijders C, Hulsewe KW, Hoofwijk AG et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. Ann Surg. 2015;261(2):345-52. doi:10.1097/sla.0000000000000628.

2. Fried LP, Hadley EC, Walston JD, Newman AB, Guralnik JM, Studenski S et al. From bedside to bench: research agenda for frailty. Sci Aging Knowledge Environ. 2005;2005(31):pe24. doi:10.1126/sageke.2005.31.pe24.

3. Peng P, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. J Gastrointest Surg. 2012;16(8):1478-86. doi:10.1007/s11605-012-1923-5.

4. Psutka SP, Carrasco A, Schmit GD, Moynagh MR, Boorjian SA, Frank I et al. Sarcopenia in patients with bladder cancer undergoing radical cystectomy: impact on cancer-specific and all-cause mortality. Cancer. 2014;120(18):2910-8. doi:10.1002/cncr.28798.

5. Sabel MS, Lee J, Cai S, Englesbe MJ, Holcombe S, Wang S. Sarcopenia as a prognostic

factor among patients with stage III melanoma. Ann Surg Oncol. 2011;18(13):3579-85. doi:10.1245/s10434-011-1976-9.

6. Del Fabbro E, Parsons H, Warneke CL, Pulivarthi K, Litton JK, Dev R et al. The relationship between body composition and response to neoadjuvant chemotherapy in women with operable breast cancer. Oncologist. 2012;17(10):1240-5. doi:10.1634/theoncologist.2012-0169.

7. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629-35. doi:10.1016/s1470-2045(08)70153-0.

8. Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y et al. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg. 2013;100(11):1523-30. doi:10.1002/bjs.9258.

9. Sharma P, Zargar-Shoshtari K, Caracciolo JT, Fishman M, Poch MA, Pow-Sang J et al. Sarcopenia as a predictor of overall survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. Urol Oncol. 2015;33(8):339.e17-23. doi:10.1016/j.urolonc.2015.01.011.

10. Fukushima H, Nakanishi Y, Kataoka M, Tobisu KI, Koga F. Prognostic significance of sarcopenia in metastatic renal cell carcinoma patients. J Urol. 2015. doi:10.1016/j.juro.2015.08.071.

11. Antoun S, Baracos VE, Birdsell L, Escudier B, Sawyer MB. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. Ann Oncol. 2010;21(8):1594-8. doi:10.1093/annonc/mdp605.

12. Huillard O, Mir O, Peyromaure M, Tlemsani C, Giroux J, Boudou-Rouquette P et al. Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients. Br J Cancer. 2013;108(5):1034-41. doi:10.1038/bjc.2013.58.

13. 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. doi:10.1371/journal.pone.0037563.

14. 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(12):1539-47. doi:10.1200/jco.2012.45.2722.

15. McMillan DC. An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. Proc Nutr Soc. 2008;67(3):257-62. doi:10.1017/s0029665108007131.

16. Proctor MJ, Morrison DS, Talwar D, Balmer SM, O'Reilly DS, Foulis AK et al. An

inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. Br J Cancer. 2011;104(4):726-34. doi:10.1038/sj.bjc.6606087.

17. Lamb GW, Aitchison M, Ramsey S, Housley SL, McMillan DC. Clinical utility of the Glasgow Prognostic Score in patients undergoing curative nephrectomy for renal clear cell cancer: basis of new prognostic scoring systems. Br J Cancer. 2012;106(2):279-83. doi:10.1038/bjc.2011.556.

18. Ramsey S, Lamb GW, Aitchison M, Graham J, McMillan DC. Evaluation of an inflammation-based prognostic score in patients with metastatic renal cancer. Cancer. 2007;109(2):205-12. doi:10.1002/cncr.22400.

19. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. The New England journal of medicine. 2007;356(2):115-24. doi:10.1056/NEJMoa065044.

20. Thompson Coon JS, Liu Z, Hoyle M, Rogers G, Green C, Moxham T et al. Sunitinib and bevacizumab for first-line treatment of metastatic renal cell carcinoma: a systematic review and indirect comparison of clinical effectiveness. Br J Cancer. 2009;101(2):238-43. doi:10.1038/sj.bjc.6605167.

21. Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS et al. EAU guidelines on renal cell carcinoma: the 2010 update. Eur Urol. 2010;58(3):398-406. doi:10.1016/j.eururo.2010.06.032.

22. Antoun S, Lanoy E, Iacovelli R, Albiges-Sauvin L, Loriot Y, Merad-Taoufik M et al. Skeletal muscle density predicts prognosis in patients with metastatic renal cell carcinoma treated with targeted therapies. Cancer. 2013;119(18):3377-84. doi:10.1002/cncr.28218.

23. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol (1985). 2004;97(6):2333-8. doi:10.1152/japplphysiol.00744.2004.

24. Kondo T, Takagi T, Kobayashi H, Iizuka J, Nozaki T, Hashimoto Y et al. Superior tolerability of altered dosing schedule of sunitinib with 2-weeks-on and 1-week-off in patients with metastatic renal cell carcinoma--comparison to standard dosing schedule of 4-weeks-on and 2-weeks-off. Jpn J Clin Oncol. 2014;44(3):270-7. doi:10.1093/jjco/hyt232.

25. Pfizer Japan. Sutent Appropriate Use Guideline. Japan: Pfizer Japan; 2012.

26. Li H, Samawi H, Heng DY. The use of prognostic factors in metastatic renal cell carcinoma. Urol Oncol. 2015. doi:10.1016/j.urolonc.2015.08.003.

27. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. J Appl

Physiol (1985). 2000;89(1):104-10.
28. Miki S, Iwano M, Miki Y, Yamamoto M, Tang B, Yokokawa K et al. Interleukin-6 (IL-6) functions as an in vitro autocrine growth factor in renal cell carcinomas. FEBS Lett. 1989;250(2):607-10.
29. Koo AS, Armstrong C, Bochner B, Shimabukuro T, Tso CL, deKernion JB et al. Interleukin-6 and renal cell cancer: production, regulation, and growth effects. Cancer Immunol Immunother. 1992;35(2):97-105.
30. Cuadros T, Trilla E, Sarro E, Vila MR, Vilardell J, de Torres I et al. HAVCR/KIM-1 activates the IL-6/STAT-3 pathway in clear cell renal cell carcinoma and determines tumor progression and patient outcome. Cancer Res. 2014;74(5):1416-28. doi:10.1158/0008-5472.can-13-1671.
31. Trikha M, Corringham R, Klein B, Rossi JF. Targeted anti-interleukin-6 monoclonal antibody therapy for cancer: a review of the rationale and clinical evidence. Clin Cancer Res. 2003;9(13):4653-65.
32. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab. 2012;16(2):153-66. doi:10.1016/j.cmet.2012.06.011.
33. Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. Am J Med. 2006;119(6):526.e9-17. doi:10.1016/j.amjmed.2005.10.049.
34. Bromwich E, McMillan DC, Lamb GW, Vasey PA, Aitchison M. The systemic inflammatory response, performance status and survival in patients undergoing alpha-interferon treatment for advanced renal cancer. Br J Cancer. 2004;91(7):1236-8. doi:10.1038/sj.bjc.6602152.
35. Cushen SJ, Power DG, Teo MY, Maceneaney P, Maher MM, McDermott R et al. Body Composition by Computed Tomography as a Predictor of Toxicity in Patients With Renal Cell Carcinoma Treated With Sunitinib. Am J Clin Oncol. 2014. doi:10.1097/coc.0000000000000061.
36. Najjar YG, Mittal K, Elson P, Wood L, Garcia JA, Dreicer R et al. A 2 weeks on and 1 week off schedule of sunitinib is associated with decreased toxicity in metastatic renal cell carcinoma. Eur J Cancer. 2014;50(6):1084-9. doi:10.1016/j.ejca.2014.01.025.
37. Atkinson BJ, Kalra S, Wang X, Bathala T, Corn P, Tannir NM et al. Clinical outcomes for patients with metastatic renal cell carcinoma treated with alternative sunitinib schedules. J Urol. 2014;191(3):611-8. doi:10.1016/j.juro.2013.08.090.
38. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. The New England journal of medicine. 2013;369(8):722-31. doi:10.1056/NEJMoa1303989.

39. Escudier B, Porta C, Bono P, Powles T, Eisen T, Sternberg CN et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(14):1412-8. doi:10.1200/jco.2013.50.8267.
40. Kacevska M, Robertson GR, Clarke SJ, Liddle C. Inflammation and CYP3A4-mediated drug metabolism in advanced cancer: impact and implications for chemotherapeutic drug dosing. Expert Opin Drug Metab Toxicol. 2008;4(2):137-49. doi:10.1517/17425255.4.2.137.

Figure legends

Figure 1: Patient selection flow-chart.

Figure 2: Progression-free survival after sunitinib treatment initiation according to sarcopenia status.

The survival rate was calculated using the Kaplan-Meier method and compared using the log-rank test ($p = 0.0004$). SU: sunitinib

Figure 3: Overall survival after sunitinib treatment initiation according to sarcopenia status. The survival rate was calculated using the Kaplan-Meier method and compared using the log-rank test ($p = 0.0019$). SU: sunitinib

Figure 4: Progression-free survival after sunitinib treatment initiation according to mGPS. The survival rate was calculated using the Kaplan-Meier method and compared using the log-rank test ($p < 0.0001$). mGPS: modified Glasgow prognostic score; SU: sunitinib

Figure 5: Overall survival after sunitinib treatment initiation according to mGPS. The survival rate was calculated using the Kaplan-Meier method and compared using the log-rank test ($p < 0.0001$). mGPS: modified Glasgow prognostic score; SU: sunitinib

Figure 6: Cumulative incidence of experiencing dose-limiting toxicities after sunitinib treatment initiation according to sarcopenia status. The cumulative incidence was calculated using the Kaplan-Meier method and compared using the log-rank test ($p = 0.741$). SU: sunitinib

Figure 7: Cumulative incidence of experiencing dose-limiting toxicities after sunitinib treatment initiation according to mGPS. The cumulative incidence was calculated using the Kaplan-Meier method and compared using the log-rank test ($p = 0.164$). SU: sunitinib

Figure 1: Patient selection flow-chart

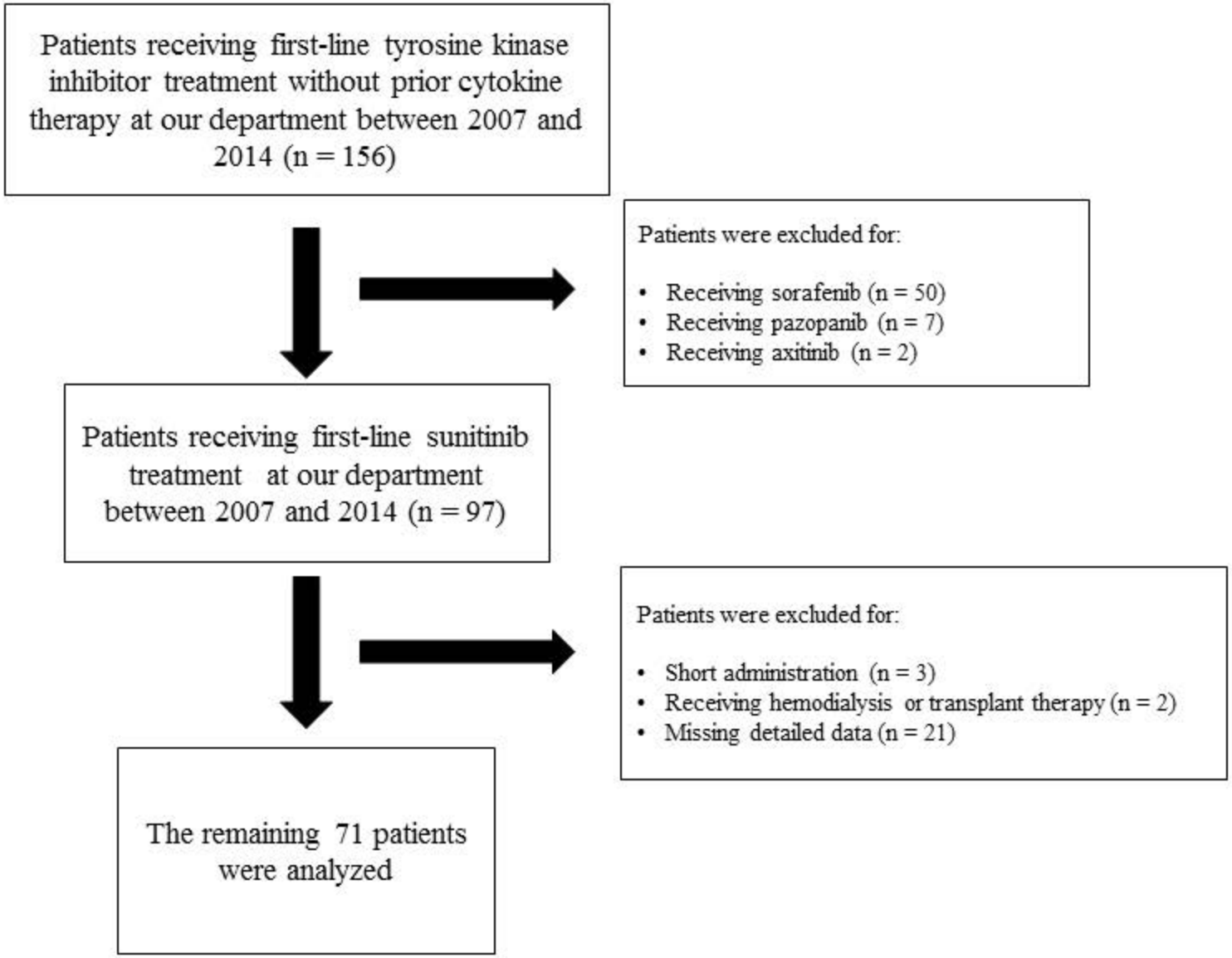


Figure 2: Progression-free survival after sunitinib treatment initiation according to sarcopenia status

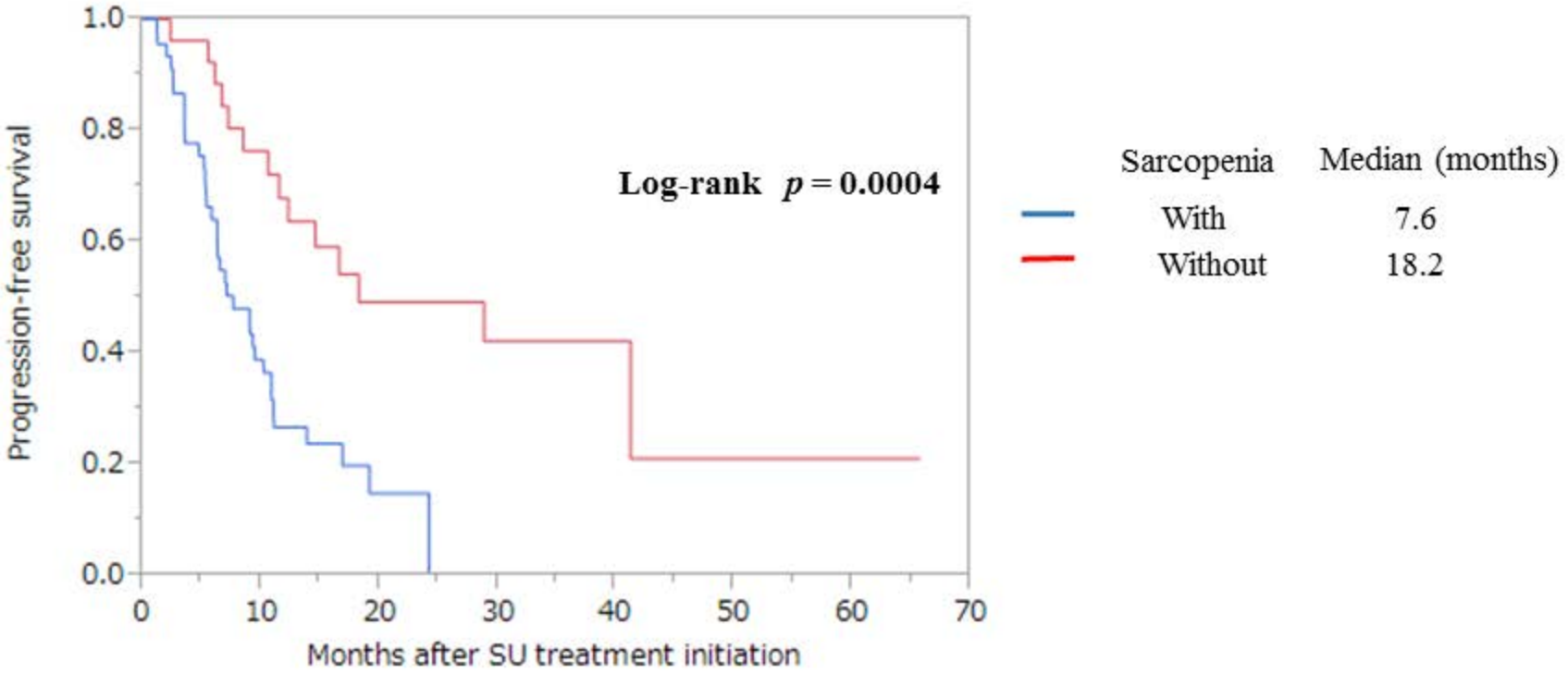


Figure 3: Overall survival after sunitinib treatment initiation according to sarcopenia status

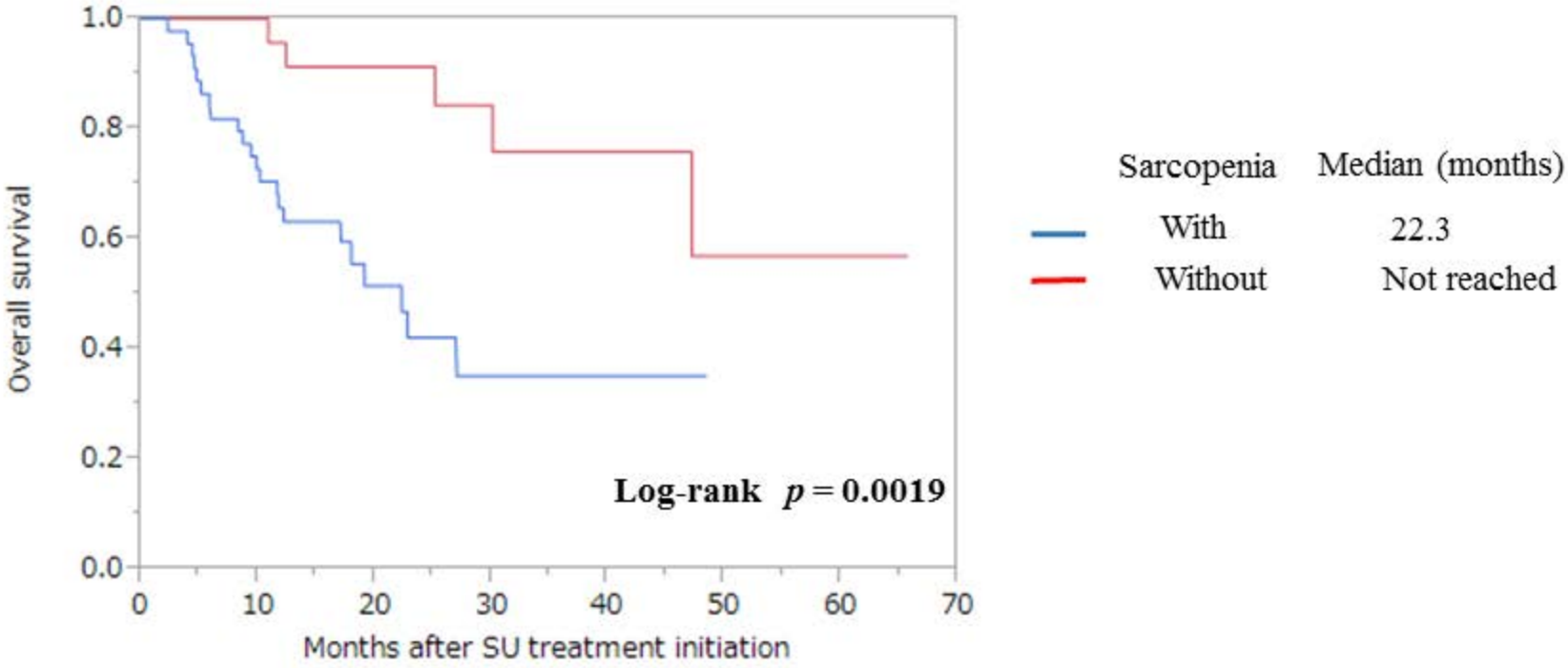


Figure 4: Progression-free survival after sunitinib treatment initiation according to mGPS

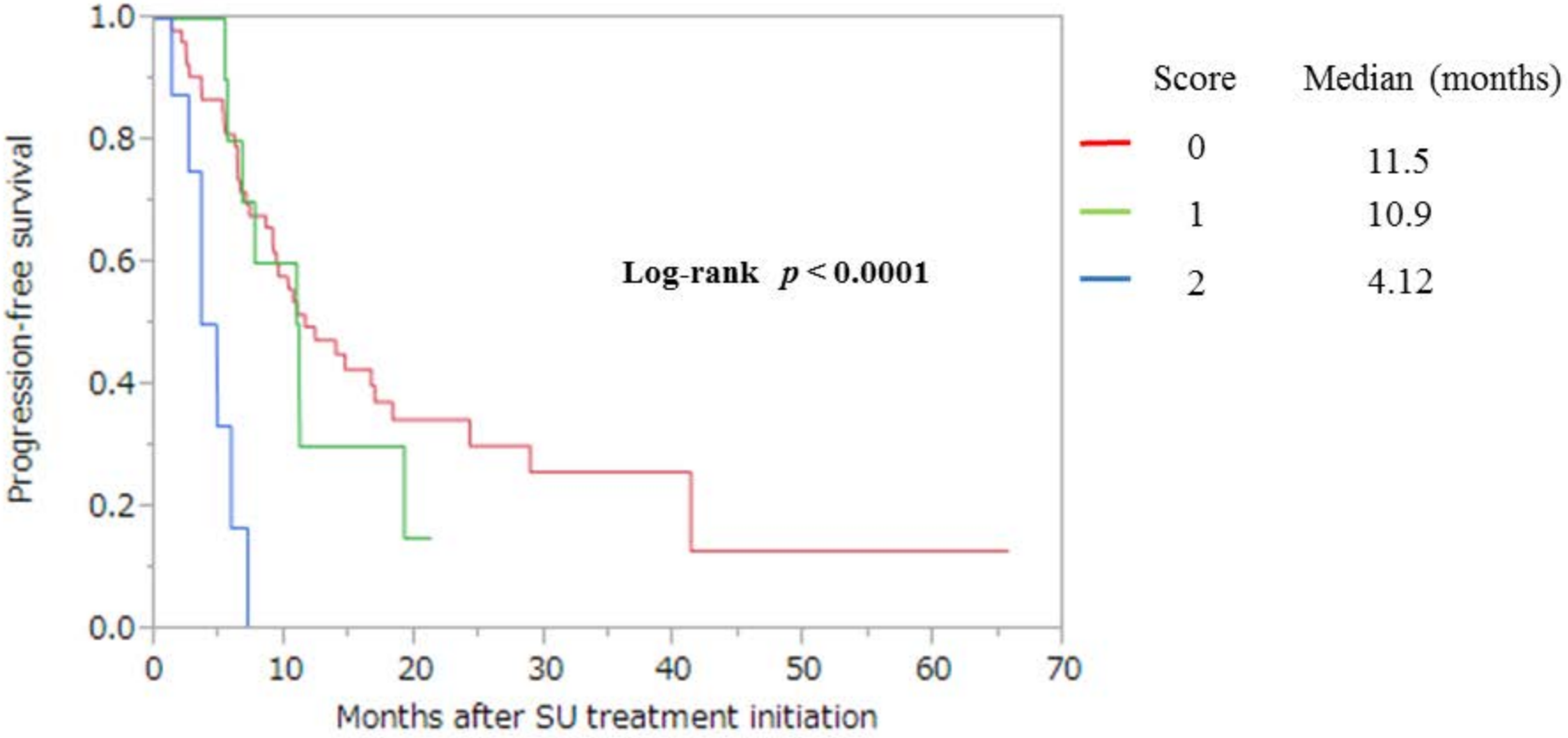


Figure 5: Overall survival after sunitinib treatment initiation according to mGPS

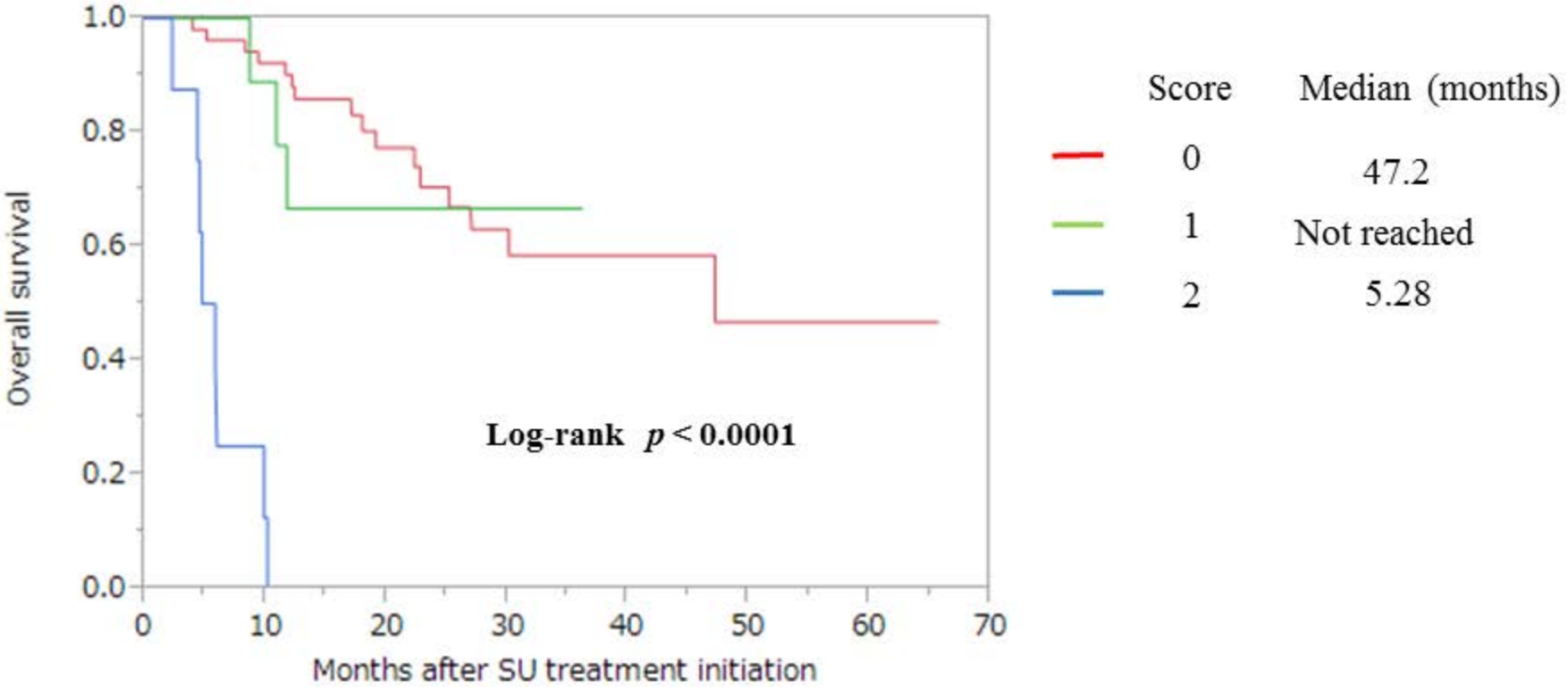
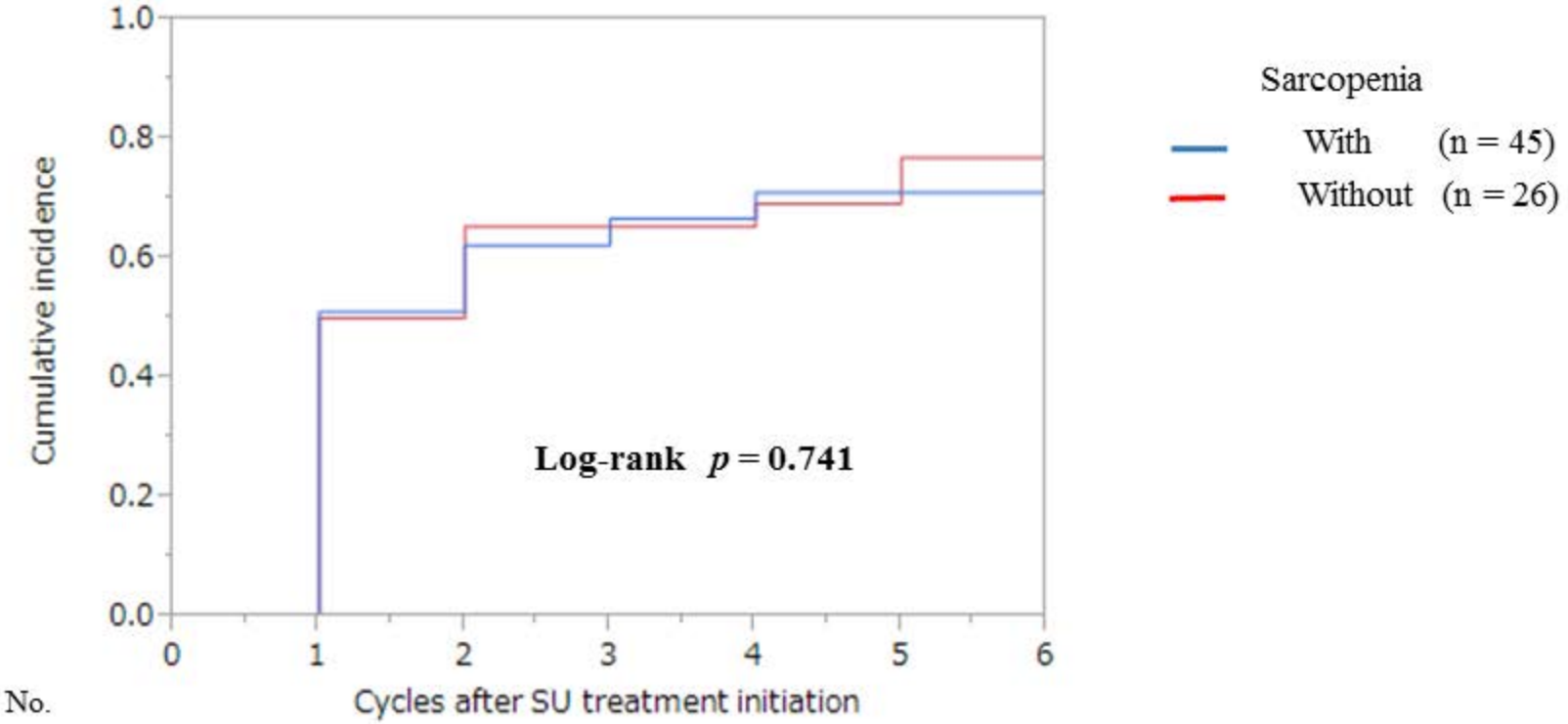


Figure 6: Cumulative incidence of dose-limiting toxicities after sunitinib treatment initiation according to sarcopenia status



No.							
With	0	23	28	30	32	32	32
Without	0	13	17	17	18	20	20

Figure 7: Cumulative incidence of dose-limiting toxicities after sunitinib treatment initiation according to mGPS

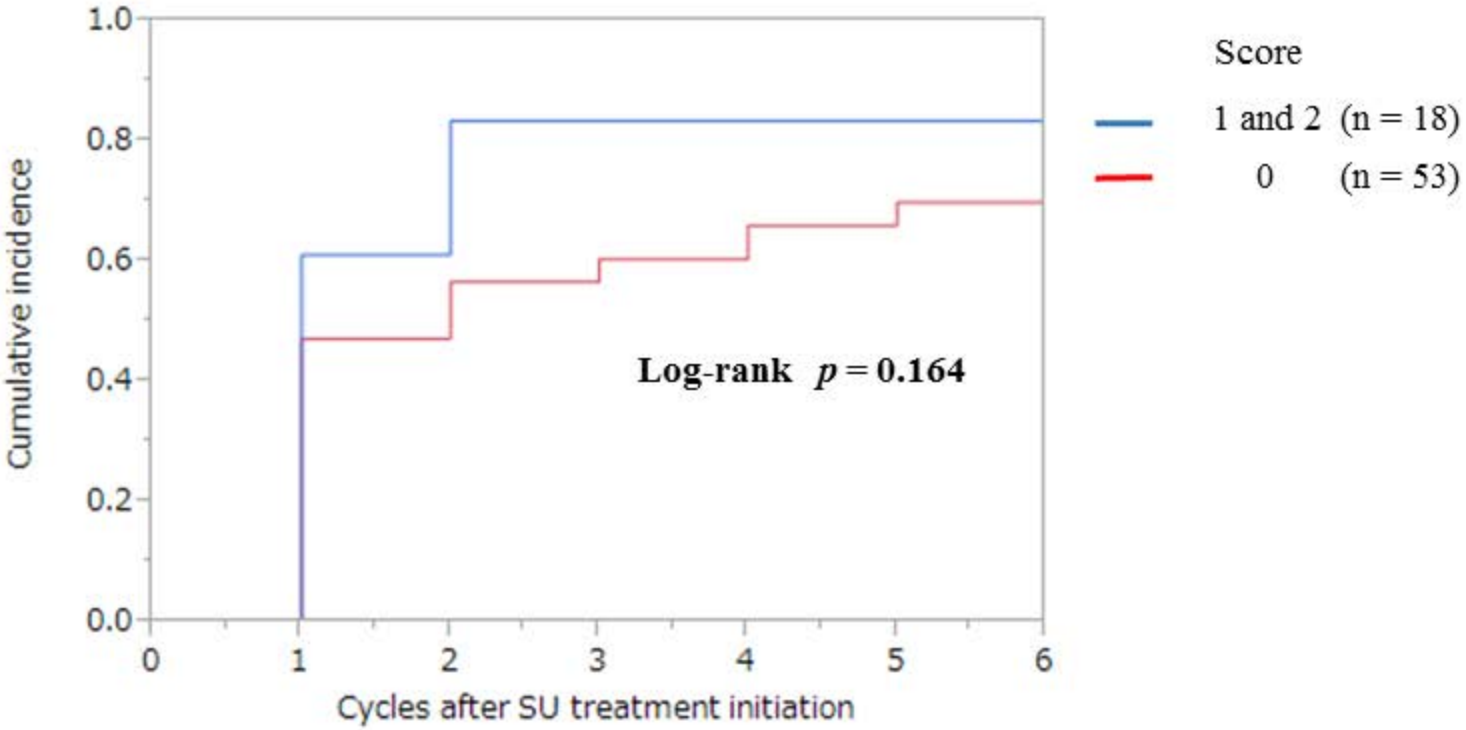


Table 1

Table 1: Patient characteristics

	All (n = 71)	With sarcopenia (n = 45)	Without sarcopenia (n = 26)	P-value
Sex				0.0025
Male	50 (70.4%)	26 (57.8%)	24 (92.3%)	
Female	21 (29.6%)	19 (42.2%)	2 (7.69%)	
Mean age at SU treatment initiation, years (median, range)	64.0 (64.0, 31 - 79)	65.6 (64.0, 31 - 79)	61.0 (63.0, 31 - 73)	0.0194
Pathology				0.0787
CCC	58 (81.7%)	34 (75.6%)	24 (92.3%)	
Non-CCC	13 (18.3%)	11 (15.5%)	2 (7.69%)	
CCC with spindle cell	3 (4.23%)	2 (4.44%)	1 (3.85%)	
CCC with sarcomatoid	1 (1.41%)	1 (2.22%)	0	
PRCC type 2	5 (7.04%)	4 (8.89%)	1 (3.85%)	
Medullary carcinoma	1 (1.41%)	1 (2.22%)	0	
Unknown	3 (4.23%)	3 (6.67%)	0	
Radical nephrectomy				0.251
Yes	64 (90.1%)	39 (86.7%)	25 (96.2%)	
No	7 (9.86%)	6 (13.3%)	1 (3.85%)	
Karnofsky performance status, %				0.642
≥ 80	64 (90.1%)	40 (88.9%)	24 (92.3%)	
< 80	7 (9.86%)	5 (11.1%)	2 (7.69%)	
Time from diagnosis to treatment, days				0.418
≥ 365	20 (28.2%)	11 (24.4%)	9 (34.6%)	
< 365	51 (71.8%)	34 (75.6%)	17 (65.4%)	
MSKCC risk				0.267
Favorable	17 (23.9%)	9 (20.0%)	8 (30.8%)	
Intermediate	39 (54.9%)	24 (53.3%)	15 (57.7%)	
Poor	15 (21.1%)	12 (26.7%)	3 (11.5%)	
Number of metastatic sites				0.0480
Solitary	32 (45.1%)	16 (35.6%)	16 (61.5%)	
Multiple	39 (54.9%)	29 (64.4%)	10 (38.5%)	
pT stage				0.282
pT1-2	21 (29.6%)	11 (24.4%)	10 (38.5%)	
pT1a	5 (7.04%)	3 (6.67%)	2 (7.69%)	
pT1b	6 (8.45%)	3 (6.67%)	3 (11.5%)	
pT2a	7 (9.86%)	3 (6.67%)	4 (15.4%)	
pT2b	3 (4.23%)	2 (4.44%)	1 (3.85%)	
pT3-4	50 (70.4%)	34 (75.6%)	16 (61.5%)	
pT3a	27 (38.0%)	19 (42.2%)	8 (30.8%)	
pT3b	10 (14.1%)	5 (11.1%)	5 (19.2%)	
pT3c	6 (8.45%)	5 (11.1%)	1 (3.85%)	
pT4	7 (9.86%)	5 (11.1%)	2 (7.69%)	
Mean height, m (median, range)	1.63 (1.63, 1.44 - 1.86)	1.61 (1.61, 1.46 - 1.86)	1.66 (1.67, 1.44 - 1.81)	0.0183
Mean Weight, kg (median, range)	63.0 (64.0, 40.0 - 109.0)	59.7 (58.3, 40 - 80.1)	68.6 (67.9, 43 - 109)	0.0030
Mean BMI, kg/m^2 (median, range)	23.6 (23.2, 17.8 - 43.7)	22.9 (22.8, 17.8 - 30.7)	24.9 (24.1, 20.7 - 43.7)	0.0431
Mean Skeletal muscle, cm^2 (median, range)	112.1 (112.03, 54.91 - 187.3)	96.2 (95.8, 54.9 - 142.8)	139.7 (137.5, 88.7 - 187.3)	<0.0001
Mean SMI, cm^2/m^2 (median, range)	41.8 (41.8, 24.4 - 66.3)	36.6 (35.8, 24.4 - 48.5)	50.7 (48.9, 42.8 - 66.3)	<0.0001
Mean SMD, HU (median, range)	35.7 (33.7, 12.0 - 92.2)	34.2 (33.3, 12.0 - 58.2)	38.5 (35.8, 12.6 - 92.2)	0.197
The mGPS at the time of SU treatment initiation				0.0534
0	53 (74.6%)	30 (66.7%)	23 (88.5%)	
1	10 (14.1%)	7 (15.6%)	3 (11.5%)	
2	8 (11.3%)	8 (17.8%)	0	
Mean serum eGFR level at SU treatment initiation, mL/min/1.73m^2 (median, range)	48.4 (48.5, 12.2 - 88.9)	46.6 (47.4, 12.2 - 72.3)	51.7 (54.5, 19.6 - 88.9)	0.194
Mean serum CRP level at SU treatment initiation, mg/dL	1.59 (0.39, 0.02 – 15.3)	1.98 (0.56, 0.02 – 15.3)	0.90 (0.24, 0.04 – 7.14)	0.174
Mean serum albumin level at SU treatment initiation, g/dL	4.08 (4.10, 2.3 – 5.0)	3.90 (4.0, 2.3 – 5.0)	4.38 (4.4, 3.6 – 4.9)	<0.0001
Mean follow-up period after SU treatment initiation, months (median, range)	20.2 (17.0, 2.24 - 65.6)	16.0 (13.7, 2.24 - 48.4)	27.4 (23.8, 5.95 - 65.6)	0.0012

SU, sunitinib; CCC, clear cell carcinoma; PRCC, papillary renal cell carcinoma; MSKCC, Memorial Sloan-Kettering Cancer Center; BMI, body mass index; SMI, skeletal muscle index; SMD, skeletal muscle density; HU, Hounsfield unit; mGPS, modified Glasgow prognostic score; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein

Table 2

Table 2: Univariate and multivariate analyses of progression-free survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Sex				
Male	Reference	-		
Female	1.15 (0.61-2.07)	0.660		
Age	1.00 (0.97-1.03)	0.880		
Pathology				
CCC	Reference	-	Reference	-
Non-CCC	2.62 (1.29-5.00)	0.0094	1.82 (0.81-3.93)	0.146
Karnofsky performance status, %				
≥ 80	0.15 (0.066-0.38)	0.0003	0.50 (0.14-1.88)	0.300
< 80	Reference	-	Reference	-
Time from diagnosis to treatment, days				
≥ 365	Reference	-	Reference	-
< 365	2.59 (1.34-5.50)	0.0038	0.95 (0.27-6.02)	0.942
MSKCC		0.0007		0.269
Favorable	0.43 (0.18-0.90)	0.0251	0.43 (0.096-3.00)	0.343
Intermediate	Reference	-	Reference	-
Poor	2.34 (1.18-4.44)	0.0159	1.90 (0.71-4.66)	0.193
Number of metastatic sites				
Solitary	Reference	-	Reference	-
Multiple	2.04 (1.14-3.73)	0.0160	1.58 (0.77-3.34)	0.214
pT stage				
pT1-2	Reference	-	Reference	-
pT3-4	1.91 (1.02-3.83)	0.0421	1.18 (0.56-2.64)	0.664
Sarcopenia				
No	Reference	-	Reference	-
Yes	3.15 (1.66-6.41)	0.00003	2.54 (1.19-5.65)	0.0163
SMD				
High muscle attenuation	Reference	-		
Low muscle attenuation	1.10 (0.62-1.97)	0.754		
The mGPS		0.0017		0.522
0	0.14 (0.059-0.39)	0.0004	0.71 (0.19-2.71)	0.614
1	0.19 (0.063-0.58)	0.0045	0.47 (0.11-2.08)	0.321
2	Reference	-	Reference	-
Serum eGFR level, mL/min/1.73m^2	1.00 (0.98-1.02)	0.891		

HR, hazard ratio; CI, confidence interval; CCC, clear cell carcinoma; MSKCC, Memorial Sloan-Kettering Cancer Center; SMD, skeletal muscle density; mGPS, modified Glasgow prognostic score; eGFR, estimated glomerular filtration rate

Table 3

Table 3: Univariate and multivariate analyses of overall survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Sex				
Male	Reference	-		
Female	1.35 (0.57-2.95)	0.480		
Age	1.00 (0.96-1.04)	0.963		
Pathology				
CCC	Reference	-	Reference	-
Non-CCC	2.49 (1.02-5.54)	0.0455	4.27 (1.30-14.6)	0.0173
Karnofsky performance status, %				
≥ 80	0.25 (0.11-0.68)	0.0094	2.59 (0.63-11.7)	0.190
< 80	Reference	-	Reference	-
Time from diagnosis to treatment, days				
≥ 365	Reference	-	Reference	-
< 365	3.14 (1.20-10.7)	0.0172	1.55 (0.24-32.1)	0.689
MSKCC		0.0011		0.239
Favorable	0.41 (0.093-1.26)	0.126	1.51 (0.13-40.4)	0.760
Intermediate	Reference	-	Reference	-
Poor	3.28 (1.43-7.38)	0.0058	3.19 (0.83-12.2)	0.0908
Number of metastatic sites				
Solitary	Reference	-	Reference	-
Multiple	2.28 (1.04-5.27)	0.0385	2.61 (0.91-7.91)	0.0748
pT stage				
pT1-2	Reference	-	Reference	-
pT3-4	4.48 (1.56-18.9)	0.0035	3.27 (0.84-17.6)	0.0917
Sarcopenia				
No	Reference	-	Reference	-
Yes	4.29 (1.72-13.0)	0.0012	2.29 (0.73-8.16)	0.157
SMD				
High muscle attenuation	Reference	-		
Low muscle attenuation	1.86 (0.82-4.77)	0.140		
The mGPS		<0.0001		0.0012
0	0.033 (0.0092-0.10)	<0.0001	0.069 (0.014-0.31)	0.0004
1	0.048 (0.0089-0.20)	<0.0001	0.053 (0.0059-0.34)	0.0014
2	Reference	-	Reference	-
Serum eGFR level, mL/min/1.73m^2	0.98 (0.96-1.01)	0.138		

HR, hazard ratio; CI, confidence interval; CCC, clear cell carcinoma; MSKCC, Memorial Sloan-Kettering Cancer Center; SMD, skeletal muscle density; mGPS, modified Glasgow prognostic score; eGFR, estimated glomerular filtration rate

Table 4

Table 4: Comparisons of sunitinib safety and tolerability between sarcopenic and non-sarcopenic patients during the first cycle

	All (n = 71)	With sarcopenia (n = 45)	Without sarcopenia (n = 26)	*p*-value
Initial dose				0.0920
50 mg	21 (29.6%)	11 (24.4%)	10 (38.5%)	
37.5 mg	35 (49.3%)	21 (46.7%)	14 (53.8%)	
25 mg	15 (21.1%)	13 (28.9%)	2 (7.69%)	
RDI during first cycle				0.128
≥ 75%	38 (53.5%)	21 (46.7%)	17 (65.4%)	
< 75%	33 (46.5%)	24 (53.3%)	9 (34.6%)	
DLT				0.928
With	36 (50.7%)	23 (51.1%)	13 (50.0%)	
Without	35 (49.3%)	22 (48.9%)	13 (50.0%)	
Prevalence of selected toxicities				
Fatigue				
Grade 2	8 (11.3%)	6 (13.3%)	2 (7.69%)	0.469
Grade 3	0	0	0	-
HFS				
Grade 2	5 (7.04%)	2 (4.44%)	3 (11.5%)	0.260
Grade 3	0	0	0	-
Hepatic disorder				
Grade 2	1 (1.41%)	0	1 (3.85%)	0.186
Grade 3	2 (2.82%)	1 (2.22%)	1 (3.85%)	0.690
Neutropenia				
Grade 2	2 (2.82%)	2 (4.44%)	0	0.276
Grade 3	5 (7.04%)	3 (6.67%)	2 (7.69%)	0.871
Thrombocytopenia				
Grade 2	9 (12.7%)	4 (8.89%)	5 (19.2%)	0.207
Grade 3	7 (9.86%)	5 (11.1%)	2 (7.69%)	0.642
Number of patients with grade 2	26 (36.6%)	15 (33.3%)	11 (42.3%)	0.450
Number of patients with grade 3	14 (19.7%)	10 (22.2%)	4 (15.4%)	0.485
RDI during six cycles				0.302
≥ 75%	24 (33.8%)	13 (28.9%)	11 (42.3%)	
< 75%	47 (66.2%)	32 (71.1%)	15 (57.7%)	
Treatment after DLT				0.194
Reduction of dose	31 (86.1%)	18 (40.0%)	13 (100.0%)	
Discontinuation of sunitinib	4 (11.1%)	4 (17.4%)	0	
Switching to other targeted agents	1 (2.78%)	1 (4.35%)	0	

RDI, relative dose intensity; DLT, dose-limiting toxicities; HFS, hand-foot syndrome

Table 5

Table 5 : Comparisons of sunitinib safety and tolerability between mGPS 0 and mGPS 1 and 2

	All (n = 71)	mGPS 1 and 2 (n = 18)	mGPS 0 (n = 53)	*p*-value
Initial dose				0.396
50 mg	21(29.6%)	7 (38.9%)	14 (26.4%)	
37.5 mg	35 (49.3%)	9 (50.0%)	26 (49.1%)	
25 mg	15 (21.1%)	2 (11.1%)	13 (24.5%)	
RDI during first cycle				0.372
≥ 75%	38 (53.5%)	8 (44.4%)	30 (56.6%)	
< 75%	33 (46.5%)	10 (55.6%%)	23 (43.4%)	
DLT				0.307
With	36 (50.7%)	11 (61.1%)	25 (47.2%)	
Without	35 (49.3%)	7 (38.9%)	28 (52.8%)	
Prevalence of selected toxicities				
Fatigue				
Grade 2	8 (11.3%)	2 (11.1%)	6 (11.3%)	0.981
Grade 3	0	0	0	-
HFS				
Grade 2	5 (7.04%)	2 (11.1%)	3 (5.66%)	0.435
Grade 3	0	0	0	-
Hepatic disorder				
Grade 2	1 (1.41%)	1 (5.56%)	0	0.254
Grade 3	2 (2.82%)	0	2 (3.77%)	0.403
Neutropenia				
Grade 2	2 (2.82%)	0	2 (3.77%)	0.403
Grade 3	5 (7.04%)	0	5 (9.43%)	0.177
Thrombocytopenia				
Grade 2	9 (12.7%)	4 (22.2%)	5 (9.43%)	0.159
Grade 3	7 (9.86%)	4 (22.2%)	3 (5.66%)	0.0635
Number of patients with grade 2 toxicities	26 (36.6%)	8 (44.4%)	18 (34.0%)	0.425
Number of patients with grade 3 toxicities	14 (19.7%)	4 (22.2%)	10 (18.9%)	0.757
RDI during six cycles				0.774
≥ 75%	24 (33.8%)	7 (38.9%)	17 (32.1%)	
< 75%	47 (66.2%)	11 (61.1%)	36 (67.9%)	
With DLT	**All (n = 36)**	**mGPS 1 and 2 (n = 11)**	**mGPS 0 (n = 25)**	
Treatment after DLT				0.763
Reduction of dose	31 (86.1%)	10 (90.9%)	21 (84.0%)	
Discontinuation of sunitinib	4 (11.1%)	1 (9.09%)	3 (12.0%)	
Switching to other targeted agents	1 (2.78%)	0	1 (4.00%)	

mGPS, modified Glasgow prognostic score; RDI, relative dose intensity; DLT, dose-limiting toxicities; HFS, hand-foot syndrome