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ORIGINAL ARTICLE

Sarcopenia is associated with survival in patients with urothelial carcinoma treated with systemic chemotherapy

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Abstract

Background Sarcopenia impacts perioperative outcomes and prognosis in various carcinomas. We aimed to investigate whether sarcopenia at the time of chemotherapy induction in patients with urothelial carcinoma is associated with prognosis.

Methods We evaluated patients treated with chemotherapy for urothelial carcinoma between April 2013 and February 2018 at our institution and affiliated centers. Skeletal muscle mass (total psoas muscle, paraspinal muscle, and total skeletal muscle areas) were used to calculate the total psoas muscle index, paraspinal muscle index, and skeletal muscle index. All participants were grouped as per cutoff points set at the median value for each sex. Overall survival was evaluated using Cox regression analysis.

Results Of the 240 patients, 171 were men and 69 were women; mean age during chemotherapy was 71 years (range: 43–88); and 36, 56, and 148 patients were at stages II, III, and IV, respectively. Paraspinal muscle index was most associated with the prognosis; groups with lower paraspinal muscle index were defined as sarcopenic (men: ≤ 20.9 cm^2/m^2, women: ≤ 16.8 cm^2/m^2). The overall survival was significantly longer in the non-sarcopenia group including all stages ($p=0.001$), and in stage III ($p=0.048$) and IV ($p=0.005$) patients. There was no significant difference among stage II patients ($p=0.648$). After propensity score matching, survival was still significantly longer in the non-sarcopenia group ($p=0.004$).

Conclusions Paraspinal muscle index measurements obtained during chemotherapy induction for urothelial carcinoma were independent prognostic factors. The absence of sarcopenia may lead to long-term survival in patients undergoing chemotherapy for urothelial carcinoma.

Keywords Sarcopenia · Urothelial carcinoma · Prognostic factors

Introduction

Approximately, 20,000 new cases of urothelial carcinoma (UC) are diagnosed, and 7000 deaths attributed to UC occur annually in Japan [1]. Systemic chemotherapy is the standard treatment for advanced UC and involves administration of gemcitabine and cisplatin (GC) or a combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), with GC being preferred because of its lower toxicity [2].

In general, locally advanced bladder cancer is also treated with neoadjuvant chemotherapy (NAC) to shrink the tumor, followed by radical cystectomy depending on the tumor size, cancer stage, and response to NAC [3]. The 2021 European Urological Association guidelines make a strong recommendation to "Offer post-operative systemic platinum-based chemotherapy to patients with muscle-invasive UTUC [4]."

However, most UC patients are older adults, and physiological changes associated with aging affect pharmacokinetics and drug sensitivity. In older adults, there is a large variation among individual patients, and it is desirable to examine the life expectancy before starting chemotherapy, and then consider whether drug therapy or dose adjustment is necessary; however, there is no clear indicator [5].

Recent geriatrics reports show that sarcopenia is associated with a worse prognosis and outcome in various diseases. The concept of sarcopenia was proposed by Rosenberg, who described the phenomenon as "age-related decrease in muscle mass" [6].

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On average, it is estimated that 5–13% of older adults aged 60–70 years are affected by sarcopenia. The numbers increase to 11–50% for those aged ≥ 80 years [7].

Sarcopenia is considered to have a prognostic impact in oncology, and there has been a recent surge in reports of sarcopenia being associated with poor prognosis and outcomes in urology. Although, many studies report on the relationship between sarcopenia and surgical outcomes and survival for localized bladder cancer, few have discussed the overall survival (OS) of patients treated with systemic chemotherapy for advanced UC.

We have previously reported that sarcopenia at the time of chemotherapy induction is a prognostic factor [8], but in this study, we used multiple indices in a multicenter setting.

Materials and methods

Patients

We retrospectively reviewed 240 patients with UC who received first-line chemotherapy (GC or GCa) at our institution and affiliated facilities between April 2013 and February 2018. Most UC patients received gemcitabine 1000 mg/m^2 on days 1, 8, and 15 plus cisplatin 70 mg/m^2 on day 2. On the other hand, cisplatin-unfit patients [with estimated glomerular filtration rate < 60 mL/min and Eastern Cooperative Oncology Group performance status (ECOG-PS) ≥ 2] received gemcitabine 1000 mg/m^2 on days 1, 8, and 15 plus carboplatin with an area under the curve of 5, according to the Calvert formula, on day 2.

Variables evaluated included age at first chemotherapy session, sex, ECOG-PS, T stage, N stage, M stage, diabetes status, smoking habits, body mass index (BMI), body surface area (BSA), pre-treatment blood biochemical data (Hgb, PLT, albumin, CRP, eGFR), and platinum drug type.

This study was approved by the Ethics Committee of Tottori University of Medicine (Approval No. 18A038).

Image analysis

All patients underwent computed tomography (CT) before chemotherapy to evaluate for sarcopenia. The cross-sectional area of the skeletal muscle at the level of the third lumbar vertebra (L3) was evaluated using the OsiriX DICOM viewer. Three parameters of skeletal muscle mass were assessed: total psoas area (TPA) (Fig. 1a); paraspinal muscle area (PSMA) including total psoas, quadratus lumborum, erector spinae, and multifidus (Fig. 1b); and skeletal muscle area (SMA) including the paraspinal, transverse abdominis, external and internal oblique abdominis, and rectus abdominis (Fig. 1c). To assess sarcopenia, these muscle areas were normalized by the square of height to calculate the total psoas muscle index (TPI) (cm^2/m^2), paraspinal muscle index (PSMI) (cm^2/m^2), and skeletal muscle index (SMI) (cm^2/m^2). For each index, the median value for each sex was set as the cutoff point. For SMI, patients were classified as sarcopenic according to sex-specific international consensus reference values [9].

Statistics

The background and pre-treatment factors of patients and their OS were analyzed. Univariate and multivariate analyses were performed, and odds ratios were analyzed using logistic regression models. Survival curves were constructed using Kaplan–Meier analysis, and the log-rank test and Cox regression model were used for comparison between the two groups.

Thereafter, propensity score matching analyses were performed to reduce confounding bias. Propensity score matching analysis is a popular approach that uses the propensity score calculated by a logistic regression model to

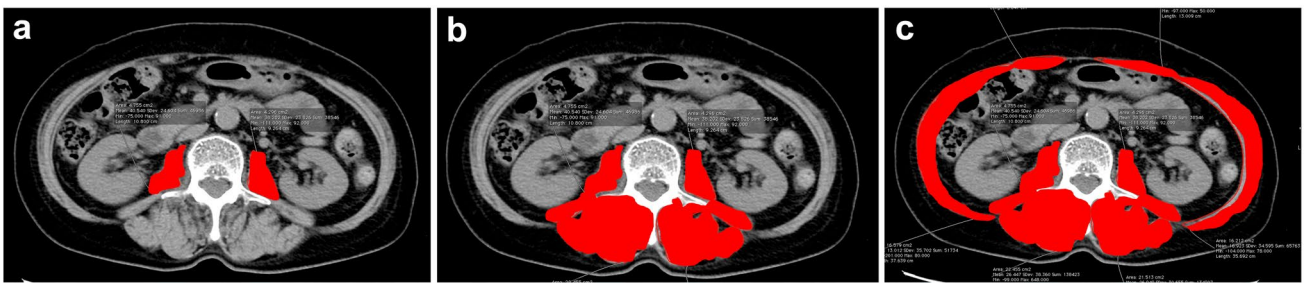

Fig. 1 Three muscle areas measured in the axial image of a computed tomography scan at L3 were normalized with square of the height and defined as **a** total psoas muscle index, **b** paraspinal muscle index, and **c** skeletal muscle index, respectively. **a** The cross-sectional area at L3 of the total psoas muscle (bilateral psoas muscle). **b** The cross-sectional area at L3 of the paraspinal muscle (including total psoas, quadratus lumborum, erector spinae, and multifidus muscle). **c** The cross-sectional area at L3 of the skeletal muscle (including paraspinal muscle, transversus abdominus, external and internal obliques, and rectus abdominus)

form matched sets with similar distributions [10]. The caliper width was set to the standard deviation of the propensity score, multiplied by 0.2. Age, sex, tumor location, T stage, N stage, M stage, surgery, and ECOG-PS were entered as covariates in the corresponding 1:1 propensity score matching model. For all tests, p values < 0.05, were considered statistically significant. Statistical analysis was conducted using SPSS Statistics software (version 24.0; SPSS Inc.).

Results

Patients

The patient characteristics before chemotherapy is shown in Table 1.

Of the 240 patients, 171 were men and 69 were women, with a mean age of 71 years (range: 43–88 years). Thirty-six patients were stage II for neoadjuvant chemotherapy, 56 were stage III for neoadjuvant or adjuvant chemotherapy, and 148 were stage IV. A total of 78 patients had tumors in the upper urinary tract, 139 in the lower urinary tract, and 22 in both. The median cutoffs of TPA were ≤ 4.35 and ≤ 2.7 cm^2/m^2, of PSMI were ≤ 20.9 and ≤ 16.8 cm^2/m^2, and of SMI were ≤ 39.3 and ≤ 30.8 cm^2/m^2 for men and women, respectively. Patients were also evaluated according to the international consensus reference values for men and women (men: SMI < 55 cm^2/m^2; women: SMI < 39 cm^2/m^2) [9].

Overall survival before propensity score matching

Figure 2 shows the Kaplan–Meier curve comparing the OS of the higher and lower groups of TPA, PSMI, and SMI. Setting the international standard of SMI as the cutoff, 14 patients were in the non-sarcopenia group and 226 patients were in the sarcopenia group, with no significant difference in OS (no figure, $p = 0.176$). Because the index mostly associated with OS was the PSMI, we adopted the median cutoffs of PSMI (men: PSMI ≤ 20.9 cm2/m2; women: PSMI ≤ 16.8 cm2/m2) as a criterion for sarcopenia. The total mean number of cycles of chemotherapy in patients with and without sarcopenia was, respectively, 4.16 and 3.63 ($p = 701$) for stage II, 4.00 and 3.65 ($p = 0.717$) for stage III, and 3.25 and 3.97 ($p = 0.138$) for stage IV. The log-rank test revealed that the OS of all patients in the non-sarcopenia group was significantly longer than that of those in the sarcopenia group ($p = 0.001$). Furthermore, the OS was not significantly different among stage II patients between the sarcopenia and non-sarcopenia groups ($p = 0.648$); however, stage III and IV patients in the non-sarcopenia group had significantly longer OS than those in the sarcopenia group (p = 0.048 and $p = 0.005$, respectively) (Fig. 2e–h).

Sarcopenia was significantly associated with lower OS in multivariate analysis using the Cox regression model [hazard ratio (HR) of death = 1.948, 95% confidence interval (CI): 1.193–3.179, $p = 0.008$]. M stage, CRP level, and albumin level at the time of chemotherapy induction were also independent prognostic factors (Table 2).

Propensity score adjustment for patient characteristics

To further examine the accuracy of the analysis results, propensity score matching was performed between the two groups, with the corresponding clinicopathological characteristics (age, sex, tumor site, T stage, N stage, M stage, surgery, and ECOG-PS) as covariates. The matching ratio was set at 1:1, and 194 patients (97 with sarcopenia and 97 without sarcopenia) were matched. The right side of Table 1 shows the clinicopathological characteristics of the two groups after propensity score adjustment, showing that there was no significant difference between the two groups for all confounding factors ($p > 0.05$).

Overall survival following propensity score matching

After propensity score matching, in all stages, the OS was significantly longer in the non-sarcopenia group ($p = 0.004$). By stage, there was no significant difference in stage II patients ($p = 0.684$); however, stage III and IV patients in the non-sarcopenia group had significantly longer OS ($p = 0.045$ and $p = 0.039$, respectively). The Kaplan–Meier curve after propensity score matching is shown in Fig. 3.

Furthermore, sarcopenia was significantly associated with OS in the multivariate Cox proportional hazards model after propensity score matching (HR of death = 1.728, 95% CI: 1.014–2.946, $p = 0.044$; Table 3). M stage, Hgb, and CRP levels at the time of chemotherapy induction were other independent predictors of OS.

Discussion

In 1989, Rosenberg et al. proposed the term "sarcopenia" (Greek: "sarx" or flesh + "penia" or loss) to describe the age-related decrease of muscle mass [6]. Sarcopenia is considered as important as frailty in the field of geriatrics because it directly affects the quality of life and prognosis of older adults [11]. According to the clinical definition by the European Working Group on Sarcopenia in Older People (EWGSOP): (1) loss of muscle strength indicates possible sarcopenia, (2) loss of both muscle strength and skeletal muscle mass indicates confirmed sarcopenia), and (3) sarcopenia accompanied by (1) and (2), and loss of physical

Table 1 The baseline characteristics before and after propensity score matching according to sarcopenia (sarcopenia criteria; men: PSMI ≤ 20.9 cm^2/m^2; women: PSMI ≤ 16.8 cm^2/m^2)

Characteristic	Original cohort			Propensity score matched cohort		
	Sarcopenia (–)	Sarcopenia (+)	*p* value	Sarcopenia (–)	Sarcopenia (+)	*p* value
Age (years, mean range)	70.02 (43–87)	71.32 (52–88)	0.26	71.49 (43–87)	70.11(52–88)	0.244
Age (≦75, > 75)			0.419			0.365
≦75	80	74		61	67	
> 75	40	46		36	30	
Gender			0.887			0.872
Male	85	86		71	70	
Female	35	34		26	27	
Location			0.612			0.714
Upper tract	43	36		54	57	
Bladder	67	72		33	28	
Both	10	12		10	12	
T stage			0.495			0.765
≦T2	38	43		34	36	
≧T3	82	77		63	61	
N stage			0.603			1
N0	65	69		56	56	
N1 + N2	55	51		41	41	
M stage			0.195			0.749
M0	91	82		26	28	
M1	29	38		71	69	
Diabetes			0.688			0.174
Yes	15	13		14	8	
No	105	107		83	89	
Smoking			0.053			0.062
Yes	68	53		56	43	
No	52	67		41	54	
BMI (kg/m2, mean range)	23.26 (17.76–30.88)	20.81 (13.32–27.70)	< 0.001	23.22 (18.08–30.88)	20.9 (15.56–27.70)	< 0.001
BSA (m^2, mean range)	1.699 (1.351–2.284)	1.614 (1.176–2.090)	< 0.001	1.697 (1.351–2.284)	1.642 (1.176–2.090)	0.005
Alb (g/dL, mean range)	3.836 (2.6–4.8)	3.616 (1.80–4.60)	0.001	3.817 (2.60–4.80)	3.644 (1.80–4.60)	0.023
eGFR (mL/min, mean range)	58.17 (6.52–121.45)	61.55 (3.59–132.49)	0.192	57.28 (6.52–121.45)	62.19 (3.59–132.49)	0.093
CRP (mg/dL, mean range)	1.053 (0.00–18.2)	1.59(0.00–17.02)	0.13	1.23(0.00–18.20)	1.433 (0.00–17.02)	0.608
Surgery			0.518			1
Yes	59	54		47	47	
No	61	66		50	50	
Type of platinum			0.502			0.55
Cisplatin	79	74		60	64	
Carboplatin	41	46		37	33	
ECOG-PS			0.156			1
0	99	90		80	80	
≧1	21	30		17	17	

activity is considered severe. In addition, sarcopenia caused by aging is defined as primary sarcopenia, while that caused by other factors is defined as secondary sarcopenia [12]. In patients with cancer, the inflammatory cytokines released by cancer cells result in a hyper inflammatory state, which can lead to consumptive sarcopenia. In addition, pain and fatigue caused by cancer can indirectly cause sarcopenia via decreased activity (disuse syndrome). In advanced cancers with cachexia, muscle mass also decreases due to decreased protein synthesis [9]. In this study, there was a tendency for muscle mass to decrease as the cancer stage increased; however, the difference was not significant (data not shown).

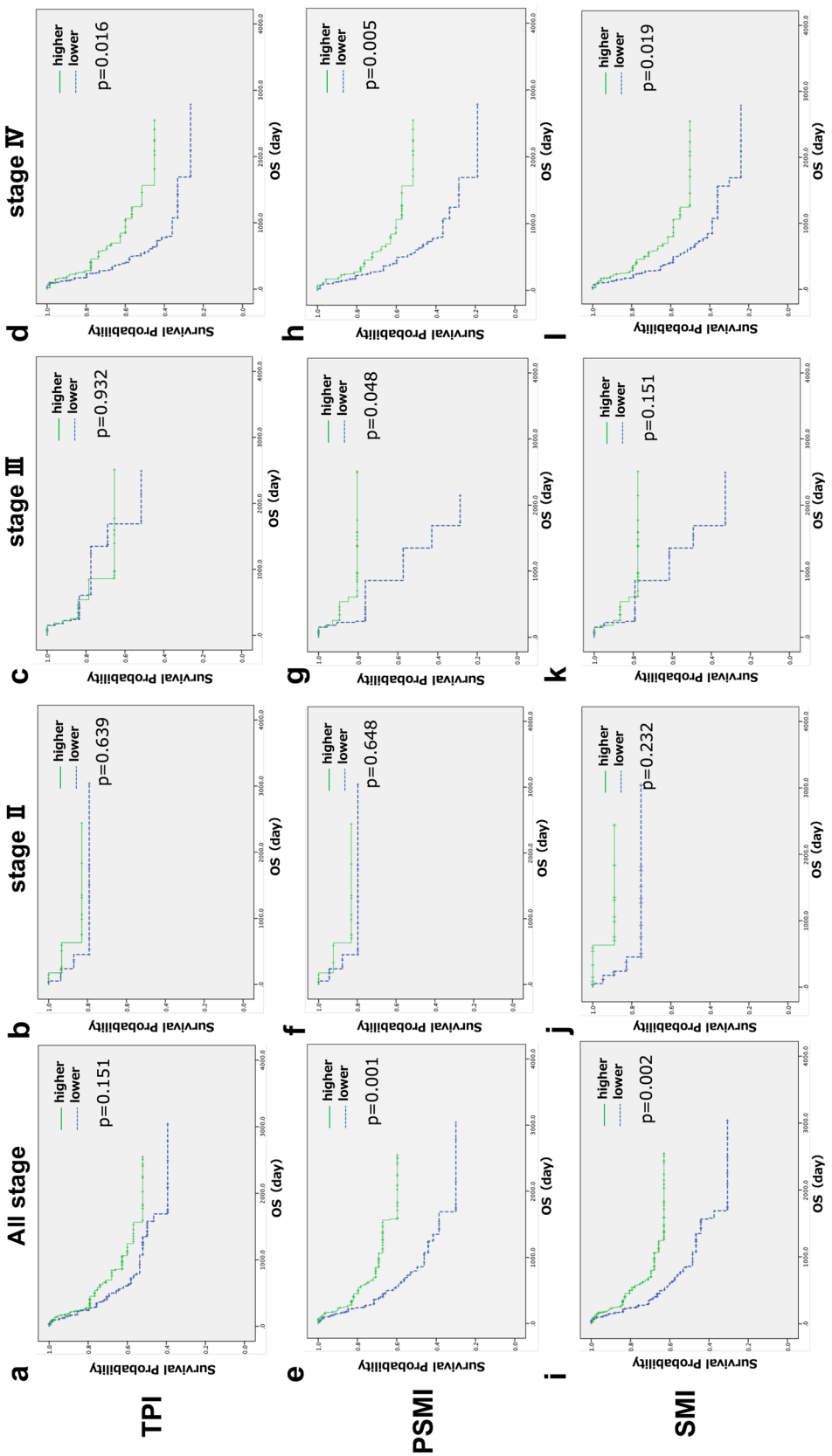

Fig. 2 Kaplan–Meier curves of overall survival divided into a lower group and a higher group as per the cutoff values for total psoas muscle area **a–d**, paraspinal muscle index **e–h** and skeletal muscle index **i–l**: **a**, **e**, **i** All stages, **b**, **f**, **j** stage II, **c**, **g**, **k** stage III, and **d**, **h**, **l** stage IV. All p values were extracted from log-rank tests

Table 2 Univariate and multivariate Cox regression models predicting overall survival

	Univariate	Multivariate		
	p value	*p* value	95% CI	Odds ratio
Age (years)	0.292			
Gender (female vs male)	0.516			
T stage (≦T2 vs ≧T3)	0.052			
N stage	0.1			
M stage	0.000	0.000	1.623–4.484	2.639
BMI (kg/m^2)	0.731			
BSA (m^2)	0.27			
Type of platinum (CDDP vs CBDCA)	0.256			
Diabetes	0.662			
PS	0.001	0.118		
Hgb (mg/dL)	0.000	0.14		
PLT (/μl)	0.856			
CRP (mg/dL)	0.000	0.000	1.598–4.571	2.703
Alb (g/dL)	0.000	0.018	1.112–3.113	1.866
eGFR	0.493			
Sarcopenia	0.001	0.008	1.193–3.179	1.948

Thus, patients with carcinoma can easily develop secondary sarcopenia as cancer progresses.

The parameters of sarcopenia are muscle mass and function. The measurable parameters are considered to be muscle mass, muscle strength, and physical ability, and it is important to repeat measurements from the same individual over the long term using the same measurement method to check for changes [13]. Although, muscle strength and physical ability are difficult to assess retrospectively, there are several ways to assess muscle mass. EWGSOP recommends CT, magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DXA), and bioelectrical impedance analysis (BIA). CT and MRI are used in general clinical practice and are considered the gold standard for measuring muscle mass in research, and many studies have measured the area of muscle mass at the level of L3. It is also easy to obtain in retrospective studies, as CT and MRI are performed for staging purposes in cancer cases [9]. Theoretically, the most reliable image-based evaluation method should be to perform CT/MRI of the whole body and measure all muscle mass, but this is not practical because of cost and radiation exposure [14].

In this study, we retrospectively analyzed the CT images obtained before the introduction of chemotherapy. Three parameters of skeletal muscle mass were calculated: TPI (cm^2/m^2), PSMI (cm^2/m^2), and SMI (cm^2/m^2), and the median of each was used as the cutoff. For SMI, patients were classified as sarcopenic according to sex-specific international consensus reference values [9]. Although, TPI is easily measured and several reports in the field of urology consider it a prognostic indicator, there is no international standard to define sarcopenia [9, 15]. Although there are few reports of PSMI use in oncology, it was reported to be associated with the risk of back pain in orthopedics and with survival after liver transplantation in gastrointestinal surgery [16–18]. SMI is currently the most widely used index of sarcopenia in oncology, with numerous reports and international standards for cutoff values [9, 12, 15]. However, in this study, 224 patients (93.3%) were defined as having sarcopenia based on international consensus reference values, which is a significant different from previous reports on the prevalence of sarcopenia. This may be due to the difference in body size between Asians and the cohort of 2115 cancer patients treated at a cancer treatment center serving northern Alberta, Canada, which is the source of the international consensus [19]. In our cohort, sarcopenia, evaluated using the median SMI and PMSI, was significantly associated with mortality. Since PMSI is simpler than SMI and is more associated with mortality, we adopted PSMI as a criterion for sarcopenia and conducted various studies.

The importance of sarcopenia in geriatrics has been recognized since early times, and it has recently been reported that sarcopenia is associated with poor prognosis and outcomes in various diseases [15]. The number of reported

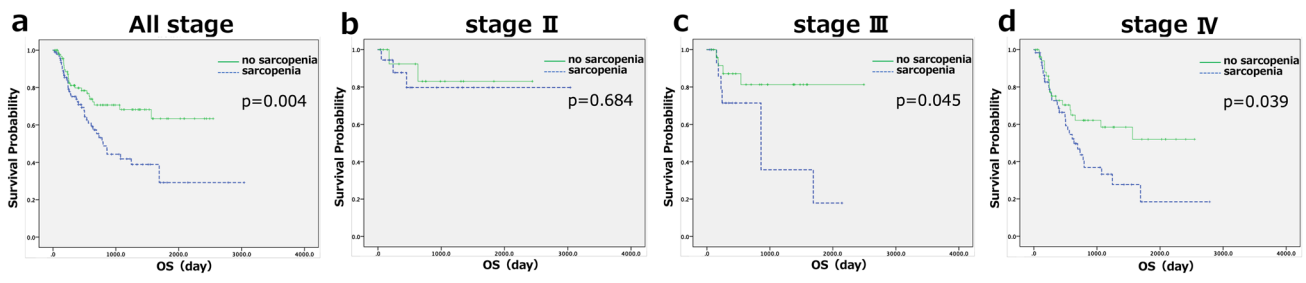

Fig. 3 Kaplan–Meier curves of overall survival divided into a lower group and a higher group as per the cutoff values of PSMI after propensity score matching. **a** All stage, **b** stage II, **c** stage III, and **d** stage IV. All *p* values were extracted from log-rank tests

Table 3 Univariate and multivariate Cox regression models predicting overall survival after propensity score matching

	Univariate	Multivariate		
	p value	*p* value	95% CI	Odds ratio
Age (years)	0.975			
Gender (female vs male)	0.673			
T stage (≦T2 vs ≧T3)	0.021	0.222		
N stage	0.181			
M stage	0.000	0.000	1.580–4.842	2.766
BMI (kg/m^2)	0.287			
BSA (m^2)	0.090			
Type of platinum (CDDP vs CBDCA)	0.092			
Diabetes	0.720			
PS	0.006	0.194		
Hgb (mg/dL)	0.001	0.247		
PLT (/μl)	0.37			
CRP (mg/dL)	0.000	0.007	1.244–4.049	2.244
Alb (g/dL)	0.000	0.104		
eGFR	0.173			
Sarcopenia	0.006	0.024	1.092–3.472	1.949

sarcopenia studies in oncology has increased remarkably since the beginning of the 2010s. Sarcopenia studies in oncology can be categorized into several types. The first is a study to investigate the impact of primary sarcopenia on cancer prognosis and treatment efficacy, especially in cases of early stage cancer. The second is a study to evaluate the impact of secondary sarcopenia caused by therapeutic interventions for cancer (surgery, chemotherapy, etc.) on treatment outcomes and prognosis. The third study evaluated the impact of sarcopenia on the prognosis of patients with advanced cancer.

In the field of urology, studies on the relationship between sarcopenia and prognosis before total cystectomy or total nephroureterectomy are the most common, corresponding to the first above [20–36]. Several studies have evaluated changes in muscle mass before and after total cystectomy and NAC, which corresponds to the second point above [37–40]. Several studies have evaluated the impact of sarcopenia in advanced or metastatic urothelial carcinoma, which falls within the scope of the third category of studies mentioned above [14, 16, 41–43].

In this report, we examined the prognostic impact of sarcopenia on 92 patients who received perioperative chemotherapy at stage III or lower and 148 patients who received induction chemotherapy at stage IV, as assessed by PSMI values, and it was a study that corresponds to the first and third categories of studies stated above. It is the largest reported stage IV case to date, and there are few reports that use PSMI to assess sarcopenia in urological oncology. In our study, the presence of sarcopenia at the time of chemotherapy induction was associated with a poor prognosis overall (all stages). When evaluated by stage, sarcopenia was associated with poor prognosis in stages III and IV but the association was not significant in stage II. Sarcopenia remained an independent prognostic factor after propensity score matching to remove confounders. One of the reported reasons for this finding is that sarcopenia is associated with chemotherapy toxicity, leading to dose reductions, dose delays, or even chemotherapy discontinuation [44, 45]. Therefore, patients with sarcopenia may not fully benefit from chemotherapy. In addition, patients with sarcopenia are susceptible to infections [46]. Sarcopenia itself may be a factor in the poor prognosis of cancer patients through these mechanisms.

As mentioned above, evidence of sarcopenia as a prognostic factor in bladder cancer has been accumulating. Since PSMI is relatively easy to measure, sarcopenia screening can be performed routinely in clinical practice.

Our study has some limitations. First, this was a retrospective study. Second, we used PSMI determined using pre therapy CT to define sarcopenia. Currently, there is no optimal evaluation method for sarcopenia, and a clear definition of sarcopenia has not been established. Therefore, future studies may be needed to accurately define sarcopenia. Despite these limitations, we were able to draw some useful conclusions from our data.

In conclusion, there have been few reports in the field of oncology that have evaluated the prognosis of patients with sarcopenia using PSMI as an index, but this study showed that PSMI is useful as a marker for predicting the prognosis of patients with UC treated with chemotherapy. Despite this study's retrospective design and the need for further validation of its findings in a larger prospective cohort, our findings are evidence that the absence of sarcopenia increases the possibility of long-term survival in patients who are administered chemotherapy for UC.

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Declarations

Conflict of interest The authors have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The need for informed consent was waived because of the retrospective nature of the study.

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