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Prognostic Impact of Skeletal Muscle Radiodensity in Advanced Urothelial Carcinoma Undergoing Avelumab Maintenance Therapy

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Abstract

Background/Aim: A significant survival benefit was found for avelumab maintenance therapy *versus* best supportive care in patients with advanced urothelial carcinoma who attained disease control after platinum-based chemotherapy in the JAVELIN Bladder 100 trial. Although patients generally tolerate avelumab maintenance therapy, some patients experience rapid progression and prognostic factors are not well established.

Patients and Methods: In this retrospective study, we investigated the prognostic significance of computed tomography–derived body composition indicators in 57 patients with advanced urothelial carcinoma who received avelumab maintenance therapy after first-line platinum-based chemotherapy. These patients were from within a cohort of 85 patients who underwent first-line platinum-based chemotherapy. Patients were divided into two groups based on a low or high skeletal muscle radiodensity (SMD). Prognostic factors were determined using univariate and multivariate analyses.

Results: Among patients treated with avelumab, median progression-free survival (PFS) was 6.4 months in the high SMD group *versus* 4.8 months in the low skeletal muscle radiodensity group, while median overall survival (OS) was not reached *versus* 16.7 months, respectively. In a Cox proportional hazards model, only low SMD indicated a worse prognosis for PFS [hazard ratio (HR)=2.07, 95% confidence interval (CI)=1.06-4.04], while low SMD plus a high

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neutrophil–lymphocyte ratio were independent predictors for worse OS (HR=2.29, 95%CI=1.04-5.05 and HR=2.44, 95%CI=1.11-5.37, respectively).

Conclusion: SMD is a potential prognostic factor for advanced urothelial carcinoma cases undergoing avelumab maintenance therapy.

Keywords: Avelumab, carcinoma, computed tomography, skeletal muscle, urinary bladder.

Introduction

Bladder cancer ranks as the ninth most commonly diagnosed malignancy worldwide. It represents ≈3% of all tumors and, globally, is thirteenth as a cause of death due to cancer (1). Over the past decade, immune checkpoint inhibitors (ICIs) have transformed the therapeutic landscape of advanced urothelial carcinoma (UC), beginning with the introduction of pembrolizumab in a post-platinum setting (2). As an antibody to programmed death-ligand 1 (PD-L1), avelumab was endorsed in 2020 by the United States Food and Drug Administration for use as first-line maintenance therapy in those who showed controlled disease after platinum-based chemotherapy, based on the results of the JAVELIN Bladder 100 trial (3). In Japan, avelumab was approved in February 2021 and is recommended in the Japanese Urological Association treatment guidelines (4). Although avelumab maintenance therapy significantly improves survival, a substantial proportion of patients still experience early disease progression. Accordingly, reliable prognostic indicators are needed to determine those patients who will likely derive durable benefit from avelumab.

Growing evidence indicates that various body composition indicators can influence cancer prognosis and antitumor immune responses. Sarcopenia, characterized by a depletion of skeletal muscle mass, strength and function (5), is prevalent across cancer populations and is associated with inferior outcomes, including reduced survival and poorer response to ICIs in many malignancies (6-11). Myosteatosis, defined as increased intramuscular fat infiltration and impaired muscle quality, is also a negative prognostic factor in multiple malignancies, including those treated with ICIs (12-17). Cross-sectional computed tomography (CT) at the third lumbar vertebrae (L3) level allows the objective quantification of skeletal muscle mass, expressed as the skeletal muscle index (SMI) (18, 19), as well as the assessment of muscle quality using skeletal muscle radiodensity (SMD) (20, 21). A low SMI reflects sarcopenia whereas low a SMD corresponds to myosteatosis. However, evidence regarding the use of body composition in the prognosis of advanced UC cases undergoing avelumab maintenance therapy remains scarce. Therefore, this investigation sought to assess the prognostic significance of sarcopenia and myosteatosis in patients with advanced UC treated with avelumab.

Patients and Methods

Patient enrolment. Patients with advanced UC affecting the upper urinary tract or urinary bladder who received first-line platinum-based chemotherapy at Nagoya City University Hospital or two related institutions between January 2019 and November 2023 were retrospectively identified. Among them, patients who subsequently received avelumab maintenance therapy after its approval in Japan were included in the survival and safety analyses. Specimens were assessed using histological staining and diagnoses made. Case selection criteria were as follows: i) a diagnosis of advanced UC and one cycle of first-line chemotherapy; ii) unenhanced CT that was performed at the end of first-line chemotherapy; and iii) biopsied primary lesions or those that were surgically removed. We collected data and assessed it retrospectively. This

retrospective investigation was approved by the ethics committee of Nagoya City University Hospital (Approval No. 60-18-0060). Patients were able to discontinue this study at any time. This study was undertaken in accordance with the Declaration of Helsinki (2013 Fortaleza revision).

Therapy. Gemcitabine and cisplatin (GC) was used as first-line therapy. The treatment of patients with a GC regimen was based on the following criteria: no significant hearing loss, <2 grade neuropathy, creatinine clearance ≥ 60 ml/min, and no symptoms of heart failure in accordance with New York Heart Association class III or greater. Treatment with gemcitabine and carboplatin was used if any criteria were not met. The size of tumors was based on CT imaging. Patients underwent a physical examination. The Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. were used to assess patient responses to treatments. Patients who achieved no disease progression (complete response, partial response, or stable disease) after first-line treatment received avelumab switch maintenance therapy (10 mg/kg by intravenous infusion every two weeks) if hematologic, hepatic, and renal functions were satisfactory. Disease progression as per RECIST criteria or adverse events (AEs) that were not well tolerated meant that treatment was stopped. Progression-free survival (PFS) referred to the interval from the start of avelumab maintenance treatment to progression. Overall survival (OS) was defined as the interval from the initiation of avelumab maintenance treatment to death from any cause or the date of last follow-up. Reports of AEs was based on National Cancer Institute Common Terminology Criteria for AEs, version 4.0. Patient data, retrieved from medical records of the abovementioned organizations, included: sex, age, height and weight, tumor location (upper urinary tract or urinary bladder), radical surgery of primary site, visceral and lymph node metastasis, Eastern Cooperative Oncology Group performance status (ECOG–PS), and serum blood variables at the end of first-line treatment.

Image protocols. Unenhanced CT images at the conclusion of first-line chemotherapy of study participants were obtained. Parameters for CT images included: 5-mm slices, 120 kVp. For each patient, an axial image of L3 with both transverse processes observed was obtained. The area of skeletal muscle (including paraspinal, psoas, rectus abdominis, transversus abdominis, and internal and external oblique muscles) was based on Hounsfield unit (HU) thresholds of –29 and +150. After normalization by height squared, this was reported as the SMI (cm^2/m^2). For each whole cross-sectional muscle area, mean skeletal muscle radiation attenuation was reported as the SMD (HU). All image analyses were performed using Image J 1.54 (National Institute of Health, Bethesda, MD, USA

Statistical analysis. The basis of cutoff values for the SMI defining sarcopenia was an Asian-based definition (<36.2 cm^2/m^2 used for males; <29.6 cm^2/m^2 used for females) (22). As there is no clear standard cutoff for the SMD validated in patients with cancer, patients were placed into two groups based on the sex-specific median of the SMD, which corresponds to 28.5 HU for males and 24.8 HU for females. A Fisher's exact test or a Mann–Whitney *U*-test was used to determine differences based on categorical parameters. To determine cumulative rates of PFS and OS, Kaplan–Meier curves were used. To calculate significant differences log-rank test was used. Univariate and multivariate analyses based on Cox proportional hazard regression analyses were used. Cut-off values used for each prognostic factor were derived from other investigations: age (≥65 *vs.* <65 years), serum C-reactive protein (CRP) levels (≥0.3 *vs.* <0.3 mg/dl), and a neutrophil–lymphocyte ratio (NLR) (≥3 *vs.* <3). Statistical significance was set at $p<0.05$ and all tests were two-tailed. The data collected was evaluated using a EZR statistical program (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (23).

Results

Patient characteristics and oncological outcomes. We enrolled a total of 85 patients with advanced UC on first-line

Table I. *Characteristics of patients segregated by low and high skeletal muscle radiodensity (SMD) status.*

Characteristics	Low SMD group (n=42)	High SMD group (n=43)	*p*-Value
Median age, years (IQR)	75.5 (71-80)	75 (71-78)	0.65
Sex, n (%)			
Male	31 (73.8)	32 (74.4)	1.00
Female	11 (26.2)	11 (25.6)	
Median BMI, kg/m^2 (IQR)	22.6 (20.2-25.9)	21.6 (19.9-25.1)	0.39
Regimen of first-line chemotherapy, n (%)			
GC	24 (57.1)	25 (58.1)	1.00
GCarb	18 (42.9)	18 (41.9)	
Median number of cycles in first-line chemotherapy, n (IQR)	4 (4-5)	4 (4-6)	0.63
ECOG–PS, n (%)			
0	27 (64.3)	33 (76.7)	0.21
1	11 (26.2)	10 (23.3)	
2	3 (7.1)	0 (0)	
3	1 (2.4)	0 (0)	
Primary site, n (%)			
Upper tract	16 (38.1)	18 (41.9)	0.93
Bladder	24 (57.1)	23 (53.5)	
Both	2 (4.8)	2 (4.6)	
Lymph node metastasis, n (%)	29 (69.0)	32 (74.4)	0.64
Existence of visceral metastasis, n (%)			
Lung	7 (16.7)	13 (30.2)	0.20
Bone	13 (31.0)	16 (37.2)	0.65
Liver	4 (9.5)	3 (7.0)	0.71
Resection of primary site, n (%)	18 (42.9)	18 (41.9)	1.00
Response to first-line chemotherapy			
CR	1 (2.4)	4 (9.3)	0.20
PR	13 (31.0)	7 (16.3)	
SD	14 (33.3)	20 (46.5)	
PD	14 (33.3)	12 (27.9)	
Median laboratory parameters (IQR)			
Leukocyte counts, cells/μl	6,300 (4,700-8,600)	5,200 (4,300-6,500)	0.16
Neutrophil counts, cells/μl	4,000 (2,800-6,100)	3,000 (2,400-4,200)	0.097
Lymphocyte counts, cells/μl	1,020 (760-1450)	1,300 (880-1,600)	0.49
NLR	3.4 (2.6-6.1)	2.4 (1.6-4.7)	**0.021**
Albumin, g/dl	3.6 (3.3-3.9)	3.7 (3.5-4.1)	0.093
LDH, IU/l	217 (204-254)	205 (172-245)	0.076
CRP, mg/dl	0.43 (0.17-3.30)	0.38 (0.16-1.04)	0.43

BMI: Body mass index; CR: complete response; CRP: C-reactive protein; ECOG–PS: Eastern Cooperative Oncology Group performance status; GC: gemcitabine and cisplatin; GCarb: gemcitabine and carboplatin; IQR: interquartile range; LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio; PD: progressive disease; PR: partial response; SD: stable disease; SMD: skeletal muscle radiodensity. Statistically significant values are shown in bold.

therapy. Of these, 57 patients underwent avelumab treatment. Based on the cut-off value, the total cohort was divided into low (n=42) and high (n=43) SMD groups. Table I outlines the characteristics of all patients. Most patient characteristics did not differ significantly between groups after first-line treatment. However, when compared to the low SMD group, the high SMD group showed a significantly lower NLR among laboratory parameters. In the cohort of patients treated with avelumab, a significant difference was not found in PFS from the start of avelumab maintenance treatment between low and high SMI groups (Figure 1A). However, the median PFS was significantly superior for the high SMD group [median 6.4 months, 95% confidence interval (CI)=4.70-not reached (NR)] in comparison to the low SMD group (median 4.8 months, 95%CI=2.30-6.21; Figure 1B). Similarly, no significant difference in OS was

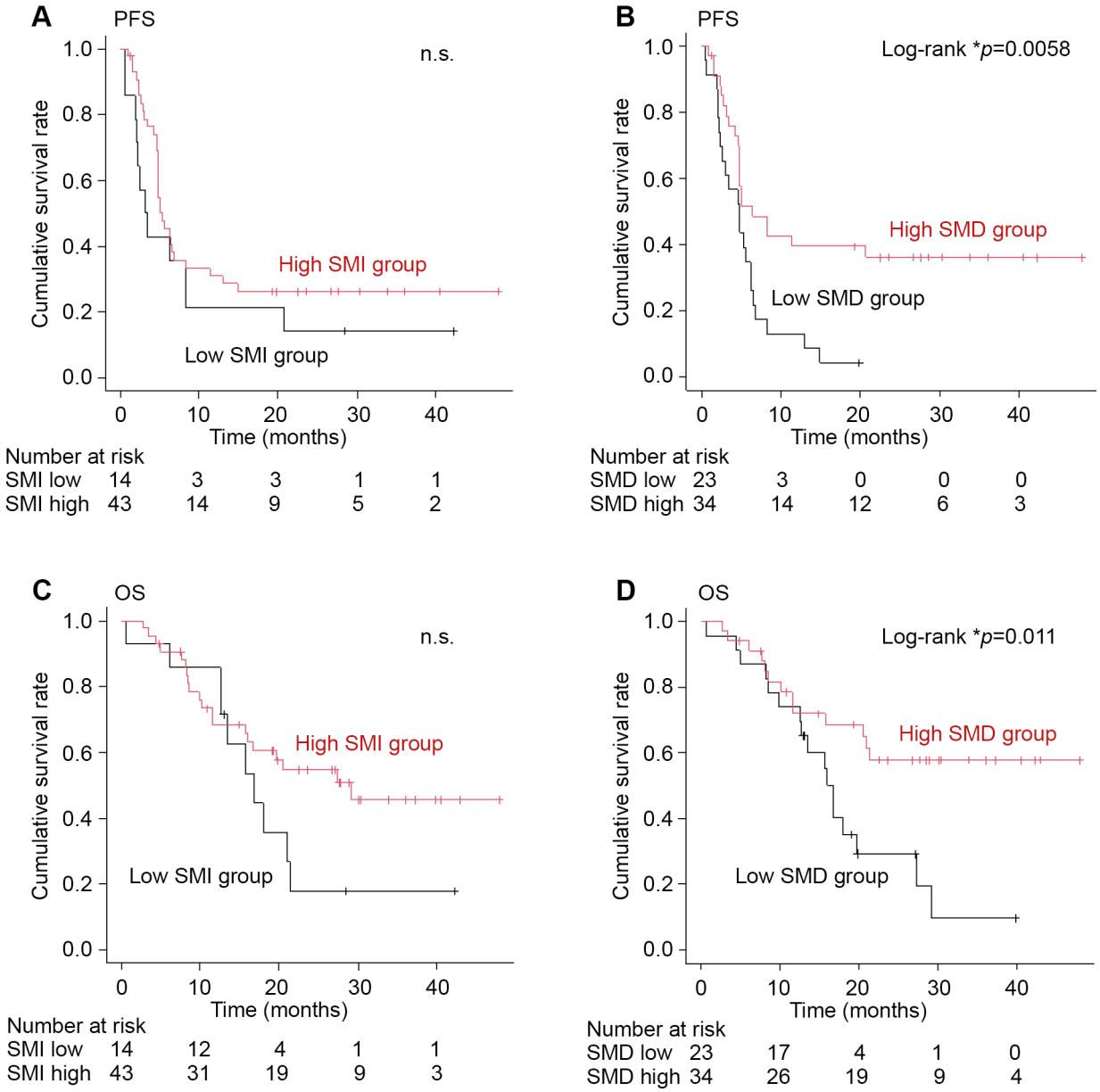

Figure 1. *Survival according to skeletal muscle index (SMI) and skeletal muscle radiodensity (SMD) during avelumab maintenance. Kaplan–Meier survival-probability curves for progression-free survival (PFS) by SMI (A) and SMD (B), and overall survival (OS) by SMI (C) and SMD (D); lines indicate estimates and ticks indicate censoring. n.s.: Not significant.*

noted between low and high SMI groups (Figure 1C). However, the median OS for the high SMD group from the initiation of avelumab maintenance treatment was significantly superior (median NR, 95%CI=15.8-NR) compared to the low SMD group (median 16.7 months, 95%CI=12.6-19.7; Figure 1D) group. Univariate and multivariate analyses showed how low SMD was the sole independent prognostic factor for worse PFS [hazard ratio (HR)=2.07, 95%CI=1.06-4.04; Table II). In addition, low SMD and high NLR were independent prognostic factors for

Table II. *Baseline parameters and progression-free survival analyzed using univariate and multivariate analyses in 57 patients treated with avelumab.*

Parameters	Univariate			Multivariate		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age, ≥65 *vs.* <65 years	1.42	0.51-3.97	0.51	1.06	0.36-3.08	0.91
Sex, Male *vs.* female	1.08	0.55-2.14	0.83	1.15	0.57-2.32	0.70
BMI, <18.5 *vs.* ≥18.5	1.06	0.42-2.69	0.90	-	-	-
Primary site, Bladder *vs.* others	1.07	0.59-1.93	0.83	-	-	-
Resection of primary site, yes *vs.* no	0.87	0.48-1.58	0.65	-	-	-
Existence of liver metastasis, yes *vs.* no	0.66	0.09-4.79	0.68	-	-	-
NLR, ≥3.0 *vs.* <3.0	1.82	1.00-3.30	0.049	1.41	0.72-2.75	0.31
Serum CRP levels, ≥0.3 *vs.* <0.3	0.95	0.52-1.73	0.86	-	-	-
SMI, <36.2 *vs.* ≥36.2 (29.6 for females)	1.49	0.77-2.91	0.24	-	-	-
SMD <28.5 *vs.* ≥28.5 (24.8 for females)	2.31	1.25-4.28	0.0075	2.07	1.06-4.04	**0.034**

BMI: Body mass index; CI: confidence interval; CRP: C-reactive protein; HR: hazard ratio; NLR: neutrophil–lymphocyte ratio; SMD: skeletal muscle radiodensity; SMI: skeletal muscle index. Statistically significant values are shown in bold.

Table III. *Baseline parameters and overall survival analyzed using univariate and multivariate analyses in 57 patients treated with avelumab.*

Parameters	Univariate			Multivariate		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age, ≥65 *vs.* <65 years	1.06	0.32-3.51	0.92	0.58	0.16-2.08	0.40
Sex, Male *vs.* female	1.67	0.68-4.09	0.26	2.03	0.81-5.07	0.13
BMI, <18.5 *vs.* ≥18.5	0.78	0.24-2.59	0.69	-	-	-
Primary site, Bladder *vs.* others	1.14	0.56-2.32	0.71	-	-	-
Resection of primary site, yes *vs.* no	0.96	0.47-1.94	0.90	-	-	-
Existence of liver metastasis, yes *vs.* no	1.03	0.14-7.60	0.98	-	-	-
NLR, ≥3.0 *vs.* <3.0	2.53	1.24-5.17	0.011*	2.44	1.11-5.37	**0.026**
Serum CRP levels, ≥0.3 *vs.* <0.3	1.12	0.55-2.28	0.75	-	-	-
SMI, <36.2 *vs.* ≥36.2 (29.6 for females)	1.73	0.80-3.72	0.16	-	-	-
SMD <28.5 *vs.* ≥28.5 (24.8 for females)	2.53	1.21-5.29	0.014*	2.29	1.04-5.05	**0.040**

BMI: Body mass index; CI: confidence interval; CRP: C-reactive protein; HR: hazard ratio; NLR: neutrophil-lymphocyte ratio; SMD: skeletal muscle radiodensity; SMI: skeletal muscle index. Statistically significant values are shown in bold.

worse OS (HR=2.29, 95%CI=1.04-5.05 and HR=2.44, 95%CI=1.11-5.37, respectively; Table III).

Adverse events. Adverse events associated with avelumab switch maintenance treatment were analysed (Table IV). Among grade ≥3 AEs, rash (4.3%) and diarrhoea (4.3%) in the low SMD group, and pancreatitis (2.9%) and encephalitis (2.9%) in the high SMD group were recognized. Of these AEs, only encephalitis was uncontrollable and led to death. Since the total incidences of AEs were fundamentally low, AEs were not significantly different between the two groups.

Discussion

Since the approval of avelumab maintenance therapy based on the JAVELIN Bladder 100 (JB100) phase 3 trial, several large real-world studies from various countries, including Japan, have described its efficacy and safety (24-27). Previous studies have identified potential prognostic factors for PFS and OS following avelumab initiation, such as ECOG-PS, CRP, metastatic sites, and inflammatory markers, including interleukin-8, NLR, and the systemic immune-inflammation index (28, 29). However, body composition parameters reflecting sarcopenia and

Table IV. *Comparison of adverse events between low and high skeletal muscle radiodensity (SMD) groups.*

Adverse events	Low SMD group (n=23)		High SMD group (n=34)		*p*-Values for total incidences	*p*-Values for incidences of grade 3-4 AEs
	No. of Pts, n (%)	No. of grade 3-4 Pts, n (%)	No. of Pts, n (%)	No. of grade 3-4 Pts, n (%)		
Infusion reaction	6 (26.1)	0 (0)	6 (17.6)	0 (0)	0.52	NA
Rash	3 (13.0)	1 (4.3)	1 (2.9)	0 (0)	0.29	0.40
Diarrhea	1 (4.3)	1 (4.3)	1 (2.9)	0 (0)	1.00	0.40
Hyperthyroidism	0 (0)	0 (0)	1 (2.9)	0 (0)	1.00	NA
Hypothyroidism	1 (4.3)	0 (0)	6 (17.6)	0 (0)	0.22	NA
Hypopituitarism	0 (0)	0 (0)	1 (2.9)	0 (0)	1.00	NA
Fatigue	2 (8.7)	0 (0)	0 (0)	0 (0)	0.16	NA
Interstitial pneumoniae	0 (0)	0 (0)	1 (2.9)	0 (0)	1.00	NA
Arthritis	0 (0)	0 (0)	2 (5.9)	0 (0)	0.51	NA
Pancreatitis	0 (0)	0 (0)	1 (2.9)	1 (2.9)	1.00	1.00
Encephalitis	0 (0)	0 (0)	1 (2.9)	1 (2.9)	1.00	1.00
Others	2 (8.7)	0 (0)	1 (2.9)	0 (0)	0.56	NA

AE: Adverse events; NA: not applicable; Pts: patients.

myosteatosis, such as skeletal muscle mass and radiodensity, have not been evaluated in this setting. In this retrospective study, we demonstrated that low SMD at the initiation of avelumab maintenance therapy was significantly associated with worse PFS and OS.

Several studies across various cancer types, including UC, have reported that a low SMD is associated with poor outcomes in patients treated with immune checkpoint inhibitors (13-15). Skeletal muscle has an important role in modulating the tumor microenvironment. This is because it secretes various myokines, including irisin and interleukin-15, which influence the immune response (30-32). Reduced muscle quality may result in decreased secretion of these myokines to promote tumor growth and suppress anti-tumor immunity to affect patient survival. In the present study, the SMI, a representative CT-derived marker of sarcopenia, was not significantly associated with prognosis. To date, two studies from Japan have evaluated the prognostic effect of the SMI in patients with advanced UC, each adopting either the international or Prado definition for sarcopenia (33, 34). A recent large-scale cohort investigation by Taguchi *et al.* (35) suggested that ethnic-specific cutoffs for low muscle mass were appropriate, leading to increased accuracy in the classification of patients and in predicting a prognosis; therefore, we applied cutoff values for an Asian-based definition by Fujiwara *et al.* in the current analysis. Survival and SMI in our cohort were not significantly associated. This may partly be explained by patient selection bias since individuals who were eligible for avelumab maintenance therapy generally had favorable disease control and relatively preserved muscle mass. In addition, recent studies have demonstrated that SMD and SMI are not always correlated, and that low SMD is more closely associated with frailty and impaired muscle strength even when muscle mass is preserved (36-38). SMD may better capture the functional and immunologic decline that influences patient outcomes.

Regarding clinicopathologic parameters besides sarcopenia, NLR ≥3 was revealed to be an independent prognostic factor for worse OS as also shown by previous studies (28). The NLR is a biomarker of systemic inflammation caused by cancer progression (39). Whereas NLR represents a tumor-related factor, the SMD reflects a host-related factor; therefore, evaluating patients from both perspectives may lead to a more comprehensive assessment of prognosis.

After the findings of the EV-302 phase 3 trial (40), enfortumab vedotin and pembrolizumab (EV + PEM) is used as first-line therapy in the United States and is the

preferred choice in updated treatment guidelines, including those in Japan. The toxicity profile of EV + PEM includes peripheral neuropathy, hyperglycemia, and serious skin reactions; a considerable proportion of patients have difficulty continuing EV + PEM due to these toxicities. Furthermore, the optimal subsequent therapy after EV + PEM remains unclear. Even in this new therapeutic era, maintenance therapy with relatively favorable efficacy and safety profiles continues to offer meaningful benefits. As real-world sequential treatment data continue to accumulate, the optimal therapeutic sequence is expected to be better defined in the future.

Nevertheless, for patients who receive platinum-based induction chemotherapy and achieve disease control, avelumab maintenance remains an important therapeutic option. Recent Japanese real-world studies have reported favorable effectiveness and manageable safety of avelumab maintenance and have evaluated clinically relevant patient and disease features, including age, performance status, timing of treatment initiation, and organ-specific responses (41-43). In addition, real-world studies addressing first-line platinum-based chemotherapy have highlighted the clinical relevance of the number of induction cycles and of subsequent treatment opportunities in patients who remain progression-free after initial therapy (44, 45). These observations support the need for practical prognostic indicators at the transition to maintenance therapy; in this context, SMD may provide additional information reflecting host condition.

Study limitations. First, it is retrospective in nature and uses a relatively small sample size limiting the generalizability of our results. Second, the cutoff value for SMD was determined using the median of our cohort, which might be specific to this study population. Further studies with larger cohorts are needed to establish an appropriate universal cutoff value.

Conclusion

Our findings indicate that SMD, a convenient and reproducible CT-derived marker, may provide valuable prognostic information in patients with advanced UC treated with avelumab maintenance therapy.

Conflicts of Interest

The Authors have no relevant financial or non-financial interests to disclose. The authors have full control of all primary data and agree to allow the journal to review the data if requested.

Authors' Contributions

Conceptualization, Shimizu N, Naiki T; Methodology, Naiki T; Validation, Naiki-Ito A; Formal Analysis, Sugiyama Y.; Data Curation, Nagai T, Etani T, Suzuki H, Tsubouchi Y, Morikawa T, Gonda M, Aoki M, Ishikawa D; Writing – Original Draft Preparation, Shimizu N; Writing – Review & Editing, Naiki T; Supervision, Ando R, Yasui T. All Authors read and approved the final manuscript.

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No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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