

Association Between Body Mass Index and Outcomes in Patients With Urothelial Carcinoma Treated With Pembrolizumab

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Abstract. *Background/Aim:* We aimed to clarify the association between body mass index (BMI) and clinical outcomes of pembrolizumab treatment for advanced urothelial cancer (UC). *Patients and Methods:* We retrospectively reviewed the records of patients with advanced UC who received pembrolizumab after chemotherapy between March 2018 and December 2021. Patients were divided according to BMI into the non-overweight group (BMI <25 kg/m²) and the overweight group (BMI ≥25 kg/m²). We compared the two groups' tumour response, survival rates, and incidence of immune-related adverse events (irAEs) and investigated the factors predicting survival. *Results:* Of 84 eligible patients, 63 (75%) and 21 (25%) were in the non-overweight and overweight groups, respectively. Although the objective response rate was higher in the overweight group (55%) than that in the non-overweight group (29%), the difference was not significant. Progression-free survival (PFS) was significantly longer in the overweight group (median 15.2 months) than that in the non-overweight group (median 4.8 months; $p=0.01$). Overall survival was also longer in the overweight group (median 36.1 months) compared to that in the non-overweight group (13.4 months), but the difference was not significant

($p=0.11$). Multivariable analysis showed that overweight was significantly associated with favourable PFS. Any and severe (grade 3) irAEs were observed in 15 (24%) and 5 (7.9%) patients in the non-overweight group, respectively, and in 8 (38%) and 2 (9.5%) patients in the overweight group, respectively, but the differences were not significant. *Conclusion:* BMI was associated with oncological outcomes in patients with advanced UC who received pembrolizumab but not with the development of irAEs.

Immune checkpoint inhibitor (ICI) plays an important role in the management of several malignancies. In one study, pembrolizumab, an ICI that targets programmed cell death protein 1 (PD-1), provided a survival benefit in patients with advanced urothelial cancer (UC) that had recurred or progressed after platinum-based chemotherapy (1). Pembrolizumab is thus recommended as second-line therapy for patients with advanced UC and has been widely used. However, the number of patients with advanced UC who benefit from pembrolizumab has been limited; an objective response rate of only 21.1% has been reported (2). In addition, a substantial number of patients experience immune-related adverse events (irAEs). Therefore, the biomarkers that predict tumour response or survival in patients who receive pembrolizumab must be identified. Several predictive biomarkers, including blood cell count markers, such as neutrophil/lymphocyte ratio (3, 4), C-reactive protein level (5, 6) or its kinetics (7), and nutritional status-based markers (8, 9) have been identified in patients with advanced UC treated with pembrolizumab.

Body mass index (BMI) may be associated with the clinical outcomes of ICI treatment for several malignancies

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Table I. Patient characteristics according to body mass index.

Characteristics	Total cohort	Non-overweight	Overweight
n	84	63	21
Median age, years (IQR)	74 (68-80)	74 (68-78)	79 (70-81)
Sex, n			
Male	62 (74%)	46 (73%)	16 (76.2%)
Female	22 (26%)	17 (27%)	5 (23.8%)
Median BMI (IQR)	22.4 (20.0-24.8)	20.7 (19.5-23.0)	26.3 (25.6-27.4)
ECOG-PS, n			
0	53 (63%)	40 (63%)	13 (62%)
≥1	31 (37%)	23 (37%)	8 (38%)
Haemoglobin, n			
≥10 g/dl	49 (58%)	34 (54%)	15 (71%)
<10 g/dl	35 (42%)	29 (46%)	6 (29%)
Primary site, n			
UUT	42 (50%)	32 (51%)	10 (48%)
Bladder	38 (45%)	28 (44%)	10 (48%)
Both	4 (4.8%)	3 (4.8%)	1 (4.8%)
Number of metastases, n			
≤1	38 (45%)	28 (44%)	10 (48%)
≥2	46 (55%)	35 (56%)	11 (52%)
Liver metastasis, n			
Absence	67 (80%)	51 (81%)	16 (76%)
Presence	17 (20%)	12 (19%)	5 (24%)
Radical surgery, n			
None	36 (43%)	29 (46%)	7 (33%)
Performed	48 (57%)	34 (54%)	14 (67%)
Number of prior treatments, n			
1	75 (89%)	56 (89%)	19 (90%)
2	9 (11%)	7 (11%)	2 (10%)
Type of prior chemotherapy, n			
Perioperative	20 (24%)	14 (22%)	6 (29%)
Others	64 (76%)	49 (78%)	15 (71%)
Time since prior chemotherapy, n			
≥3 months	37 (44%)	27 (43%)	10 (48%)
<3 months	47 (56%)	36 (57%)	11 (52%)

BMI: Body mass index; ECOG-PS: Eastern Cooperative Oncology Group performance status; IQR: interquartile range; UUT: upper urinary tract.

(10-12). In patients with UC treated with ICI, however, few studies have focused on BMI (13); therefore, the effect of BMI on clinical outcomes remains unclear.

Our aim was to clarify the association between BMI and clinical outcomes in patients who received pembrolizumab for advanced UC.

Patients and Methods

Study design and ethics statement. This retrospective, multicenter study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the University of Occupational and Environmental Health, Kitakyushu, Japan (UOEHCRB20-180). Informed consent was obtained through an opt-out function on the study website; patients who opted out were excluded from the study.

Patients and data collection. We retrospectively reviewed the medical records of consecutive patients with advanced UC who received pembrolizumab after chemotherapy between March 2018 and December 2021. All patients, who received treatment at one academic centre or one of six general hospitals, had histologically confirmed UC. Clinical and laboratory data were collected from the patients' records.

Treatment and follow-up examinations. Pembrolizumab was administered at a fixed dosage of 200 mg every 3 weeks or 400 mg every 6 weeks, continued until disease progression or the occurrence

Table II. Best response of each group according to body mass index.

	Non-overweight	Overweight	p-Value
Complete response (%)	0 (0)	1 (5.0)	0.10
Partial response (%)	17 (29)	10 (50)	
Stable disease (%)	11 (19)	2 (10)	
Progressive disease (%)	30 (51)	7 (35)	
Total (%)	58 (100)	20 (100)	

of intolerable adverse events. Computed tomography of the chest and abdomen was performed at baseline and every 2-3 months to evaluate the therapeutic effect. To evaluate the tumour response, we used the Response Evaluation Criteria in Solid Tumours, version 1.1. We classified irAEs according to the Common Terminology Criteria for Adverse Events, version 4.0.

Outcomes. BMI was calculated as body weight (in kilograms) divided by height squared (square metres). According to the World Health Organisation (WHO) criteria (14) for classifying BMI, the patients were divided into an overweight group (BMI ≥25 kg/m²) and a non-overweight group (BMI <25 kg/m²). We compared the two groups' tumour responses, rates of progression-free survival (PFS), rates of overall survival (OS), and incidences of irAEs. In addition, we investigated factors associated with PFS and OS.

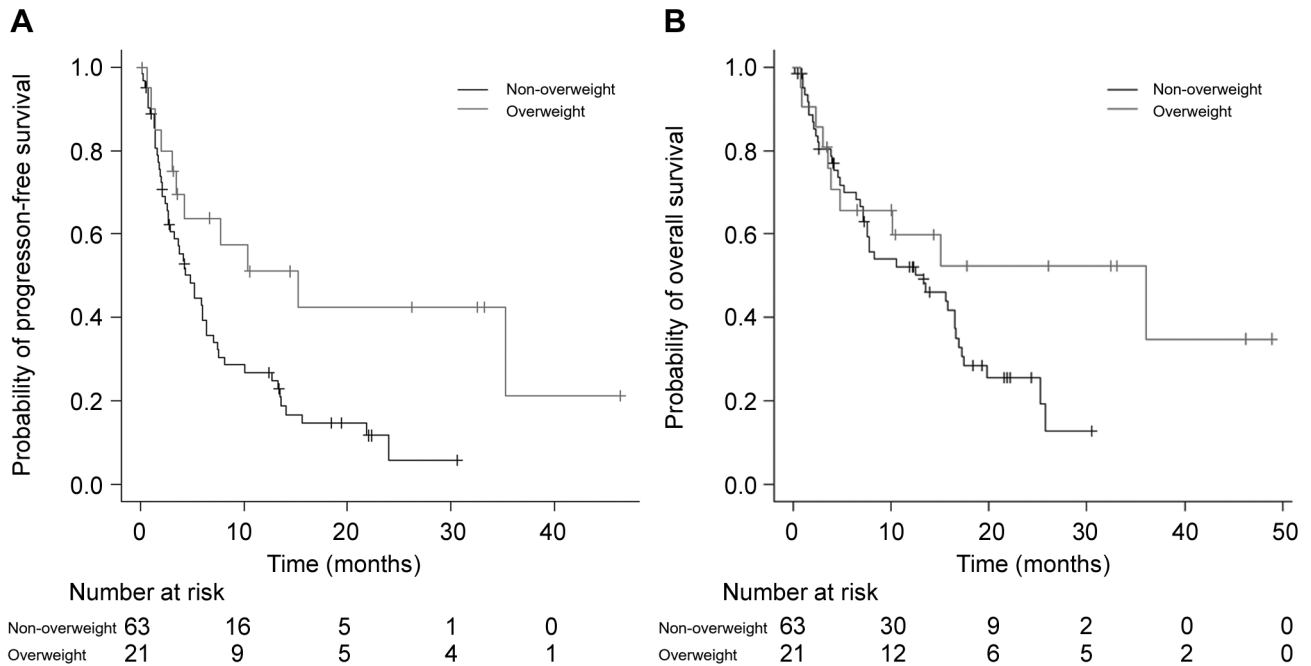


Figure 1. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B), stratified by body mass index.

Statistical analysis. To perform between-group comparisons of tumour response, and incidence of irAEs, we used the Fisher’s exact test for nominal variables. PFS and OS were calculated from the first date of pembrolizumab administration to the date of disease progression and the last follow-up or death from any cause, respectively. The Kaplan–Meier method was used to estimate survival curves and the log-rank test to compare these curves. In performing univariable and multivariable analyses, the Cox proportional hazards regression model was used to identify PFS- or OS-associated factors. A p -value of <0.05 was considered statistically significant. For all statistical analyses, EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria) was used (15).

Results

Patient characteristics. A total of 84 patients with advanced UC received pembrolizumab after chemotherapy during the study period. Patient characteristics are summarised in Table I. Sixty-three (75%) patients were in the non-overweight group, and 21 (25%) were in the overweight group. The maximum BMI in our patient population was 29.0 kg/m². We found no obvious differences in patient characteristics between the two groups.

Tumour response. A complete response was observed in only one patient, who was in the overweight group; partial responses were observed in 17 patients (29%) in the non-

overweight group and 10 (50%) in the overweight group. Although the objective response rate was higher in the overweight group (55%) than that in the non-overweight group (29%), the difference was not significant (Table II).

Clinical events and subsequent therapy. The median length of follow-up was 9.2 months. Among patients in the non-overweight group, the cancers progressed in 42, and 51 died during the study period. Of those with cancer progression, 18 underwent subsequent therapy: 10 received platinum-based chemotherapy, 2 received paclitaxel–gemcitabine, and 6 received enfortumab vedotin.

Among patients in the overweight group, the cancers progressed in 10, and 11 died during the study period. Of those with cancer progression, 2 received enfortumab vedotin after pembrolizumab.

Survival analyses. PFS was significantly longer in the overweight group (median 15.2 months) than that in the non-overweight group (median 4.8 months; $p=0.01$). OS was also longer in the overweight group (median 36.1 months) than that in the non-overweight group (median 13.4 months); however, the difference was not significant ($p=0.11$; Figure 1). According to the multivariable analysis, whereas higher BMI (overweight) was significantly associated with favourable PFS (Table III), no significant association was found between BMI and OS (data not shown).

Table III. Results of univariable and multivariable analyses to predict progression-free survival.

Characteristic	Univariable		Multivariable	
	Hazard ratio (95%CI)	p-Value	Hazard ratio (95%CI)	p-Value
Age (continuous)	0.98 (0.96-1.00)	0.12	1.00 (0.97-1.03)	0.97
Sex (female)	2.36 (1.34-4.15)	0.003	2.54 (1.33-4.85)	0.005
BMI (overweight)	0.43 (0.22-0.85)	0.02	0.39 (0.18-0.83)	0.02
ECOG-PS of ≥ 1	1.49 (0.89-2.50)	0.13	1.30 (0.75-2.25)	0.35
Presence of liver metastasis	2.27 (1.29-4.00)	0.005	2.54 (1.28-5.02)	0.008
Haemoglobin (<10 g/dl)	2.94 (1.67-5.17)	<0.001	0.80 (0.41-1.55)	0.51
Time since prior therapy (<3 months)	1.83 (1.09-3.06)	0.02	1.23 (0.71-2.13)	0.45

BMI: Body mass index; CI: confidence interval; ECOG-PS: Eastern Cooperative Oncology Group performance status.

Immune-related adverse events. Any and severe (grade 3) irAEs were observed in 15 (24%) and 5 (7.9%) patients in the non-overweight group, respectively, and in 8 (38%) and 2 (9.5%) patients in the overweight group, respectively. The differences between the two groups were not significant (Table IV).

Discussion

In this study, we demonstrated an association between BMI and the clinical outcomes of pembrolizumab treatment for advanced UC. PFS was significantly longer in the overweight group compared to that in the non-overweight group. The overweight group had a better objective response rate and longer OS than did the non-overweight group, although the difference was not significant. In contrast, the incidence of irAEs did not differ between the groups.

The association between BMI and oncological outcomes has been investigated for several malignancies that were treated with ICI. Although some studies demonstrated better outcomes in patients with high BMIs than in those with normal or low BMIs (10-12, 16), no association between BMI and oncological outcomes was reported (17-19). In one of the few studies of patients with UC, Ishihara et al. found no relation between BMI and either tumour response or survival (13).

In our study, PFS was significantly longer in the overweight group. Although the association between obesity and favourable oncological outcomes is not fully understood, paradoxical effects of obesity on T cell function and on the efficacy of ICI have been demonstrated in preclinical models. Obesity results in increased immune aging, tumor progression, and PD-1-mediated T cell dysfunction. However, obese models displayed greater therapeutic efficacy of ICI than control models. The improved responsiveness in obese models was associated with a significant increase in the total number of tumor-infiltrating T cells and increased frequency of CD8+ T cells in the tumour microenvironments (20).

Table IV. Immune-related adverse events in each group according to body mass index.

Immune-related adverse events	Non-overweight (n=63)	Overweight (n=21)	p-Value
Any grade	15 (24%)	8 (38%)	0.26
Grade 3	5 (7.9%)	2 (9.5%)	1.00

The association between BMI and the development of irAEs has been investigated. Increased numbers of irAEs in patients with high BMIs have been reported (10, 21); however, no effect of BMI on the incidence of irAEs was observed in our study or in others (13, 22). The development of irAEs was associated with the efficacy of ICI treatment, according to a study of several malignancies, including UC (23). Our results indicate that ICI is a reasonable treatment option for patients with high BMIs because they are efficacious and do not increase the risk of irAEs. Furthermore, in another study, better PFS was observed among patients with metastatic cancer who gained weight during ICI treatment than in those who did not gain weight (24). Thus, nutritional support might be helpful to patients who receive ICI treatment.

This study had several limitations. First, it was a retrospective study with a relatively small cohort; therefore, selection biases may have occurred. Second, we did not investigate the changes in BMI; some patients might have gained or lost weight during the treatment periods with pembrolizumab. Third, our patients as a group had a median BMI of 22.4 kg/m², which is relatively low, and patients who had obesity (BMI ≥ 30 kg/m²) according to the WHO criteria were not included. Thus, the association between obesity and clinical outcomes of ICI treatment remains unclear.

In conclusion, oncological outcomes were better in patients with high BMIs and advanced UC who received

pembrolizumab than in those with lower BMIs. In contrast, BMI was not associated with the development of irAEs. Therefore, BMI is useful for predicting the efficacy of ICI treatment in patients with UC.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Ikko Tomisaki: conceptualisation, data curation, formal analysis, investigation, methodology, project administration, and writing – original draft. Mirii Harada: data curation. Shigeru Sakano: data curation. Michikazu Terado: data curation. Ryoichi Hamasuna: data curation. Shuji Harada: data curation. Hiroomi Matsumoto: data curation. Souichiro Akasaka: data curation. Yujiro Nagata: data curatio. Akinori Minato: data curation. Ken-ichi Harada: supervision. Naohiro Fujimoto: supervision and writing – review and editing.

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