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Cachexia Index Is a Prognostic Indicator in Patients With Metastatic Urothelial Carcinoma Treated With Systemic Chemotherapy

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Abstract. *Background/Aim: Cancer cachexia is associated with poor prognosis in patients with metastatic urothelial carcinoma (mUC). The objective of the study was to assess the cachexia index (CXI), which is a new indicator assessing the status of cancer cachexia, as a prognostic indicator for mUC patients treated with gemcitabine plus cisplatin (GC) chemotherapy. Patients and Methods: The study included 55 patients with mUC who underwent GC chemotherapy between 2008 and 2022 as first-line chemotherapy. The CXI at the start of chemotherapy was determined as follows: CXI=(serum albumin × skeletal muscle mass index)/(neutrophil count/lymphocyte count). Patients were categorized into two groups based on a median CXI value (CXI-high and CXI low). We used Kaplan–Meier curves and multivariate Cox proportional hazards regression models to assess the association between the CXI and overall survival (OS). Results: At the start of GC chemotherapy, significant differences were not found in patients' characteristics. The median OS was significantly shorter in the CXI-low group [10.0 months (95% confidence interval (CI)=5.1-12.8)] than in the CXI-high group [22.3 months (95% CI=13.6-NA), p<0.05]. Multivariate analysis revealed that low CXI was a predictor of a poor prognosis [hazard ratio (HR)=2.25, 95% CI=1.12-4.52, p<0.05]. Conclusion: CXI might be useful as a prognostic indicator for patients with mUC undergoing first-line GC chemotherapy.*

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Metastatic urothelial carcinoma (mUC), which encompasses malignancies of the urinary tract, such as the bladder, renal pelvis, and ureter, is a highly malignant cancer with a 5-year survival rate of approximately 6% (1). Cisplatin-based systemic chemotherapy has been the gold-standard treatment for mUC for the past decades (2, 3). Recently, immune checkpoint inhibitors (ICI), such as pembrolizumab and avelumab, have been approved for the treatment of mUC (4, 5). Moreover, enfortumab vedotin, which is an antibody–drug conjugated agent targeting nectin-4, has been approved for a post-platinum and ICI setting (6). However, no drastic improvement in clinical outcome has been noted. Thus, cisplatin-based chemotherapy has remained the cornerstone of treatment for mUC.

Both decreased skeletal muscle mass and malnutrition caused by chronic inflammation due to cancer are parts of the syndrome of symptoms that characterize cancer cachexia. The European Palliative Care Research Collaborative has defined cancer cachexia as "a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (7). Cancer cachexia has been reported to appear in >30% of patients with a diagnosis of cancer, and in 50-80% of patients with advanced cancer (7). Clinical features of cancer cachexia that are pivotal include: systemic inflammation, a poor nutritional status, and a reduction in

skeletal muscle mass. In patients with UC, approximately 70% are observed with cancer cachexia, especially skeletal muscle loss (8). Cancer cachexia is associated with increased treatment-related toxicity, reduced treatment efficacy, and a poor prognosis. We previously described the relationship between nutritional status, a reduction in skeletal muscle mass, and clinical outcomes in patients with mUC (9-13). Therefore, careful attention should be paid to patients with mUC in terms of cancer cachexia.

The cachexia index (CXI) is a new indicator of cancer cachexia that is calculated by the following equation: CXI=serum albumin (g/dl) × skeletal muscle index (SMI, cm^2/m^2)/neutrophil to lymphocyte ratio (NLR). These variables incorporate the clinical measures of crucial features of cancer cachexia, such as nutritional status, skeletal muscle mass, and systemic inflammation. Several reports exist describing CXI as a useful prognostic indicator for patients with cancer, such as those with lung cancer, hepatocellular carcinoma, and lymphomas (14-16). In this study, we aimed to assess the usefulness of CXI as an indicator of prognosis in patients with mUC who underwent gemcitabine plus cisplatin chemotherapy.

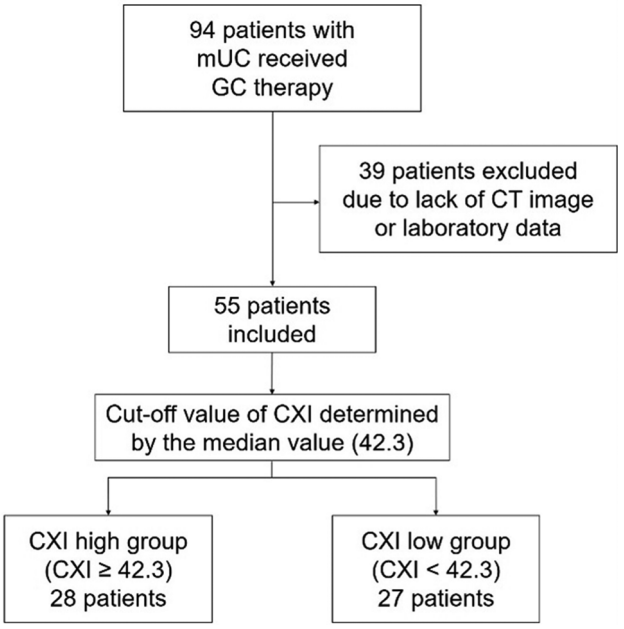

Figure 1. *Flow chart of the patient accrual process. CXI, Cachexia index, GC, gemcitabine plus cisplatin.*

Patients and Methods

Study design and treatment. Patient records were retrospectively reviewed to identify those with mUC who had received gemcitabine plus cisplatin chemotherapy as a first-line treatment between 2008 and 2022 at our hospital. A total of 94 patients were identified. Nineteen patients were excluded due to a lack of computed tomography (CT) imaging conducted within one month before GC therapy. For 20 patients, CXI could not be calculated at the start of GC therapy due to a lack of laboratory data and they were therefore excluded, leaving a final of 55 patients. The Ethics committee of the Nagoya City University Hospital endorsed this study (approval no. 60-18-0060), which was performed using histopathological evaluation and with patient consent. Previously performed routine pathological diagnoses were the source of specimens used in this study. Patients were free to opt-out. This study was undertaken according to the Declaration of Helsinki (2013 Fortaleza revision). In this study, gemcitabine and cisplatin (GC) were used as first-line chemotherapy. This consisted of 1,000 mg/m^2 of gemcitabine that was given on days 1, 8, and 15, plus 70 mg/m^2 of cisplatin that was given on days 1 or 2. Adverse events during GC therapy were classified in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Calculation of neutrophil-lymphocyte ratio, skeletal muscle mass index, and cachexia index. The neutrophil to lymphocyte ratio was determined as follows: NLR=number of peripheral neutrophils/number of peripheral lymphocytes. The SMI was calculated as follows: SMI=the area of skeletal muscle at the third lumbar vertebra (cm^2)/height squared (m^2) (13). The CXI was determined as follows: CXI=serum albumin (g/dl) × SMI (cm^2/m^2)/NLR.

Statistical analyses. Data were calculated as a mean with 95% confidence intervals (CI), ranges, medians, or frequencies (%). Statistical significance was set at $p<0.05$. Fisher's exact test was used to assess differences in patient characteristics. Mann-Whitney *U*-test was used to assess continuous variables. Overall survival (OS) and progression-free survival (PFS) calculated using a Kaplan–Meier method and log-rank test. Univariate and multivariate Cox regression analyses were used to assess the factors associated with OS. GraphPad Prism 9 software and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) were used in the statistical analyses performed (17).

Results

Patient characteristics. In this study, 55 patients were analyzed. The median CXI was calculated as 42.3 (range=1.8-305.0). Therefore, patients were divided into two groups according to the median CXI value: CXI-low and CXI-high (Figure 1). Patient characteristics are listed in Table I. The two groups did not show any significant differences with regard to age, sex, Eastern Cooperative Oncology Group Performance status (ECOG-PS), origin organ of urothelial carcinoma, and metastasis sites. However, the mean hemoglobin level in the CXI-low group was significantly lower than that in the CXI-high group. Since the calculation of CXI is based on albumin, NLR, and SMI values, the mean NLR was significantly higher, and mean albumin and SMI levels were significantly lower in the CXI-low group.

CXI was a prognostic indicator for overall survival of mUC patients. The median OS of the CXI-low group was significantly shorter than that of the CXI-high group (10.0

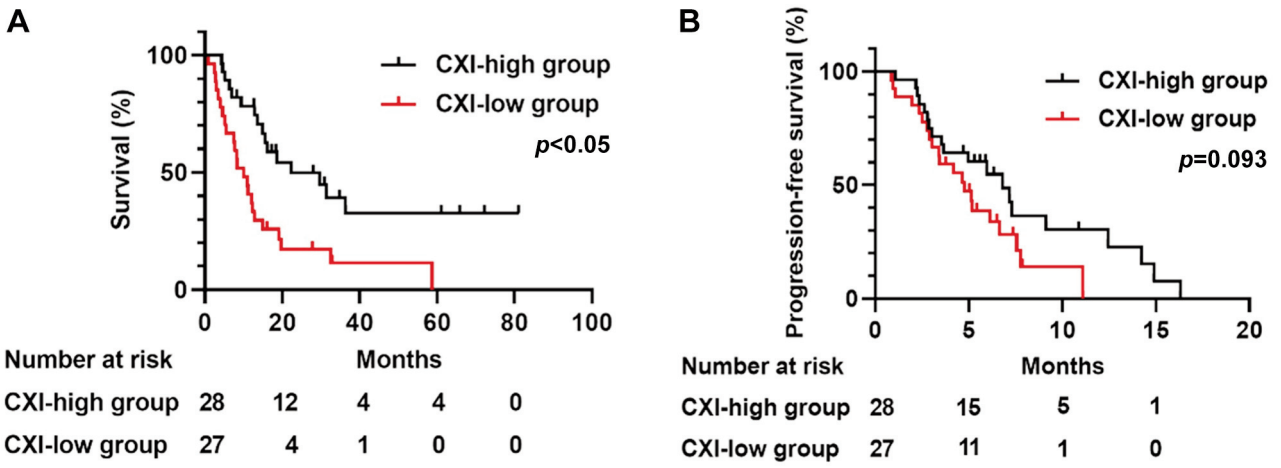

Figure 2. *Kaplan–Meier curves showing (a) overall survival and (b) progression-free survival. Patients were divided into two groups based on a CXI value of 42.3. CXI, Cachexia index.*

Table I. *Patient characteristics.*

Characteristics		CXI-high group (n=28)	CXI-low group (n=27)	*p*-Value
Median age, years (range)		70 (55-85)	71 (53-84)	0.595
Sex, n (%)	Male	21 (75.0)	19 (70.4)	0.768
	Female	7 (25.0)	8 (29.6)	
ECOG-PS, n (%)	0	17 (60.7)	13 (48.1)	0.609
	1	7 (25.0)	9 (33.3)	
	2	1 (3.6)	3 (11.1)	
	NA	3 (1.07)	2 (7.4)	
Origin organ of urothelial carcinoma, n (%)	Bladder	19 (67.9)	15 (55.6)	0.412
	Upper urinary tract	9 (32.1)	12 (44.4)	
Metastasis, n (%)	Liver	2 (7.1)	5 (18.5)	0.252
	Lung	10 (35.7)	10 (37.0)	1
	Others	3 (10.7)	9 (33.3)	0.055
	Lymph nodes	21 (75.0)	19 (70.4)	0.768
Serum hemoglobin, g/dl (range)		12.55 (9.10-15.80)	10.70 (8.10-14.00)	<0.001
Serum albumin, g/dl (range)		3.75 (2.60-4.50)	2.90 (2.30-4.00)	<0.001
Median neutrophil count, /mm^3 (range)		3.4 (1.90-8.70)	7.00 (3.40-24.30)	<0.001
Median lymphocyte count, /mm^3 (range)		1.40 (0.70-3.10)	0.9 (0.30-1.80)	<0.001
Median NLR (range)		2.52 (0.94-4.42)	6.80 (3.88-81.00)	<0.001
Median SMI, cm^2/m^2 (range)		53.86 (29.75-71.99)	40.62 (30.17-59.01)	<0.001
Median CXI (range)		67.35 (42.31-305.08)	17.56 (1.82-42.30)	<0.001

CXI, Cachexia index; ECOG-PS, Eastern Cooperative Oncology Group Performance status; NA, not assessable; NLR, neutrophil lymphocyte ratio; SMI, skeletal mass index.

months *vs*. 22.3 months, $p<0.05$, Figure 2a). The median PFS of the CXI-low group tended to be shorter than those of CXI-high group (6.7 months *vs*. 4.7 months, $p=0.093$, Figure 2b). All patients in CXI-high group received subsequent treatment, whereas seven patients (25.9%) in CXI-low group died during GC therapy ($p<0.05$, Table II). Clinical efficacy and safety profiles are summarized in Table II and Table III. The best overall response (BOR) did not statistically differ between the two groups. We calculated the average relative dose intensity (RDI) and the RDI of gemcitabine and cisplatin, respectively; however, a statistical difference between CXI-high and CXI-low groups was not noted. The adverse events that occurred during GC therapy are shown in Table III. The frequency of grade ≥3 anemia was significantly higher in the CXI-low group than in the CXI-high group. In comparison, the frequency of all grades of a

Table II. *The clinical outcome and relative dose intensity of GC therapy.*

		CXI-high group (n=28)	CXI-low group (n=27)	*p*-Value
Best overall response, n (%)	CR	0 (0.0)	0 (0.0)	0.611
	PR	8 (29.6)	11 (40.7)	
	SD	13 (48.16)	10 (37.0)	
	PD	6 (22.2)	6 (22.2)	
	NA	1 (3.6)	0 (0.0)	
No. of patient died during GC therapy, n (%)		0 (0.0)	7 (25.9)	<0.05
Average RDI, % (range)		75.1 (57.3, 101.0)	79.2 (56.3, 98.9)	0.686
RDI of gemcitabine% (range)		65.4 (47.4, 101.3)	67.1 (37.2, 100.2)	0.662
RDI of cisplatin % (range)		87.5 (67.3, 102.6)	91.6 (59.8, 102.5)	0.893

CXI, Cachexia index; CR, complete response; GC, gemcitabine plus cisplatin; NA, not assessable; PD, progressive disease; PR, partial response; RDI, relative dose intensity; SD, stable disease.

Table III. *Profile of adverse events during GC therapy.*

Adverse events	CXI-high group (n=28)		CXI-low group (n=27)	
	No. of all grade Pts, n (%)	No. of grade 3-4 Pts, n (%)	No. of all grade Pts, n (%)	No. of grade 3-4 Pts, n (%)
Neutropenia	24 (85.7)	17 (60.7)	25 (92.6)	15 (55.6)
Anemia	27 (96.4)	9 (32.1)	27 (100)	17 (63.0)*
Thrombocytopenia	27 (96.4)	15 (53.6)	26 (96.3)	17 (63.0)
AST increase	13 (46.4)	0 (0.0)	12 (44.4)	3 (11.1)
ALT increase	18 (64.3)	1 (3.6)	20 (74.1)	1 (3.7)
Creatinine increase	27 (96.4)*	0 (0.0)	19 (70.4)	1 (3.7)

AST, Aspartate aminotransferase; ALT, alanine aminotransferase; CXI, cachexia index; GC, gemcitabine plus cisplatin; Pts, patients; *p<0.05, statistically significant.

creatinine increase was greater in the CXI-high compared to CXI-low group. Treatment histories are summarized in Table IV. Statistical differences in prior and subsequent treatments were not noted between the two groups.

Univariate and multivariate analyses of patients who received GC. Table V shows Cox proportional hazard regression analyses of baseline parameters and OS in 55 patients treated with GC therapy. Hemoglobin <10 mg/dl, the existence of liver metastasis, and CXI-low group correlated with OS in univariate analysis. Multivariate analysis revealed that only the CXI-low group was a risk factor for OS [hazard ratio (HR)=2.25, p<0.05].

Discussion

In this investigation, we found that CXI acted as a prognostic indicator for the OS of patients with mUC treated with GC therapy.

Several research groups have analyzed the relationships between clinical outcome, such as the efficacy and safety of chemotherapy and inflammatory status (18), skeletal muscle mass (13, 19), and nutritional status (9, 11, 20), respectively. However, such factors are cachexia-related parameters and therefore expected to intimately interact with each other. Since cancer cachexia has a complex pathophysiology, CXI would be an ideal index that gives a better estimate of ongoing cachexia. In mUC, a poor prognosis has been reported in patients with serum albumin levels less than the lower limit of normal, hemoglobin levels of <10 mg/dl, the existent of liver metastasis, or ECOG PS≥1 (21). In this study, an analysis by multivariate cox regression highlighted a low CXI as an independent prognostic factor for patients with mUC even though according for these factors. Thus, CXI might be a novel prognostic indicator for mUC treated with GC therapy.

We compared efficacy and safety profiles, such as BOR, RDI, and adverse event profiles between CXI-low and high groups. The BOR and RDI did not show a significant difference between the two groups. Cancer cachexia has been reported to reduce the efficacy of chemotherapy in various cancer types (22). Despite the same BOR or RDI, the shorter median OS of patients in the CXI-low group is suggested to be affected by cancer cachexia. In this cohort, the incidence of anemia ≥G3 is statistically greater in the CXI-low

Table IV. *Treatment history of patients*.

Treatment		CXI-high group (n=28)	CXI-low group (n=27)	*p*-Value
Prior treatment				
Neoadjuvant GC therapy, n (%)		5 (17.9)	3 (11.1)	0.595
Radical resection, n (%)		17 (60.7)	13 (48.1)	0.768
Adjuvant GC therapy, n (%)		10 (35.7)	3 (11.1)	0.055
Subsequent chemotherapy				
Cytotoxic agent, n (%)	Gemcitabine+carboplatin	3 (10.7)	2 (7.4)	0.060
	Gemcitabine+docetaxel	15 (53.6)	10 (37.0)	
	Gemcitabine+paclitaxel	5 (17.9)	2 (7.4)	
Immune checkpoint inhibitor, n (%)	Avelumab	8 (28.6)	6 (22.2)	0.180
	Pembrolizumab	14 (50.0)	6 (22.2)	
Antibody–drug conjugated agent, n (%)	Enfortumab vedotin	6 (21.4)	4 (14.8)	0.729

GC, Gemcitabine plus cisplatin; CXI, cachexia index.

Table V. *Univariate and multivariate cox regression analysis for overall survival outcomes*.

Parameters	Univariate			Multivariate		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age at start of a treatment, ≥65 *vs*. <65 years	0.88	0.46-1.67	0.423			
Sex, male *vs*. female	1.07	0.55-2.12	0.836			
Albumin, <4.0 g/dl *vs*. ≥4 g/dl	2.01	0.71-5.69	0.19			
Hemoglobin, <10 mg/dl *vs*. ≥10 mg/dl	2.01	1.01-4.32	0.046	1.41	0.65-3.08	0.383
ECOG-PS ≥1 *vs*. 0	1.55	0.81-3.00	0.189			
Liver metastasis, yes *vs*. no	2.75	1.19-6.28	0.017	1.75	0.73-4.20	0.210
CXI, low group *vs*. high group	2.70	1.42-5.15	0.002	2.25	1.12-4.52	0.023

CI, Confidence interval; CXI, cachexia index; ECOG-PS, Eastern Cooperative Oncology Group Performance status; HR, hazard ratio.

compared to CXI-high group. Cancer cachexia is associated with a higher incidence of adverse events during cancer therapy (7, 8, 15, 23). Therefore, careful monitoring of adverse events might be needed depending on the value of the CXI. We also compared treatment histories between the two groups. The systemic chemotherapy used for mUC has substantially changed over the past few years. In addition to the use of cytotoxic agents, such as gemcitabine and cisplatin, ICIs are also widely used in the treatment of mUC (4, 5). Moreover, enfortumab vedotin, an antibody–drug conjugate, is available as a third-line agent (6). Efficacy of subsequence chemotherapy after platinum-based regimen or ICIs have also been discussed (24-26). However, in our cohort, a difference in treatment history, including in the use of ICIs and enfortumab vedotin, was not noted between the two groups. In fact, 25.7% of patients in CXI-low group died and could not receive subsequent treatment. These indicate that patients who had a low CXI at the start of first-line chemotherapy might not be benefit from these drugs. Therefore, the status of cachexia should be assessed in detail in order to make the most appropriate treatment decisions.

There are several limitations in this study. We divided patients into two groups based on a median value of CXI of 42.3. Therefore, the optimal cut-off value of CXI might require further investigation. In comparison, Karmali *et al*. reported a cut-off value of 49.8 in patients with lymphoma (16). Goh *et al*. reported a cut-off value of 53 in patients who had hepatocellular carcinoma and who underwent systemic chemotherapy (15). Jafri *et al*. reported a cut-off value of 35 in patients with advanced non-small cell lung cancer (14). Based on these reports; our cut-off value would be considered acceptable. In addition, owing to the retrospective nature of this study, bias was not controllable in patient's selection. Therefore, a prospective interventional study is needed to verify our findings.

Conclusion

In conclusion, we revealed that a low CXI might be useful as a prognostic indicator for patients with mUC under GC therapy, thereby, highlighting the importance of assessing the status of cachexia to make treatment decisions.

Conflicts of Interest

The Authors wish to declare that they have no conflicts of interest.

Authors' Contributions

Conceptualization, Y.M. and T.N; Data curation, Y.M.; Formal analysis, Y.M. and Y.S.; Funding acquisition, Y.M.; Investigation, Y.M., Y.S., Y.T., K.O., T.E., T.N., M.I., Y.K., and N.I.; Methodology, Y.M., T.N., and Y.S.; Project administration, Y.M.; Supervision, Y.H., T.Y. and Y. F-H; Validation, Y.M.; Visualization, Y.M.; Roles/Writing - original draft, Y.M., T.N. and Y.S.; Writing - review & editing, Y.M., T.N., Y.H., T.Y. and Y.F-H. All the Authors have read and approved the manuscript and agree with its submission to this journal.

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