

Original Article

# Prognostic value of nutritional indices and body composition parameters including sarcopenia in patients treated with radiotherapy for urothelial carcinoma of the bladder

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## Abstract

**Purpose:** To assess the prognostic importance of sarcopenia in survival in patients with high-risk urothelial carcinoma of the bladder (UCB) who were unfit for radical cystectomy or systemic chemotherapy and were, therefore, treated with radiotherapy only.

**Methods:** We evaluated 94 patients treated with transurethral resection of the bladder and radiotherapy for UCB. Sarcopenia, identified from pretreatment computed tomography scans, was defined as a skeletal muscle index of  $<39 \text{ cm}^2/\text{m}^2$  for women and  $<55 \text{ cm}^2/\text{m}^2$  for men. Body mass index -adjusted definition of sarcopenia was used to evaluate for sarcopenic obesity. Univariate models were used to assess the association between body composition and nutritional parameters with survival outcomes.

**Results:** Overall, 68 patients were eligible for the final analysis, and 49 (72%) patients were sarcopenic. After body mass index adjustment of the definition of sarcopenia, its prevalence changed to 53.8% in women and 52.7% in men. Median age was 82 (interquartile range [IQR] 75–86) years, with a median, age-adjusted comorbidity index of 7.5 (IQR 6–10). The median time of follow-up was 12.5 (IQR 5.1–23.5) months. There were 42 (61.7%) patients who died of any cause and 19 (45.2%) who died because of UCB during the study period. Of all the body composition and nutritional parameters investigated, sarcopenic obesity was associated with cancer-specific survival (hazard ratio 5.0, 95% confidence interval 1.4–16.7,  $P = 0.01$ ) and a low prognostic nutritional index was associated with overall survival (hazard ratio 0.46, 95% confidence interval 0.2–0.9,  $P = 0.02$ ).

**Conclusion:** In patients who are too high risk for the standard treatment of UCB, sarcopenia is highly prevalent, but not prognostic of survival. Nevertheless, sarcopenic obesity and the prognostic nutritional index might act as prognostic markers for patients with UCB undergoing radiotherapy. © 2018 Elsevier Inc. All rights reserved.

**Keywords:** Urothelial bladder cancer; Sarcopenia; Radiotherapy; Nutrition; Body composition; Survival

## 1. Introduction

Bladder cancer is the ninth most commonly diagnosed malignancy worldwide. The most common histology is urothelial carcinoma of the bladder (UCB), accounting for

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approximately 90% of all bladder cancers. The estimated incidence is 430,000 per year and shows a strong male predominance [1].

Radical cystectomy (RC) is the standard treatment for muscle-invasive bladder cancer and for high-risk, non-muscle-invasive bladder cancer [2]. While RC results in sustained disease control in more than 60% of the patients, it is also associated with significant morbidity and mortality, especially in elderly patients [3].

Therefore, for patients who are too high risks for RC, bladder-preserving trimodal therapy is a treatment option in selected patients. It is comprised of maximal transurethral resection of the bladder (TURB), radiotherapy (RT) and platinum-based systemic chemotherapy [4–6]. Due to the complexity of bladder-preserving trimodal therapy, careful patient selection is of paramount importance in order to maximize therapy efficacy and minimize side effects [6–8]. Several biomarkers have been investigated over the last few years [9,10]. However, none of these tools have been implemented into standard clinical practice due to limitations in study design and the lack of a structured, phased approach to development and validation [11,12]. In this context, the prognostic importance of sarcopenia and poor nutritional status has been evaluated in patients treated with RC and correlated with poor overall survival (OS) [13,14]. Data regarding the prognostic role of sarcopenia and nutritional indices in patients treated with RT for UCB are lacking.

In this study, we investigated the prognostic value of sarcopenia, sarcopenic obesity, and nutritional indices in a cohort of patients considered unfit for RC or systemic chemotherapy and therefore treated with RT with curative intent.

## 2. Materials and methods

### 2.1. Patient data collection

After obtaining institutional review board approval (#2056/2016), we retrospectively reviewed the charts of 94 patients with high-risk bladder cancer, where we included patients with clinical tumor stage  $\geq T2$  and non-muscle-invasive tumors at highest risk of progression [15,16]. No patients with evidence of distant metastatic disease were included. They were treated with RT for UCB between 2004 and 2015 at our tertiary referral center. Overall, 3 patients were excluded because full data were not available for the measurement of the skeletal muscle areas, 3 were lost to follow-up, and 20 received concurrent chemotherapy. The final cohort consisted of 68 patients with UCB, who were clinically considered unfit for RC and/or chemotherapy because of comorbidities and low general health condition and were thus treated with RT only.

In our cohort, all patients underwent TURB for primary UCB according to guideline recommendations at that time [17]. A second-look resection was performed after the first

resection based on pathologic and intraoperative findings. Concomitant upper urinary tract urothelial carcinoma was excluded with a radiological work-up in all patients. All surgical specimens were processed according to standard pathologic procedures and staged based on the 2009 Tumor-Node-Metastasis (TNM) classification. Tumor grade was assigned according to the 1973 World Health Organization system. A standard radiation schedule included external beam radiation to the bladder and pelvic lymph nodes. The target dose of 45 to 50 Gray (Gy) was reached in 5 weeks, with 1.8 to 2 Gy single doses were given for 5 days a week. Subsequently, a tumor boost was given in 1.8 to 2 Gy single doses at 5 to 7 days, resulting in a total boost of 9 to 14 Gy. Radiation was mostly done with 4-field box technique after 3D planning of the procedure. Age-adjusted Charlson comorbidity index (CMI) was calculated, and patients were classified according to the American Society of Anaesthesiologists' physical status group by reviewing perioperative anesthesia protocols for each patient [18,19]. A follow-up schedule was not standardized because of the retrospective nature of the study. Nevertheless, patients generally underwent physical examination, cytology, cystoscopy, and radiologic work-up every 3 months within the first 2 years, semiannually from the second to the fifth year, and then, annually thereafter. In case of suspicious lesions at cystoscopy, patients underwent re-TURB. Disease recurrence was defined as the first tumor relapse in the bladder regardless of tumor stage or occurrence of distant metastases. Cause of death was coded according to chart review and/or death certificate [20].

### 2.2. Image analysis and assessment of nutritional markers

Two trained investigators measured the skeletal muscle area, as well as fat areas from preradiation computed tomography scans at the level of the third lumbar vertebra [21]. Images were analyzed using the image processing application OsiriX (version 6.0.2; Bernex, Switzerland) and the regions of interest were defined by using their specific Hounsfield units (skeletal muscle area  $-29$  to  $150$ , subcutaneous fat area  $-190$  to  $-30$ , and visceral fat area  $-150$  to  $-50$ ). The skeletal muscle area was normalized to the square of the height ( $m^2$ ) to create the skeletal muscle index (SMI). A gender-specific, international consensus definition was used to stratify patients with regard to the presence of sarcopenia: women with an SMI of  $<39 \text{ cm}^2/m^2$  and men with a SMI  $<55 \text{ cm}^2/m^2$  [22] were defined as sarcopenic. We also assessed sarcopenia with body mass index (BMI)-incorporated cut-off values of SMI, according to definition to Martin et al. in order to assess for the condition of sarcopenic obesity. BMI-adjusted sarcopenia was therefore defined as SMI  $<43 \text{ cm}^2/m^2$  for males with BMI  $<25 \text{ kg}/m^2$ ,  $<53 \text{ cm}^2/m^2$  for males with BMI  $\geq 25 \text{ kg}/m^2$  and  $<41 \text{ cm}^2/m^2$  for females [23]. To evaluate the body skeletal muscle volume, we used the formula skeletal muscle volume =  $0.166 \times$  skeletal muscle area +  $4.142$ , and,

for the adipose tissue volume,  $ATV = 0.068 \times (\text{subcutaneous fat area} + \text{visceral fat area}) + 2.142$  [24]. To estimate the distribution of body composition (fat areas and skeletal muscle area), the visceral-to-subcutaneous fat area ratio and the visceral fat-to-muscle area ratio were calculated, respectively.

Two nutritional indices were calculated using laboratory data collected within 30 days prior to radiation therapy. The prognostic nutritional index (PNI) was calculated by the formula:  $0.005 \times \text{lymphocyte count (per mm}^3) + 10 \times \text{serum albumin concentration (g/dl)}$  [25]. For the controlling nutritional status, total cholesterol (mg/dl), lymphocytes (per  $\text{mm}^3$ ), and serum albumin (g/dl) [8,9,26] were summed. The BMI was calculated by weight (in kg) divided by height squared.

### 2.3. Outcome of interest and statistical analysis

Continuous variables are presented using median and interquartile range (IQR) and categorical variables with numbers and proportions. The primary outcome of interest was OS, defined as time from RT start to death due to any cause. The secondary outcome was cancer-specific survival (CSS). Sarcopenic vs. nonsarcopenic patients were compared by using the Kruskal–Wallis equality-of-populations rank test. Univariate Cox proportional hazards regression analyses were used to evaluate the association of sarcopenia, body composition parameters, and nutritional indices with OS and CSS. Kaplan–Meier curves were used to graphically visualize the survival function. Multivariate analyses were omitted due the low number of events. A  $P$  value  $<0.05$  was considered statistically significant and all tests were 2-sided. STATA v14 (StataCorp, College Station, TX) was used for statistical analyses.

## 3. Results

### 3.1. Patient characteristics

Demographic data and clinicopathological features are summarized in Table 1. The histological report from the TURB revealed muscle-invasive bladder cancer in 91.1% of the patients, the other 6 patients had pT1 bladder cancer, 3 with high grade and 3 associated with bladder carcinoma in situ (CIS). None of the patients displayed neither lymph node metastases nor distant metastasis on pretreatment imaging, albeit in 9 patients the lymph node status was not precisely evaluable. For our primary outcome, 49 patients were disease free after TURB and RT with curative intent. Additionally, during a median follow-up time of 13.5 (IQR 7.3–31.5) months, of these 49 patients who were disease free, only 8 patients experienced a recurrence of disease. The median time of follow-up was 12.5 (IQR 5.1–23.5) months for all patients who were alive at their last follow-up. In our study population, 42 patients of 68

Table 1

Clinicopathologic features of 68 patients with high-risk urinary bladder cancer clinically considered unfit for radical cystectomy and/or systemic chemotherapy and treated, therefore, with radiotherapy. Clinical lymph node status was only evaluable for 59 of 68 patients.

Variable	Median	IQR
Age (y)	82	75–86
CMI	7.5	6–10
BMI ( $\text{kg/m}^2$ )	25.2	22.9–29.6
Dose pelvis (Gy)	45	45–48.6
Dose bladder (Gy)	59.8	55–65
SMA ( $\text{cm}^2$ )	136.4	114.7–154.8
SFA ( $\text{cm}^2$ )	138.5	95.6–186.8
VFA ( $\text{cm}^2$ )	190.5	81.5–266.8
CONUT	1583	1009–1969
PNI	45.2	41.7–50.3
SMI ( $\text{cm}^2/\text{m}^2$ )	46.3	40.3–53.2
ATV (l)	25.6	15.7–33.3
SMV (l)	26.7	23.1–29.8
VSR	1.1	0.6–1.7
VMR	1.4	0.6–1.9

Variable	n	%
Male gender	55	80.9
Hydronephrosis	14	20.6
ASA		
1	5	7.4
2	17	25.0
3	44	64.7
4	2	2.9
Clinical tumor stage		
T1	6	8.9
T2	56	82.4
T3	5	7.4
T4	1	1.5

$n = 68$ .

ASA = American Society of Anaesthesiologists' classification; ATV = adipose tissue volume; BMI = body mass index; CMI = comorbidity index; CONUT = controlling nutritional status; PNI = prognostic nutritional index; SFA = subcutaneous fat area; SM = skeletal muscle volume; SMA = skeletal muscle area; SMI = skeletal muscle index, VFA = visceral fat area, VMR = visceral to skeletal muscle ratio; VSR = visceral to subcutaneous fat ratio.

(61.7%) died during follow-up, including 19 patients (45.2%) who died of UCB.

### 3.2. Pretreatment body composition and nutritional markers

The median BMI was in the normal range at  $25.2 \text{ kg/m}^2$  (IQR 23.0–29.6). Despite that, the overall prevalence of sarcopenia was 72% ( $n = 49$ ). Six women (46.2%) and 43 men (78.2%) were sarcopenic, with a median SMI of 40.8 (IQR 37.3–46.3) and 47.6 (IQR 40.7–54.6), respectively. Using the BMI-adjusted definition for sarcopenia, the overall prevalence of sarcopenia changed to 52.9% ( $n = 36$ ) and was detected in 29 men (52.7%) and 7 women (53.8%). We compared the body composition parameters of sarcopenic to nonsarcopenic patients and found that the only

statistically significant difference was between the parameters related to muscle mass. The evaluation for differences between patients, where BMI-incorporated cut-off values of SMI for defining sarcopenia was used, revealed that non-sarcopenic patients had higher PNI values (43.4 vs. 46.1,  $P = 0.02$ ; Table 2). The boxplot shown in Fig. 1 demonstrates the distribution of the SMI of survivors vs. deceased patients. The SMI between the groups did not differ significantly ( $P = 0.1$ ) in Kruskal–Wallis equality-of-populations rank test.

### 3.3. Prognostic value of body composition and nutritional markers

Univariate Cox regression analysis examining sarcopenia was neither significantly associated with OS (hazard ratio [HR] 1.31, 95% confidence interval [CI] 0.6–2.6,  $P = 0.44$ ) nor with CSS (HR 0.6, 95% CI 0.1–2.2,  $P = 0.45$ ). Within the evaluated body composition parameters and nutritional indices, PNI was the only parameter

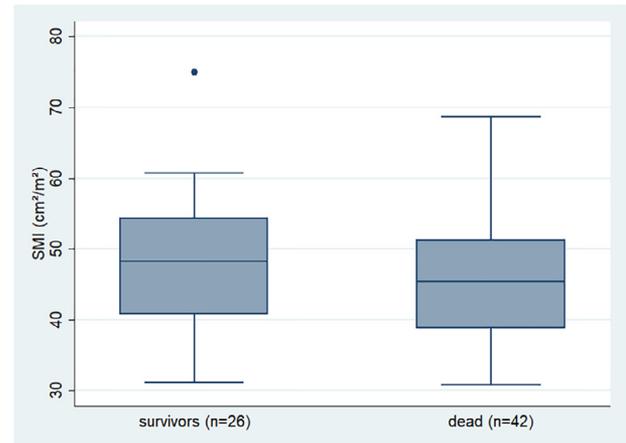


Fig. 1. Distribution of SMI in 68 patients with high-risk urinary bladder cancer clinically considered unfit for radical cystectomy and/or systemic chemotherapy and treated, therefore, with radiotherapy, stratified by alive vs. dead patients at last follow-up, with a median of 48.5 cm<sup>2</sup>/m<sup>2</sup> (IQR 40.7–55.4) for alive patients vs. deceased patients, with a median of 44.6 cm<sup>2</sup>/m<sup>2</sup> (IQR 38.7–50.0). IQR = interquartile range; SMI = skeletal muscle index.

Table 2

Comparison of nutritional and body composition parameters in 68 patients with high-risk urinary bladder cancer clinically considered unfit for radical cystectomy and/or systemic chemotherapy and treated, therefore, with radiotherapy, stratified by sarcopenic vs. nonsarcopenic [1] and BMI-adjusted sarcopenic vs. nonsarcopenic patients [2].

[1]	Sarcopenic (n = 49)		Nonsarcopenic (n = 19)		P value
	Median	IQR	Median	IQR	
SMA (cm <sup>2</sup> )	133.4	110–147.8	163.6	130.3–178.3	<0.001
SFA (cm <sup>2</sup> )	139.5	93.4–180.6	137.5	107.3–204.2	0.62
VFA (cm <sup>2</sup> )	184.5	95.6–252.2	200.1	72.8–317.8	0.75
SMI (cm <sup>2</sup> /m <sup>2</sup> )	44.6	37.7–48.5	57	47.8–60.8	<0.001
ATV (l)	25.4	16.4–32.5	28	14.4–37.0	0.75
SMV (l)	26.2	22.4–28.6	31.2	25.7–33.7	<0.001
VSR	1.15	0.72–1.77	1.05	0.4–1.5	0.4
VMR	1.6	0.9–1.9	1.2	0.4–1.9	0.24
BMI (kg/m <sup>2</sup> )	24.62	22.8–27	28.6	23.6–31.8	0.09
CONUT	1520.9	989.1–1893.3	1620.9	1534.3–2029.8	0.41
PNI	45.1	39.5–50.2	45.8	44.0–50.5	0.21

[2]	BMI-adj. sarcopenic (n = 36)		Nonsarcopenic (n = 32)		P value
	median	IQR	median	IQR	
SMA (cm <sup>2</sup> )	154.8	133.8–173.8	120.9	102.5–137.7	<0.001
SFA (cm <sup>2</sup> )	157.6	94.1–191.4	136.1	99.7–186.7	0.60
VFA (cm <sup>2</sup> )	179.7	92.6–222.6	219.4	79.1–316.8	0.29
SMI (cm <sup>2</sup> /m <sup>2</sup> )	40.62	36.1–46.8	53.9	46.9–59.2	<0.001
ATV (l)	25.3	15.7–30.0	28.49	15.4–35.1	0.52
SMV (l)	24.2	21.1–27.0	29.8	26.3–32.9	<0.001
VSR	1.01	0.61–1.56	1.3	0.6–2.1	0.25
VMR	1.5	0.8–1.8	1.3	0.4–1.9	0.46
BMI (kg/m <sup>2</sup> )	25.2	23.5–28.0	25.0	22.6–30.3	0.97
CONUT	1449.3	921.4–1893.3	1620.9	1352.8–1999.6	0.23
PNI	43.4	37.5–49.6	46.1	44.2–50.5	0.02

n = 68.

ATV = adipose tissue volume; BMI = body mass index; CONUT = controlling nutritional status; PNI = prognostic nutritional index; SMA = skeletal muscle area; SFA = subcutaneous fat area; SMI = skeletal muscle index; SMV = skeletal muscle volume; VFA = visceral fat area; VMR = visceral to skeletal muscle ratio; VSR = visceral to subcutaneous fat ratio.

significantly associated with OS. We used the median of 45.2 to dichotomize the population into low-PNI and high-PNI. Patients with low-PNI had a significantly shorter OS (HR 0.46, 95% CI 0.2–0.9,  $P = 0.02$ ) but patients with low-PNI had no shorter CSS (HR 0.56, 95% CI 0.1–1.8,  $P = 0.34$ ). The BMI-adjusted sarcopenia was not statistically associated with OS (HR 1.36, 95% CI 0.7–2.5,  $P = 0.32$ ) but we detected a significant association with CSS (HR 5.0, 95% CI 1.4–16.7,  $P = 0.01$ ; Fig. 2). Results of the univariate analyses for survival outcomes are shown in Table 3. After adjusting the model for gender and CMI, the HR was 0.50 (95% CI 0.24–1.03,  $P = 0.06$ ) with a nonstatistically significant prognostic trend for PNI. However, the PNI did only differ significantly between sarcopenic and nonsarcopenic patients ( $P = 0.02$ ) when using the BMI-adjusted definition for sarcopenia [23].

#### 4. Discussion

In this study, we assessed the effect of sarcopenia, body composition parameters, and nutritional indices on survival

in patients treated with transurethral resection and RT for UCB. Although nutritional parameters correlated with survival, there was no such association with sarcopenia.

In patients with advanced renal cancer who were undergoing radical nephrectomy, sarcopenia is associated with a higher complication rate ( $P = 0.03$ ) [27]. In metastatic renal cancer patients who were undergoing cytoreductive nephrectomy, Sharma et al. demonstrated that sarcopenia is a negative prognostic factor for OS (HR 2.13;  $P = 0.016$ ) [28]. In patients who were undergoing RC for UCB, Psutka et al. showed a significantly poorer OS after radical surgery in sarcopenic patients compared to their nonsarcopenic counterparts (39% vs. 70%;  $P = 0.003$ ) [13]. Furthermore, sarcopenia is negatively predictive for perioperative major complications, especially in women [29]. Advanced age and an impaired performance status also carry an increased risk of perioperative complications and mortality [30–33]. Regarding body composition in patients who were undergoing bladder-sparing treatment for UCB, there are data showing that baseline BMI and weight loss during four weeks of RT might have a significant influence on survival

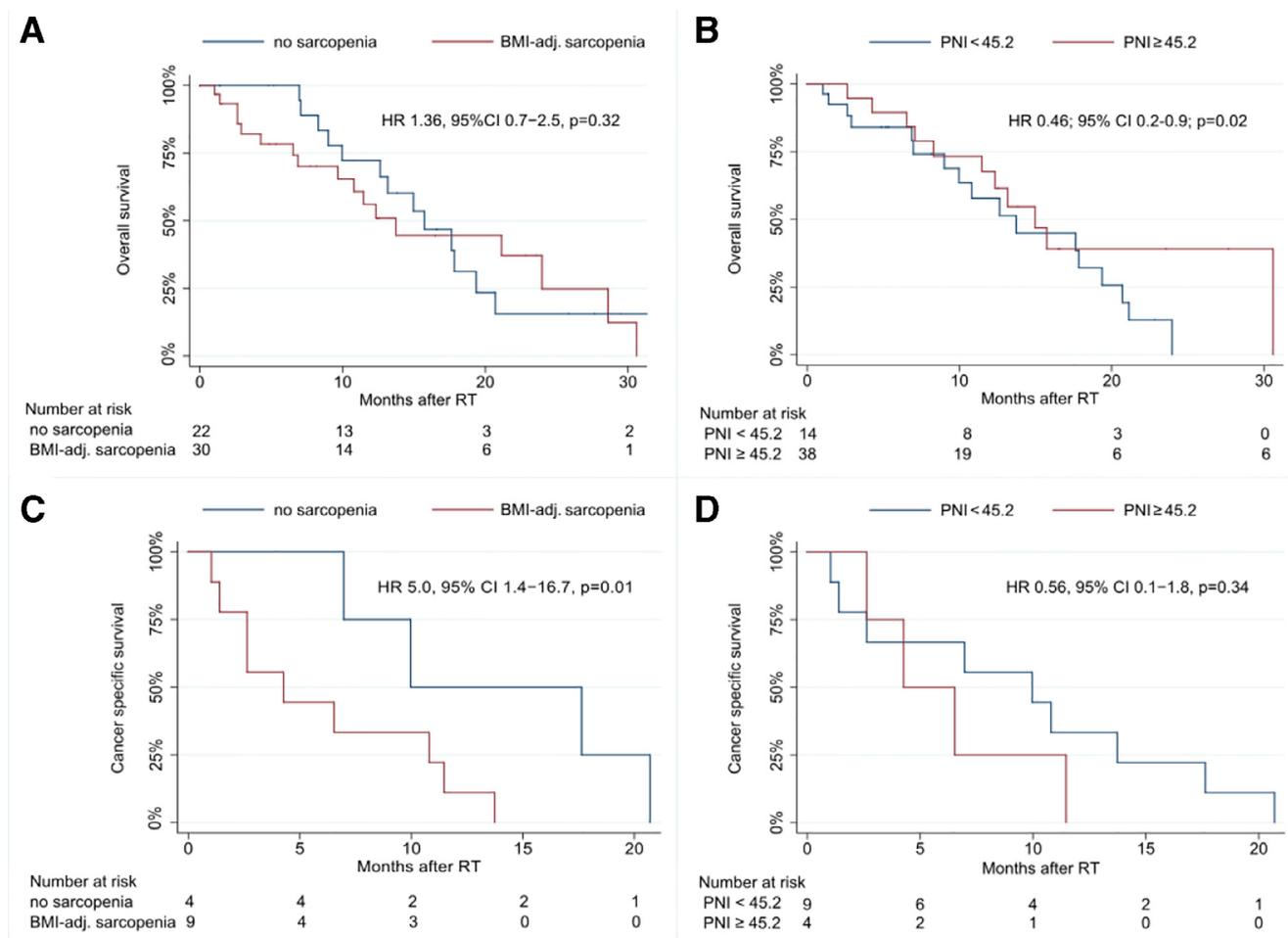


Fig. 2. Overall and cancer-specific survival of patients with high-risk urinary bladder cancer clinically considered unfit for radical cystectomy and/or systemic chemotherapy and treated, therefore, with radiotherapy, stratified by BMI-adjusted sarcopenia and prognostic nutritional index (PNI) groups. RT group survival data shown for 23.9 and 31.6 months (75% percentile levels), respectively. BMI = body mass index; RT = radiotherapy.

Table 3

Univariate Cox regression analysis evaluating the association of body composition parameters and nutritional indices with [1] overall survival and [2] cancer-specific survival in 68 patients with high-risk urinary bladder cancer clinically considered unfit for radical cystectomy and/or systemic chemotherapy and treated, therefore, with radiotherapy.

[1]	Univariate analysis for OS		
	Variable	HR	95% CI
Age	1.03	0.9–1.0	0.15
CMI	1.10	0.9–1.2	0.07
SMA (cm <sup>2</sup> )	0.99	0.9–1.0	0.51
SFA (cm <sup>2</sup> )	0.99	0.9–1.0	0.46
VFA (cm <sup>2</sup> )	0.99	0.9–1.0	0.45
SMI (cm <sup>2</sup> /m <sup>2</sup> )	0.98	0.9–1.0	0.47
Sarcopenia	1.31	0.6–2.6	0.44
BMI-adj. sarcopenia	1.36	0.7–2.5	0.32
ATV (l)	0.98	0.9–1.0	0.37
SMV (l)	0.98	0.9–1.0	0.51
VSR	1.04	0.7–1.6	0.83
VMR	0.78	0.5–1.2	0.28
BMI (kg/m <sup>2</sup> )	0.99	0.9–1.0	0.81
CONUT	0.99	0.9–1.0	0.38
PNI	0.98	0.9–1.0	0.37
PNI (<45.2)	0.46	0.2–0.9	0.02
[2]	Univariate analysis for CSS		
	Variable	HR	95% CI
Age	0.97	0.9–1.0	0.39
CMI	1.09	0.9–1.3	0.35
SMA (cm <sup>2</sup> )	0.99	0.9–1.0	0.80
SFA (cm <sup>2</sup> )	1.00	1.0–1.0	0.02
VFA (cm <sup>2</sup> )	1.00	0.9–1.0	0.48
SMI (cm <sup>2</sup> /m <sup>2</sup> )	0.98	0.9–1.0	0.73
Sarcopenia	0.60	0.1–2.2	0.45
BMI-adj. sarcopenia	5.00	1.4–16.7	0.01
ATV (l)	1.03	0.9–1.1	0.07
SMV (l)	0.98	0.8–1.1	0.80
VSR	0.90	0.4–1.9	0.80
VMR	1.39	0.7–2.5	0.29
BMI (kg/m <sup>2</sup> )	1.06	0.9–1.1	0.06
CONUT	0.99	0.9–1.0	0.43
PNI	0.98	0.9–1.0	0.17
PNI (<45.2)	0.56	0.1–1.8	0.34

n = 68.

ATV = adipose tissue volume; BMI = body mass index; CMI = comorbidity index; CONUT = controlling nutritional status; PNI = prognostic nutritional index; SFA = subcutaneous fat area; SMA = skeletal muscle area; SMI = skeletal muscle index; SMV = skeletal muscle volume; VFA = visceral fat area; VSR = visceral to subcutaneous fat ratio; VMR = visceral to skeletal muscle ratio.

[34]. Patients with larger tumors have a greater amount of weight loss compared to those with a smaller tumor [35], which could be attributable to higher metabolism.

In our analyzed patients, the median age was 82 years (IQR 75–86). A relatively high CMI of 7.5 (IQR 6–10), and 46 patients (67.6%) stratified to American Society of Anaesthesiologists' classification  $\geq 3$ , indicates that a low general health condition is a prevalent observation in our population. Similarly, the univariate analysis demonstrated

that patients with more comorbidities have a trend toward a poorer survival outcome (HR 1.1, 95% 0.9–1.2,  $P = 0.07$ ). In contrast to previous findings in the literature, the pre-treatment BMI in our cancer patients was not significantly associated with OS ( $P = 0.50$ ). The prevalence of sarcopenia is reported to be 29% to 33 % for elderly patients in the general population [36,37]. Simultaneous gain of adipose tissue and loss of skeletal muscle can occur in cancer patients and might end in the unfavorable condition of sarcopenic obesity. In women, it has been demonstrated that BMI variation does not have an association to the amount of skeletal muscle and therefore sarcopenia only needs to be BMI-adjusted in men. In our patients, after BMI-adjustment of the definition of sarcopenia according to Martin et al., the prevalence was almost equal in both sexes (53.8% in women vs. 52.7% in men). [23]. The only significant prognostic body composition parameter was BMI-adjusted sarcopenia which was associated with CSS (HR 5.0, 95% CI 1.4–16.7,  $P = 0.01$ ). A trend for longer survival is also supported by the higher SMI in the survivor group. We conclude from our findings that sarcopenia has only limited prognostic relevance for survival outcomes in elderly patients with several comorbidities, as their life expectancy is limited. Furthermore, we should be aware of the phenomenon of sarcopenic obesity as it comes along with the worst prognosis for patients.

Besides the body composition, we evaluated nutritional indices in our patients. A normal preoperative serum albumin, which is also part of the calculation formula for PNI, is associated with survival in patients undergoing RC for UCB [35,36]. In patients undergoing radiation, there are few studies supporting decreased albumin as an unfavorable prognostic biomarker [13,37]. For the calculation of the PNI, the peripheral lymphocytes and serum albumin are combined. Peripheral lymphocytes play an essential role in the cell-mediated immune response to tumor growth [38], and the serum albumin reflects nutritional intake. The controlling nutritional status calculation total serum cholesterol as a variable. However, in our patient cohort, the only significant prognostic nutritional index was the PNI (HR 10.3; 95% CI 1.1–95.8;  $P = 0.04$ ). Patients with a PNI <45.2 had a poorer OS than those with a higher PNI (HR 0.5; 95% CI 0.3–0.8;  $P = 0.01$ ). This finding supports the study of Peng et al. [36], suggesting that PNI might be a novel reliable index for patients with UCB OS that is easy to assess and modified.

Our study has several limitations that need to be considered when interpreting our results. The retrospective nature of this single center study and the small sample size with may introduce selection bias. Though sarcopenia might have a prognostic value in younger patients who undergo RT as an organ-sparing alternative treatment, because only 68 patients were eligible for the final analysis, the study was underpowered which could also explain why no statistically significant association of sarcopenia with survival outcomes was found. Weight loss throughout the course of the RT and

neutrophil to lymphocyte ratio are also known prognostic factors for UCB patients, but were not evaluated in our study, and therefore may be confounders. Furthermore, those patients who underwent RT after transurethral resection of their bladder tumor were included. This cohort is, therefore, only a subgroup of UCB patients who received suboptimal therapy because of their comorbidities. In addition, the follow-up time was short, with a median time of 12.5 months (IQR 5.1–23.5). Despite these limitations, to our knowledge, this is the first study to investigate the association of nutritional and body composition parameters, including sarcopenia, with survival outcomes in UCB patients undergoing RT. It should initiate further validation studies with larger patient cohorts that should include younger, more medically fit patients.

## 5. Conclusion

Sarcopenia is not a suitable surrogate biomarker for survival in UCB patients who are treated with RT only. This could be due to advanced age and/or the high number of comorbidities, which influence OS more than the presence of sarcopenia. Our findings underline the importance of sarcopenic obesity and state its prognostic value for CSS in patients undergoing RT for high-risk bladder cancer. Furthermore, PNI might act as prognostic biomarker for patients with UCB.

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