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Sarcopenia as a comorbidity-independent predictor of survival following radical cystectomy for bladder cancer

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Abstract

Background A multicentre study was conducted to investigate the impact of sarcopenia as an independent predictor of oncological outcome after radical cystectomy for bladder cancer.

Methods In total, 500 patients with available digital computed tomography scans of the abdomen obtained within 90 days before surgery were identified. The lumbar skeletal muscle index was measured using pre-operative computed tomography. Cancer-specific survival (CSS) and overall survival (OS) were estimated using Kaplan–Meier curves. Predictors of CSS and OS were analysed by univariable and multivariable Cox regression models.

Results Based on skeletal muscle index, 189 patients (37.8%) were classified as sarcopenic. Patients with sarcopenia were older compared with their counterparts ($P = 0.002$), but both groups were comparable regarding to gender, comorbidity, tumor, node, metastasis (TNM) stage, and type of urinary diversion (all $P > 0.05$). In total, 234 (46.8%) patients died, and of these, 145 (29.0%) died because of urothelial carcinoma of the bladder. Sarcopenic patients had significantly worse 5 year OS (38.3% vs. 50.5%; $P = 0.002$) and 5 year CSS (49.5% vs. 62.3%; $P = 0.016$) rates compared with patients without sarcopenia. Moreover, sarcopenia was associated independently with both increased all-cause mortality (hazard ratio, 1.43; 95% confidence interval 1.09–1.87; $P = 0.01$) and increased cancer-specific mortality (hazard ratio, 1.42; 95% confidence interval, 1.00–2.02; $P = 0.048$). Our results are limited by the lack of prospective frailty assessment.

Conclusions Sarcopenia has been shown to be an independent predictor for OS and CSS in a large multicentre study with patients undergoing radical cystectomy for bladder cancer.

Keywords Frailty; Skeletal muscle mass; Bladder cancer; Prognosis; Urinary bladder neoplasm

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Introduction

Radical cystectomy (RC) with bilateral pelvic lymph node dissection is the gold-standard treatment for muscle invasive urothelial carcinoma of the bladder (UCB) and for high-risk non-muscle invasive UCB resistant to intravesical therapy.[1,2] Despite curative intent, RC only provides 5 year overall survival (OS) rates of approximately 60%.[1,2] Besides histopathological characteristics, comorbidity has also been shown to affect patient outcome after RC.[3,4]

Frailty is defined as a clinical syndrome suggesting decreased physiological reserve.[5] Sarcopenia is the paucity of muscle mass, which is a key component of frailty.[6] Muscle mass decrease is directly responsible for functional impairment with loss of strength, increased likelihood of falling, and loss of autonomy.[7]

Sarcopenia has already been investigated in different tumour entities. So far, sarcopenia was identified as a poor prognostic factor in patients undergoing surgical treatment for tumours of the respiratory tract, gastrointestinal tract, malignant melanoma, UCB, and upper urinary tract urothelial carcinoma.[8–13] Furthermore, sarcopenia has been shown to be an independent prognostic factor of survival after RC for UCB, and it was strongly associated with early complications following RC.[11,13,14] However, only single-centre studies with limited patient numbers or inadequate sarcopenia classifications are available.[11,13]

The aim of our study was to assess the prevalence of adequately assessed sarcopenia in a large multicentre study and to investigate its association with OS and cancer-specific survival (CSS) in patients undergoing RC for UCB.

Patients and methods

Patients

After Institutional Review Board approval and obtaining ethics approval, 860 patients who underwent RC for UCB at three tertiary institutions between 2004 and 2014 were retrospectively identified. In 709 patients, computed tomography (CT) of the abdomen was performed as pre-operative staging, 142 were not available as digital file, 33 were not performed within 90 days prior to RC, and 32 patients had to be excluded because of poor image quality. Of 860 patients, seven patients had neoadjuvant chemotherapy (NAC) prior to RC, of whom four patients did not have a CT after completion of NAC. Three patients had a CT after NAC, but only two were available as digital file. Because of the small number, inhomogeneity of this subgroup and risk of confounding, patients who underwent NAC were excluded. The final study cohort consisted of a total of 500 patients.

All tumours were histologically confirmed as UCB. Tumour staging was performed according to the seventh edition of the American Joint Committee on Cancer/Union Internationale Contre le Cancer TNM classification.[15]

Follow-up regimens were conducted according to institutional protocols. The cause of death was determined by chart review. A patient with metastatic disease at the time of death was categorized as having died of disease.

Pre-operative computed tomography-based muscle measurement

Sarcopenia was determined by a surrogate marker: the cross-sectional skeletal muscle surface (cm^2) at the level of the third lumbar vertebra (L3) on two consecutive transversal CT images on which both vertebral spines were visible.[16] Computed tomography images were contrast enhanced or unenhanced 3- to 5-mm-thick multiplanar reconstructions on the axial plane. Of note, the partial volume effect can be neglected because of the almost cylindrical expansion of the musculature. Measurements were performed using Osirix™ version 7.0 (32 bit; http://www.osirix-viewer.com). The 'Grow Region (2D/3D Segmentation)' tool was used to automatically select all skeletal muscle mass in one transversal CT image. The distinction between different tissues is based on Hounsfield units. A threshold range of −30 to +110 Hounsfield units was used for skeletal muscle.[16] Muscles measured were the psoas, paraspinal, transverse abdominal, external oblique, internal oblique, and rectus abdominis muscles (*Figure* 1A and 1B). Manual adjustment of the selected areas was performed if necessary. The averages of the two measurements were used for calculations.

Sarcopenia

Muscle area (cm^2) was normalized for height in metres squared (m^2) and reported as lumbar skeletal muscle index (SMI) (cm^2/m^2) According to Martin *et al.*[8], sarcopenia was defined as SMI of <43 cm^2/m^2 for men with body mass index (BMI) <25 kg/m^2, SMI <53 cm^2/m^2 for men with BMI ≥ 25 kg/m^2, and SMI <41 cm^2/m^2 for women.

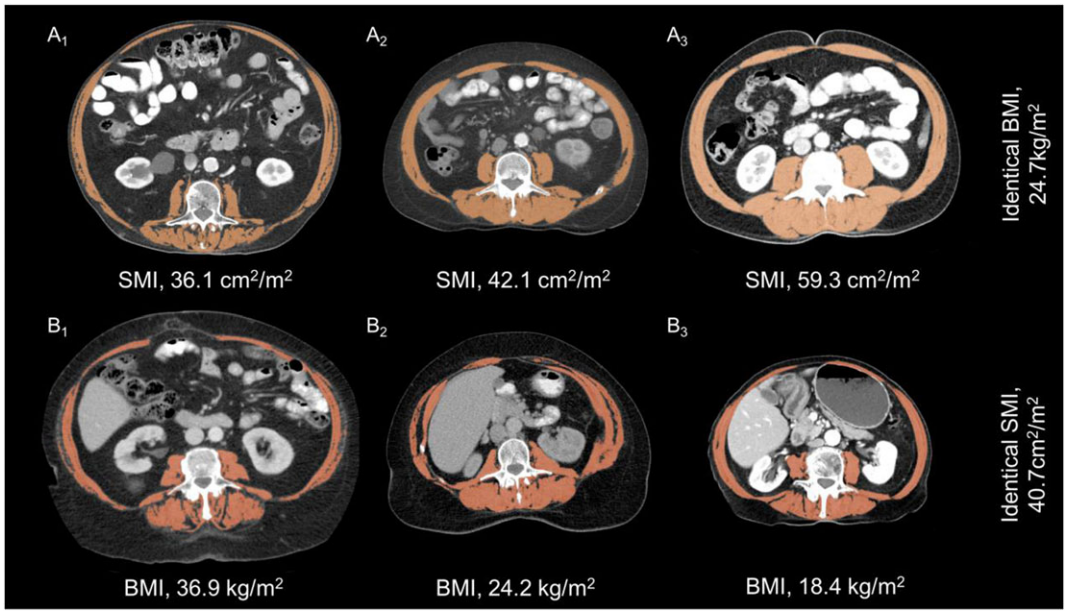
Comorbidity assessment

Comorbidity was assessed based on the information from patients' files according to the Adult Comorbidity Evaluation 27 (ACE-27), which is a validated 27-item comorbidity instrument for patients undergoing RC for UCB.[3,17]

Statistical analysis

Frequencies are presented as absolute numbers and percentages. Continuous data are presented as median with interquartile range (IQR). Differences between groups were analysed using the Pearson's χ^2 test for dichotomous parameters and the Wilcoxon–Mann–Whitney *U* test for continuous data. Survival analysis was performed with Kaplan–Meier and Cox regression analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by univariable and multivariable Cox regression analyses. For the calculation of significant predictors of survival, univariable analyses with clinically relevant parameters were performed. Significant predictors ($P < 0.05$) based on univariable analyses were included into a multivariable Cox regression analysis. *P*-values <0.05 were considered significant. To assess the validity of the Cox models, the proportional hazards assumption of each predictor variable was verified by using the Grambsch–Therneau residual-based test.[18] The type of relationship

Figure 1 (A and B) Axial computed tomography images at the third lumbar vertebra region with skeletal muscle highlighted in orange. (A_1–A_3) depict variation in skeletal muscle index (SMI) for male patients with identical body mass indices (BMIs) (24.7 kg/m^2) and different SMIs. (B_1–B_3) depict variation in BMI for sarcopenic female patients (SMI of 40.7 cm^2/m^2) and different BMIs. The orange regions represent the skeletal muscle, identified by attenuation limits of −29 to 110 Hounsfield units. The SMI is calculated by dividing the cross-sectional area of skeletal muscle (cm^2) by the patient's height squared (m^2).



between SMI and OS was tested by restricted cubic splines with 5 knots at percentiles 5%, 27.5%, 50%, 72.5% and 95% as suggested by Frank Harrell in a multivariable Cox regression model.[19] Optimal stratification, a statistical method similar to receiver operator curve analysis, was used to solve specific threshold values for SMI. Optimal stratification is based on log-rank statistics that best separate patients with respect to time to death.[20] Skeletal muscle index thresholds were already published by Martin *et al.*[8], but these values were solved in a cohort of 1.473 patients with a diagnosis of gastrointestinal or respiratory tract cancer, of whom 50% had metastatic disease. In our study, we defined threshold values related to OS for SMI, and thresholds for SMI were examined by sex and BMI and compared with the existing cut-offs. Cox regression analyses were carried out with the threshold values published by Martin *et al.*[8] Statistical analyses were conducted with SAS (version 9.4; SAS Institute, Cary, NC, USA) and R 3.2.2 for Windows (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/).

Results

The median SMI among women in the study cohort was 42.3 cm^2/m^2 (IQR, 38.1–48.1 cm^2/m^2), whereas the median SMI in men was 52.2 cm^2/m^2 (IQR, 46.8–58.1 cm^2/m^2). The overall prevalence of sarcopenia in the study population was 37.8% (189/500 patients), including 43.4% of women (43/99) and 36.2% of men (145/401). Sarcopenic patients were significantly older (median pre-operative age of 73 vs. 70 years; $P = 0.002$) but were otherwise similar regarding to comorbidity (ACE-27), TNM stage, urinary diversion, lymphovascular invasion (LVI), carcinoma *in situ*, days between CT and surgery, administration of adjuvant chemotherapy, and soft tissue surgical margins ($P > 0.05$ for all, *Table* 1). In addition, median BMI was significantly lower in sarcopenic patients compared with their counterparts (26.0 vs. 27.0 kg/m^2; $P < 0.001$). Patient characteristics are depicted in *Table* 1.

Calculated threshold values for SMI associated with lower survival in the current cohort are listed in *Table* 2. Spline curves of adjusted HR for OS show a linear correlation between 48 and 55 cm^2/m^2, while in the lower and upper quartiles, a change of SMI shows no further effect on OS (*Figure* 2). The calculated threshold values from the current cohort differed only to a little extent to the published threshold values from Martin *et al.*[8] (*Table* 2).

The median follow-up for survivors was 35 months (IQR, 20–58 months). The median overall follow-up of patients was 22 months (IQR, 10–45 months). Two hundred thirty-four (46.8%) patients died, with 145 (29%) of these dying because of UCB. In addition, patients with sarcopenia had a significantly decreased 5 year OS (38.3% vs. 50.5%, $P = 0.002$, *Figure* 3A) and CSS (49.5% vs. 62.3%, $P = 0.016$, *Figure* 3B) compared with non-sarcopenic patients.

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Table 1 Patient characteristics of sarcopenic and non-sarcopenic patients

Variables	Entire cohort (n = 500)	Sarcopenic patients (n = 189)	Non-sarcopenic patients (n = 311)	P-value
Median age at RC (IQR)	72 (65.00–78.00)	73 (66–79)	70 (63–77)	0.002
Male, n (%)	401 (80.2)	146 (77.25)	255 (82.0)	0.197
Days between CT and RC, median (IQR)	18 (8–33)	16 (6–33)	20 (10–33)	0.110
Median BMI (kg/m^2) (IQR)	26.3 (23.7–29.4)	26.0 (23.2–27.9)	27.0 (23.8–30.5)	<0.001
Underweight (<20.00)	26 (5.2)	17 (9.0)	9 (2.9)	<0.001
Normal weight (20.00–24.99)	160 (32.0)	51 (27.0)	109 (35.0)	
Overweight (25.00–29.99)	207 (41.4)	103 (54.5)	104 (33.4)	
Obese (>29.99)	107 (21.4)	18 (9.5)	89 (28.6)	
ACE-27, n (%); missing n = 3				
ACE-27: 0 (no comorbidity)	104 (20.9)	39 (20.6)	65 (21.1)	0.737
ACE-27: 1 (mild comorbidity)	154 (31.0)	64 (33.9)	90 (29.2)	
ACE-27: 2 (moderate comorbidity)	143 (28.8)	51 (27.0)	92 (29.9)	
ACE-27: 3 (severe comorbidity)	96 (19.3)	35 (18.5)	61 (19.8)	
Urinary diversion, n (%)				
Ileal conduit	249 (49.8)	85 (45.0)	164 (52.7)	0.236
Colon conduit	52 (10.4)	21 (11.1)	31 (10.0)	
Ileal neobladder	131 (26.2)	50 (26.5)	81 (26.0)	
Sigmoid neobladder	19 (3.8)	10 (5.3)	9 (2.9)	
Pouch	15 (3.0)	5 (2.6)	10 (3.2)	
Ureterocutaneostomy	34 (6.8)	18 (9.5)	16 (5.1)	
Pathological tumour stage, n (%)				
pTa	3 (0.6)	1 (0.6)	2 (0.6)	0.753
pTis	28 (5.6)	9 (4.8)	19 (6.1)	
pT1	66 (13.2)	29 (15.3)	37 (11.9)	
pT2	179 (35.8)	63 (33.3)	116 (37.3)	
pT3	161 (32.2)	65 (34.4)	96 (30.9)	
pT4	63 (12.6)	22 (11.6)	41 (13.2)	
Pathological nodal classification, n (%)				
pN0	368 (73.6)	140 (74.1)	228 (73.3)	0.985
pN1	45 (9.0)	16 (8.5)	29 (9.3)	
pN2	67 (13.4)	25 (13.2)	42 (13.5)	
pN3	4 (0.8)	2 (1.1)	2 (0.6)	
pNx	16 (3.2)	6 (3.2)	10 (3.2)	
Presence of carcinoma *in situ*, n (%)	171 (34.2)	61 (32.3)	110 (35.4)	0.479
Presence of lymphovascular invasion, n (%)	200 (40.0)	73 (38.6)	127 (40.8)	0.624
Soft tissue surgical margin				
R0	453 (90.6)	168 (88.9)	285 (91.6)	
R1	41 (8.2)	18 (9.5)	23 (7.4)	0.569
R2	6 (1.2)	3 (1.6)	3 (1.0)	
Adjuvant chemotherapy, n (%)	65 (13.0)	21 (11.1)	44 (14.1)	0.328

RC, radical cystectomy; IQR, interquartile range; BMI, body mass index; ACE-27, Adult Comorbidity Evaluation 27; CT, computed tomography.

Table 2 Skeletal muscle index threshold values significantly associated with low overall survival in the current study cohort and the cohort of Martin *et al.*[8]

	Current study cohort SMI (cm^2/m^2)		Martin *et al.*[8] SMI (cm^2/m^2)	
BMI (kg/m^2)	Men	Women	Men	Women
<25	48	40	43	41
≥25	52	43	53	41

In univariable analysis, age, sarcopenia, higher ACE-27, higher pathological tumour (pT) stage, lymph node metastasis, LVI, positive surgical margins, and adjuvant chemotherapy were significantly associated with decreased OS and CSS after RC for UCB (*Tables* 3 and 4). In the multivariable Cox regression analysis, age, comorbidity (ACE-27), pathological tumour and nodal stage, LVI, surgical margin rates, and administration of adjuvant chemotherapy as additional covariates, the presence of sarcopenia remained significantly associated with increased all-cause mortality after RC (HR, 1.43; 95% CI 1.09–1.87; P = 0.01). This model provides a c-index of 0.754. The same multivariable model with the SMI cut-offs derived from our cohort provides a c-index of 0.760. In addition, sarcopenia was also significantly associated with increased cancer-specific mortality (HR, 1.42; 95% CI, 1.00–2.02; P = 0.048) after adjusting for age, ACE-27, pathological tumour and nodal stage, LVI surgical margin rates after RC, and administration of adjuvant chemotherapy (*Table* 4). The

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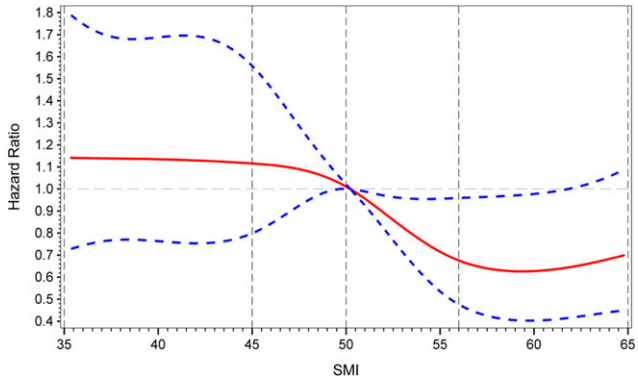
Figure 2 Restricted cubic spline with 5 knots at percentiles 5%, 27.5%, 50%, 72.5%, and 95% (vertical dotted lines) showing the relationship between skeletal muscle index (SMI) (cm^2/m^2) and hazard ratios of overall survival (red line). Ninety-five per cent confidence interval is indicated by the dotted blue lines. The model is adjusted for significant covariates depicted in *Table* 3.



multivariable model regarding CSS provides a c-index of 0.802, and the multivariable model with our SMI cut-offs provides a c-index of 0.801. No violations of the proportional hazards assumption and the linearity assumption were found.

Discussion

The aim of the present study was to assess the frequency of sarcopenia and determine its impact on survival in a large multicentre cohort of patients undergoing RC for UCB. We defined sarcopenia by sex-specific and BMI-specific threshold values according to the Martin criteria, which were determined from 1473 cancer patients using optimal stratification of lower survival and therefore represents the most accurate CT-derived sarcopenia classification.[8]

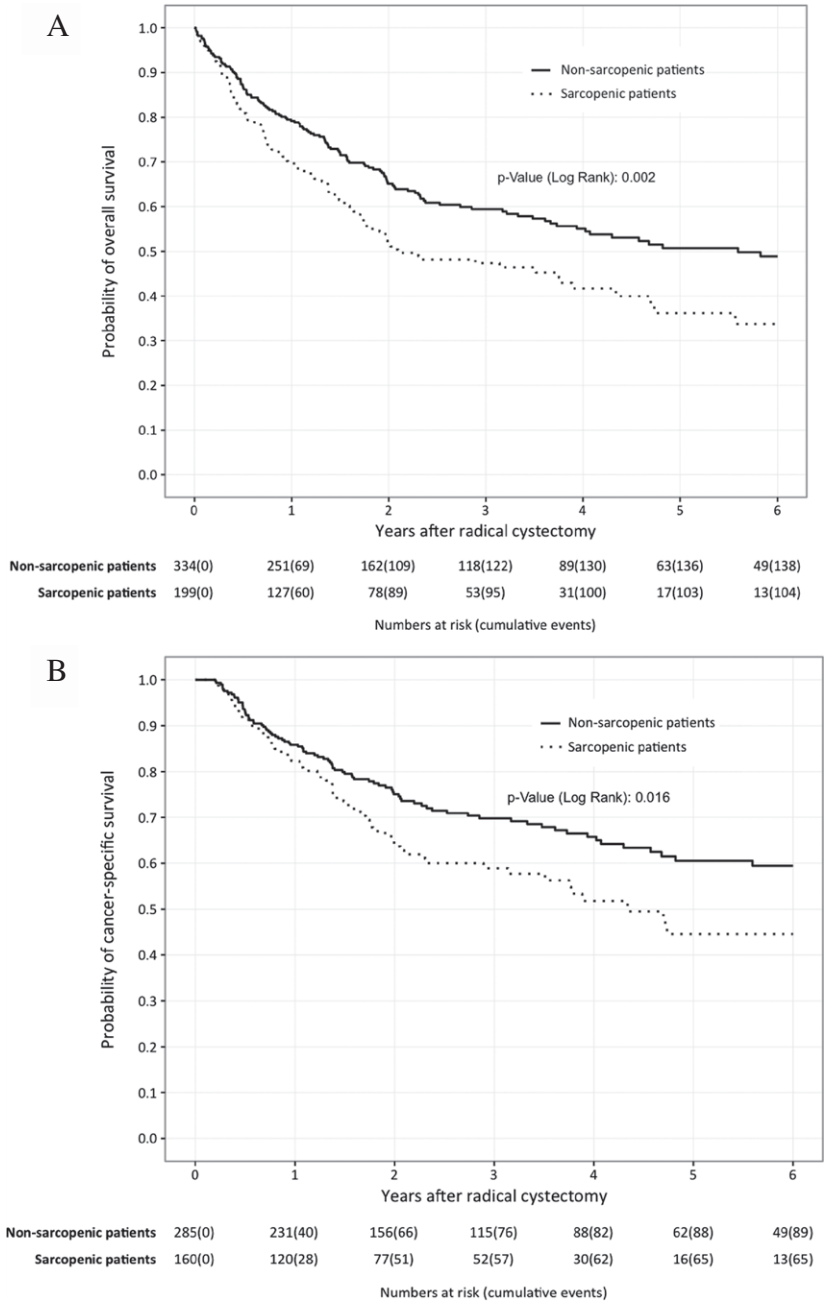
Thirty-seven per cent of the patients in our cohort were classified as sarcopenic. In a recently published Japanese single-centre study of 136 patients undergoing RC for UCB, 65 patients (47.8%) were classified as sarcopenic.[13] Although in both cohorts sarcopenia has been classified according to the Martin criteria, differences in sarcopenia frequencies might be explained because of the retrospective and non-consecutive fashion of the cohorts. In contrast, Psutka *et al*.[11] reported a study of 205 patients, of whom 141 patients (68.8%) were sarcopenic according to the criteria defined by Fearon *et al*.[6] The applied classification by Psutka *et al*.[11] has two important drawbacks: first, the used CT-based threshold values were converted from dual energy X-ray absorptiometry based threshold values, which were defined as values two standard deviations below the sex-specific means in young healthy adults. This conversion was based on only 31 patients, who underwent both dual energy X-ray absorptiometry and CT.[21,22] Second, the threshold values were not BMI specific. The threshold values reported from Martin *et al*.[8] (*Table* 2) were calculated from a large patient cohort with a diagnosis of gastrointestinal and respiratory tract cancer, of whom 50% had metastatic disease. To investigate whether these established SMI threshold values are suitable for non-metastatic bladder cancer patients, SMI threshold values from our cohort were calculated, which differed only to a little extent compared with the established values from Martin *et al*.[8] (*Table* 2). In addition, the predictive capacity for OS and CSS showed only a minimal improvement and confirms the applicability in bladder cancer patients.

The most important finding in the current study is the independent association of sarcopenia and increased cancer-specific mortality (HR, 1.42; 95% CI, 1.00–2.02; P = 0.048) and increased all-cause mortality (HR, 1.43; 95% CI 1.09–1.87; P = 0.01). These results are in concordance with the previous published literature. Psutka *et al*.[11] were able to demonstrate that sarcopenia was an independent predictor of CSS (HR 2.14; 95% CI 1.24–3.71; P = 0.007) and OS (HR 1.93; 95% CI 1.23–3.00; P = 0.004). Hirasawa *et al*.[13] demonstrated that sarcopenia was an independent predictor of CSS in a single-centre cohort of 136 patients (HR 2.3; 95% CI 1.2–4.4; P = 0.015). However, this study was limited by a small sample size and a small number of events (n = 42), and therefore, an overfitting bias in the multivariate analysis must be taken into account. In contrast, a study reported by Smith *et al*.[10] including 200 patients undergoing RC for UCB could not demonstrate an association between survival and sarcopenia, which was classified by the total psoas area. However, their study was limited by a median follow-up of 16 months, and sarcopenia was assessed by total psoas area, which is lacking validated threshold values. Even in metastatic UCB, sarcopenia was shown to be an independent predictor of poor CSS (HR 2.07; 95% CI 1.01–4.67; P = 0.045).[23]

Comorbidity indices such as the ACE-27 score and the Charlson comorbidity index have been evaluated as predictors for survival after RC for UCB.[3,4] Our findings clearly demonstrate that sarcopenia is an important predictor of survival in UCB independent of the degree of comorbidity. Assessment of sarcopenia by calculation of SMI is quick and simple using free software and CT images without special training. Furthermore, sarcopenia is a highly objective measure because one can estimate the composition of the human body using CT with a precision error of 1.4%.[24]

Sarcopenia has important implications for clinical practice, because the decline of skeletal muscle mass is potentially reversible.[25] Adequate calorie and protein intake, combined with resistance training, are the key components in the management of sarcopenic patients.[26,27] A prospective Japanese single-centre study demonstrated that sarcopenic patients older than 65 years undergoing gastrectomy for gastric cancer had significantly lower caloric and

Figure 3 (A and B) Kaplan–Meier plots depicting overall survival and cancer-specific survival in sarcopenic and non-sarcopenic patients undergoing radical cystectomy for urothelial carcinoma of the bladder.



protein intake per day and had significantly more severe complications.[28] Interestingly, the same research group investigated 22 sarcopenic patients undergoing gastrectomy for gastric cancer and established a pre-operative exercise and nutritional support programme, which resulted in a significantly higher calorie and protein intake per day and increased handgrip strength.[29] In addition, four of the 22 investigated patients became non-sarcopenic after the support programme. In the previously mentioned study by Hirasawa *et al.*,[13] it was demonstrated that sarcopenic patients showed significantly lower haemoglobin levels than non-sarcopenic patients. As recently shown in a randomized controlled trial, patients with iron-deficiency anaemia undergoing major open abdominal surgery showed significantly reduced blood transfusions and length of hospital stay, when administered perioperative intravenous iron.[30]

Table 3 Univariate and multivariable Cox regression models addressing prediction of overall survival after radical cystectomy for urothelial carcinoma of the bladder

	Univariate analysis			Multivariable analysis		
Variables	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Age at RC (continous)	1.043	1.03–1.06	<0.001	1.03	1.01–1.04	0.002
Gender (reference: male)	1.28	0.94–1.74	0.123	—	—	—
Presence of sarcopenia (reference: absence)	1.50	1.16–1.94	0.002	1.43	1.09–1.87	0.01
pT stage						
pT2 (reference: ≤pT1)	1.12	0.71–1.78	0.633	0.98	0.61–1.58	0.94
pT3 (reference: ≤pT1)	3.36	2.19–5.14	<0.001	1.95	1.22–3.14	0.006
pT4 (reference: ≤pT1)	4.46	2.78–7.17	<0.001	2.11	1.20–3.70	0.009
Presence of CIS (reference: absence)	0.78	0.59–1.02	0.071	—	—	—
Presence of LVI (reference: absence)	2.86	2.20–3.72	<0.001	1.72	1.25–2.38	0.001
Positive soft tissue surgical margin (reference: negative)	4.39	3.14–6.147	<0.001	2.41	1.63–3.55	<0.001
pN stage						
pN+ (reference: pN0)	3.15	2.39–4.14	<0.001	1.73	1.24–2.41	0.001
pNx (reference: pN0)	2.90	1.60–5.24	<0.001	1.81	0.98–3.34	0.056
ACE-27						
ACE-27: 1 (reference: ACE-27 0)	1.22	0.81–1.84	0.333	1.14	0.76–1.70	0.526
ACE-27: 2 (reference: ACE-27 0)	1.60	1.08–2.37	0.019	1.56	1.04–2.34	0.033
ACE-27: 3 (reference: ACE-27 0)	1.60	1.08–2.37	0.004	1.75	1.12–2.73	0.013
Adjuvant chemotherapy (reference: not administered)	1.64	1.17–2.28	0.004	0.83	0.55–1.23	0.347
Body mass index						
Underweight (reference: normal weight)	0.80	0.59–1.08	0.140	—	—	—
Overweight (reference: normal weight)	0.81	0.57–1.16	0.258	—	—	—
Obese (reference: normal weight)	1.15	0.65–2.03	0.625	—	—	—

CI, confidence interval; RC, radical cystectomy; CIS, carcinoma *in situ*; LVI, lymphovascular invasion; ACE-27, Adult Comorbidity Evaluation 27.

Table 4 Univariate and multivariable Cox regression models addressing the prediction of cancer-specific survival after radical cystectomy for urothelial carcinoma of the bladder

	Univariate analysis			Multivariable analysis		
Variables	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Age at RC (continous)	1.03	1.01–1.05	0.002	1.01	0.99–1.033	0.206
Gender (reference: male)	1.32	0.89–1.96	0.163	—	—	—
Presence of sarcopenia (reference: absence)	1.49	1.07–2.07	0.018	1.42	1.00–2.02	0.048
pT stage						
pT2 (reference: ≤pT1)	1.64	0.80–3.35	0.184	1.33	0.64–2.77	0.442
pT3 (reference: ≤pT1)	6.71	3.46–13.02	<0.001	3.54	1.73–7.24	0.001
pT4 (reference: ≤pT1)	8.57	4.20–17.46	<0.001	3.20	1.41–7.27	0.005
Presence of CIS (reference: absence)	0.78	0.55–1.11	0.164	—	—	—
Presence of LVI (reference: absence)	3.72	2.65–5.22	<0.001	1.81	1.20–2.73	0.005
Positive soft tissue surgical margin (reference: negative)	5.89	3.92–8.83	<0.001	3.24	2.01–5.23	<0.001
pN stage						
pN+ (reference: pN0)	4.14	2.95–5.81	<0.001	1.79	1.19–2.70	0.005
pNx (reference: pN0)	2.57	1.12–5.91	0.026	1.75	0.74–4.15	0.202
ACE-27						
ACE-27: 1 (reference: ACE-27 0)	1.15	0.70–1.89	0.588	1.13	0.68–1.89	0.639
ACE-27: 2 (reference: ACE-27 0)	1.34	0.82–2.20	0.249	1.49	0.90–2.50	0.130
ACE-27: 3 (reference: ACE-27 0)	1.74	1.04–2.92	0.036	1.81	1.03–3.17	0.039
Adjuvant chemotherapy (reference: not administered)	2.72	1.87–3.94	<0.001	1.11	0.70–1.75	0.67
Body mass index						
Underweight (reference: normal weight)	0.85	0.59–1.24	0.394	—	—	—
Overweight (reference: normal weight)	0.75	0.47–1.19	0.221	—	—	—
Obese (reference: normal weight)	0.79	0.34–1.84	0.587	—	—	—

CI, confidence interval; RC, radical cystectomy; CIS, carcinoma *in situ*; LVI, lymphovascular invasion; ACE-27, Adult Comorbidity Evaluation 27; BMI, body mass index.

Perioperative iron transfusion could therefore complement the nutritional support programme in sarcopenic patients with iron-deficiency anaemia. In addition, the prevention of muscle loss is a necessary precondition for autonomy for older people. Food supplements with proteins, leucine, vitamin D, and antioxidants delay progression of sarcopenia and also stimulate muscular protein synthesis.[31,32] Alternatively, anabolic hormones such as testosterone, oestrogen, and growth factors can play a role in the prevention, delay, and regression of sarcopenia.[32]

To the best of our knowledge, this is the largest and first multicentre study (n = 500) reporting sarcopenia as a prognostic factor in patients undergoing RC, classifying sarcopenia according to the Martin criteria.[8] A further strength of the current paper is that the multivariate model was adjusted for comorbidity, which is an independent predictor of survival after RC for UCB.[3] In our analyses, ACE-27 was used as quantification tool for comorbidity, as it is the most accurate comorbidity index and it has been robustly evaluated in 17 712 cancer patients.[17]

Our study is not free of limitations. In this survey, we collected data from 500 patients in a non-consecutive fashion due to its retrospective nature. In addition, the current study was limited by the finding that many of the patients who underwent RC during 2004–2014 did not have digital CT scans available for SMI analysis and therefore were excluded from the final analysis. Given its retrospective nature, we were unable to correlate SMI with other metrics of frailty such as performance status on patient questionnaires or walking speed or grip strength tests and nutritional status. To overcome this limitation, a prospective multicentre study should be performed to acquire a consecutive patient cohort with a prospective frailty assessment. However, the assessment of skeletal muscle mass was not limited because of the prospective acquisition of CT images. A further notable limitation of the study is the reduced frequency of patients undergoing NAC, which have therefore not been included in the final analysis. Even though NAC frequencies of 20% have been reported in the USA in 2010, a prospective European RC study from 2011 demonstrated frequency rates of 2%, which is in concordance with our study.[33,34] However, to investigate the impact of sarcopenia in patients undergoing NAC, further studies are needed.

Taken together, sarcopenia is an objective risk factor for prediction of CSS and OS in patients with UCB undergoing RC. The identification of patients with sarcopenia is important as their outcome may be improved by pre-operative exercise and nutritional support programmes prior to RC.

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The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015.[35]

Conflict of interest

None declared.

References

1. Madersbacher S, Hochreiter W, Burkhard F, Thalmann GN, Danuser H, Markwalder R, et al. Radical cystectomy for bladder cancer today—a homogeneous series without neoadjuvant therapy. *J Clin Oncol: Official Journal of the American Society of Clinical Oncology* 2003;**21**:690–696.
2. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol: Official Journal of the American Society of Clinical Oncology* 2001;**19**:666–675.
3. Mayr R, May M, Martini T, Lodde M, Comploj E, Pycha A, et al. Comorbidity and performance indices as predictors of cancer-independent mortality but not of cancer-specific mortality after radical cystectomy for urothelial carcinoma of the bladder. *Eur Urol* 2012;**62**:662–670.
4. Boorjian SA, Kim SP, Tollefson MK, Carrasco A, Cheville JC, Thompson RH, et al. Comparative performance of comorbidity indices for estimating perioperative and 5-year all cause mortality following radical cystectomy for bladder cancer. *J Urol* 2013;**190**:55–60.
5. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *The Journals of Gerontology Series A, Biol Sci Med Sci* 2001;**56**:M146–M156.
6. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;**12**:489–495.
7. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 2002;**50**:889–896.
8. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013;**31**:1539–1547.
9. Sabel MS, Lee J, Cai S, Englesbe MJ, Holcombe S, Wang S. Sarcopenia as a prognostic factor among patients with stage III melanoma. *Ann Surg Oncol* 2011;**18**:3579–3585.
10. Smith AB, Deal AM, Yu H, Boyd B, Matthews J, Wallen EM, et al. Sarcopenia as a predictor of complications and survival following radical cystectomy. *J Urol* 2014;**191**:1714–1720.
11. Psutka SP, Carrasco A, Schmit GD, Moynagh MR, Boorjian SA, Frank I, et al. Sarcopenia in patients with bladder cancer undergoing radical cystectomy: impact on cancer-specific and all-cause mortality. *Cancer* 2014;**120**:2910–2918.
12. Ishihara H, Kondo T, Omae K, Takagi T, Iizuka J, Kobayashi H, et al. Sarcopenia predicts survival outcomes among patients with urothelial carcinoma of the upper urinary tract undergoing radical nephroureterectomy: a retrospective multi-institution study. *Int J Clin Oncol* 2016;**22**:136–144.
13. Hirasawa Y, Nakashima J, Yunaiyama D, Sugihara T, Gondo T, Nakagami Y, et al. Sarcopenia as a novel preoperative prognostic predictor for survival in patients with bladder cancer undergoing radical cystectomy. *Ann Surg Oncol* 2016;**23**:1048–1054.
14. Wan F, Zhu Y, Gu C, Yao X, Shen Y, Dai B, et al. Lower skeletal muscle index and early complications in patients undergoing radical cystectomy for bladder cancer. *World J Surg Oncol* 2014;**12**:14.
15. Sobin LHG, MK, Wittekind C, International Union against Cancer. ed. 7. *TNM Classification of Malignant Tumours*. Hoboken, NJ: Wiley-Blackwell; 2010.
16. Reisinger KW, van Vugt JL, Tegels JJ, Snijders C, Hulsewé KW, Hoofwijk AG, et al. Functional compromise reflected by

sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. *Ann Surg* 2014;**261**:345–52.
17. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA* 2004;**291**:2441–2447.
18. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994;**81**: 515–526.
19. Harrell FE. Regression Modeling Strategies. In *With Applications to Linear Models, Logistic Regression, and Survival Analysis*. Springer Series in Statistics. New York: Springer; 2001.
20. Williams, BA, Mandrekar, JN, Mandrekar, SJ, Cha, SS, Furth, AF. Finding optimal cutpoints for continuous covariates with binary and time-to-event outcomes, in technical report series #79. 2006: Rochester, MN
21. Gallagher D, Visser M, De Meersman RE, Sepúlveda D, Baumgartner RN, Pierson RN, et al. Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. *J Appl Physiol (1985)* 1997;**83**:229–239.
22. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008;**33**:997–1006.
23. Taguchi S, Akamatsu N, Nakagawa T, Gonoi W, Kanatani A, Miyazaki H, et al. Sarcopenia evaluated using the skeletal muscle index is a significant prognostic factor for metastatic urothelial carcinoma. *Clin Genitourin Cancer* 2016;**14**:237–243.
24. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol (1985)* 1998;**85**:115–122.
25. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010;**39**:412–423.
26. Morley JE, Argiles JM, Evans WJ, Bhasin S, Cella D, Deutz NE, et al. Nutritional recommendations for the management of sarcopenia. *J Am Med Dir Assoc* 2010;**11**:391–396.
27. Peterson MD, Sen A, Gordon PM. Influence of resistance exercise on lean body mass in aging adults: a meta-analysis. *Med Sci Sports Exerc* 2011;**43**:249–258.
28. Fukuda Y, Yamamoto K, Hirao M, Nishikawa K, Nagatsuma Y, Nakayama T, et al. Sarcopenia is associated with severe postoperative complications in elderly gastric cancer patients undergoing gastrectomy. *Gastric Cancer* 2016;**19**:986–993.
29. Yamamoto K, Nagatsuma Y, Fukuda Y, Hirao M, Nishikawa K, Miyamoto A, et al. Effectiveness of a preoperative exercise and nutritional support program for elderly sarcopenic patients with gastric cancer. *Gastric Cancer* 2016.
30. Froessler B, Palm P, Weber I, Hodyl NA, Singh R, Murphy EM. The important role for intravenous iron in perioperative patient blood management in major abdominal surgery: a randomized controlled trial. *Ann Surg* 2016;**264**:41–46.
31. Robinson S, Cooper C, Aihie Sayer A. Nutrition and sarcopenia: a review of the evidence and implications for preventive strategies. *J Aging Res* 2012;**2012**:510801.
32. Waters DL, Baumgartner RN, Garry PJ, Vellas B. Advantages of dietary, exercise-related, and therapeutic interventions to prevent and treat sarcopenia in adult patients: an update. *Clin Interv Aging* 2010;**5**:259–270.
33. Reardon ZD, Patel SG, Zaid HB, Stimson CJ, Resnick MJ, Keegan KA, et al. Trends in the use of perioperative chemotherapy for localized and locally advanced muscle-invasive bladder cancer: a sign of changing tides. *Eur Urol* 2015;**67**:165–170.
34. Martini T, Gilfrich C, Mayr R, Burger M, Pycha A, Aziz A, et al. The use of neoadjuvant chemotherapy in patients with urothelial carcinoma of the bladder: current practice among clinicians. *Clin Genitourin Cancer* 2016;**15**:356–362.
35. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015. *J Cachexia Sarcopenia Muscle* 2015;**6**:315–316.