Original Article

Sarcopenia in Patients With Bladder Cancer Undergoing Radical Cystectomy

Impact on Cancer-Specific and All-Cause Mortality

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BACKGROUND: The authors evaluated sarcopenia as a predictor of cancer-specific survival (CSS) and overall survival (OS) among patients with urothelial cancer of the bladder undergoing radical cystectomy (RC). **METHODS:** The lumbar skeletal muscle index (SMI) of 205 patients treated with RC for urothelial cancer between 2000 and 2007 was measured. Sarcopenia was classified according to international consensus definitions (SMI of < 55 cm^2/m^2 for men and < 39 cm^2/m^2 for women). The CSS and OS were estimated using the Kaplan-Meier method and compared with the log-rank test. Variables associated with CSS and all-cause mortality were summarized with hazard ratios (HRs). **RESULTS:** Of 205 patients, 141 (68.8%) were sarcopenic. Patients with sarcopenia were older, but were otherwise similar to patients without sarcopenia with respect to sex, Charlson comorbidity index, American Society of Anesthesiologists score, Eastern Cooperative Oncology Group performance status, receipt of neoadjuvant chemotherapy, TNM stage of disease, and tumor grade ($P > .05$ for all). The median follow-up was 6.7 years, during which time 135 patients died, including 91 who died of bladder cancer. Sarcopenic patients had significantly worse 5-year CSS (49% vs 72%; $P = .003$) and OS (39% vs 70%; $P = .003$) compared with patients without sarcopenia. Moreover, sarcopenia was found to be independently associated with both increased CSS (HR, 2.14; $P = .007$) and all-cause mortality (HR, 1.93; $P = .004$) on multivariable analysis. **CONCLUSIONS:** The presence of sarcopenia was found to significantly increase a patient's risk of CSS and all-cause mortality after undergoing RC for bladder cancer. ***Cancer*** **2014;120:2910-8.** *© 2014 American Cancer Society.*

KEYWORDS: sarcopenia, mortality, frailty, bladder cancer, radical cystectomy, survival.

INTRODUCTION

In 2013, bladder cancer was diagnosed among 72,570 individuals in the United States, resulting in 15,210 deaths.[1] Bladder cancer most commonly affects the elderly and those with significant comorbidity and impaired performance status.[2-4] Radical cystectomy (RC) remains the gold standard of treatment in patients with muscle-invasive urothelial carcinoma (UC). Unfortunately, even in contemporary series, overall survival (OS) rates at 5 years after RC are 42% to 58%,[5,6] with 90-day mortality rates of up to 9% reported at high-volume centers.[3]

Of central importance in treatment planning is consideration of the patient-related factors that impact a patient's ability to tolerate a major surgical intervention such as RC. Recent studies have highlighted the substantial contribution of comorbidity and performance status to surgical outcomes as well as inferior long-term survival after RC.[7,8] However, comorbidity and performance status remain generally subjective measures that can be difficult to define and even more challenging to standardize. Accordingly, the reliability of the most widely accepted and commonly used scoring systems, including the Charlson comorbidity index (CCI), the American Association of Anesthesiologists (ASA) score, and the Eastern Cooperative Oncology Group (ECOG) performance status, has been questioned with respect to their ability to identify those patients at highest risk of perioperative morbidity and mortality.[9]

Involuntary weight loss and cachexia, which are hallmarks of advanced malignancy, have long been associated with diminished survival.[10] Sarcopenia specifically describes the severe wasting of skeletal muscle, and is classified according to

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sex-specific international consensus definitions based on the skeletal muscle index (SMI), which may be reproducibly measured on axial computed tomography (CT).[11] Recently, sarcopenia has been associated with markedly worse OS and cancer-specific survival (CSS) in patients with melanoma as well as breast, pancreatic, colorectal, and hepatobiliary cancer.[12-18] Taken together, these findings suggest that sarcopenia may function as an objective composite measure, representing both the burden of comorbidity as well as overall frailty. As such, sarcopenia has been touted as an important feature to be considered in not only treatment planning and decision-making regarding fitness for surgery but also in counseling patients regarding expected outcomes.

Therefore, the objective of the current study was to describe the prevalence of sarcopenia in a cohort of patients with bladder cancer who were treated with RC, and to evaluate the impact of sarcopenia on both CSS and OS.

MATERIALS AND METHODS

After Institutional Review Board approval, we identified 414 patients treated with RC using standard techniques for nonmetastatic (M0) UC at the study institution between 2000 and 2007. Axial CT images obtained within 30 days of surgery previously have been found to accurately represent muscle status at the time of surgery,[14] and are the preferred imaging modality for analysis of sarcopenia.[19] For 198 patients, preoperative digital axial CT images were not available within 30 days of surgery, and therefore these patients were excluded. To assess for possible bias introduced by the missing digital imaging, clinicopathologic features and survival of patients with missing data were compared with patients comprising the analytic cohort. An additional 11 patients had CT images that were unable to be analyzed due to CT artifact due to patient malposition on the scanner or poor image quality, leaving 205 patients available for analysis. The median time between the date of the scan and the surgical date was 12 days (interquartile range [IQR], 6 days-22 days).

Two radiologists (G.D.S. and M.R.M.) identified the single axial image at the level of the third lumbar vertebrae (L3) on which both transverse processes were fully observed, which was then converted to the Digital Imaging and Communications in Medicine (DICOM) format. The cross-sectional area of all skeletal muscle at L3 including the rectus abdominus; internal, external, and lateral obliques; psoas; quadratus lumborum; and erector spinae muscles was measured using the attenuation thresholds of −29 Hounsfield units (HU) to +150 HU[20] with Slice-O-Matic software (version 5.0; TomoVision, Montreal, Quebec, Canada). Image analysis was performed by 1 investigator (S.P.P.) who was blinded to patient outcomes. Figure 1 depicts representative axial CT images at the level of L3 in 2 patients with and without sarcopenia, but with a similar body mass index (BMI).

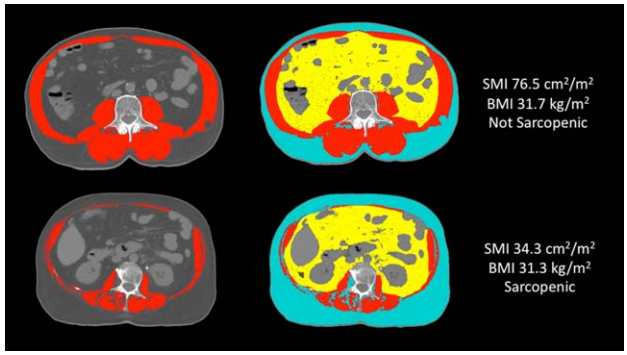

Figure 1. Two analyzed axial computed tomography images at the third lumbar vertebrae depict (A) a male patient with sarcopenia (skeletal muscle index [SMI] of 76.5 cm^2/m^2) compared with (B) a male patient with a normal SMI (SMI of 34.3 cm^2/m^2) with similar body mass indices (BMIs) (BMI of 31.7 kg/m^2 vs 31.3 kg/m^2). The red regions represent the skeletal muscle, identified by attenuation limits of −29 Hounsfield units (HU) to 150 HU. The SMI is calculated by dividing the cross-sectional area of skeletal muscle by the patient's height squared. The yellow and blue regions represent visceral and intramuscular/subcutaneous adipose tissue, identified within attenuation limits of −150 HU to −30 HU and −190 HU to −30 HU, respectively.

The lumbar SMI was calculated by normalizing skeletal muscle area by height (m^2) and reported as cm^2/m^2. The sex-specific international consensus definitions of sarcopenia, based on 2 standard deviations below the norm for young healthy adults (SMI of < 55 cm^2/m^2 for men and < 39 cm^2/m^2 for women), were used to classify patients as sarcopenic versus not sarcopenic.[19]

Statistical Analysis

Clinicopathological variables were compared between the sarcopenic and nonsarcopenic patients, including age, race, sex, BMI (in kg/m^2), ECOG performance status, ASA score, CCI, history of preoperative systemic chemotherapy or radiotherapy, preoperative serum albumin and hemoglobin, pathological tumor and lymph node stage, tumor grade (grade 1 or 2 vs 3), extent of lymph node dissection, lymphovascular invasion (LVI), and pathological surgical margin status. All pathological specimens were rereviewed by a single genitourinary pathologist (J.C.C.). Continuous features were summarized with medians and IQRs and were compared between patients with and without sarcopenia using the Wilcoxon rank sum test.

TABLE 1. Comparison of Clinicopathological Features Between Patients With and Without Sarcopenia

Feature	Nonsarcopenic Patients N = 64 (31.2%)	Sarcopenic Patients N = 141 (68.9%)	Total N = 205	*P*
Median age at RC (IQR)	67.5 (59.0-75.5)	72 (67-78)	71 (63-78)	.002
Sex, no. (%)				
Female	12 (18.8)	15 (10.6%)	27 (13.2%)	.11
Male	52 (81.3)	126 (89.4%)	178 (86.8%)	
Median preoperative albumin, g/dL (IQR)[a]	4.2 (3.6-4.4)	4.0 (3.6-4.3)	4.1 (3.6-4.3)	.42
Median preoperative hemoglobin, g/dL (IQR)	13.9 (12.6-14.9)	13.8 (12.4-14.7)	13.8 (12.4-14.8)	.46
Median BMI, kg/m^2 (IQR)	31.2 (28.1-34.7)	27 (23.9-29.5)	27.7 (24.6-31.3)	<.0001
Charlson comorbidity index, no. (%)				
≤2	20 (31.3)	39 (27.7)	59 (28.8)	.52
3-4	10 (15.6)	16 (11.3)	26 (12.7)	
≥5	34 (53.1)	86 (61)	120 (58.5)	
ASA score, no. (%)				
1	0 (0)	1 (0.7)	1 (0.5)	.53
2	24 (37.5)	62 (44)	86 (42)	
≥3	40 (62.5)	78 (55.3)	118 (57.6)	
ECOG performance status, no. (%)				
Missing	1	1	2	.78
0	51 (81)	115 (82.1)	166 (81.8)	
1	9 (14.3)	16 (11.4)	25 (12.3)	
≥2	3 (4.8)	9 (6.4)	12 (5.9)	
Preoperative systemic therapy, no. (%)	5 (7.8)	13 (9.4)	18 (8.8)	.74
Preoperative radiotherapy, no. (%)	2 (3.1)	5 (3.5)	7 (3.4)	.88
Pathologic tumor stage, no. (%)				
≤pT1	24 (37.5)	52 (36.9)	76 (37.1)	.56
pT2	13 (20.3)	31 (22)	44 (21.5)	
pT3	24 (37.5)	44 (31.2)	68 (33.2)	
pT4	3 (4.7)	14 (9.9)	17 (8.3)	
Pathologic N classification, no. (%)				
pN0/x	53 (82.8)	115 (81.6)	168 (82)	.83
pN1	11 (17.2)	26 (18.4)	37 (18)	
Classification of primary tumor grade,[b] no. (%)				
Missing	0	1	1	.10
Grade 1/2	35 (54.7)	59 (42.1)	94 (46.1)	
Grade 3	29 (45.3)	81 (57.9)	110 (53.9)	
Lymphovascular invasion, no. (%)	13 (24.5)	37 (31.4)	50 (29.2)	.36
Median no. of lymph nodes dissected (IQR)	10 (4-24)	12 (5-18)	11 (5-20)	.49
Positive peripheral tumor margin, no. (%)	1 (1.8)	7 (5.7)	8 (4.5)	.25

Abbreviations: ASA, American Association of Anesthesiologists; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; RC, radical cystectomy.

[a] Serum albumin was assessed within the 90 days prior to surgery or 14 days postoperatively and was available for a total of 102 patients, 68 of whom were sarcopenic and 34 of whom were not sarcopenic. The median time between the collection of albumin and surgery was 14 days (IQR, 7 days-23 days).

[b] WHO 1999 grading system.

Categorical features were summarized with frequency counts and percentages and compared using the chi-square test and Cochran-Armitage test for trend.

The primary outcomes of interest were CSS and OS. Disease and vital statuses for patients in our institutional Cystectomy Registry are updated yearly by direct contact with the patient and verified with the patient's local physician. Cause of death is confirmed via death certificate.

CSS and OS were estimated using the Kaplan-Meier method and compared with the log-rank test. Disease recurrence was defined as local pelvic tumor recurrence or distant metastasis occurring > 30 days after RC, excluding metachronous upper tract cancers. Associations with time to death from any cause and death from UC were evaluated by univariable and multivariable Cox proportional hazards regression models and summarized with hazards ratios (HRs) and 95% confidence intervals (95% CIs). All features that were found to be statistically significant predictors on univariable analysis for both outcomes of interest were included in the final multivariable models.

Statistical analyses were performed using the SAS software package (SAS Institute Inc, Cary, NC). All tests were 2-sided, with a P value < .05 considered to be statistically significant.

RESULTS

The median SMI among women in the study cohort was 38.4 cm^2/m^2 (IQR, 35.5 cm^2/m^2-42.5 cm^2/m^2), whereas

the median SMI in men was 49.8 cm^2/m^2 (IQR, 45 cm^2/m^2-55.7 cm^2/m^2). The overall prevalence of sarcopenia within the population in the current study was 68.8% (141 of 205 patients), including 55.6% of women (15 of 27 women) and 70.8% of men (126 of 178 men). Sarcopenic patients were significantly older (median preoperative age of 72 years vs 67.5 years; $P = .002$), but were otherwise similar with respect to sex, perioperative serum albumin and hemoglobin levels, CCI, ASA score, ECOG performance status, receipt of preoperative chemotherapy or radiotherapy, TNM stage, and tumor grade ($P > .05$ for all) (Table 1). As expected, BMI was found to be significantly lower in those patients with sarcopenia compared with those who did not have sarcopenia (27 kg/m^2 vs 31.2 kg/m^2; $P < .0001$). It is interesting to note that these median BMI levels were consistent with sarcopenic patients being overweight and nonsarcopenic patients being obese by the World Health Organization definitions.[21]

The median follow-up for survivors was 6.7 years (IQR, 5.9 years-10.2 years), during which time a total of 75 patients experienced non-upper tract UC recurrence and 135 patients died, including 91 who died of UC. It is interesting to note that patients with sarcopenia had a significantly inferior 5-year CSS (49% vs 72%; $P = .003$) (Fig. 2 Top) and OS (39% vs 70%; $P = .003$) (Fig. 2 Bottom). In fact, the trend toward a difference in OS manifested within 90 days after surgery, such that the all-cause mortality rate within 90 days was 7.8% among patients with sarcopenia (11 of 141 patients) versus 1.6% in nonsarcopenic patients (1 of 64 patients) ($P = .07$). The specific details related to the postoperative courses and causes of death for these 12 patients are presented in Table 2.

On univariable analysis, the presence of sarcopenia as well as higher CCI, pathological T classification, lymph node positivity, LVI, tumor grade, and positive surgical margins were found to be significantly associated with a patient's risk of death from bladder cancer (Table 3). Although incremental BMI approached statistical significance on univariable analysis, it was not found to be significant in the multivariable model. It is interesting to note that on multivariable analysis, after adjusting for BMI, CCI, pathological tumor and nodal stage, LVI, tumor grade, and margin status, the presence of sarcopenia remained associated with a > 2-fold increased risk of death from bladder cancer (HR, 2.2; 95% CI, 1.2-3.6 [$P = .003$]).

We also noted that older age at the time of surgery, the presence of sarcopenia, higher BMI, CCI, ECOG performance status, ASA score, pT and N classifications, LVI, and positive surgical margins were significantly associated with decreased OS on univariable analysis (Table 4). On multivariable analysis, the presence of sarcopenia was found to be independently associated with all-cause mortality (HR, 2.1; 95% CI, 1.3-3.4 [$P = .005$]) after adjusting for all variables that were found to be significant predictors on the univariable model.

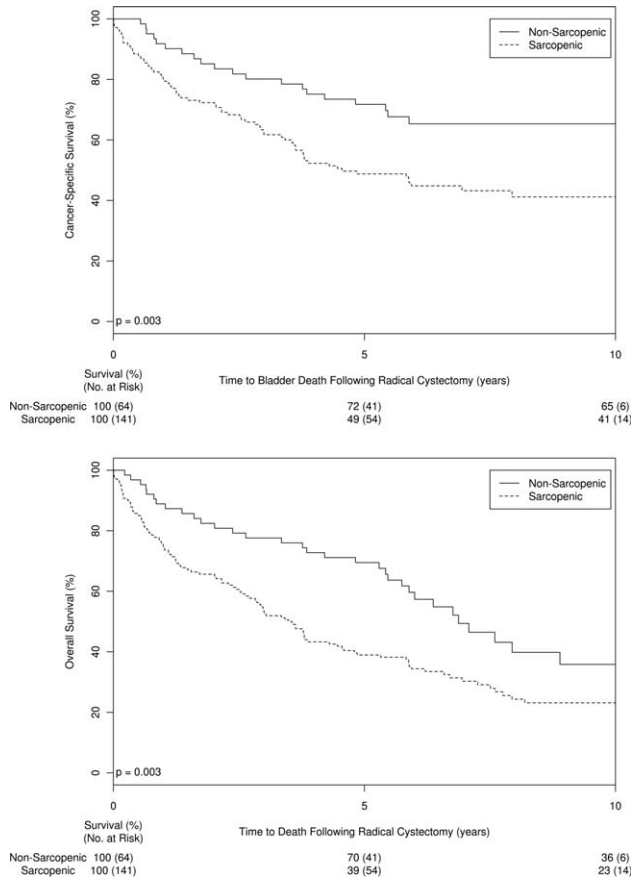

Figure 2. Kaplan-Meier curves depicting (*Top*) cancer-specific survival and (*Bottom*) overall survival are shown in patients with and without sarcopenia.

DISCUSSION

Sarcopenia represents a stereotypical response to both nutrient deprivation and systemic stress, resulting in critical anatomic and functional deficits.[22] In the current study, we assessed sarcopenia as a novel risk factor for mortality among patients with UC undergoing RC. We noted several findings of interest. First, we determined that in this cohort of patients with UC who were surgically managed, 68.9% of patients were classified as sarcopenic preoperatively.[19] We defined sarcopenia according to the international sex-specific consensus definitions put forth by Fearon et al, which are based on absolute muscularity

TABLE 2. Perioperative Course and Causes of Death for the Patients Who Died Within 90 Days of Surgery

Sarcopenic (Yes/No)	Patient No.	Sex	Age at Surgery, Years	SMI, cm^2/m^2	BMI, kg/m^2	pTNM Stage/ Histologic Grade	Time From Surgery to Death, Days	Significant Postoperative Events	Cause of Death[a]
Yes	1	Male	80	45.4	23.0	T4NxM0/High	71	POD 30: rapid development of metastatic disease in the lungs, liver, and malignant pleural effusion noted 1 mo after surgery. POD 60: admission for pneumonia, failure to thrive. POD 65: abdominal pain, constipation, prerenal azotemia, edema.	Bladder cancer Renal failure
Yes	2	Male	72	41.3	21.2	T4N0M0/High	44	POD 7: discharged after uncomplicated hospital course followed by rapid development of metastatic disease.	Bladder cancer
Yes	3	Male	55	49.8	37	T4N1M0/High	63	POD 6: superficial wound infection. POD 18: wound drainage determined to be intraabdominal abscess with enterocutaneous fistula, treated with percutaneous drainage. POD 40: seizure in the setting of acute renal failure with hyponatremia and hyperkalemia in the setting of obstructed right ureter, treated with percutaneous nephrostomy tube. Developed small bowel obstruction, found to have rapid development of intraperitoneal metastatic disease.	Bladder cancer
Yes	4	Male	79	41.3	28.6	T4N0M0/High	71	POD 26: failure to thrive and diarrhea with fecal incontinence. POD 30: admitted with fever, intraabdominal abscess, found to have enterocutaneous fistula, underwent exploratory laparotomy, drainage, and bowel resection; discharged to home hospice with metastatic disease.	Bladder cancer
Yes	5	Male	67	47.5	26.9	T3N0M0/High	70	POD 29: readmitted with abdominal pain, found to have diffuse peritoneal metastases resulting in bowel obstruction, which necessitated PEG tube placement. Rapid development of metastasis accompanied by ARF, enterococcal urinary tract infection, and pneumonia.	Bladder cancer
Yes	6	Male	74	46.4	31.4	T3NxM0/High	29	POD 10: readmitted with sepsis.	Bladder cancer Failure to thrive
Yes	7	Male	70	51.7	28.4	T3N0M0/High	54	POD 8: resumption of bowel function after prolonged postoperative ileus, large bilateral PE and disseminated intravascular coagulation, necessitating intubation with TPN complicated by Pseudomonas pneumonia and bacteremia. POD 33: bowel perforation treated operatively. Patient died after exploratory laparotomy.	Bowel obstruction and perforation
Yes	8	Male	67	39.9	22.4	T4N1M0/High	2	POD 1: developed mental status changes, found to have large basilar artery stroke, resulting in infarct to majority of the bilateral cerebella, with extensive mass effect and impingement of the brain stem. POD 2: care withdrawn.	Stroke (basilar artery)
Yes	9	Male	94	43.5	24.6	T4NxM0/High	60	POD 13: readmitted with abdominal pain and nausea/vomiting complicated by aspiration pneumonia. Chronic aspiration diagnosed.	Aspiration pneumonia
Yes	10	Female	69	37.4	45	T3N0M0/High	59	POD 5: postoperative DVT and PE despite indwelling IVC filter. POD 34: readmitted with large open incisional wound (fascia intact) with urinary leakage and ARF resulting in hyperkalemia for which the patient was initiated on hemodialysis, non-STEMI, sacral decubitus ulcer, worsening delirium, poor nutrition, UTI.	Myocardial infarction, failure to thrive, infected sacral decubitus ulcer
Yes	11	Male	70	48.3	30.3	T4N0M0/High	5	POD 6: cardiopulmonary arrest with unsuccessful resuscitation.	Cardiorespiratory failure (pulmonary embolism vs myocardial infarction, autopsy declined)
No	12	Male	76	57.1	46.2	T2N0M0/High	82	POD 6: developed periincisional erythema. POD 9: fascial dehiscence repaired. POD 22: discharged with wound vacuum device.	Bladder cancer

Abbreviations: ARF, acute renal failure; BMI, body mass index; DVT, deep vein thrombosis; IVC, inferior vena cava; PE, pulmonary embolism; PEG, percutaneous endoscopic gastrostomy; POD, postoperative day; SMI, skeletal muscle index; STEMI, ST-segment elevation myocardial infarction; TPN, total parenteral nutrition; UTI, urinary tract infection.

[a] Validated by communication with the patient's family and primary physician as well as by death certificate.

TABLE 3. Univariable and Multivariable Cox Proportional Hazards Analysis of Variables Associated With Patients' Risk of Death From Bladder Cancer After RC

	Univariable Analysis		Multivariable Analysis	
Feature	HR (95% CI)	*P*	HR (95% CI)	*P*
Sarcopenia (reference: no)	2.067 (1.26-3.40)	.004	2.14 (1.24-3.71)	.007
Age	1.02 (1.00-1.04)	.12		
Sex (reference: female)	1.77 (0.86-3.67)	.12		
BMI	0.96 (0.93-1.0)	.05	1.00 (0.97-1.05)	.70
Charlson comorbidity index	1.09 (1.03-1.53)	.004	1.05 (0.99-1.12)	.13
ECOG performance status	1.16 (0.79-1.71)	.45		
ASA score	1.43 (0.94-2.18)	.09		
T classification				
T2 (reference: ≤pT1)	1.81 (0.97-3.40)	.06	1.76 (0.91-3.41)	.09
T3 (reference: ≤pT1)	2.33 (1.67-4.99)	.0002	2.34 (1.25-4.38)	.008
T4 (reference: ≤pT1)	11.19 (5.71-21.94)	<.0001	7.79 (3.53-17.20)	<.0001
Lymph node positive (reference: negative)	2.34 (1.47-3.75)	.0004	1.63 (0.99-2.68)	.06
LVI (reference: no)	2.45 (1.60-3.74)	<.0001	1.04 (0.66-1.66)	.85
Tumor grade (reference: grade 1/2)	1.62 (1.11-2.60)	.007	1.51 (0.96-2.38)	.08
Positive surgical margins (reference: no)	5.68 (2.73-11.82)	<.0001	2.62 (1.21-5.66)	0.01

Abbreviations: 95% CI, 95% confidence interval; ASA, American Association of Anesthesiologists; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; HR, hazards ratio; LVI, lymphovascular invasion; RC, radical cystectomy.

TABLE 4. Univariable and Multivariable Cox Proportional Hazards Analysis of Variables Associated With Patients' Risk of Death (All-Cause) After RC

	Univariable Analysis		Multivariable Analysis	
Feature	HR (95% CI)	*P*	HR (95% CI)	*P*
Sarcopenia (reference: no)	1.80 (1.21-2.66)	.004	1.93 (1.23-3.00)	.004
Age	1.03 (1.01-1.05)	.004	1.01 (0.99-1.04)	.17
Sex (reference: female)	1.1 (0.68-1.79)	.7		
BMI	0.96 (0.93-0.99)	.01	1.00 (0.96-1.03)	.76
Charlson comorbidity index	1.10 (1.05-1.15)	.0002	1.05 (1.00-1.11)	.06
ECOG performance status	1.60 (1.23-2.51)	.0007	1.31 (0.96-1.78)	.09
ASA score	1.76 (1.23-2.51)	.002	1.51 (0.99-2.28)	.05
T classification				
T2 (reference: ≤ pT1)	1.68 (1.03-2.72)	.04	1.58 (0.95-2.64)	.08
T3 (reference: ≤pT1)	2.48 (1.62-3.81)	<.0001	2.17 (1.32-3.56)	.0002
T4 (reference: ≤pT1)	6.40 (3.50-11.70)	<.0001	4.37 (2.12-9.01)	<.0001
Lymph node positive (reference: negative)	1.95 (1.30-2.94)	.001	1.5 (0.95-2.37)	.08
LVI (reference: no)	1.92 (1.33-2.77)	.0005	1.21 (0.81-1.81)	.35
Tumor grade (reference: grade 1/2)	1.62 (1.14- 2.29)	.007	1.09 (0.74-1.60)	.66
Positive surgical margins (reference: no)	3.78 (1.84-7.76)	.0003	1.55 (0.72-3.34)	.27

Abbreviations: 95% CI, 95% confidence interval; ASA, American Association of Anesthesiologists; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; HR, hazards ratio; LVI, lymphovascular invasion; RC, radical cystectomy.

below the fifth percentile of healthy young adults.[19] In the United States and Europe, the prevalence of sarcopenia has been reported to be 5% to 13% among individuals aged 60 years to70 years, and 11% to 50% in those aged > 80 years.[23] The high prevalence of sarcopenia in this UC cohort, combined with the elevated overall CCI, ASA score, and ECOG performance status, illustrates the poor overall health condition among patients with UC undergoing RC. In addition, it is interesting to note the high prevalence of sarcopenia that occurred in this cohort despite the finding that the median BMI of the study population overall was 27.1 kg/m^2, which is consistent with overweight by the World Health Organization criteria and underscores the finding that, in the current era of epidemic obesity, sarcopenia may be occult.[14]

The second and most significant finding of the current study is that sarcopenia was independently associated with increased risks of postoperative CSS and all-cause mortality. Indeed, the trend toward an increased risk of death among sarcopenic patients in the current study was apparent within

as little as 90 days after RC was performed, thereby highlighting the potential importance of using SMI to risk-stratify patients before surgery. Although all of these patients experienced complicated postoperative courses, with death resulting from cardiopulmonary failure or stroke in 3 patients and infectious complications in 2 patients, the primary cause of death in 7 of the 12 patients in the current study was rapid progression of bladder cancer.

The relationship between sarcopenia and decreased survival has previously been described in other malignancies. For example, Peng et al[9] reported that sarcopenia was independently associated with an increased risk of all-cause mortality in a population of 296 patients with surgically resected pancreatic cancer, with a median survival of 18 months noted among nonsarcopenic patients compared with 13.7 months in those with sarcopenia ($P = .01$). In addition, in their multivariable analysis, sarcopenia was found to be associated with a 67% increase in the risk of all-cause mortality at 3 years (HR, 1.67; 95% CI, 1.28-2.07 [$P < .001$]).[9] Similarly, Harimoto et al observed decreased OS among sarcopenic patients undergoing partial hepatectomy for hepatocellular carcinoma (71% vs 83.7%; $P = .001$).[24] Likewise, in the series of Martin et al of 1471 patients with gastrointestinal or respiratory tract cancers, the median OS was 13.0 months among patients with sarcopenia versus 20.1 months among those with normal SMI.[14] Similar detrimental effects on OS in individuals with sarcopenia have been observed in patients with pancreatic,[25] lung,[14] and colorectal carcinoma.[14] To our knowledge, few studies to date have commented on the impact of sarcopenia on CSS specifically, although inferior oncologic outcomes have been noted among patients with hepatobiliary cancer[24] and melanoma.[16]

Recently, 2 articles assessed lean muscle mass as a predictor of short-term outcomes after RC.[26,27] Wan et al demonstrated that SMI was independently associated with an increased risk of postoperative complications after RC in a contemporary series of 125 patients using a similar automated methodology to measure SMI as was used in the current analysis.[27] At the same time, Smith et al reported an increased risk of perioperative complications after RC among sarcopenic female patients alone.[26] The authors did not observe significant differences in CSS or OS between patients with and without sarcopenia. However, their study was limited by a median follow-up of only 1.4 years. Furthermore, sarcopenia was assessed by manually traced cross-sectional area of the psoas muscles, which may be subject to human error and has yet to be validated,[19] and for which to our knowledge there currently are no published consensus reference values.

In the current study, we report that sarcopenia was found to be significantly prognostic of inferior CSS and OS. Furthermore, sarcopenia remained associated with mortality, independent of the classically used composite metrics of comorbidity and performance status, such as CCI, ECOG performance status, and ASA score. The current study differs from the recently published data in that SMI was measured by assessing the full lumbar skeletal muscle complement on axial CT imaging, which has been validated against dual-energy x-ray absorptiometry[11] and in that we defined sarcopenia according to internationally accepted sex-specific consensus definitions.[19] Furthermore, the median follow-up of the current study was 6.7 years.

The substantial contribution of patient-related factors such as comorbidity and performance status to survival after RC is increasingly acknowledged.[7,8] Frailty has been proposed as a unifying measure of these features, simultaneously conveying physiological reserve, overall wellness, and vulnerability to stressors.[16,28] Although sarcopenia specifically refers to the loss of muscle mass, frailty is described as a more global phenomenon, resulting in impairment of multiple physiologic parameters resulting in a decreased ability to respond to stressors. As such, frailty has been demonstrated to independently predict risk of 30-day postoperative complications.[29,30] Unfortunately, available frailty indices, which involve either clinical measurements of weakness (eg, grip strength tests, gait speed) or patient questionnaires, are generally subjective and susceptible to both reporting and measurement bias, and thus have decreased reproducibility. Sarcopenia, which can be reliably and rapidly determined from standard cross-sectional imaging, may be able to supplant these less reliable tests. As such, it been proposed as an accurate, reproducible, and objective surrogate for frailty.[9,14,16,19,28] Furthermore, automated, density-based measurement of the lumbar SMI based on axial CT imaging is well validated against dual-energy x-ray absorptiometry scans, outperforming bioelectrical impedance analysis, and reliably predicting both whole-body fat mass and fat-free mass.[11,19] Indeed, sarcopenia represents a convenient, noninvasive way to assess a patient's risk because it is rapidly and easily obtained from standard preoperative imaging, obviating the cost or potential morbidity of additional testing.

In addition to the prognostic value, the identification of sarcopenia before RC is performed offers a potential opportunity to improve outcomes in patients with UC because skeletal muscle loss has been shown to be both modifiable and potentially reversible. Resistance training combined with light aerobic exercise successfully increase muscle mass and strength in the elderly,

improving quality of life, fitness, and performance status.[31] Nutritional interventions such as supplementing protein intake, leucine, vitamin D, and antioxidants have demonstrated preliminary success in halting the progression of sarcopenia and stimulating muscle protein synthesis and currently are the focus of many clinical trials.[23,32] Alternatively, anabolic hormones including testosterone, estrogen, and growth hormone have shown some benefit in preventing, delaying, or reversing sarcopenia.[23] For example, the oral anabolic steroid oxandrolone is approved the US Food and Drug Administration for the promotion of muscle building, wound healing, and recovery in patients with human immunodeficiency virus-related muscle wasting, severe burn trauma, alcoholic hepatitis, and chronic illness with minimal toxicity.[33]

Several limitations of the current study must be acknowledged. Given its retrospective nature, we were unable to correlate measurements of skeletal muscle wasting with other metrics of frailty such as performance status on patient questionnaires or walking speed or grip strength tests. Because anemia has been reported as a potential surrogate for frailty,[34] we assessed preoperative hemoglobin in the cohort in the current study, but did not appreciate any substantial differences between the sarcopenic and nonsarcopenic patients. However, this may have been related to confounding factors associated with UC such as preoperative hematuria, receipt of neoadjuvant chemotherapy, and coexistent anemia of chronic disease. Especially considering the high prevalence of sarcopenia in this cohort of patients, functional assessments such as grip strength could potentially be of significant additive value in the risk stratification.

Similarly, skeletal muscle wasting has been hypothesized to be strongly linked with nutritional status. Previous studies have noted that nutritional reserve, as quantified by plasma albumin level, is a significant predictive factor in perioperative outcomes after RC.[35,36] Unfortunately, plasma albumin was not routinely collected during the time period of the current study and therefore was only available in 50% of the patient cohort. As such, we did not appreciate any significant correlation between albumin levels and sarcopenic status. However, closer prospective attention to preoperative nutritional status is necessary to further evaluate the correlation between sarcopenia, protein stores, and nutritional levels.

In addition, the current study was limited by the finding that many of the patients who underwent RC during this time period did not have digital CT scans available for body composition analysis and therefore were excluded from the study. Because the study institution is a tertiary referral center, imaging may have been obtained locally or by the referring hospital. To assess for possible bias introduced by these missing data, we compared the characteristics of the patients without imaging with those of the patients in the analytic cohort and did not observe any substantial differences with regard to clinicopathological features, comorbidity, or ECOG performance status between the 2 groups with the exception that the patients for whom we had digital scans were slightly older than those without scans (71 years vs 66 years; $P < .001$). Given the association between muscle wasting and age, this may have contributed to the high overall prevalence of sarcopenia noted in the current study.

Despite these limitations, to our knowledge the current study is the first to demonstrate the independent association between sarcopenia and increased risk of mortality in patients with UC after RC. As such, we propose consideration of SMI as a modifiable feature to be included in the risk stratification of patients undergoing RC.

Going forward, the diagnosis of sarcopenia in patients scheduled to undergo RC may be used to identify those patients at risk of inferior long-term survival. Given the promising results reported in other fields in which interventions in skeletal muscle wasting have been performed and it was successfully modified, we plan to use sarcopenia as a selection factor to identify those patients who might be candidates for clinical trials testing therapeutic interventions to halt or reverse skeletal muscle wasting, as well as to identify those individuals at risk of failure to thrive who may benefit postoperatively from additional surveillance, nutritional support, and assistance with regaining functional status.

Conclusions

Sarcopenia, or extreme wasting of skeletal muscle, was found to be significantly associated with an increased risk of both CSS and all-cause mortality after RC for UC. Moreover, this association appears to be independent of commonly used comorbidity and performance status indices. The assessment of lean muscle mass is objective and quickly obtained from standard preoperative imaging. As such, we propose the inclusion of this variable in preoperative risk stratification because it may be beneficial in both treatment planning and patient counseling. Furthermore, additional investigation is needed to determine the extent that preoperative interventions to modify skeletal muscle wasting may result in improved outcomes after RC.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Frank has acted as a paid consultant for Rochester Medical Company for work performed outside of the current study.

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