The preoperative sarcopenia status is associated with lymphovascular invasion in upper tract urothelial carcinoma patients treated with radical nephroureterectomy

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Abstract

Introduction: Sarcopenia is a novel concept representing skeletal muscle wasting and has been identified as a prognostic factor for several cancers. The aims of this study were to evaluate the prognostic significance of sarcopenia and the relationship between sarcopenia and poor pathological findings in upper tract urothelial carcinoma (UTUC) patients who underwent radical nephroureterectomy (RNU).

Methods: We identified 123 UTUC patients who underwent RNU between 2003 and 2014. We assessed sarcopenia by measuring the area of skeletal muscle at the third lumber vertebra on preoperative computed tomography scans. Sarcopenia was classified based on a sex-specific consensus definition. We investigated whether sarcopenia predicts clinical outcomes such as cancer death and poor pathological findings at RNU.

Results: A total of 40.7% of patients (n=50) had sarcopenia. In a multivariate Cox regression analysis, sarcopenia was not associated with cancer-specific survival (CSS), and lymphovascular invasion (LVI) (hazard ratio 5.88; p=0.002) was the only independent risk factor for CSS. A multivariate logistic regression analysis showed that sarcopenia independently correlated with the LVI status (odds ratio 2.36; p=0.025). LVI was positive in 27 out of 50 (54%) and 25 out of 73 (34%) patients with and without sarcopenia, respectively (p=0.029).

Conclusions: Preoperative sarcopenia predicted the LVI status, which was a strong prognostic factor for UTUC patients after RNU.

Introduction

Radical nephroureterectomy (RNU) is the gold standard therapeutic modality for non-metastatic upper tract urothelial carcinoma (UTUC). Although pre-operative systematic chemotherapy and/or extended lymph node dissection during RNU may be planned to improve survival outcomes, appropriate selection criteria have not yet been established.[1] Sarcopenia is a novel concept representing a state of wasting skeletal muscle. Previous studies described sarcopenia as a novel prognostic factor for predicting survival in patients with various cancers, including colorectal cancer, pancreatic cancer, hepatocellular carcinoma, renal cell carcinoma, UC, and gastroesophageal cancer.[2-7] Only two studies have investigated the relationship between the sarcopenia status and clinical outcomes of UTUC patients treated with RNU. Furthermore, it currently remains unclear whether the pre-operative factor, the sarcopenia status predicts pathological findings in RNU specimens. This retrospective study aimed to examine the prognostic role of sarcopenia and the relationship between sarcopenia and poor pathological findings in non-metastatic and node-negative UTUC patients who underwent RNU.

Methods

Study population

A total of 181 patients were newly diagnosed with UTUC and underwent RNU between 2003 and 2014 at Keio University Hospital. Twelve patients with a follow-up period of less than 6 months were excluded from the analysis. Preoperative abdominal computed tomography (CT) scans were not performed on 37 patients at our hospital and, thus, these patients were excluded. We also excluded 9 patients who pathologically exhibited lymph node metastasis. Therefore, we ultimately identified 123 patients with pTa-4N0M0 UTUC for analyses in the present study.

Patients underwent standard RNU by an open or laparoscopic procedure with bladder cuff excision. The regional lymph nodes were dissected in patients with nodes that were enlarged in the preoperative evaluation or intraoperative inspection. Extended

lymphadenectomy was not routinely performed. Patients were assessed by urine cytology and cystoscopy every 3 months for 2 years after RNU, every 6 months for the next 3 years, and every 6 to 12 months thereafter. CT, MRI, and/or excretory urograms were also performed every 6 months for 5 years and annually thereafter.

Tumor locations were divided into 2 groups (renal pelvis and ureter) based on the dominant lesion site. Tumors were staged according to the 2002 American Joint Committee on Cancer/UICC TNM classification. Tumors were graded according to the 1973 WHO/International Society of Urological Pathology consensus classification. Lymphovascular invasion (LVI) was defined as tumor cells in an endothelial-lined space without underlying muscular walls.

Evaluation

We used preoperative plain CT imaging. Using the third lumber vertebra as a landmark, the area of skeletal muscle (cm^2) was evaluated. Skeletal muscle was identified by Hounsfield unit thresholds of -29 to +150. The skeletal muscle index (SMI) was calculated by normalizing the skeletal muscle area by height^2 (m^2) and reported as cm^2/m^2. We classified patients as having sarcopenia based on international consensus definitions (SMI<43 cm^2/m^2 among men with a BMI of <25, SMI<53 cm^2/m^2 among men with a BMI of ≥25, and SMI<41 cm^2/m^2 among women).[8] CT images were analyzed using AW volumeshare 5 (General Electric Company, Connecticut, USA).

Statistical analysis

We analyzed relationships between clinicopathological parameters and the sarcopenia status using the chi-squared test. The cancer-specific survival (CSS) rate was estimated using the Kaplan–Meier method, and analyzed with the Log-rank test. A multivariate analysis for CSS was performed using Cox's proportional hazards model with stepwise forward selection. Clinical factors included age (<70 or ≥70), sex, clinical T stage (<T3 or ≥T3), smoking history, tumor location (renal pelvis vs ureter), tumor size (<30 mm vs ≥30 mm), hydronephrosis, and sarcopenia. Pathological findings included the pathological T stage (<T3 or ≥T3), LVI, carcinoma *in situ* (CIS), and tumor grade (G1/2 vs. G3). Logistic regression methodology was used to predict poor pathological features in RNU specimens. All analyses were performed with the SPSS v. 22.0 statistical

software package (IBM Corp., Somers, NY) and $p<0.05$ was considered to be significant.

Results

Relationship between clinicopathological characteristics and sarcopenia

Table 1 shows the relationship between pre-operative clinical parameters and the sarcopenia status in 123 patients. A total of 40.7% of patients had sarcopenia (n=50). Patients with sarcopenia were significantly older and had larger tumors (≥30 mm in size) than their counterparts ($p=0.024$ and $p=0.034$, respectively). Men and smokers were less likely to have sarcopenia ($p<0.001$ and $p=0.012$, respectively) than their counterparts.

CSS according to the sarcopenia status

The median follow-up period was 4.49 years. A Kaplan-Meier curve revealed that the 5-year CSS rate of patients with sarcopenia was 77.9%, which was not significantly different from those without sarcopenia (84.0%, $p=0.203$; in Figure 1). A univariate analysis identified LVI, the tumor grade, and pathological T stage as risk factors for predicting CSS ($p<0.001$, 0.0019 and 0.003, respectively, Table 2). In a multivariate analysis, LVI ($p=0.002$, hazard ratio (HR) 5.88) was the only independent risk factor for CSS.

Predictors of poor pathological findings

Univariate and multivariate logistic regression analyses were performed to identify predictors of the poor pathological finding of LVI, which was the only independent predictor of CSS in our multivariate Cox regression analysis (Table 3). Positive LVI was confirmed at RNU in 27 out of 50 patients with sarcopenia (54%), and in 25 out of 73 of their counterparts (34%). This difference was significant ($p=0.029$). A multivariate logistic regression analysis showed that sarcopenia independently correlated with LVI ($p=0.025$, odds ratio (OR)=2.36).

Discussion

We investigated the prognostic significance of sarcopenia and the relationship between sarcopenia and the pathological factor, LVI, which was the only independent risk factor for cancer death in 123 UTUC patients who underwent RNU. The results obtained demonstrated that among the pre-operative clinical factors tested, only sarcopenia was independently associated with LVI positivity in surgical specimens of RNU.

Two previous studies investigated the relationship between sarcopenia and prognosis of advanced UC including bladder cancer and UTUC. One of these studies reported that sarcopenia predicted poor CSS in 100 metastatic UC patients treated with systemic chemotherapy, 28 (44%) of whom had metastatic UTUC.[9] The other study identified sarcopenia as an independent predictor for overall survival in 88 UC patients with cT4 and/or metastasis to the lymph nodes/distant organs, 46 (52%) of whom had UTUC.[10] There have only been two studies on the prognostic significance of sarcopenia with a focus on the UTUC patient population that underwent RNU. Ishihara et al. reported that 90 out of 137 (65.7%) UTUC patients who underwent RNU were diagnosed with sarcopenia and were predicted to have worse relapse-free survival, CSS, and overall survival, and this relationship was slightly stronger for patients with a higher pT stage.[11] Fukushima et al. showed that 47 out of 81 (58%) UTUC patients treated with RNU had sarcopenia, and correlations between the presence or absence of sarcopenia and cancer-specific death as well as overall death were observed in patients with locally advanced disease (≥pT3 or pN+), but not in those with organ-confined disease (<pT3N0/x).[12] On the other hand, our study did not show the independence of sarcopenia on the prediction of cancer-specific death after RNU in patients with UTUC. The main reason for this difference was presumably due to the different study populations and designs. Our study focused on non-metastatic UTUC patients and excluded pathological node-positive patients, leading to a more favorable population. In the present study, the CSS rate was higher than in other studies; the 5-year CSS rate of patients with sarcopenia was 77.9% in our study, 57.1% in that by Ishihara et al., and 69% in that by Fukushima et al.. Another reason was that the strong prognostic indicator of LVI[13-15] was not evaluated by Ishihara et al.. In our study, LVI was the only independent predictor for cancer-specific death and sarcopenia independently predicted

the LVI status.

A close relationship was observed between LVI, which is the first step of metastasis, and sarcopenia in the present study and appears to be supported by the concept that the tumor micro-metastatic environment is closely associated with sarcopenia. In the process of micro-metastasis, tumor tissue produces various proinflammatory cytokines such as IL-6, TNF-α, IL-1β, and IFN-γ.[16-18] These cytokines activate systematic inflammation and metabolic abnormalities affecting host immunity and have been suggested to subsequently lead to sarcopenia, which is one of physical findings of cachexia. Furthermore, sarcopenia may easily change the state of the microenvironment to micro-metastasis by stimulating epithelial-mesenchymal transition.[16, 19-21] The tumor micro-metastatic environment may induce sarcopenia, which may, in turn, promote tumor micro-invasion. Therefore, we speculate that tumor micro-invasion and sarcopenia enhance each other.

A previous study revealed that neoadjuvant chemotherapy before radical cystectomy for bladder cancer contributed to the extension of survival.[22-24] Since UTUC is the same histological type of UC, neoadjuvant chemotherapy for UTUC is expected to be effective.[25] Martin et al. previously showed that neoadjuvant chemotherapy achieved significant pathological downstaging and complete remission in 14% of UTUC surgical specimens.[26] Furthermore, Porten et al. demonstrated that neoadjuvant chemotherapy significantly improved overall survival and CSS in patients with UTUC.[27] Since kidney function decreases after RNU, neoadjuvant cisplatin-based chemotherapy may be recommended for patients predicted to have poor pathological features and, thus, a poor prognosis.[26] Several studies have reported the therapeutic effects of lymph node dissection in locally advanced UTUC. Kondo et al. showed that complete lymphadenectomy improved CSS in patients with pT3 or higher.[28] Moreover, Roscigno et al. found that not performing lymphadenectomy was strongly associated with poor survival in patients expected to have pT2-4 UTUC.[29] Our results showing that the preoperative factor, sarcopenia is a strong predictor of poor pathological features, such as LVI, may provide useful preoperative information for the appropriate selection of candidates for neoadjuvant chemotherapy and wide lymph node dissection.

The present study has several limitations. A relatively small number of patients was

examined at a single institution. In our study, sarcopenia, the pathological T stage, and tumor grade were not identified as prognostic factors, which contrasts with previous findings,[30-32] and may be attributed to the small size of our study. In addition, since the present study was retrospective in nature, there was a possibility of unknown bias. Another limitation is that we utilized the definition of sarcopenia widely used in other studies; however, this definition has not yet been fully confirmed in Japanese populations.

Conclusions

Preoperative sarcopenia predicted the LVI status, which was a strong prognostic factor for UTUC patients after RNU. The pre-operative factor, the sarcopenia status may provide useful information for selecting candidates for neoadjuvant chemotherapy or decision making regarding surgical options.

References

1. Roupret M, Babjuk M, Comperat E, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update. *Eur Urol*. 2015;68:868-79.
2. Boer BC, de Graaff F, Brusse-Keizer M, et al. Skeletal muscle mass and quality as risk factors for postoperative outcome after open colon resection for cancer. *Int J Colorectal Dis*. 2016;31:1117-24.
3. Choi Y, Oh DY, Kim TY, et al. Skeletal Muscle Depletion Predicts the Prognosis of Patients with Advanced Pancreatic Cancer Undergoing Palliative Chemotherapy, Independent of Body Mass Index. *PLoS One*. 2015;10:e0139749.
4. Fujiwara N, Nakagawa H, Kudo Y, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. *J Hepatol*. 2015;63:131-40.
5. Psutka SP, Boorjian SA, Moynagh MR, et al. Decreased Skeletal Muscle Mass is Associated with an Increased Risk of Mortality after Radical Nephrectomy for Localized Renal Cell Cancer. *J Urol*. 2016;195:270-6.
6. Psutka SP, Boorjian SA, Moynagh MR, et al. Mortality after radical cystectomy: impact of obesity versus adiposity after adjusting for skeletal muscle wasting. *J Urol*. 2015;193:1507-13.
7. Tamandl D, Paireder M, Asari R, et al. Markers of sarcopenia quantified by computed tomography predict adverse long-term outcome in patients with resected oesophageal or gastro-oesophageal junction cancer. *Eur Radiol*. 2016;26:1359-67.
8. Martin L, Birdsell L, Macdonald N, 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;31:1539-47.
9. Fukushima H, Yokoyama M, Nakanishi Y, et al. Sarcopenia as a prognostic biomarker of advanced urothelial carcinoma. *PLoS One*. 2015;10:e0115895.
10. Taguchi S, Akamatsu N, Nakagawa T, et al. Sarcopenia Evaluated Using the Skeletal Muscle Index Is a Significant Prognostic Factor for Metastatic

Urothelial Carcinoma. *Clin Genitourin Cancer*. 2016;14:237-43.

11. Ishihara H, Kondo T, Omae K, 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*. 2017;22:136-44.
12. Fukushima H, Nakanishi Y, Kataoka M, et al. Prognostic significance of sarcopenia in upper tract urothelial carcinoma patients treated with radical nephroureterectomy. *Cancer Med*. 2016;5:2213-20.
13. Godfrey MS, Badalato GM, Hruby GW, et al. Prognostic indicators for upper tract urothelial carcinoma after radical nephroureterectomy: the impact of lymphovascular invasion. *BJU Int*. 2012;110:798-803.
14. Kikuchi E, Margulis V, Karakiewicz PI, et al. Lymphovascular invasion predicts clinical outcomes in patients with node-negative upper tract urothelial carcinoma. *J Clin Oncol*. 2009;27:612-8.
15. Novara G, Matsumoto K, Kassouf W, et al. Prognostic role of lymphovascular invasion in patients with urothelial carcinoma of the upper urinary tract: an international validation study. *Eur Urol*. 2010;57:1064-71.
16. Inacio Pinto N, Carnier J, Oyama LM, et al. Cancer as a Proinflammatory Environment: Metastasis and Cachexia. *Mediators Inflamm*. 2015;2015:791060.
17. Pop VV, Seicean A, Lupan I, et al. IL-6 roles - Molecular pathway and clinical implication in pancreatic cancer - A systemic review. *Immunol Lett*. 2016;181:45-50.
18. Sakuma K, Aoi W, Yamaguchi A. Molecular mechanism of sarcopenia and cachexia: recent research advances. *Pflugers Arch*. 2017;469:1-19.
19. Prado CM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res*. 2009;15:2920-6.
20. Tisdale MJ. Loss of skeletal muscle in cancer: biochemical mechanisms. *Front Biosci*. 2001;6:D164-74.
21. Wolfe RR. The underappreciated role of muscle in health and disease. *Am J Clin Nutr*. 2006;84:475-82.

22. Advanced Bladder Cancer Meta-analysis C. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet*. 2003;361:1927-34.
23. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med*. 2003;349:859-66.
24. Kitamura H, Tsukamoto T, Shibata T, et al. Randomised phase III study of neoadjuvant chemotherapy with methotrexate, doxorubicin, vinblastine and cisplatin followed by radical cystectomy compared with radical cystectomy alone for muscle-invasive bladder cancer: Japan Clinical Oncology Group Study JCOG0209. *Ann Oncol*. 2014;25:1192-8.
25. Green DA, Rink M, Xylinas E, et al. Urothelial carcinoma of the bladder and the upper tract: disparate twins. *J Urol*. 2013;189:1214-21.
26. Matin SF, Margulis V, Kamat A, et al. Incidence of downstaging and complete remission after neoadjuvant chemotherapy for high-risk upper tract transitional cell carcinoma. *Cancer*. 2010;116:3127-34.
27. Porten S, Siefker-Radtke AO, Xiao L, et al. Neoadjuvant chemotherapy improves survival of patients with upper tract urothelial carcinoma. *Cancer*. 2014;120:1794-9.
28. Kondo T, Nakazawa H, Ito F, et al. Impact of the extent of regional lymphadenectomy on the survival of patients with urothelial carcinoma of the upper urinary tract. *J Urol*. 2007;178:1212-7.
29. Roscigno M, Shariat SF, Margulis V, et al. Impact of lymph node dissection on cancer specific survival in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy. *J Urol*. 2009;181:2482-9.
30. Lehmann J, Suttmann H, Kovac I, et al. Transitional cell carcinoma of the ureter: prognostic factors influencing progression and survival. *Eur Urol*. 2007;51:1281-8.
31. Lughezzani G, Burger M, Margulis V, et al. Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. *Eur Urol*. 2012;62:100-14.

32. Petrelli F, Yasser Hussein MI, Vavassori I, et al. Prognostic Factors of Overall Survival in Upper Urinary Tract Carcinoma: A Systematic Review and Meta-analysis. *Urology*. 2016;100:9-15.

Figures and Tables

Fig.1. Cancer-specific survival according to the presence or absence of sarcopenia.

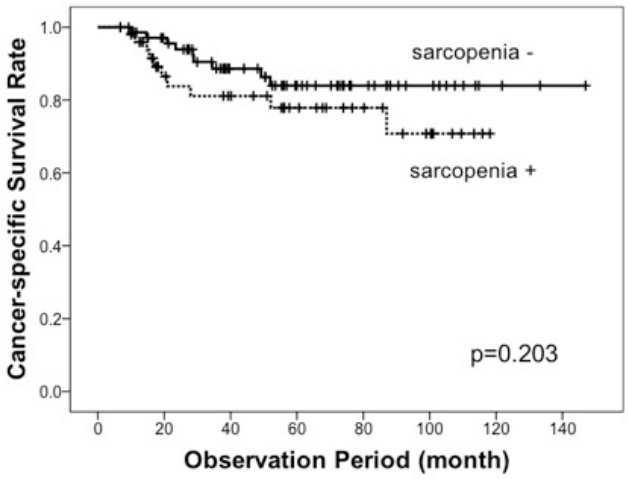

Table 1. Preoperative clinical parameters in 123 patients according to the sarcopenia status

Characteristics	Total		Sarcopenia				p
			Yes		No		
	n	%	n	%			
No. of patients	123		50		73		
Age							0.024
<70 years	44	35.8	12	24	32	43.8	
≥70 years	79	64.2	38	76	41	56.2	
Sex							<0.001
Male	96	78	31	62	65	89	
Female	27	22	19	38	8	11	
Clinical T stage							0.189
<T3	75	61	27	54	48	65.8	
≥T3	48	39	23	46	25	34.2	
Smoking							0.012
Yes	66	53.7	20	40	46	63	
No	57	46.3	30	60	27	37	
Location							0.470
Pelvis	69	56.1	30	60	39	53.4	

Ureter	54	43.9	20	40	34	46.6	
Size							0.034
<30 mm	73	59.3	24	48	49	67.1	
≥30 mm	50	40.7	26	52	24	32.9	
Hydronephrosis							0.760
Positive	66	53.7	26	52	40	54.8	
Negative	57	46.3	24	48	33	45.2	

Table 2. Univariate and multivariate Cox regression analyses for cancer-specific death

	Univariate	**Multivariate**	
	p	**p**	**HR (95% CI)**
Preoperative			
Age (≥70 years vs. <70 years)	0.672		
Sex (male vs. female)	0.438		
Clinical T stage (≥T3 vs. <T3)	0.058		
Smoking (yes vs. no)	0.803		
Location (pelvis vs. ureter)	0.874		
Size (≥30 mm vs. <30 mm)	0.287		
Hydronephrosis (positive vs. negative)	0.719		
Sarcopenia (yes vs. no)	0.203		
Postoperative			
CIS (positive vs. negative)	0.303		
LVI (positive vs. negative)	<0.001	0.002	5.88 (1.95–17.86)
Tumour grade (Grade 3 vs. 1/2)	0.019		
Pathological T stage (≥T3 vs. <T3)	0.003		

CI: confidence interval; CIS: carcinoma in situ; HR: hazard ratio; LVI: lymphovascular invasion.

Table 3. Univariate and multivariate logistic regression analyses of preoperative factors for the prediction of LVI in surgical specimens

	Univariate	Multivariate	
	p value	**p value**	**OR (95% CI)**
Age (≥70 years vs. <70 years)	0.594		
Sex (male vs. female)	0.484		
Clinical T stage (≥T3 vs. <T3)	0.078		
Smoking (yes vs. no)	0.741		
Location (pelvis vs. ureter)	0.501		
Size (≥30 mm vs. <30 mm)	0.071		
Hydronephrosis (positive vs. negative)	0.062		
Sarcopenia (yes vs. no)	0.029	0.025	2.36 (1.11–5.03)

CI: confidence interval; LVI: lymphovascular invasion; OR: odds ratio.