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Sarcopenia predicts survival outcomes among patients with urothelial carcinoma of the upper urinary tract undergoing radical nephroureterectomy: a retrospective multi-institution study

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Abbreviations

UC, urothelial carcinoma; RNU, radical nephroureterectomy; UCUT, urothelial carcinoma of the upper urinary tract; HU, Hounsfield units; SMI, skeletal muscle index; BMI, body mass index; LND, lymphadenectomy; RFS, relapse-free survival; CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval

Abstract

Background: We aimed to evaluate the effect of sarcopenia, a condition of low muscle mass, on the survival among patients who were undergoing radical nephroureterectomy (RNU) for urothelial carcinoma of the upper urinary tract (UCUT).

Methods: We retrospectively reviewed consecutive patients with UCUT (cT[any]N0M0) who underwent RNU between 2003 and 2013 at our department and its affiliated institutions. Preoperative computed tomography images were used to calculate each patient's skeletal muscle index, an indicator of whole-body muscle mass. Sarcopenia was defined according to the sex-specific consensus definitions, based on the patient's skeletal muscle and body mass indexes. We analyzed the relapse-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) after RNU to identify factors that predicted patient survival.

Results: A total of 137 patients were included, and 90 patients (65.7%) were diagnosed with sarcopenia. Compared to the non-sarcopenic patients, the sarcopenic patients had a significant inferior 5-year RFS (48.8% vs. 79.6%, $p = 0.0002$), CSS (57.1% vs. 92.6%, $p < 0.0001$), and OS (48.2% vs. 90.6%, $p < 0.0001$). Multivariate analyses revealed that sarcopenia was an independent predictor of shorter RFS, CSS, and OS (all, $p < 0.0001$).

Conclusions: Sarcopenia was an independent predictor of survival among patients with UCUT who were undergoing RNU.

Key words

Sarcopenia, urothelial carcinoma, upper urinary tract, nephroureterectomy, survival, biomarker

Introduction

Sarcopenia is a state of degenerative skeletal muscle wasting, and has recently been recognized as an important physiological change that occurs during the development of cancer cachexia [1,2]. Sarcopenia is associated with a poor physical condition [3], reduced tolerance of anti-cancer therapy [4,5], more frequent surgical complications [6-10], and poorer patient survival [8,11-13]. Although sarcopenia occurs during normal aging, it can be exacerbated by the hypercatabolic state and inflammatory response that are caused by malignancy [14]. The diagnosis of sarcopenia is confirmed using sex-specific consensus definitions that were suggested in a study of a large Canadian cohort, based on the combination of skeletal muscle and body mass indexes that are calculated using imaging findings [1]. These methods provide an objective subclinical measurement of patient frailty and nutritional status, and can be used to gauge an individual's physical condition.

Sarcopenia can affect patient survival, even in localized cancers (i.e., no metastasis) if the tumor was removed using curative therapy [13,15-17], although patients with localized cancers are thought to be less affected by cachexia, compared to patients with advanced cancers. In addition, the association between sarcopenia and survival has been reported among patients with urothelial carcinoma (UC). Nevertheless, there were few studies regarding the correlation between sarcopenia and survival among patients who are undergoing radical nephroureterectomy (RNU) for UC of the upper urinary tract (UCUT).

This retrospective multi-institution study aimed to investigate the effect of sarcopenia on survival among a cohort of patients with localized UCUT who were undergoing RNU.

Materials and methods

The internal Ethics Review Board of Tokyo Women's Medical University- Aoyama Hospital Tokyo Women's Medical University (ID: 3696), and Saiseikai Kawaguchi General Hospital (ID: 27-11) approved this retrospective study's protocol. The study was performed in accordance with the principals that are outlined in the Declaration of Helsinki. Between October 2003 and December 2013, we performed RNU for 238 patients with non-metastatic UCUT (cT[any]N0M0) at our department and its affiliated institutions. However, the present study excluded patients who had received hemodialysis therapy (n = 11), who had prior UC (n = 41), or who had received neoadjuvant chemotherapy (n = 11). We also excluded patients with missing preoperative imaging data (n = 9) or missing follow-up data (n = 32). Thus, 137 patients were included in the present study (Figure 1).

Clinical and laboratory data were extracted from an electronic database and the patients' medical records. Staging of the tumor was performed according to the Union for International Cancer Control TNM classification [18]. The preoperative stage was determined based on computed tomography findings, and all preoperative imaging was performed within 2 months before the surgery. Surgery was performed based on the procedure for the management of urothelial tumors of the renal pelvis and

ureter, as described in *Campbell's Urology* [19]. Open standard nephroureterectomy and retroperitoneoscopic surgery were performed in conjunction with open distal ureter and bladder cuff removal at our institutions. All tumors were confirmed to be UC using histology.

Imaging methods and definitions of sarcopenia

The cross-sectional areas of the lumbar skeletal muscle complement (including the rectus abdominus; bilateral internal, external, and lateral obliques; psoas; quadratus lumborum; and erector spinae) were identified using attenuation thresholds of -29 Hounsfield units (HU) and +150 HU with a Toshiba Aquilion 64 multidetector scanner (Toshiba, Tochigi, Japan). Manual scripting was used to define the area of interest at each 1-mm level, and the areas of interest were then summed. L3 was set as a landmark, and the mean value for two consecutive images was computed for each patient and normalized for stature: skeletal muscle index (SMI) (cm^2/m^2) = (skeletal muscle cross-sectional area at L3)/ ($height^2$) [11,20]. SMI was assessed as a continuous variable, and used as an indicator of whole-body muscle mass, as a previous study has demonstrated that the total lumbar-skeletal muscle cross-sectional area is linearly correlated with whole-body muscle mass [21]. Based on the international sex-specific consensus definitions of sarcopenia, we stratified the patients as sarcopenic and non-sarcopenic according to their body mass index (BMI), using a threshold lumbar SMI of < 43 cm^2/m^2 among men with a BMI of <25 kg/m^2, < 53 cm^2/m^2 among men with a BMI of >25 kg/m^2, and < 41

cm^2/m^2 among women [1]. All imaging analyses were performed by one investigator (HI) who was blinded to the other clinical parameters and patient outcomes.

Protocol for regional lymphadenectomy

We simultaneously performed regional lymphadenectomy (LND; named template-based LND) with the RNU for patients with cT[any]N0M0 UCUT, except for patients with severe comorbidities or at an advanced age [22,23]. The right renal hilar, paracaval, retrocaval, and interaortocaval nodes were dissected for tumors of the right pelvis and tumors of the right upper and middle ureter. The left renal hilar and para-aortic nodes were dissected for tumors of the left renal pelvis and tumors of the left upper and middle ureter. The lower boundary of the template was defined as the level of the inferior mesenteric artery for pelvic tumors, and as the aortic bifurcation for upper and middle ureter tumors. The ipsilateral common iliac, external iliac, obturator, and internal iliac nodes were included for tumors of the lower ureter. Dissection of the presacral nodes was not necessary for patients with lower ureteral cancer. All LNDs were performed as an open procedure, and the lymph node specimens were sampled en bloc with the surrounding adipose tissue.

Adjuvant chemotherapy

Adjuvant chemotherapy was considered when we observed nodal involvement and/or disease

infiltrating the surrounding adipose tissue. However, the final decision was made based on the patients' comorbidities, performance status, and willingness to receive chemotherapy. Chemotherapy consisted of 1-3 cycles of methotrexate, vinblastine, doxorubicin, and cisplatin, or 1-3 cycles of gemcitabine and cisplatin.

Perioperative complications

Perioperative complications were evaluated up to 90 days after surgery, and were graded using the Clavien-Dindo classification [24].

Statistical analysis

Continuous variables were analyzed using the Mann-Whitney *U*-test, and categorical variables were analyzed using the χ^2 test or Fisher's exact test. Relapse-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) after RNU were calculated using the Kaplan-Meier method, and compared between the sarcopenic and non-sarcopenic patients, respectively. To clarify the association between tumor stages and sarcopenia, the potential of sarcopenia as a prognostic factor was assessed according to tumor stage (pT and pN) based on Kaplan-Meier survival curves. We performed multivariate analyses to identify factors that were associated with RFS, CSS, and OS using Cox proportional hazards regression models. RFS was defined as the time from the RNU to the first

instance of local recurrence, metastasis, or death due to any cause. CSS and OS were defined as the time from the RNU to death due to cancer-related causes or any cause, respectively. Risk was expressed as the hazard ratio (HR) with 95% confidence interval (CI). All analyses were performed using the JMP software (version 11; SAS Institute Inc., Cary, NC, USA), and differences with a *p*-value of < 0.05 were considered statistically significant.

Results

Patient characteristics

The patients' characteristics are summarized in Table 1. Ninety patients were sarcopenic (65.7%). The sarcopenic patients were significantly older (mean age: 75.3 years vs. 68.5 years, $p < 0.0001$), and were significantly more likely to be female (46.7% vs. 12.8%, $p < 0.0001$), compared to the non-sarcopenic patients. The sarcopenic patients also exhibited a significantly shorter height (1.58 m vs. 1.63 m, $p = 0.0015$), lighter weight (55.6 kg vs. 64.6 kg, $p < 0.0001$), lower BMI (22.2 kg/m^2 vs. 24.1 kg/m^2, $p < 0.0001$), smaller skeletal muscle area (90.4 cm^2 vs. 129.3 cm^2, $p < 0.0001$), and lower SMI (35.8 cm^2/m^2 vs. 48.1 cm^2/m^2, $p<0.0001$). However, when we compared the sarcopenic and non-sarcopenic patients, there were no significant differences in the tumor site, LND status, pT stage, pN stage, tumor grade, frequency of adjuvant chemotherapy, or Charlson comorbidity index (all, $p > 0.05$).

The sarcopenic patients exhibited a significantly shorter follow-up period (mean follow-up: 36.5

months vs. 58.0 months, $p < 0.0001$). During the follow-up, tumor recurrence or metastasis was observed in 50 patients (36.5%), and the numbers of deaths due to cancer or any cause were 35 (25.6%) and 43 (31.4%), respectively. These rates were significantly higher among the sarcopenic patients (RFS: $p = 0.0007$; CSS: $p = 0.0001$; OS: $p < 0.0001$).

Patient survival

Figure 2 shows the Kaplan-Meier curves for patient survival after RNU according to sarcopenia status. Sarcopenia was associated with a significantly shorter RFS (5-year survival: 48.8 % vs. 79.6 %, $p = 0.0002$), CSS (57.1 % vs. 92.6 %, $p < 0.0001$), and OS (48.2 % vs. 90.6 %, $p < 0.0001$). Figure 3 shows Kaplan-Meier survival curves according to pT stage and sarcopenia status. The results indicated that for 26 non-sarcopenic patients with tumor stage < pT3, 34 sarcopenic patients with stage < pT3, 21 non-sarcopenic patients with stage ≥ pT3, and 56 sarcopenic patients with stage ≥ pT3, the 5-year RFS rates were 95.7%, 87.5%, 62.6%, and 25.4%, respectively; the 5-year CSS rates were 100.0%, 82.4%, 83.1%, and 39.3%, respectively; and the 5-year OS rates were 100.0%, 70.6%, 79.2%, and 32.4%, respectively. Among the 60 patients with tumor stage < pT3, sarcopenia was significantly associated with inferior OS ($p = 0.0120$), whereas among the 77 patients with tumor stage ≥ pT3, sarcopenia was significantly associated with inferior RFS, CSS, and OS ($p = 0.0025$, 0.0008, 0.0007, respectively). Figure 4 shows Kaplan-Meier survival curves according to the pN stage and sarcopenia

status. For 41 non-sarcopenic patients with tumor stage pNx or 0, 83 sarcopenic patients with stage pNx or 0, 6 non-sarcopenic patients with stage ≥ pN1, and 7 sarcopenic patients with stage ≥ pN1, the 3-year RFS rates were 92.3%, 53.2%, 22.2%, and 0.00%, respectively; the 5-year CSS rates were 97.2%, 60.6%, 40.0%, and 0.00%, respectively; and the 5-yaer OS rates were 97.2%, 51.2%, 33.3%, and 0.00%, respectively. Among the 124 patients with tumor stage pNx or 0, sarcopenia was significantly associated with inferior RFS, CSS, and OS (all, $p < 0.0001$), whereas among the 13 patients with tumor stage ≥ pN1, sarcopenia was significantly associated with inferior CSS ($p = 0.0331$).

Perioperative complications

The perioperative complications according to sarcopenia status are shown in Table 2. Perioperative complications were observed in 11 of the 90 sarcopenic patients (12.2%), compared to in 7 of the 47 non-sarcopenic patients (14.9%). Two sarcopenic patients and 2 non-sarcopenic patients experienced Grade ≥3 complications. One sarcopenic patient underwent drainage under radiographic guidance for lymphorrhea (Grade 3a), and the other sarcopenic patient received an ileus tube under radiographic guidance (Grade 3a). One non-sarcopenic patient underwent colostomy for a rectum perforation (Grade 3b), the other non-sarcopenic patient underwent surgical drainage and hemodialysis for severe renal failure due to sepsis that was caused by a retroperitoneal abscess (Grade 4). There were no

significant differences in the rates of all-grade or Grade ≥3 perioperative complications ($p = 0.607$ and $p = 0.66$, respectively).

Predictors of patient survival

Multivariate analyses revealed that sarcopenia was an independent predictor of shorter RFS (HR: 5.18, $p < 0.0001$), CSS (HR: 13.3, $p < 0.0001$), and OS (HR: 12.1, $p < 0.0001$). The pT and pN stages were also independent predictors of all endpoints (all, $p < 0.05$). Moreover, a LND status was an independent predictor of longer OS (HR: 2.22, $p = 0.0380$) (Table 3).

Discussion

To our knowledge, this multi-institution retrospective study is the first to evaluate the relationship between sarcopenia and survival outcomes among patients who were undergoing RNU for UCUT. We found that sarcopenia was significantly associated with poor patient survival, although there were no significant differences in the rates of perioperative complications when we compared the sarcopenic and non-sarcopenic patients.

Recent studies have suggested that sarcopenia is a novel biomarker for survival among patients with malignancies. In this context, malignancy can result in a hypercatabolic state that is caused by tumor metabolism, systematic inflammation, and other tumor-mediated effects [25]. When combined with

other cancer-mediated effects, such as anorexia, fatigue, decreased functional status, and immobility, this hypercatabolic state can lead to the depletion of skeletal muscle and the development of sarcopenia. Furthermore, sarcopenia may have an effect on survival among patients with advanced or metastatic cancers [5,26-29]. For example, Sharma et al. [27] reported that sarcopenia predicted OS after cytoreductive nephrectomy for metastatic renal cell carcinoma, and Prado et al. [5] reported that sarcopenia predicted toxicity and time to tumor progression among patients with metastatic breast carcinoma who were treated using chemotherapy. Interestingly, this effect is also observed in localized cancers [15-17], which are thought to exhibit less severe inflammatory responses or nutritional disorders, compared to advanced or metastatic cancers. Moreover, recent studies have reported that sarcopenia was associated with both tumor relapse (i.e., RFS or disease-free survival) and mortality outcomes, such as CSS [15,17] or OS [13,15,17], among patients who were undergoing curative surgery. However, only a few studies have examined the effect of sarcopenia on RFS or disease-free survival. Harimoto et al. [13] observed decreased RFS among sarcopenic patients who were undergoing curative partial hepatectomy for hepatocellular carcinoma. Similarly, Miyamoto et al. [16] reported that sarcopenia negatively affected survival among patients who were undergoing curative resection for stage I-III colorectal cancer. Furthermore, our data revealed that sarcopenia was significantly correlated with RFS, CSS, and OS among patients with UCUT who were undergoing curative surgery. Although these results are interesting, they are difficult to explain. One possible

explanation is that sarcopenia may be induced by a systematic inflammatory response or nutritional disorder, and may directly promote or accelerate tumor progression or dissemination. Thus, sarcopenic patients may have micrometastases that cannot be detected using routine radiological examinations. Moreover, experimental investigations have revealed inflammatory and immune cells in tumors, such as dendritic cells, macrophages, and lymphocytes, which produced cytokines and other factors that promoted tumor growth and affected survival [30-32].

Sarcopenia can predict survival outcomes in UC, as Psutka et al. [15] reported that sarcopenia significantly increased the risk of mortality after radical cystectomy for bladder cancer. Furthermore, other groups have also reported that sarcopenia was an independent biomarker among patients with advanced or metastatic UC, which included bladder carcinoma or UCUT [26,29]. Moreover, Fukushima et al. [26] suggested that sarcopenia was a useful predictor of shorter OS in advanced or metastatic UC (UCUT and bladder carcinoma combined). These results agree with our findings that sarcopenia was an independent predictor of survival after RNU for localized UCUT, after we adjusted for well-known risk factors, such as pT and pN [33-35].

We also found that the prognostic potential of sarcopenia as a survival biomarker was higher for more invasive UCUT. Thus, the association between sarcopenia and survival tended to be stronger for patients with higher pT stage (≥ pT3) (Table 3); however, the significance of an association between sarcopenia and pN stage could not be statistically evaluated because of a small number of patients

with tumor stage ≥ pN1. We speculate that patient's age may be a factor, since the present study included some patients with low stage cancer (i.e., pTa or 1), for whom sarcopenia could have been induced by age-related physiological changes rather than cancer. The distinction between age-related and cancer-mediated sarcopenia is important but difficult to detect because the sarcopenic status may be affected by a combination of various factors such as aging, cancer-mediated chronic inflammation, and treatment-associated fatigue. The multivariate analysis showed that statistical significance of sarcopenia as a prognostic factor remained after adjusting for age; however, further studies separately evaluating the impact of age-related and cancer-mediated sarcopenia are needed.

The present study has several limitations. First, we used a retrospective design, which limits the level of provided evidence, and the analyzed patient population was small. Second, the retrospective design precludes any analysis of other parameters of muscle mass wasting (i.e., cachexia), such as history of weight loss [1], or reduced walking speed or grip strength [36], which are common symptoms of cachexia and are significantly associated with outcomes [1,6]. Third, we used BMI-adjusted cut-off values for SMI to define sarcopenia, which were established in a Canadian patient cohort [1]. However, it is not clear whether these values are accurate when they are used in a non-Canadian population. Therefore, future studies may be needed to identify the appropriate SMI cut-off values for the Japanese population. Furthermore, prospective studies are needed to validate the predictive value of sarcopenia, and to account for other parameters of cachexia, among patients with UCUT who are undergoing RNU.

Conclusions

Sarcopenia was an independent predictor of survival among patients with localized UCUT who were undergoing RNU. The advantage of this parameter is that sarcopenia can be easily evaluated without extra cost or effort, as it is quantified using routine imaging tests. Moreover, we found that sarcopenia remained an independent predictor after adjustment for tumor staging factors (pT and pN) and age. Therefore, this new biomarker may effectively predict the outcome of UCUT before performing surgery. Nevertheless, careful follow-up is needed to monitor the postoperative course of patients with sarcopenia.

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Conflicts of Interest

All authors have no conflicts of interest to declare.

References

1. Martin L, Birdsell L, Macdonald N et al (2013) Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 31:1539-1547
2. Fearon K, Strasser F, Anker SD et al (2011) Definition and classification of cancer cachexia: an international consensus. The Lancet Oncology 12:489-495
3. Moses AW, Slater C, Preston T et al (2004) Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. British journal of cancer 90:996-1002
4. Huillard O, Mir O, Peyromaure M et al (2013) Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients. British journal of cancer 108:1034-1041
5. Prado CM, Baracos VE, McCargar LJ et al (2009) Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clinical cancer research : an official journal of the American Association for Cancer Research 15:2920-2926
6. Huang DD, Wang SL, Zhuang CL et al (2015) Sarcopenia, as defined by low muscle mass, strength and physical performance, predicts complications after surgery for colorectal cancer. Colorectal Dis 17:O256-264
7. Sharma P, Zargar-Shoshtari K, Caracciolo JT et al (2015) Sarcopenia as a predictor of complications in penile cancer patients undergoing inguinal lymph node dissection. World journal of urology 33:1585-1592
8. Joglekar S, Nau PN, Mezhir JJ (2015) The impact of sarcopenia on survival and complications in surgical oncology: A review of the current literature. J Surg Oncol 112:503-509
9. Ida S, Watanabe M, Yoshida N et al (2015) Sarcopenia is a Predictor of Postoperative Respiratory Complications in Patients with Esophageal Cancer. Ann Surg Oncol 22:4432-4437
10. Smith AB, Deal AM, Yu H et al (2014) Sarcopenia as a predictor of complications and survival following radical cystectomy. The Journal of urology 191:1714-1720
11. Prado CM, Lieffers JR, McCargar LJ et al (2008) Prevalence and clinical implications

of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. The Lancet Oncology 9:629-635

12. Sabel MS, Lee J, Cai S et al (2011) Sarcopenia as a prognostic factor among patients with stage III melanoma. Ann Surg Oncol 18:3579-3585
13. Harimoto N, Shirabe K, Yamashita YI et al (2013) Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg 100:1523-1530
14. Prado CM, Wells JC, Smith SR et al (2012) Sarcopenic obesity: A Critical appraisal of the current evidence. Clin Nutr 31:583-601
15. Psutka SP, Carrasco A, Schmit GD et al (2014) Sarcopenia in patients with bladder cancer undergoing radical cystectomy: impact on cancer-specific and all-cause mortality. Cancer 120:2910-2918
16. Miyamoto Y, Baba Y, Sakamoto Y et al (2015) Sarcopenia is a Negative Prognostic Factor After Curative Resection of Colorectal Cancer. Ann Surg Oncol 22:2663-2668
17. Psutka SP, Boorjian SA, Moynagh MR et al (2016) Decreased Skeletal Muscle Mass is Associated with an Increased Risk of Mortality after Radical Nephrectomy for Localized Renal Cell Cancer. The Journal of urology 195:270-276
18. Sobin L, Wittekind C (2002) International Union Against Cancer (UICC): TNM classification of malignant tumors 6th edition. New York: Willey–Liss
19. Sagalowsky A, Jarrett T (2002) Management of urothelial tumors of the renal pelvis and ureter. Campbell's urology 4:2845-2875
20. Antoun S, Lanoy E, Iacovelli R et al (2013) Skeletal muscle density predicts prognosis in patients with metastatic renal cell carcinoma treated with targeted therapies. Cancer 119:3377-3384
21. Shen W, Punyanitya M, Wang Z et al (2004) Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol (1985) 97:2333-2338
22. Kondo T, Hara I, Takagi T et al (2014) Template-based lymphadenectomy in urothelial carcinoma of the renal pelvis: a prospective study. Int J Urol 21:453-459
23. Kondo T, Nakazawa H, Ito F et al (2007) Impact of the extent of regional lymphadenectomy on the survival of patients with urothelial carcinoma of the upper urinary tract. The Journal of urology 178:1212-1217; discussion 1217
24. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205-213
25. Roubenoff R, Hughes VA (2000) Sarcopenia: current concepts. J Gerontol A Biol Sci

Med Sci 55:M716-724
26. Fukushima H, Yokoyama M, Nakanishi Y et al (2015) Sarcopenia as a prognostic biomarker of advanced urothelial carcinoma. PloS one 10:e0115895
27. Sharma P, Zargar-Shoshtari K, Caracciolo JT et al (2015) Sarcopenia as a predictor of overall survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. Urologic oncology 33:339.e317-323
28. Fukushima H, Nakanishi Y, Kataoka M et al (2016) Prognostic Significance of Sarcopenia in Patients with Metastatic Renal Cell Carcinoma. The Journal of urology 195:26-32
29. Taguchi S, Akamatsu N, Nakagawa T et al (2015) Sarcopenia Evaluated Using the Skeletal Muscle Index Is a Significant Prognostic Factor for Metastatic Urothelial Carcinoma. Clinical genitourinary cancer
30. Grivennikov S, Karin E, Terzic J et al (2009) IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell 15:103-113
31. Coussens LM, Werb Z (2002) Inflammation and cancer. Nature 420:860-867
32. Lin WW, Karin M (2007) A cytokine-mediated link between innate immunity, inflammation, and cancer. J Clin Invest 117:1175-1183
33. Margulis V, Shariat SF, Matin SF et al (2009) Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer 115:1224-1233
34. Li CC, Chang TH, Wu WJ et al (2008) Significant predictive factors for prognosis of primary upper urinary tract cancer after radical nephroureterectomy in Taiwanese patients. European urology 54:1127-1134
35. Bolenz C, Shariat SF, Fernandez MI et al (2009) Risk stratification of patients with nodal involvement in upper tract urothelial carcinoma: value of lymph-node density. BJU Int 103:302-306
36. Waters DL, Baumgartner RN, Garry PJ et al (2010) Advantages of dietary, exercise-related, and therapeutic interventions to prevent and treat sarcopenia in adult patients: an update. Clin Interv Aging 5:259-270

Figure legends

Figure 1: Flow-chart for the present study. RNU, radical nephroureterectomy; UCUT, urothelial

carcinoma of the upper urinary tract; UC, urothelial carcinoma

Figure 2: Kaplan-Meier estimates of (a) relapse-free survival, (b) cancer-specific survival, and (c) overall survival according to sarcopenia status among 137 patients with urothelial carcinoma of the upper urinary tract (cT［any］N0M0).

Red and blue lines represent patients with and without sarcopenia, respectively.

Figure 3: Kaplan-Meier estimates of (a) relapse-free survival, (b) cancer-specific survival, and (c) overall survival according to the pT stage and sarcopenia status among 137 patients with urothelial carcinoma of the upper urinary tract (cT［any］N0M0).

Blue, red, yellow, and green lines represent patients with stage < pT3 without sarcopenia (n = 26), stage < pT3 with sarcopenia (n = 34), stage ≥ pT3 without sarcopenia (n = 21), and stage ≥ pT3 with sarcopenia (n = 56), respectively. RNU, radical nephroureterectomy

Figure 4: Kaplan-Meier estimates of (a) relapse-free survival, (b) cancer-specific survival, and (c) overall survival according to the pN stage sarcopenia status among 137 patients with urothelial carcinoma of the upper urinary tract (cT［any］N0M0).

Blue, red, yellow, and green lines represent patients with stage pNx or 0 without sarcopenia (n = 41),

stage pNx or 0 with sarcopenia (n = 83), stage ≥ pN1 without sarcopenia (n = 6), and stage ≥ pN1 with sarcopenia (n = 7), respectively. RNU, radical nephroureterectomy

Figure 1: Flow-chart for the present study

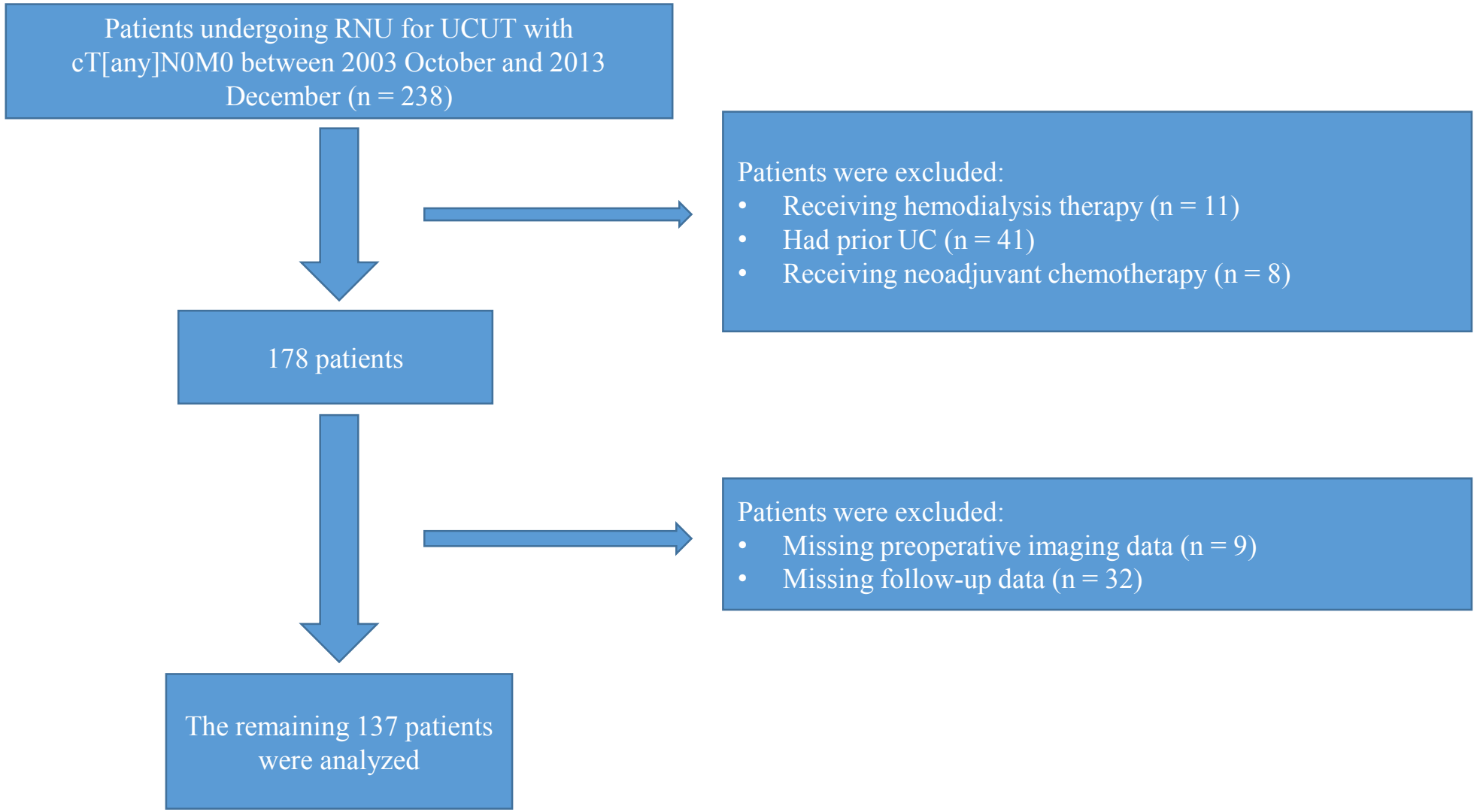


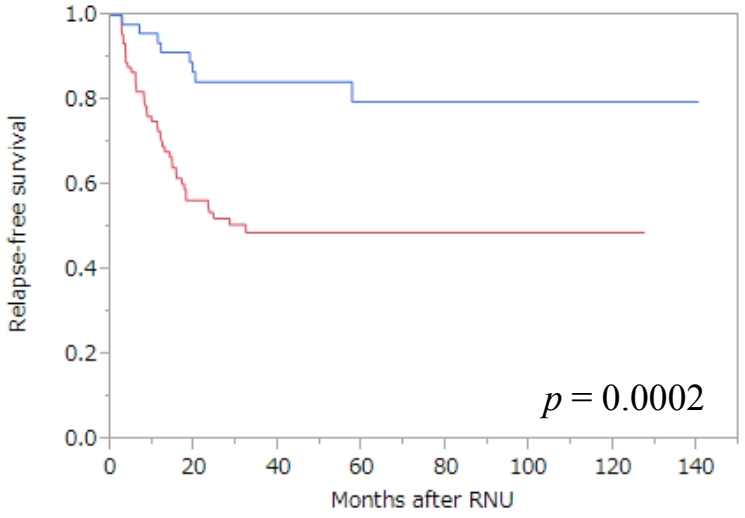
Table 1: Patient characteristics

Variable	All (n = 137)	With sarcopenia (n = 90)	Without sarcopenia (n = 47)	*p*
Mean age, years (median, range)	72.8 (73.0, 39-92)	75.3 (78.0, 39-92)	68.5 (70.0, 52.0-87.0)	<0.0001
Sex Male Female	 89 (65.0%) 48 (35.0%)	 48 (53.3%) 42 (46.7%)	 41 (87.2%) 6 (12.8%)	<0.0001
Sites of tumor Pelvis Ureter	 79 (57.7%) 58 (42.3%)	 50 (55.6%) 40 (44.4%)	 29 (61.7%) 18 (38.3%)	0.586
LND Yes No	 54 (39.4%) 83 (60.6%)	 32 (35.6%) 58 (64.4%)	 22 (46.8%) 25 (53.2%)	0.269
pT stage < pT3 ≥ pT3	 60 (43.8%) 77 (56.2%)	 34 (37.8%) 56 (62.2%)	 26 (55.3%) 21 (44.7%)	0.0693
pN stage pNx or 0 ≥ pN1	 124 (90.5%) 13 (9.49%)	 83 (92.2%) 7 (7.78%)	 41 (87.2%) 6 (12.8%)	0.368
Grade of tumor Low grade High grade	 34 (24.8%) 103 (75.2%)	 19 (21.1%) 71 (78.9%)	 15 (31.9%) 32 (68.1%)	0.211
Mean height, m (median, range)	1.60 (1.61, 1.33-1.85)	1.58 (1.57, 1.38-1.85)	1.63 (1.64, 1.33-1.8)	0.0015
Mean weight, kg (median, range)	58.7 (57.0, 32-98.4)	55.6 (55.0, 32.0-81.0)	64.6 (63.0, 45.6-98.4)	<0.0001
Mean BMI, kg/m^2 (median, range)	22.8 (22.7, 14.4-32.9)	22.2 (22.0, 14.4-31.8)	24.1 (23.8, 17.5-32.9)	<0.0001
Mean skeletal muscle area, cm^2 (median, range)	103.7 (100.0, 38.7-202.9)	90.4 (84.4, 38.7-151.8)	129.3 (130.0, 81.5-202.9)	<0.0001
Mean SMI, cm^2/m^2 (median, range)	40.0 (40.6, 20.3-67.3)	35.8 (34.8, 20.3-50.7)	48.1 (46.1, 41.0-67.3)	<0.0001
Adjuvant chemotherapy Yes No	 16 (11.7%) 121 (88.3%)	 12 (13.3%) 78 (86.7%)	 4 (8.51%) 43 (91.5%)	0.577
Charlson comorbidity index < 3 ≥ 3	 122 (89.0%) 15 (11.0%)	 80 (88.9%) 10 (11.1%)	 42 (89.4%) 5 (10.6%)	1.000
Mean follow-up period, months (median, range)	43.9 (34.7, 2.83-140.3)	36.5(26.7, 2.83-129.8)	58.0 (49.2, 10.4-140.3)	<0.0001
Tumor recurrence or metastasis Yes No	 50 (36.5%) 87 (63.5%)	 42 (46.7%) 48 (53.3%)	 8 (17.0%) 39 (83.0%)	0.0007
Died from cancer Yes No	 35 (25.6%) 102 (74.5%)	 32 (35.6%) 58 (64.4%)	 3 (6.38%) 44 (93.6%)	0.0001
Died from any cause Yes No	 43 (31.4%) 94 (68.6%)	 39 (43.3%) 51 (56.7%)	 4 (8.51%) 43 (91.5%)	<0.0001

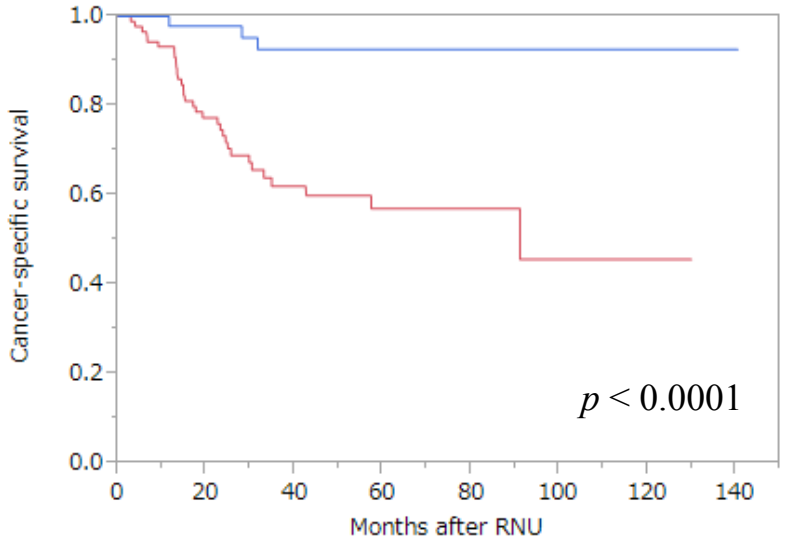
LND, lymphadenectomy; CIS, carcinoma *in situ*; LVI, lymphovascular invasion; CRP, C-reactive protein; BMI, body mass index; SMI, skeletal muscle index;

Figure 2: Kaplan-Meier estimates of (a) relapse-free survival, (b) cancer-specific survival, and (c) overall survival according to sarcopenia status among 137 patients with urothelial carcinoma of the upper urinary tract (cT[any]N0M0)

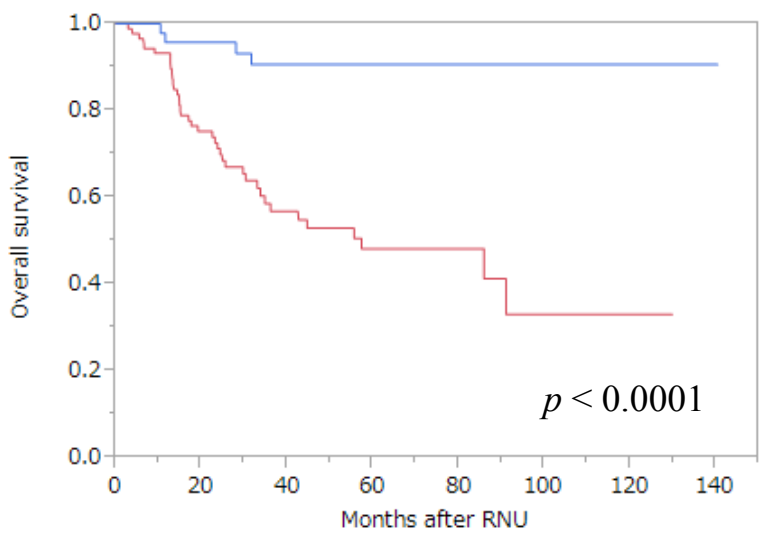
(a)



(b)



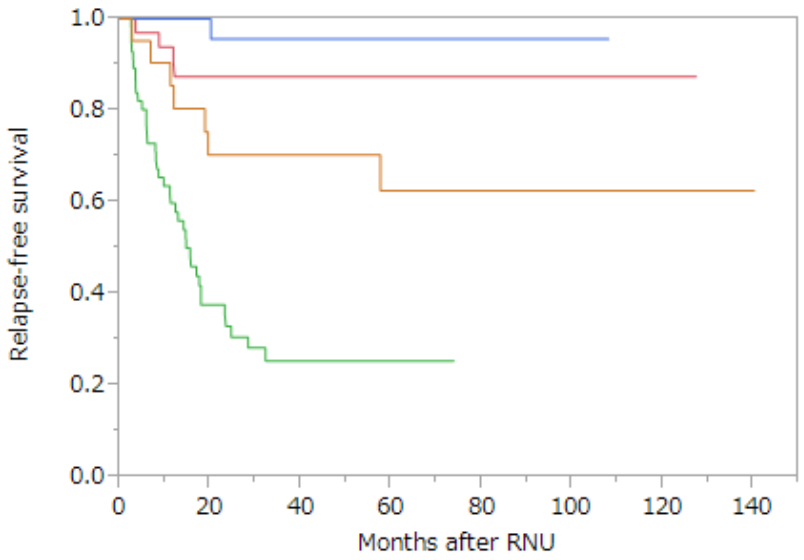
(c)



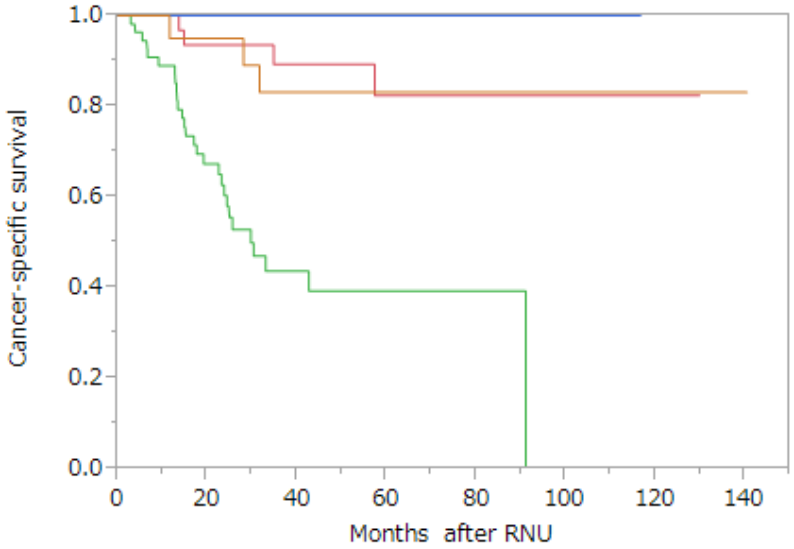
Sarcopenia status	5-year survival	5-year survival	5-year survival
Yes (n = 90)	48.8 %	57.1 %	48.2 %
No (n = 47)	79.6 %	92.6 %	90.6 %

Figure 3: Kaplan-Meier estimates of (a) relapse-free survival, (b) cancer-specific survival, and (c) overall survival according to the pT stage and sarcopenia status among 137 patients with urothelial carcinoma of the upper urinary tract (cT[any]N0M0)

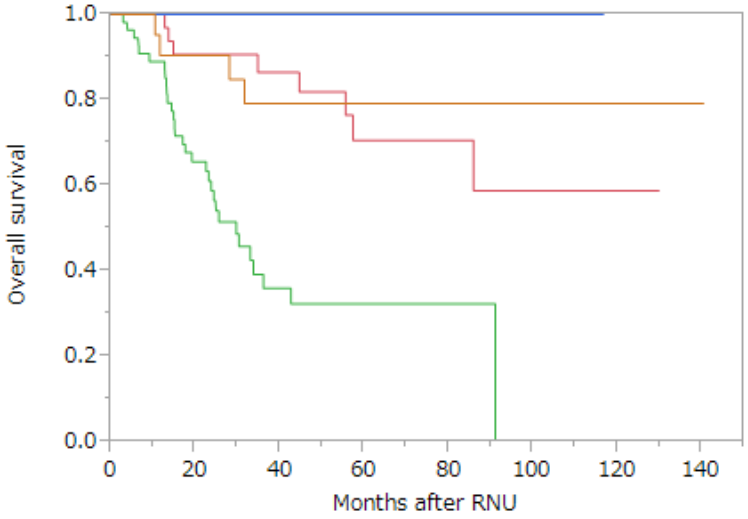
(a)



(b)

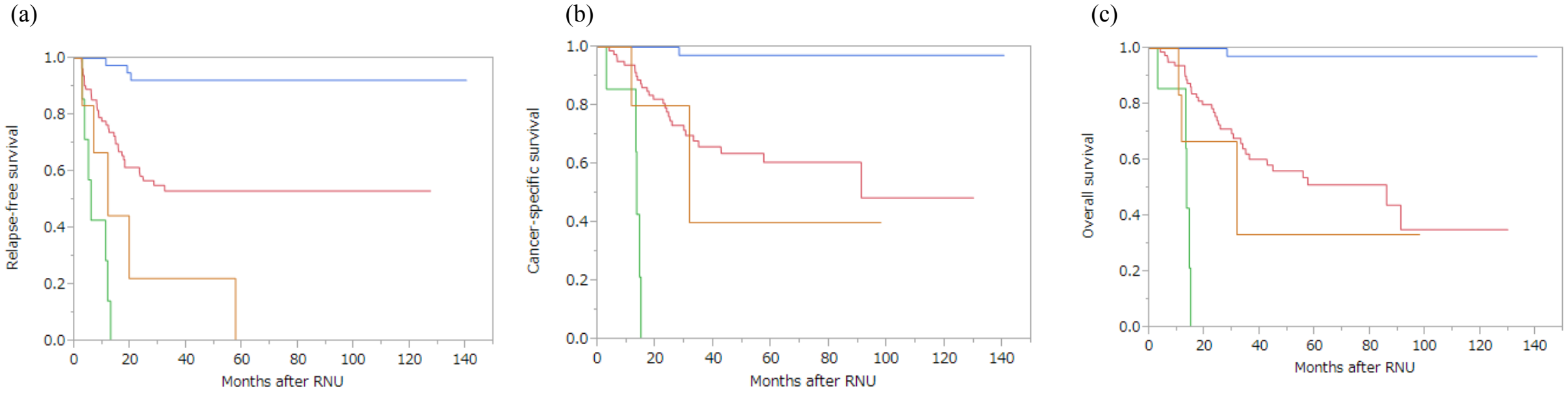


(c)



pT stage with/without sarcopenia	5-year survival	5-year survival	5-year survival
< pT3 without sarcopenia (n =26)	95.7 %	100.0 %	100.0 %
< pT3 with sarcopenia (n = 34)	87.5 %	82.4 %	70.6 %
	$p = 0.245$	$p = 0.0688$	$p = 0.0120$
≥ pT3 without sarcopenia (n = 21)	62.6 %	83.1 %	79.2 %
≥ pT3 with sarcopenia (n = 56)	25.4 %	39.3 %	32.4 %
	$p = 0.0025$	$p = 0.0008$	$p = 0.0007$

Figure 4: Kaplan-Meier estimates of (a) relapse-free survival, (b) cancer-specific survival, and (c) overall survival according to the pN stage and sarcopenia status among 137 patients with urothelial carcinoma of the upper urinary tract (cT[any]N0M0)



pN stage
with/without sarcopenia

	3-year survival	5-year survival	5-year survival
pNx or 0 without sarcopenia (n = 41)	92.3 %	97.2 %	97.2 %
pNx or 0 with sarcopenia (n = 83)	53.2 %	60.6 %	51.2 %
	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
≥ pN1 without sarcopenia (n = 6)	22.2 %	40.0 %	33.3 %
≥ pN1 with sarcopenia (n = 7)	0.00 %	0.00 %	0.00 %
	$p = 0.0901$	$p = 0.0331$	$p = 0.109$

Table 2: Perioperative complications according to sarcopenia status

Clavien-Dindo classification	All (n = 137)	With sarcopenia (n = 90)	Without sarcopenia (n = 47)	*p*
Grade 1 Femoral nerve paralysis Bleeding Lymphorrhea Others	8 (5.84%) 2 (1.46%) 2 (1.46%) 1 (0.73%) 3 (2.19%)	5 (5.56%) 1 (1.11%) 2 (2.22%) 1 (1.11%) 1 (1.11%)	3 (6.38%) 1 (2.13%) 0 0 2 (4.26%)	
Grade 2 Bleeding Infection Ileus	6 (4.38%) 3 (2.19%) 2 (1.46%) 1 (0.73%)	4 (4.44%) 3 (3.33%) 1 (1.11%) 0	2 (4.26%) 0 1 (2.13%) 1 (2.13%)	
Grade 3a Lymphorrhea Ileus	2 (1.46%) 1 (0.73%) 1 (0.73%)	2 (2.22%) 1 (1.11%) 1 (1.11%)	0 0 0	
Grade 3b Rectal perforation	1 (0.73%)	0	1 (2.13%)	
Grade 4a Retroperitoneal abscess	1 (0.73%)	0	1 (2.13%)	
Incidence (all grades)	18 (13.1%)	11 (12.2%)	7 (14.9%)	0.66
Incidence (grade ≥3)	4 (2.92%)	2 (2.22%)	2 (4.26%)	0.607

Table 3: Multivariate analyses of relapse-free survival, cancer-specific survival, and overall survival among137 patients with urothelial carcinoma of the upper urinary tract (cT[any]N0M0)

	RFS HR (95% CI)	***p***	**CSS HR (95% CI)**	***p***	**OS HR (95% CI)**	***p***
Age	0.99 (0.95 – 1.02)	0.490	1.00 (0.96 – 1.05)	0.859	1.01 (0.97 – 1.06)	0.504
LND Yes No	 Ref. 1.89 (0.95 – 3.84)	 - 0.0712	 Ref. 1.72 (0.76 – 4.03)	 - 0.192	 Ref. 2.22 (1.04 – 4.94)	 - 0.0380
pT < pT3 ≥ pT3	 Ref. 6.15 (2.47 – 18.8)	 - <0.0001	 Ref. 5.21 (1.79 – 19.6)	 - 0.0015	 Ref. 3.78 (1.55 – 10.4)	 - 0.0028
pN pNx or 0 ≥ pN1	 Ref. 7.45 (3.27 – 16.5)	 - <0.0001	 Ref. 8.58 (2.92 – 23.9)	 - 0.0002	 Ref. 9.25 (3.42 – 23.8)	 - <0.0001
Grade of tumor Low grade High grade	 Ref. 3.10 (0.85 – 20.0)	 - 0.0923	 Ref. 2.34 (0.58 – 15.8)	 - 0.252	 Ref. 1.23 (0.42 – 4.13)	 - 0.717
Sarcopenia Yes No	 5.18 (2.36 – 12.7) Ref.	 <0.0001	 13.3 (4.10 – 61.7) Ref.	 <0.0001	 12.1 (4.31 – 44.2) Ref.	 <0.0001 -

RFS, relapse-free survival; CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; LND, lymphadenectomy

Table 1: Patient characteristics

Variable	**All (n = 137)**	**With sarcopenia (n = 90)**	**Without sarcopenia (n = 47)**	***p***
Mean age, years (median, range)	72.8 (73.0, 39-92)	75.3 (78.0, 39-92)	68.5 (70.0, 52.0-87.0)	<0.0001
Sex				<0.0001
Male	89 (65.0%)	48 (53.3%)	41 (87.2%)	
Female	48 (35.0%)	42 (46.7%)	6 (12.8%)	
Sites of tumor				0.586
Pelvis	79 (57.7%)	50 (55.6%)	29 (61.7%)	
Ureter	58 (42.3%)	40 (44.4%)	18 (38.3%)	
LND				0.269
Yes	54 (39.4%)	32 (35.6%)	22 (46.8%)	
No	83 (60.6%)	58 (64.4%)	25 (53.2%)	
pT stage				0.0693
< pT3	60 (43.8%)	34 (37.8%)	26 (55.3%)	
≥ pT3	77 (56.2%)	56 (62.2%)	21 (44.7%)	
pN stage				0.368
pNx or 0	124 (90.5%)	83 (92.2%)	41 (87.2%)	
≥ pN1	13 (9.49%)	7 (7.78%)	6 (12.8%)	
Grade of tumor				0.211
Low grade	34 (24.8%)	19 (21.1%)	15 (31.9%)	
High grade	103 (75.2%)	71 (78.9%)	32 (68.1%)	
Mean height, m (median, range)	1.60 (1.61, 1.33-1.85)	1.58 (1.57, 1.38-1.85)	1.63 (1.64, 1.33-1.8)	0.0015
Mean weight, kg (median, range)	58.7 (57.0, 32-98.4)	55.6 (55.0, 32.0-81.0)	64.6 (63.0, 45.6-98.4)	<0.0001
Mean BMI, kg/m^2 (median, range)	22.8 (22.7, 14.4-32.9)	22.2 (22.0, 14.4-31.8)	24.1 (23.8, 17.5-32.9)	<0.0001
Mean skeletal muscle area, cm^2 (median, range)	103.7 (100.0, 38.7-202.9)	90.4 (84.4, 38.7-151.8)	129.3 (130.0, 81.5-202.9)	<0.0001
Mean SMI, cm^2/m^2 (median, range)	40.0 (40.6, 20.3-67.3)	35.8 (34.8, 20.3-50.7)	48.1 (46.1, 41.0-67.3)	<0.0001
Adjuvant chemotherapy				0.577
Yes	16 (11.7%)	12 (13.3%)	4 (8.51%)	
No	121 (88.3%)	78 (86.7%)	43 (91.5%)	
Charlson comorbidity index				1.000
< 3	122 (89.0%)	80 (88.9%)	42 (89.4%)	
≥ 3	15 (11.0%)	10 (11.1%)	5 (10.6%)	
Mean follow-up period, months (median, range)	43.9 (34.7, 2.83-140.3)	36.5(26.7, 2.83-129.8)	58.0 (49.2, 10.4-140.3)	<0.0001
Tumor recurrence or metastasis				0.0007
Yes	50 (36.5%)	42 (46.7%)	8 (17.0%)	

No	87 (63.5%)	48 (53.3%)	39 (83.0%)	
Died from cancer				0.0001
Yes	35 (25.6%)	32 (35.6%)	3 (6.38%)	
No	102 (74.5%)	58 (64.4%)	44 (93.6%)	
Died from any cause				<0.0001
Yes	43 (31.4%)	39 (43.3%)	4 (8.51%)	
No	94 (68.6%)	51 (56.7%)	43 (91.5%)	

LND, lymphadenectomy; CIS, carcinoma *in situ*; LVI, lymphovascular invasion; CRP, C-reactive protein; BMI, body mass index; SMI, skeletal muscle index

Table 2: Perioperative complications according to sarcopenia status

Clavien-Dindo classification	**All (n = 137)**	**With sarcopenia (n = 90)**	**Without sarcopenia (n = 47)**	***p***
Grade 1	8 (5.84%)	5 (5.56%)	3 (6.38%)	
Femoral nerve paralysis	2 (1.46%)	1 (1.11%)	1 (2.13%)	
Bleeding	2 (1.46%)	2 (2.22%)	0	
Lymphorrhea	1 (0.73%)	1 (1.11%)	0	
Others	3 (2.19%)	1 (1.11%)	2 (4.26%)	
Grade 2	6 (4.38%)	4 (4.44%)	2 (4.26%)	
Bleeding	3 (2.19%)	3 (3.33%)	0	
Infection	2 (1.46%)	1 (1.11%)	1 (2.13%)	
Ileus	1 (0.73%)	0	1 (2.13%)	
Grade 3a	2 (1.46%)	2 (2.22%)	0	
Lymphorrhea	1 (0.73%)	1 (1.11%)	0	
Ileus	1 (0.73%)	1 (1.11%)	0	
Grade 3b				
Rectal perforation	1 (0.73%)	0	1 (2.13%)	
Grade 4a				
Retroperitoneal abscess	1 (0.73%)	0	1 (2.13%)	
Incidence (all grades)	18 (13.1%)	11 (12.2%)	7 (14.9%)	0.66
Incidence (grade ≥3)	4 (2.92%)	2 (2.22%)	2 (4.26%)	0.607

Table 3: Multivariate analyses of relapse-free survival, cancer-specific survival, and overall survival among137 patients with urothelial carcinoma of the upper urinary tract (cT[any]N0M0)

	RFS **HR (95% CI)**	***p***	**CSS** **HR (95% CI)**	***p***	**OS** **HR (95% CI)**	***p***
Age	0.99 (0.95 – 1.02)	0.490	1.00 (0.96 – 1.05)	0.859	1.01 (0.97 – 1.06)	0.504
LND		0.0712		0.192		0.0380
Yes	Ref.		Ref.		Ref.	
No	1.89 (0.95 – 3.84)		1.72 (0.76 – 4.03)		2.22 (1.04 – 4.94)	
pT		<0.0001		0.0015		0.0028
< pT3	Ref.		Ref.		Ref.	
≥ pT3	6.15 (2.47 – 18.8)		5.21 (1.79 – 19.6)		3.78 (1.55 – 10.4)	
pN		<0.0001		0.0002		<0.0001
pNx or 0	Ref.		Ref.		Ref.	
≥ pN1	7.45 (3.27 – 16.5)		8.58 (2.92 – 23.9)		9.25 (3.42 – 23.8)	
Grade of tumor		0.0923		0.252		0.717
Low grade	Ref.		Ref.		Ref.	
High grade	3.10 (0.85 – 20.0)		2.34 (0.58 – 15.8)		1.23 (0.42 – 4.13)	
Sarcopenia		<0.0001		<0.0001		<0.0001
Yes	5.18 (2.36 – 12.7)		13.3 (4.10 – 61.7)		12.1 (4.31 – 44.2)	
No	Ref.		Ref.		Ref.	

RFS, relapse-free survival; CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; LND, lymphadenectomy