Preoperative controlling nutritional status (CONUT) score as a novel predictive biomarker of survival in patients with localized urothelial carcinoma of the upper urinary tract treated with radical nephroureterectomy

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Highlights

- The CONUT score's prediction of patient survival after RNU is unknown.
- The CONUT score was associated with RFS, CSS, and OS after RNU for localized UTUC.
- The CONUT score helps predict RFS, CSS, and OS after RNU for localized UTUC.
- The score's impact remains after adjusting for tumor-specific factors and CRP.
- There was a close relationship between sarcopenia and CONUT score.

Preoperative Controlling Nutritional Status (CONUT) score as a novel predictive biomarker of survival in patients with localized urothelial carcinoma of the upper urinary tract treated with radical nephroureterectomy

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Subtitle

CONUT score in patients with UCUT after RNU

Running title

CONUT score as a predictor in UCUT after RNU

Conflict of interest

Tsunenori Kondo received honoraria from Pfizer, Bayer and Novartis. All other authors declare no conflict of interest.

Abstract

Objective: The purpose of this study was to investigate the correlation between the Controlling Nutritional Status (CONUT) score and survival of patients with localized urothelial carcinoma of the upper urinary tract (UTUC) treated with radical nephroureterectomy (RNU).

Methods and Materials: We retrospectively enrolled 107 patients. CONUT score was calculated based on the serum albumin concentration, lymphocyte count, and total cholesterol concentration. Patients were classified into two groups based on CONUT score. Relapse-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) after RNU were compared between the two groups, and predictors of survival were analyzed using Cox proportional hazards regression models.

Results: For CONUT score, the area under the curve was 0.588, and the optimal cutoff value was 3. Twenty-four patients (22.4%) had high CONUT scores. The patients with high CONUT scores had significantly shorter 5-year RFS, CSS, and OS than did those with low CONUT scores (RFS: 50.1% vs. 66.0%, CSS: 28.1% vs. 71.7%, OS: 26.4% vs. 66.8%, all $p < 0.05$). Results of the multivariable analysis, after adjustment for factors such as pT stage, pN stage, tumor grade,

presence of lymphovascular invasion, and C-reactive protein level, revealed that CONUT score was an independent predictor of CSS (hazard ratio [HR], 5.44; p = 0.0016) and OS (HR, 2.90; p = 0.0214), and showed marginal significance for predicting RFS (HR, 2.26; p = 0.0581).

Conclusions: Preoperative CONUT score helps predict survival in patients with localized UTUC treated with RNU.

Highlights

- The CONUT score's prediction of patient survival after RNU is unknown.
- The CONUT score was associated with RFS, CSS, and OS after RNU for localized UTUC.
- The CONUT score helps predict RFS, CSS, and OS after RNU for localized UTUC.
- The score's impact remains after adjusting for tumor-specific factors and CRP.
- There was a close relationship between sarcopenia and CONUT score.

Keywords: Biomarker; inflammation; nutrition; urothelial carcinoma; nephroureterectomy; survival

1. Introduction

It is well recognized that the development of cancer has a genetic basis, however, there is increasing evidence that host inflammatory responses also play an important role in cancer's development and progression [1-3]. The hyper-catabolic state and inflammatory response that are caused by malignancy also exacerbates malnutrition [1]. In this context, a prognostic biomarker representing nutritional condition is identified as an independent predictor of survival in patients with cancer. Recently, the Controlling Nutritional Status (CONUT) score, which is an index calculated from the serum albumin concentration, total peripheral lymphocyte count, and total cholesterol concentration, has received focus as a predictive biomarker of survival in patients with several cancers [4-6]. For example, in a cohort of 204 patients with stage II/ III colorectal cancer undergoing curative surgery, Iseki et al. reported that the 5-year cancer-specific survival (CSS) rate was significantly higher in the low CONUT group than in the high CONUT group (92.7% vs. 81.0%), and multivariate analyses showed that high CONUT scores independently predicted low CSS rates [4].

We previously reported that sarcopenia, which was an indicator of cancer cachexia, was significantly associated with prognosis in patients with localized

urothelial carcinoma of the upper urinary tract (UTUC) after radical nephroureterectomy (RNU) [7] . This finding suggested a relationship between malnutrition and poor prognosis in patients with UTUC after RNU, as a sarcopenic status indicates patient frailty and malnutrition caused by systematic inflammation. Thus, we investigated whether the CONUT score, which was developed to evaluate immune-nutritional status, could predict survival in patients with localized UTUC after RNU.

2. Material and methods

2.1. Study design

The Internal Ethics Review Board of Tokyo Women's Medical University approved this retrospective single-center study (ID 4204), which was performed in accordance with the principles outlined in the Declaration of Helsinki.

In our department, 200 patients overall underwent RNU for localized UTUC (i.e., cTanyN0M0) between October 2003 and March 2014. Among these patients, 42 patients who had prior UC (bladder: 36 patients, UTUC: 6 patients), 7 who received neoadjuvant chemotherapy, 10 who received hemodialysis therapy, and 34 who did not have available clinical data were excluded. The remaining 107

patients were evaluated in this study (Figure 1).

Clinical and laboratory data were extracted from an electronic database and the patient medical record. Our diagnostic strategy is largely based on a consensus guideline [8]; all patients undergo urinary cytology examination, computed tomography and/or magnetic resonance imaging (if possible, enhanced) of the chest, abdomen, and pelvis, and cystoscopy to rule out concomitant bladder tumors. Retrograde ureteropyelography, ureteroscopy or biopsy is performed only when tumor location is not clarified or the possibility of benign lesions cannot be excluded. Staging of the tumor was performed based on the Union for International Cancer Control TNM classification [9]. The preoperative stage was diagnosed based on computed tomography findings of the chest, abdomen, and pelvis. 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 [10]. Open standard nephroureterectomy and retroperitoneoscopic surgery were performed in conjunction with open distal ureter and bladder cuff removal at our institution. All tumors were confirmed to be urothelial carcinoma using histology. After RNU, patients were evaluated for recurrence by computed tomography every 6 months and for intravesical recurrence with cystoscopy and

urine cytology every 3 months for the first 2 years. Subsequently, follow-up examinations were performed every 6-12 months.

2.2. Endpoint

Relapse-free survival (RFS), CSS and overall survival (OS) after RNU were set as endpoints in this study. RFS was defined as the time from RNU to the first local recurrence, metastasis, or any-cause death. CSS and OS were defined as the time from RNU to cancer-related or any-cause death, respectively.

2.3. Defining of CONUT score

In all patients, blood samples were obtained within 2 months before RNU. The CONUT score was calculated from the serum albumin concentration, total peripheral lymphocyte count, and total cholesterol concentration, as shown in Table 1. These three parameters were evaluated from the same blood sample.

The efficacy of using the CONUT score was analyzed using the receiver operating characteristic (ROC) curve and the area under curve (AUC). The cutoff value for the CONUT score was defined using the maximum Youden index [11].

2.4 Protocol for regional lymphadenectomy

We simultaneously performed regional lymphadenectomy (LND) with RNU for patients with localized UTUC, expect for patients with severe comorbidities or at an advanced age, as described previously [12, 13]. The right renal hilar, paracaval, retrocaval, and interaortocaval nodes were dissected for right pelvic and right upper and middle ureteral tumors. The left renal hilar and para-aortic nodes were dissected for left renal pelvic and left upper and middle ureteral tumors. 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 ureteral tumors. The ipsilateral common iliac, external iliac, obturator, internal iliac and presacral nodes were included for lower ureteral tumors. All LNDs were performed as an open procedure, and the lymph node specimens were sampled en bloc with the surrounding adipose tissue.

2.5 Adjuvant chemotherapy

Adjuvant chemotherapy was considered for nodal involvement and/or disease infiltrating surrounding adipose tissue, with considering of the patients' comorbidities, performance status, and willingness to receive therapy. The

chemotherapy regimen was 1-3 cycles of methotrexate, vinblastine, doxorubicin, and cisplatin or 1-3 cycles of gemcitabine and cisplatin.

2.6 Definition of sarcopenia

Sarcopenia has been defined in detail previously [7, 14]. Briefly, preoperative computed tomography was used to calculate skeletal muscle index, which indicates whole-body muscle mass. Sarcopenia was defined using sex-specific consensus definitions, based on the patient's skeletal muscle and body mass indexes.

2.7 Statistical analysis

Data for the two groups were compared using the χ^2 test or Mann-Whitney *U* test, as appropriate. RFS, CSS, and OS curves were estimated using the Kaplan-Meier method and compared using the log-rank test. We performed multivariable analyses for RFS, CSS, and OS to assess associations between clinicopathological parameters, including CONUT score and outcomes, using Cox proportional hazards regression models. Risk was expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). All analyses were performed

using JMP software (ver. 11; SAS Institute Inc., Cary, NC, USA), and differences were considered statistically significant at a p-value of < 0.05.

3. Results

3.1 ROC curve analysis and cutoff value for CONUT score

The ROC analysis for the CONUT score showed that the AUC predicting RFS was 0.588 (Figure 2). According to the maximum Youden index value, the cutoff for CONUT score was set at 3; therefore, 24 patients with a CONUT score ≥ 3 were classified into the high CONUT score group, whereas the remaining 83 patients (i.e., those with CONUT scores < 3) were classified into the low CONUT score group.

3.2 CONUT score components

Table 2 shows the individual CONUT score components for the high and low CONUT score groups. As expected, patients in high CONUT group had higher scores for the 3 components than those in the low CONUT group.

3.3 Patients' backgrounds

Table 3 shows the patients' backgrounds. High CONUT score was significantly associated with high serum CRP level ($p = 0.0041$) and sarcopenia ($p = 0.0213$), whereas there were no significant differences in other clinicopathological parameters between the high and low CONUT score groups, including age, sex, initial symptoms, tumor site, surgical approach, pT stage, pN stage, tumor grade, presence of lymphovasular invasion (LVI), or the presence of adjuvant chemotherapy (all $p > 0.05$). Adjuvant chemotherapy was administered in 5 and 3 patients with ≥T3 stage and with both ≥T3 and ≥N1 stage, respectively. LND was performed and ≥N1 stage was observed significantly more often in patients receiving than in those not receiving adjuvant chemotherapy (LND: 100% vs. 47.5%, $p = 0.0042$; ≥N1 stage: 37.5% vs. 6.06%, $p = 0.0021$). During follow-up, 34 patients experienced cancer recurrence, and 25 and 32 patients died from cancer and any cause, respectively. These rates were non-significantly higher in patients with high CONUT scores (RFS: 41.7% vs. 28.9%; CSS: 37.5% vs. 19.3%; OS; 41.7% vs. 26.5%, all $p > 0.05$). Finally, follow-up duration was significantly shorter in the high CONUT score group than in the low CONUT score group ($p = 0.0045$), perhaps due to their shorter CSS/OS.

3.4 Survival according to CONUT score

In the 34 patients (31.8%) with cancer relapse, contralateral recurrence and local recurrence or lymph node/distance metastasis were observed in 4 (37.4%) and 30 (28.0%) patients, respectively. Chemotherapy, radiation, and metastatectomy were performed in 19, 6, and 2 patients, respectively, whereas best supportive care for reduced performance status was performed in 12 patients. There were no significant differences between high and low CONUT groups in the rates of patients undergoing each treatment (chemotherapy: 7 [70.0%] vs. 12 [50.0%], p = 0.285; radiation: 4 [16.7%] vs. 2 [20.0%], p = 0.816; metastatectomy: 1 [10.0%] vs. 1 [4.17%], p = 0.510; best supportive care: 3 [30.0%] vs. 9 [37.5%], p = 0.677). Figure 3 shows that patients with high CONUT score had significantly shorter RFS, CSS, and OS after RNU than patients with low CONUT score did (5-year RFS: 50.1% vs. 66.0%, p = 0.0395; CSS: 28.1% vs. 71.7%, p = 0.0041; OS: 26.4% vs. 66.8%, p = 0.0140).

3.5 Predictors for survival

Univariable analyses for RFS, CSS, and OS showed that pT stage, pN stage, tumor grade, presence of LVI, serum CRP level, and CONUT score were

significantly associated with survival (all $p < 0.05$), whereas other parameters, including age, sex, tumor site, surgical approach, or presence of adjuvant chemotherapy were not significantly associated with survival. Multivariable analyses showed that CONUT score was an independent predictor for CSS and OS (CSS: HR 5.44; $p = 0.0016$; OS: HR 2.90; $p = 0.0214$), whereas CONUT score marginally significantly predicted RFS (HR 2.26; $p = 0.0581$). With respect to other parameters, pT stage was significantly associated with CSS and OS (CSS: HR 12.9; $p = 0.0002$; OS: HR 3.29; $p = 0.0167$), and pN stage was significantly associated with RFS (HR 3.59; $p = 0.0080$) (Table 4).

4. Discussion

We found that the preoperative CONUT score helped predict RFS, CSS, and OS after RNU for UTUC. Importantly, we found that the CONUT score remained a significantly predictive biomarker after adjusting for tumor-specific factors (i.e., pT stage, pN stage, tumor grade, and presence of LVI), which are well-known risk factors [15, 16]. Moreover, its influence remained after adjustment for pre-treatment CRP level, which is a typical inflammatory-based biomarker that has been identified as being associated with prognosis in patients with UTUC [17, 18].

The predictive impact of CONUT score for prognosis has been previously demonstrated in colorectal cancer [4] and thoracic esophageal squamous cell carcinoma [5, 6]. After Iseki and colleagues reported the CONUT score's predictive role in patients with localized colorectal cancer [4], Toyokawa and Hirahara et al. suggested that it independently predicted RFS and OS, and was superior to other inflammation-based markers, such as the platelet/lymphocyte ratio, neutrophil/lymphocyte ratio, and modified Glasgow prognostic score, in patients with resectable thoracic esophageal squamous cell carcinoma [5, 6]. However, the predictive influence of the CONUT score on prognosis in patients with genitourinary cancers, such as UTUC, has remained controversial. Thus, to the best of our knowledge, this is the first study showing that the preoperative CONUT score was significantly associated with patient survival after RNU for localized UTUC.

The CONUT score is determined based on the serum albumin concentration, total lymphocyte count, and total cholesterol concentration. Low albuminemia was previously reported to be associated with poor prognosis in patients with cancer. Albumin concentration represents not only nutritional status but also other factors, including inflammation, caused by cancer cells [19, 20]. Numerous

studies of various cancers have investigated the predictive role of inflammation-based markers that incorporate albumin (e.g., the modified Glasgow prognostic score or CRP/albumin ratio) [14, 21, 22]. Moreover, lymphocytes play a role in the host's immunity against cancers and are thought to possess an antitumor effect by inducing cell apoptosis, suppressing tumor growth and migration, and mediating cytotoxicity [3]. T-lymphocytes play an important role in the immune response to cancer. Previous studies have indicated that high intratumoral CD8+ T-cell density was associated with better prognosis in invasive urothelial carcinoma of the bladder [23]. Moreover, patients with invasive bladder cancer had lower tumor infiltration of CD4+ and CD8+ T-cells [24], and in patients who responded to chemotherapy for bladder urothelial carcinoma, the CD4+/CD8+ ratio was significantly higher than that in those who did not respond [25]. A recent study indicated that a lower pre-treatment neutrophil/lymphocyte ratio might indicate good outcomes after neoadjuvant chemotherapy in muscle-invasive bladder cancer [26]. Finally, low serum cholesterol levels have been reported to be associated with a poor prognosis in patients with cancers [27-29]. Although it remains unclear why hypocholesterolemia is associated with a poor prognosis, there are several speculations based on previous experimental studies;

cholesterol is a crucial membrane component, and it affects membrane structure and function, including membrane fluidity and membrane protein activity [30-32]. Cholesterol metabolism is strictly regulated to maintain an appropriate cholesterol content in healthy cells. Perturbations in cholesterol metabolism can play important roles in oncogenesis and tumor development [33, 34]. Indeed, a previous experimental study suggested that membrane lipid composition plays an important role in urothelial carcinoma progression [35]. One of the sources of cholesterol is its acquisition from circulating blood via low-density lipoprotein (LDL) receptor-mediated endocytosis [36]. LDL receptor activity is reported to be elevated in patients with cancer, indicating that tumor-associated hypocholesteremia might result from increased cholesterol uptake by the neoplastic cells of neoplasms [37, 38]. Additionally, an elevated serum interleukin-6 level, which is induced by cancer cells [39], is reported to be associated with a decreased serum cholesterol level [40].

Finally, a unique aspect of this study was its demonstration of the relationship between sarcopenia and CONUT score (Table 3). Sarcopenia involves degenerative skeletal muscle wasting, and has recently been recognized as an important physiological change occurring during cancer cachexia development

[41]. Although sarcopenia occurs during normal aging, it can be exacerbated by hypercatabolic states and inflammatory responses caused by malignancy [1]. Thus, as expected, we observed a close relationship between sarcopenic status and high CONUT score, because these two markers similarly represented high inflammatory or malnutrition.

This study has several limitations. First, it was performed in a small cohort using a retrospective, single-center design. Second, because of its retrospective nature, potential factors that could possibly affect inflammation-based markers, such as comorbidities or medications, could not be completely excluded. Therefore, large-scale prospective validation studies are needed to confirm our findings. Third, a study recently reported the effect of CONUT score on cardiovascular morbidity [42], which could represent a competing risk in our analyses. Indeed, 7 patients died from non-cancer-related causes; 6 with low CONUT scores (subarachnoid hemorrhage, renal failure, colon cancer, pneumonia, abdominal aneurysm, and unknown) and 1 with a high CONUT score (heart failure). Because only 1 patient in each group died from cardiovascular disease, a competing risk of CONUT score on cardiovascular morbidity did not appear strong. Nonetheless, this possible influence should be considered. Fourth, only severe lymphocytopenia

(e.g., <800/mm^3; score 3) could result in a high CONUT score due to this marker's nature. Indeed, as shown in Table 2, only 7 (29.2%) patients had it, however, 3 had other components (i.e., low albumin and/or cholesterol); therefore, CONUT score can comprehensively represent nutritional status, although a strong influence of lymphocytopenia on high CONUT score may exist. Fifth, we found a higher rate of LVI (54 patients [50.5%]); this percentage was higher than those reported previously. Although we do not have an adequate explanation, we believe that this may have affected the analyses. Sixth, our analyses showed that 30 patients (28.0%) underwent RNU despite the presence of low-grade cancer; this may also have affected the analyses because of possible overtreatment. However, this can be partly attributed to the retrospective nature of our study. We could not diagnose low-grade cancer until RNU was performed because we do not routinely perform ureteroscopy or retrograde ureteropyelography. Seventh, the relationship between bladder recurrence and survival in patients with UTUC after RNU remains controversial [43]. In this context, bladder recurrence was not defined as relapse-free failure in reference to a previous large-scale and worldwide retrospective study [44]; however, a different definition may yield a different result. Eighth, because of the limited diagnostic accuracy of preoperative

radiological examinations, all patients who could tolerate LND underwent the procedure according to our strategy. Therefore, several patients received LND despite the presence of low-stage cancer, and this may have affected the results. Finally, the blood sample used to calculate CONUT score was obtained 34.7 ± 15.5 (mean ± standard deviation; median 32.0, range 6 – 62) days preoperatively. As the half-life of serum albumin is approximately 2-3 weeks, we should consider a possible time lag.

Conclusions

This study indicated that preoperative CONUT score helped predict prognosis in patients with localized UTUC after RNU. This biomarker is objective and non-invasive, and is easily obtained from blood samples in daily clinical practice. Thus, in addition to established prognostic factors, the CONUT score may improve postoperative follow-up performance, especially for patients with high CONUT scores.

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Conflict of interest

Tsunenori Kondo has received honoraria from Pfizer, Bayer, and Novartis. All other authors have no conflict of interest to declare.

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Figure legends

Figure 1: Flowchart showing patient selection

RNU, radical nephroureterectomy; UTUC, urothelial carcinoma of the upper urinary tract; UC, urothelial carcinoma

Figure 2: ROC curve analysis for CONUT score

We used the continuous variable CONUT as the test variable and RFS as the state variable. An investigation of the cut-off value for the CONUT score using the ROC curve showed the most appropriate cut-off value for the CONUT score to be 3 (AUC: 0.588). Thus, we set 3 as the cut-off value for the CONUT score in this study, and classified the patients into high (≥3) and low (<3) CONUT groups.
ROC, receiver operating characteristics; CONUT, Controlling Nutritional Status; RFS, relapse-free survival; AUC, area under curve

Figure 3: RFS, CSS, and OS according to CONUT score in patients with localized UTUC after RNU

Survival curves according to CONUT score. The 5-year RFS, CSS, and OS were significantly lower in patients with high CONUT scores, compared to those with low CONUT scores (RFS: 50.1% vs. 66.0%, p = 0.0395; CSS: 28.1% vs. 71.7%, p = 0.0041; OS: 26.4% vs. 66.8%, p = 0.0140).
RFS, relapse-free survival; CSS, cancer-specific survival; OS, overall survival; CONUT, Controlling Nutritional Status

Table 1: Definition of the CONUT score

Parameter	None	Light	Moderate	Sever
Serum albumin (g/dL)	≥ 3.50	3.00 – 3.49	2.50 – 2.99	< 2.50
Score	0	2	4	6
Total lymphocyte count (/mm^3)	≥ 1600	1200 - 1599	800 - 1199	< 800
Score	0	1	2	3
Total cholesterol (mg/dL)	≥ 180	140 - 179	100 - 139	< 100
Score	0	1	2	3

CONUT, Controlling Nutritional Status

Table 2: Components of the CONUT score

	Low CONUT (n = 83)	High CONUT (n = 24)
CONUT score		
0	21 (25.3%)	0
1	40 (48.2%)	0
2	22 (26.5%)	0
3	0	13 (54.2%)
4	0	6 (25.0%)
5	0	4 (16.7%)
6	0	1 (4.17%)
Albumin score		
0	82 (98.8%)	15 (62.3%)
2	1 (1.20%)	8 (33.3%)
4	0	1 (4.17%)
6	0	0
Total Lymphocyte score		
0	40 (48.2%)	2 (8.33%)
1	31 (37.8%)	3 (12.5%)
2	12 (14.5%)	12 (50.0%)
3	0	7 (29.2%)
Total cholesterol score		
0	60 (72.3%)	8 (33.3%)
1	19 (22.9%)	11 (45.8%)
2	4 (4.82%)	5 (20.8%)
3	0	0

CONUT, Controlling Nutritional Status

Table 3: Comparisons of patients' backgrounds according to CONUT score

Variable	Low CONUT (n = 83)	High CONUT (n = 24)	p
Age, years (continuous variable) [a]	72.7 ± 9.98	76.1 ± 8.65	0.166
Age, years (categorical classification)			0.0571
≥ 70 (ref. < 70)	48 (57.8%)	19 (79.2%)	
Sex			0.400
Male (ref. female)	51 (61.5%)	17 (70.8%)	
Initial symptom			0.399
Macrohematuria	52 (62.7%)	17 (70.8%)	
No symptom with urinary cytology disorder	6 (7.23%)	0	
Hydronephrosis	8 (9.64%)	5 (20.8%)	
Pain	6 (7.22%)	1 (4.17%)	
Others	11 (13.3%)	1 (4.17%)	
Tumor site			0.454
Pelvis (ref. ureter)	52 (62.7%)	13 (54.2%)	
Surgery type	66 (78.6%)	20 (20.0%)	0.878
Open (ref. laparoscopic)			
pT stage			0.882
pTis	1 (1.20%)	1 (4.17%)	
pTa	4 (4.82%)	0	
pT1	17 (20.5%)	6 (25.0%)	
pT2	14 (16.9%)	3 (12.5%)	
pT3	44 (53.0%)	12 (50.0%)	
pT4	3 (3.61%)	2 (8.33%)	
pN stage			0.413
pNx	27 (32.5%)	11 (45.8%)	
pN0	50 (60.2%)	10 (41.7%)	

pN1 pN2	3 (3.61%) 3 (3.61%)	0 3 (12.5%)	
Tumor grade High (ref. low)	 58 (69.9%)	 19 (79.2%)	0.372
LVI With (ref. without)	 42 (50.6%)	 12 (50.0%)	0.959
Adjuvant chemotherapy With (ref. without)	8 (9.52%)	0 (0.00%)	0.109
CRP, mg/dl ≥0.5 (ref. <0.5)	 10 (12.1%)	 9 (37.5%)	0.0041
Sarcopenia With (ref. without)	52 (62.7%)	21 (87.5%)	0.0213
Relapse of cancer With (ref. without)	24 (28.9%)	10 (41.7%)	0.237
Death from cancer With (ref. without)	16 (19.3%)	9 (37.5%)	0.0632
Death from any cause With (ref. without)	22 (26.5%)	10 (41.7%)	0.153
Follow-up, months [a]	46.1 ± 32.8	25.5 ± 18.4	0.0045

[a] Mean ± standard deviation

CONUT, Controlling Nutritional Status; LVI, lymphovascular invasion; CRP, C-reactive protein

Table 4: Multivariable analysis for the predictive factors for RFS, CSS, and OS in patients with localized UTUC after RNU

Variable	RFS (95% CI)	p	CSS (95% CI)	p	OS (95% CI)	p
pT stage ≥3 (ref. <3)	2.02 (0.83 – 5.51)	0.122	12.9 (3.01 – 91.3)	0.0002	3.29 (1.23 – 10.1)	0.0167
pN stage ≥1 (ref. 0 or X)	3.59 (1.43 – 8.28)	0.0080	3.11 (0.97 – 8.57)	0.0548	1.98 (0.64 – 5.11)	0.215
Tumor grade High (ref. low)	4.21 (0.99 – 28.9)	0.0525	1.88 (0.45 – 9.49)	0.390	2.64 (0.79 – 10.4)	0.117
LVI With (ref. without)	1.47 (0.61 – 4.02)	0.403	1.49 (0.48 – 4.04)	0.470	1.31 (0.50 – 3.15)	0.564
CRP, mg/dl ≥0.5 (ref.< 0.5)	1.12 (0.49 – 2.68)	0.796	1.08 (0.42 – 2.64)	0.867	1.20 (0.51 – 2.71)	0.669
CONUT ≥3 (ref. <3)	2.26 (0.97 – 4.94)	0.0581	5.44 (1.95 – 14.8)	0.0016	2.90 (1.18 – 6.75)	0.0214

RFS, relapse-free survival; CSS, cancer-specific survival; OS, overall survival; UTUC, urothelial carcinoma of the upper

urinary tract; RNU, radical nephroureterectomy; HR, hazard ratio; CI, confidence interval; LVI, lymphovascular invasion; CRP, C-reactive protein CONUT, Controlling Nutritional Status

Figure 1: Patient selection

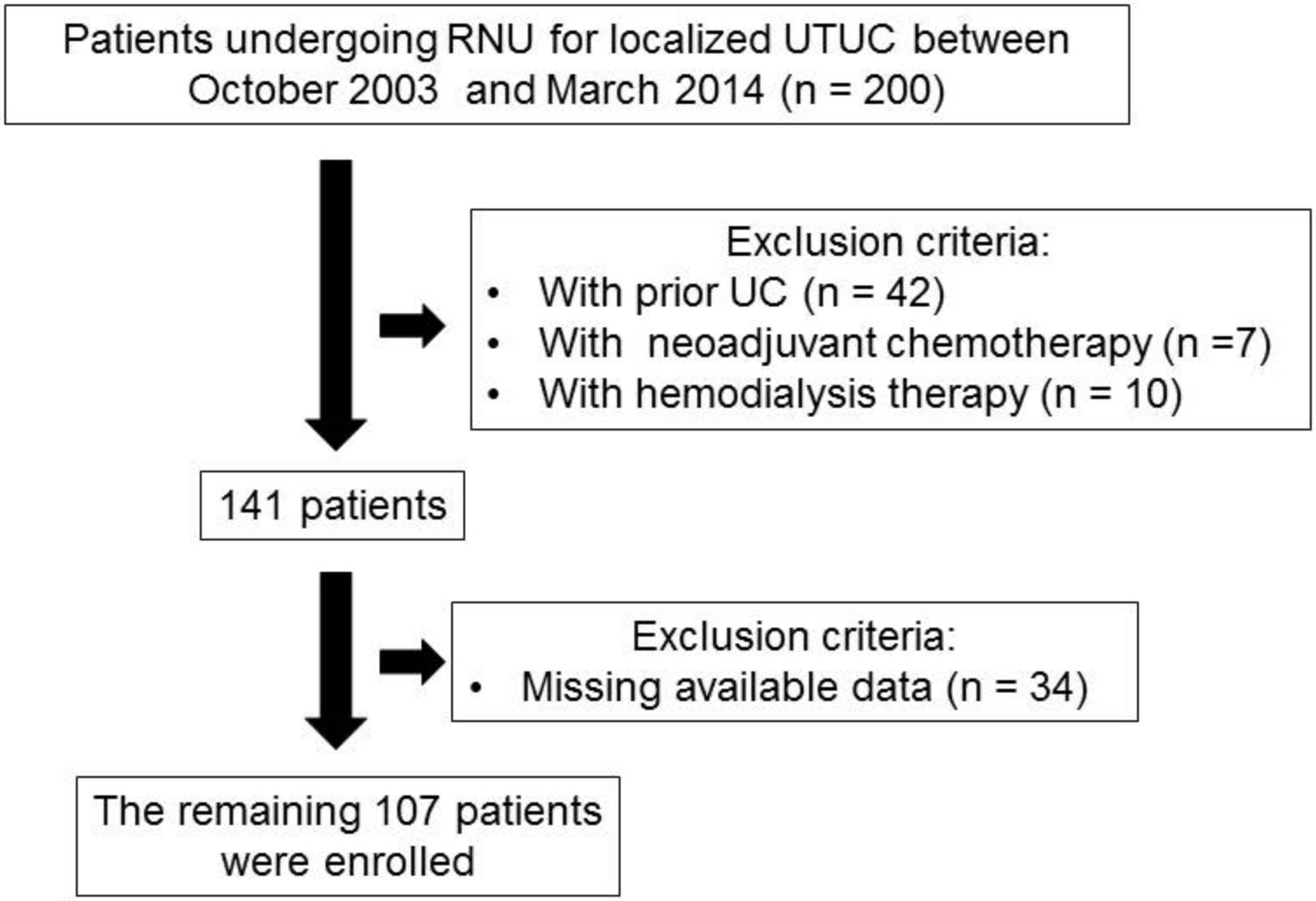


Figure 2: ROC analysis for CONUT score

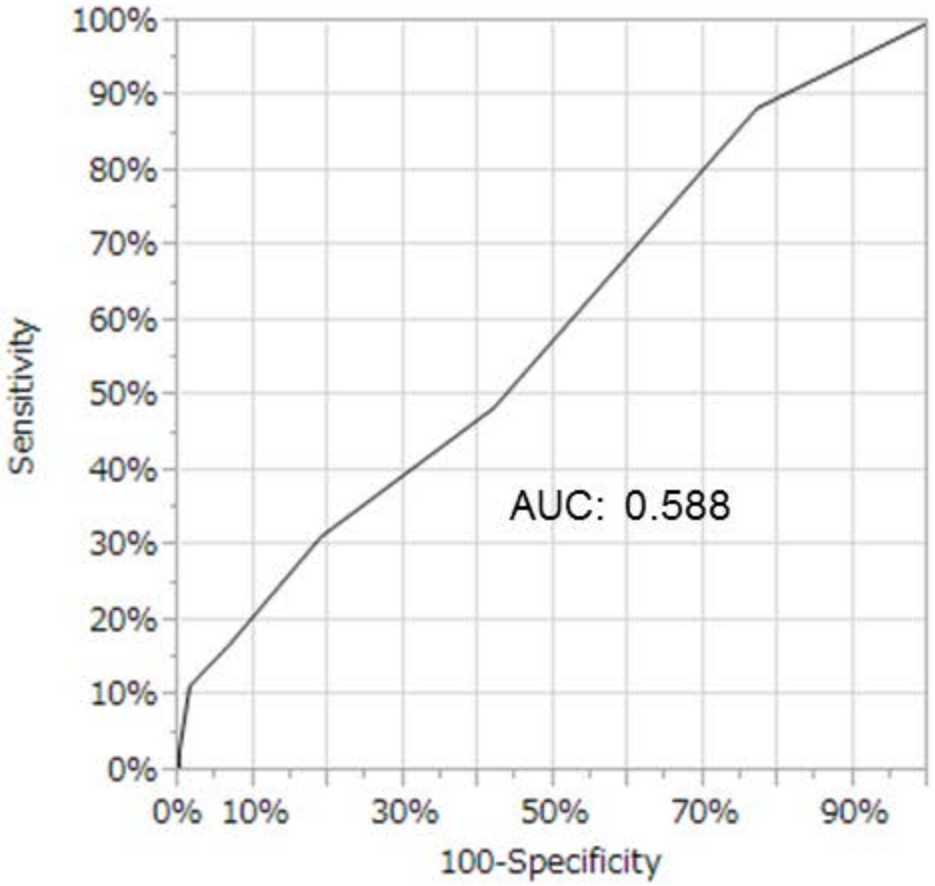
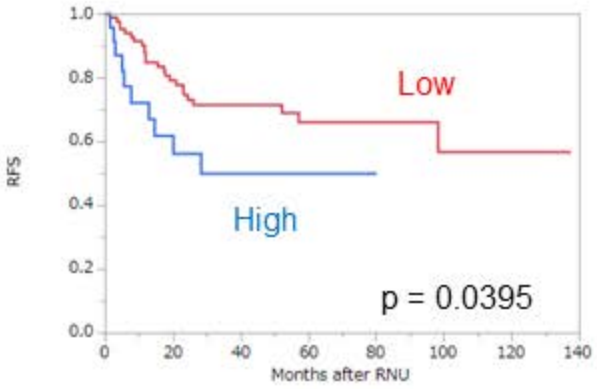


Figure 3: RFS, CSS, and OS according to CONUT score

RFS



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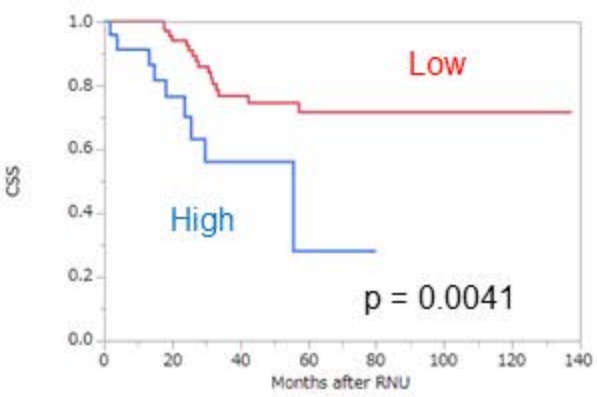
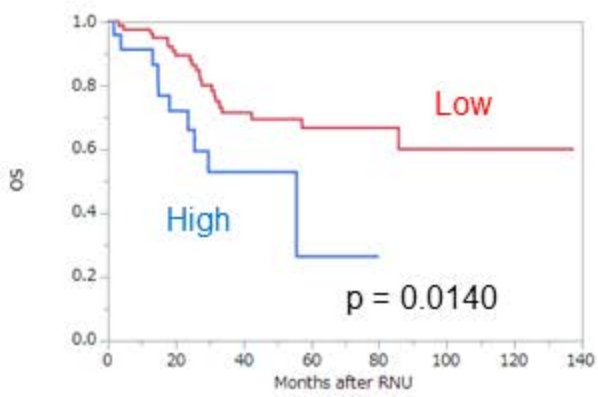


OS



5-year survival

50.1% vs. 66.0%

28.1% vs. 71.7%

26.4% vs. 66.8%