【Title】Modified Glasgow prognostic score is a pre-surgical prognostic marker of disease mortality in upper urinary tract urothelial carcinoma

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Running title: Pre-surgical mGPS in UTUC

【Abstract】

Background: To investigate the prognostic value of pre-surgical modified Glasgow prognostic score (mGPS) in upper urinary tract urothelial carcinoma (UTUC) patients treated with radical nephroureterectomy.

Methods: We retrospectively reviewed the clinical records of 273 UTUC patients treated with radical nephroureterectomy. The mGPS was evaluated based on pre-surgical serum C-reactive protein and albumin. Association of mGPS with recurrence-free survival (RFS), cancer-specific-survival (CSS) and overall survival (OS) rates were estimated using Kaplan-Meier method and log-rank test was used to compare survival outcome. Cox regression analyses were performed for the assessment of the mGPS with RFS, CSS and OS.

Results: Of total 273 patients, the mGPS 0, 1 and 2 were assigned in 216 (79%), 45 (17%) and 12 (4%), respectively. The RFS, CSS and OS of UTUC patients with mGPS 2 were significantly worse than those with mGPS 0. On univariate analysis, mGPS 2 was associated with worse RFS, CSS and OS (all P-value < 0.01). On multivariate analyses, mGPS2 was independently associated with worse CSS and OS (HR: 4.73, 95% CI: 1.31-17.2 and HR: 3.66, 95% CI: 1.08-12.4, respectively). In the subgroup analyses of advanced UTUC patients, mGPS2 was independently associated with worse RFS (HR 4.31, 95% CI: 1.69-11.1).

Conclusions: Pre-surgical mGPS independently predicts CSS and OS of UTUC patients. Therefore, assessment of pre-surgical mGPS status could help identifying the worse survivor of UTUC patients.

Mini abstract: Assessment of pre-surgical mGPS could help identifying the worse survivor of UTUC patients.

Keywords: Upper urinary tract urothelial carcinoma, Modified Glasgow prognostic score, recurrence, survival

Abbreviations & Acronyms:

mGPS = modified Glasgow prognostic score

UTUC = upper urinary tract urothelial carcinoma

RNU = radical nephroureterectomy

RFS = recurrence free survival

CSS = cancer specific survival

OS = overall survival

CRP = C-reactive protein

LND = lymph node dissection

LVI = lymphovascular invasion

IQR = Interquartile range

EAU = European association of urology

【Introduction】

Upper urinary tract urothelial cancer (UTUC) is an uncommon type of cancer, representing only 5-10% of urothelial carcinoma cases globally (1, 2). UTUC is a heterogeneous disease and owing to its rarity, poses a challenge for the development of strong evidence for treatment. There is no doubt that the gold standard for treatment of non-metastatic UTUC is radical nephroureterectomy with bladder cuff incision (RNU). Although evidence regarding the use of perioperative chemotherapy for the treatment of UTUC is lacking, it plays a crucial role in high-risk patients, and may allow kidney-sparing treatment in low-risk patients (2, 3). Therefore, accurate predictive models are essential for clinical decision-making and intensified follow-up scheduling. Unfortunately, the current risk model based on standard clinicopathologic features remains unsatisfying (4). Thus, novel biomarkers are needed to help improve prediction of disease progression.

The Glasgow prognostic score (GPS) is based on C-reactive protein (CRP) and albumin levels, which are inflammation and nutrition markers, respectively (5). Recently, GPS has been established as a prognostic marker in several cancers such as non-small cell lung and colorectal cancer (5, 6). In 2017, Inamoto et al. reported the utility of GPS as a powerful prognostic marker in UTUC, along with the other cancers (7). Modified GPS with a CRP cutoff value of 0.5 mg/dl has been proposed as a prognostic marker for colorectal cancer based on a receiver operating characteristic (ROC) analyses (8). Thereafter, it has been investigated as a prognostic factor for European patients of non-muscle invasive bladder cancer (NMIBC) (9). Recently, the utility of mGPS for predicting survival outcome of UTUC was reported by a large multicenter international cohort study from Europe and the United States (10). In Japan, a study tested the utility of several inflammation- and nutrition- status in UTUC patients for the prediction of survival outcomes, however, statistically speaking, mGPS was not associated with disease-specific survival and overall survival (OS) (11). It remains unclear whether mGPS is associated with worse oncologic and survival outcome in Japanese patients with UTUC. Therefore, we retrospectively investigated the association of a high mGPS with disease recurrence, cancer-specific survival (CSS), and OS in UTUC patients treated with RNU.

【Materials and methods】

This study was approved by the Ethics Committee of The Jikei University School of Medicine ((31-426(1008)) and Kameda Medical Center.

(Patient and study design)

We retrospectively reviewed the clinical records of 303 patients with UTUC who were treated with RNU in our institutions from 2004-2014. Twenty five, 1, and 4 patients were excluded from this study based on the following criteria: 1) lack of clinical and pathological information, 2) presence of infection before surgery, and 3) who received neoadjuvant chemotherapy before RNU, respectively. Eventually, 273 consecutive patients with UTUC were enrolled in this study. Patients with UTUC were treated using either laparoscopic- or open- RNU. Open- RNU was performed based on the discretion of the surgeon and/or when lymph node enlargement (greater than 10 mm) was suspected before surgery. Recently, we principally performed laparoscopic RNU via an intraperitoneal approach, thereafter, the bladder cuff was removed with an extra-vesical incision. In the case of prior intraperitoneal surgeries, we chose the retroperitoneal approach. We referred to the template dissection recommended by Kondo et al. for cases with lymph node dissection (12).

The pathological stage was determined according to the 2009 TNM classification system. Tumor grade was assigned as per the 1999 WHO classification.

Adjuvant chemotherapy was recommended based on the discretion of the patients' own clinicians.

Blood tests, including CRP and albumin, were undertaken within a month before RNU. Post-RNU, the patients were followed up every 3 months with physical examination, blood test, CT scan,

cystoscopy, and urine cytology for 2 years, and thereafter every 6 months.

The GPS and mGPS were calculated with serum CRP and albumin values. Previously, CRP cutoff values for GPS and mGPS were defined as 1.0 and 0.5 mg/dl, respectively (5) (8). Albumin cutoff value was 3.5 g/dl for both GPS and mGPS (5).

The GPS and mGPS were rated 0 through 2 based on serum CRP and albumin status. (8) The GPS and mGPS 0,1, and 2 were allocated if the patient had neither high CRP nor hypoalbuminemia, one of the factors, or both factors, respectively.

Preliminary validation to decide the cutoff value of CRP and albumin has been performed previously. We chose mGPS (CRP cutoff value: 0.5 mg/dl) because of the higher sensitivity compared with GPS (Data not shown).

(Statistical analysis)

Patient characteristics presented in Table 1 were compared using the chi-square test and t-test. Association of mGPS with recurrence-free survival (RFS), CSS, and OS rates were estimated using the Kaplan-Meier method, and the log-rank test was used to compare survival outcome. Univariate and multivariate Cox regression analyses were performed to identify the independent factors for RFS, CSS, and OS. All data were analyzed using STATA 14 (Stata Corp., College Station, TX). Differences were considered significant if the two-sided P values were <0.05.

【Results】

The clinical and pathological characteristics of 273 patients with UTUC are listed in Table 1. The median age was 71 years (IQR: 63-77), and approximately 70% of patients were males. Of 273 patients with UTUC, 40% were diagnosed with > pT2 stage and 30% underwent lymph node dissection. Of those, 10% were diagnosed with nodal involvement. Approximately 60% of patients with UTUC had a higher pathological tumor grade (G3), thereafter 20% of patients with UTUC underwent adjuvant chemotherapy.

When all patients were categorized into mGPS 0, 1, and 2 groups based on their pre-surgical CRP and albumin value, 216 (79%), 45 (17%), and 12 (4%) patients had mGPS scores of 0, 1, and 2, respectively.

When the baseline characteristics were compared based on the mGPS status, the UTUC patients with a high mGPS who were likely to undergo open surgery had a higher pT stage (>pT2) and lymphovascular invasion (LVI) (Table1).

The median follow-up period was 36.1 months. Overall, out of the total cases during follow-up, there were 86 recurrences, 49 cancer-specific deaths, and 70 deaths due to any causes.

The Kaplan-Meier curves showed worse survival outcome in RFS, CSS, and OS for patients with

mGPS 2 (Figure 1A, B, and C). In detail, the 5-year RFS rates for patients with mGPS 0, 1, and 2 were 49.4%, 23.8%, and 10.6%, respectively (0 vs 2: $p<0.01$) (Figure 1A). No significant difference in CSS was seen between mGPS 0 and 1, however, when the survival curve was compared between mGPS 0 and 2, there was a significant difference in CSS (0 vs 2: $p<0.01$). The 5-year CSS rates for patients with mGPS 0, 1, and 2 were 80.4%, 72.9%, and 32.3%, respectively (Figure1B). Figure 1C shows the OS curves of mGPS 0, 1, and 2. The 5-year OS rates for patients with mGPS 0, 1, and 2 were 74.4%, 57.3%, and 32.3%, respectively. Based on the statistical analyses, UTUC patients with pre-surgical mGPS of 2 had worse overall mortality than those with mGPS of 0 ($p<0.01$).

Finally, univariate and multivariate Cox regression analyses were performed to investigate the independent prognostic factors for recurrence, CSS, and OS. The results are summarized in Table 2. In univariate analyses, mGPS of 1 or 2 (ref:0) was a significant predictive factor for recurrence. In multivariate analyses, although statistically insignificant (p-value:0.06), mGPS of 2 (ref:0) was a predictive factor for recurrence. When we focused on the group with pT3-4 or any T plus nodal involvement, multivariate Cox regression analyses revealed that UTUC patients with mGPS of 2 were at 4 times a higher risk for recurrence than those with mGPS of 0(p-value:<0.01) (Table3).

The predictive factors for worse CSS and OS rates had the same trend. The univariate analyses showed that an mGPS of 2 (ref:0) was a predictive factor for worse CSS and OS rates. Eventually, the multivariate analyses demonstrated mGPS of 2 (ref:0) (HR for CSS and OS: 4.73 and 3.66) as the

independent factor (Table2).

【Discussion】

In this study, we investigated the association of mGPS with the survival outcome of Japanese UTUC patients treated with RNU. In agreement with previous studies reported, we found that mGPS of 2 was associated with worse CSS and OS in non-metastatic UTUC patients treated with RNU. Additionally, in the subgroup of pT3-4 or any T with nodal involvement, mGPS of 2 was an independent prognostic factor for disease recurrence.

EAU guidelines recommended that non-metastatic UTUC be classified into low- and high- risk based on the preoperative clinicopathological characteristics (such as hydronephrosis, tumor grade by cytology or ureteroscopic biopsy, tumor size / focality, and clinical TNM stage by CT-urography) for the indication of nephron sparling surgery (4). However, predicting the precise staging before RNU in clinical practice is challenging. Margolin et al. evaluated the discordance between ureteroscopic biopsy and pathological findings at RNU; 50% of UTUC initially diagnosed as low grade at ureteroscopic biopsy were eventually upgraded at RNU (13). Furthermore, they found the diameter of the biopsy fragment (1 mm or less) affected the underestimation of high-risk UTUC at biopsy (13). Indeed, EAU guidelines recommended diagnostic ureteroscopy and biopsy only in cases

where additional information will impact treatment decisions, such as nephron sparling surgery (14). In order to recognize the worse survivors of non-metastatic UTUC patients treated with RNU, preoperative predictive combination tools, which consist of patient-related and/or tumor-related factors and/or molecular biomarkers have been proposed (3). However, the accuracy for prediction of advanced UTUC is 67%-80% (15-17). Therefore, there is an unmet need to investigate more accurate and useful biomarkers to predict the survival outcome of UTUC patients.

In this study, we proposed mGPS as a pre-surgical biomarker for the survival outcome of patients with UTUC. The GPS is a combination marker of CRP and albumin status, which are representative inflammation and nutrition makers, respectively (5). Previously, several biomarkers such as neutrophil-to-lymphocyte ratio (18), and albumin-to-globulin ratio (19), had been proposed. We focused on mGPS since it is an ideal marker based on availability of CRP and albumin, is inexpensive, and is routinely examined before and after surgery. Generally, elevation of CRP represents a non-specific systemic inflammation. In cancer patients, CRP elevation often reflects tumor aggressiveness (20). Low albumin indicates malnutrition and poorer outcome among several types of cancers, such as colorectal and gastric cancer (21, 22). Therefore, the combination of CRP and albumin status reflects poorer outcomes in patients with cancer. Forrest et al. investigated the correlation of cumulative CRP and albumin score with survival outcomes on patients with inoperable non-small cell lung cancer. They reported that patients with elevated CRP (>10 mg/l) and low

albumin (<35 g/l) who were allocated a score of 2, had two times higher a risk for death than patients without elevated CRP and low albumin (5). McMillan et al. evaluated the association of GPS with disease mortality of lung, colon, and rectal cancer; they advocated the utility of modified GPS (which had a different definition) as a prognostic model for mortality (6). Thereafter, the utility of mGPS as the prognostic predictive model was widely evaluated for advanced stages of various cancers, such as breast, prostate, renal, and bladder cancer. As expected, mGPS significantly enhanced the difference of survival curves among all cancer types (23). In 2011, a Japanese group proposed the other criteria of mGPS with a CRP cutoff value set at 0.5 based on ROC analyses to investigate the best cutoff value of CRP and albumin; they found that mGPS was a reliable predictor of postoperative mortality of colorectal cancer (8). In 2018, Kimura et al. utilized this criterion of mGPS and demonstrated that higher mGPS was associated with worse PFS in European NMIBC patients (9). Following the previous studies, we evaluated the association of mGPS with recurrence and mortality of UTUC patients and found that pre-surgical mGPS of 2 predicted the recurrence and mortality of UTUC. Recently, a large European and US multicenter cohort study demonstrated the utility of mGPS as a useful biomarker to predict the worse prognosis for survival in UTUC patients treated with RNU (10). In detail, 2492 UTUC patients were retrospectively analyzed and mGPS of 0, 1, and 2 were allocated in 77, 21, and 1 %, respectively. They demonstrated that higher mGPS was independently associated with RFS, CSS and OS, both in a preoperative and in a postoperative

setting.

Itami et al. investigated several preoperative predictive factors in 125 UTUC Japanese patients (11). In their study, mGPS was not statistically associated with worse disease-specific survival and OS. However, the number of subjects in the study was limited. The present study included 273 patients with a similar proportion of mGPS as the western study and revealed consistent results for predictive efficacy.

Based on the results of this study, conventional prognostic tools, such as EAU risk stratification and pre-surgical mGPS would increase the accuracy of predicting non-organ confined disease. Moreover, the predictive information will be helpful to recognize the patients that are suitable to undergo perioperative chemotherapy and/or strict follow-up. However, external validation and prospective studies are warranted in the future to emphasize the role of mGPS in patients with UTUC.

This study has several limitations. The most intensive limitation was the retrospective nature of the study with a small sample size. This may have introduced a selection bias. Moreover, these results were shown by two different institutions. Owing to the small number, only 12 UTUC patients were allocated mGPS 2. This may have affected the results of this study. In addition, the pathological results were not reviewed by a central pathologist. Furthermore, we performed Cox regression analyses with mGPS and postoperative parameters such as pT stage and nodal involvement since we

did not have sufficient preoperative pathological data at ureteroscopy ((biopsy was performed in only 33 patients (12.3%)). Despite these limitations in our investigation of the association of pre-surgical mGPS status and the survival outcome of Japanese patients with UTUC, we believe our results offer beneficial information in the consideration of biomarkers in daily clinical oncology practice.

【Conclusions】

High pre-surgical mGPS was significantly associated with mortality of UTUC patients treated with RNU. Therefore, assessment of pre-surgical mGPS could help predicting the patients who will meet disease recurrence and be threaten the survival. Further external validation cohort and prospective study are warrant in the future.

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【Conflict of interest】All authors have no conflict of interest

Figure legends

Figure1: Kaplan-Meier curves for recurrence-free survival (A), cancer-specific survival (B) and overall survival (C) according to mGPS (modified Glasgow prognostic score) in 273 patients treated with radical nephrouretectomy for upper urinary tract urothelial carcinoma.

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Table1. Association of modified Glasgow prognostic score with clinicopathologic features in 273 patients treated with nephroureterectomy for upper urinary tract urothelial carcinoma					
Variables	Total	mGPS			P value
		0	1	2	
Number of patients	273	216 (79)	45 (17)	12 (4)	
Median age (IQR)	71 (63-77)	70 (62-77)	74 (66-78)	63 (70-77)	0.16
Gender, n (%)					0.14
female	72 (26)	56 (26)	10 (22)	6 (50)	
male	201 (74)	160 (74)	35 (78)	6 (50)	
Operation					0.03
Open	126 (46)	91 (42)	27 (60)	8 (66)	
Laparoscopic	147 (54)	125 (58)	18 (40)	4(34)	
Pathological T stage					<0.01
≤pT2	160 (59)	132 (62)	26 (55)	2 (14)	
>pT2	113 (41)	80 (38)	21 (45)	12 (86)	
Pathological tumor grade, n (%)					0.08
Grade3	160 (59)	120 (56)	31 (76)	9 (75)	
Lymphovascular invasion, n (%)	93 (34)	66 (30)	29 (64)	8 (75)	<0.01
Multifocality, n (%)	55 (20)	43 (20)	9 (20)	3 (25)	0.9
Tumor architecture, n (%)					0.39
Papillary	179(66)	143 (67)	28 (54)	8 (66)	
Sessile	94 (34)	70 (33)	24 (46)	4 (34)	
Nodal involvement	26 (10)	19 (9)	4 (11)	3 (25)	0.18
Tumor location, n (%)					0.13
Renal pelvis	137 (50)	108 (50)	26 (58)	3 (2)	
Ureter	136 (50)	108 (50)	19 (42)	9 (12)	
Adjuvant chemotherapy	55(20)	42(19)	11 (24)	2 (17)	0.67
IQR=interquartile range, mGPS: modified Glasgow prognostic score					

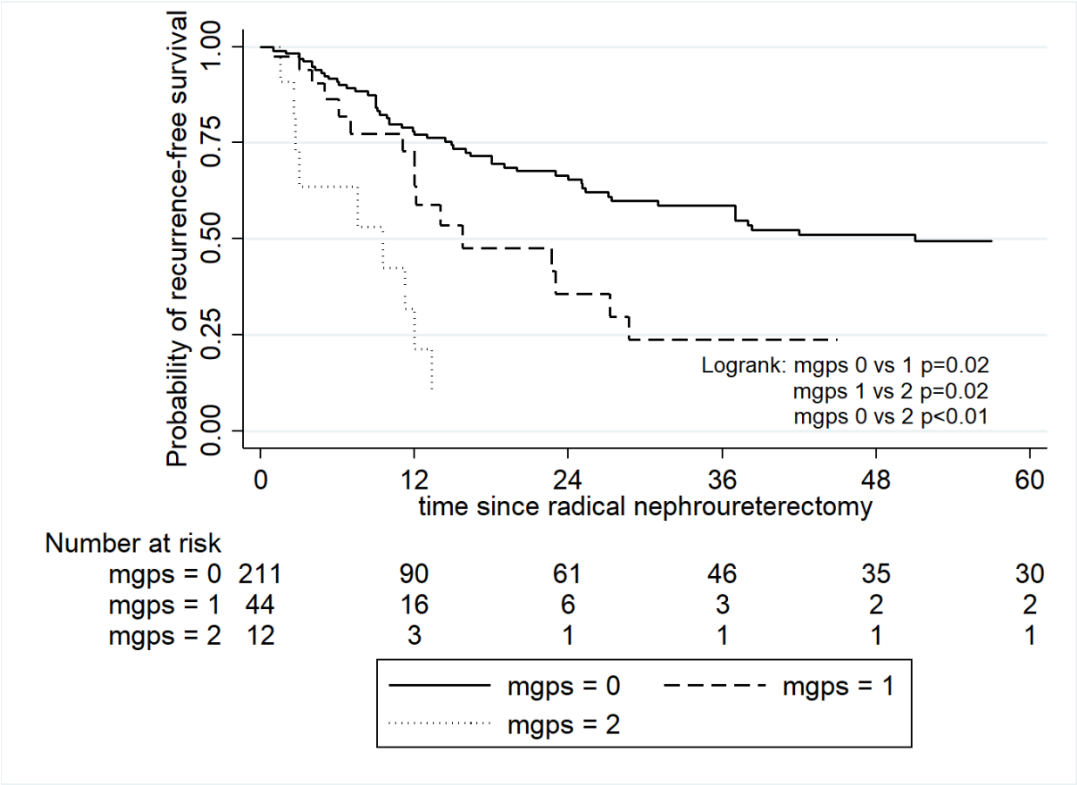
Table2.Univariable and multivariable Cox regression analyses for the prediction of recurrence-free survival (RFS), cancer specific-free survival l (CSS) and overall survival (OS) in 273 patients treated with radical nephroureterectomy for upper urinary tract urothelial carcinoma.

Variable	RFS				CSS				OS			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Age (continuous)	1.02(1.00-1.04)	0.04	1.03(1.01-1.06)	0.04	1.01 (0.99-1.05)	0.33	-	-	1.03(0.99-1.05)	0.05	-	-
Gender (ref: female)	0.66(0.42-1.03)	0.07	-	-	0.66 (0.37-1.19)	0.17	-	-	0.91(0.54-1.55)	0.74	-	-
Operation (ref: open)	0.60(0.39-0.93)	0.02	0.51(0.31-0.83)	<0.01	0.44(0.24-0.80)	<0.01	0.49(0.25-0.96)	0.04	0.44(0.26-0.74)	<0.01	0.43(0.23-0.77)	<0.01
pT stage (ref: ≤pT1)												
pT2	1.96(0.93-4.12)	0.08	0.93(0.39-2.22)	0.88	2.73(1.03-7.25)	0.04	1.82(0.52-6.47)	0.35	2.69(1.18-6.18)	0.02	1.94(0.72-5.25)	0.19
pT3	3.34(1.61-6.94)	<0.01	1.80(0.78-4.18)	0.17	2.36(0.89-6.25)	0.09	1.44(0.40-5.13)	0.58	2.48(1.09-5.64)	0.03	1.45(0.54-3.94)	0.46
pT4	5.89(1.24-27.8)	0.03	0.55(0.53-5.63)	0.61	4.56(0.88-23.5)	0.07	0.07(0.05-1.01)	0.06	3.35(0.69-16.1)	0.13	0.09(0.07-1.09)	0.06
Tumor grade3(ref:≤G2)	4.70(2.48-8.91)	<0.01	3.01(1.51-6.01)	<0.01	4.06 (1.90-8.72)	<0.01	1.87(0.83-4.22)	0.13	2.34(1.36-4.02)	<0.01	1.11(0.61-2.03)	0.73
LVI	4.64(2.88-7.48)	<0.01	2.79(1.63-4.75)	<0.01	6.93(3.58-13.4)	<0.01	3.48(1.76-6.88)	<0.01	3.86(2.34-6.36)	<0.01	2.66(1.52-4.65)	<0.01
Multifocality	0.72(0.42-1.22)	0.22	-	-	0.89(0.43-1.85)	0.76	-	-	0.82(0.44-1.53)	0.54	-	-
Tumor architecture (ref: papillary)	1.69(1.09-2.63)	0.02	1.65(1.01-2.70)	0.04	1.85(1.04-3.28)	0.04	1.54(0.81-2.94)	0.19	1.66(1.03-2.70)	0.04	1.55(0.90-2.66)	0.11
Nodal Involvement	3.44 (2.04-5.79)	<0.01	1.95(1.03-3.68)	0.04	5.51 (2.94- 10.3)	<0.01	3.93(1.81-8.54)	<0.01	4.03 (2.26-7.19)	<0.01	3.34(1.61-6.92)	<0.01
Tumor location (ref: renal pelvis)	0.75(0.48-1.16)	0.19	-	-	0.75(0.43-1.33)	0.33	-	-	0.76(0.47-1.22)	0.25	-	-
mGPS (ref: score 0)												
1	1.88(1.07-3.28)	0.03	1.39(0.72-2.71)	0.33	1.33(0.64-2.77)	0.45	1.25 (0.54-2.90)	0.61	1.80(1.03-3.14)	0.04	1.53(0.80-2.90)	0.20
2	4.49(2.20-9.14)	<0.01	2.40(0.98-5.90)	0.06	5.09(2.13-12.1)	<0.01	4.73(1.31-17.2)	0.02	3.71(1.58-8.68)	<0.01	3.66(1.08-12.4)	0.04

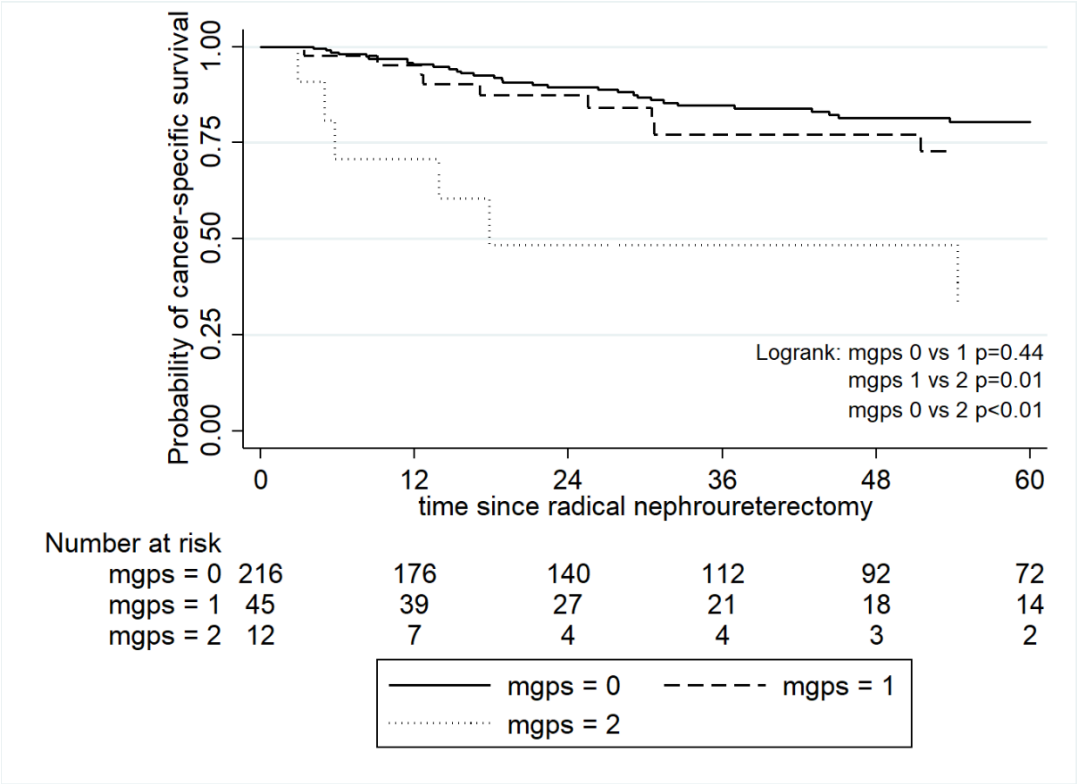
HR = Hazard Ratio; CI = Confidence Interval; LVI: lymphovascular invasion; mGPS = modified Glasgow Prognostic Score

Table3. Multivariable Cox regression analyses for the prediction of disease recurrence adjusted for clinicopathological features in patients with pathologic advanced stage.			
	patients with pT3-4 or any T with nodal involvement		
	RFS		
	HR	95%CI	p-value
mGPS (ref:0)			
1	2.61	1.11-6.10	0.03
2	4.32	1.69-11.1	<0.01
CI: confidence interval, HR: hazard ratio, mGPS: modified Glasgow prognostic score, RFS: recurrence-free survival			

A.


Probability of recurrence-free survival
0.00
0.25
0.50
0.75
1.00
0
12
24
36
48
60
time since radical nephroureterectomy
Logrank: mgps 0 vs 1 p=0.02
mgps 1 vs 2 p=0.02
mgps 0 vs 2 p<0.01
Number at risk
mgps = 0 211 90 61 46 35 30
mgps = 1 44 16 6 3 2 2
mgps = 2 12 3 1 1 1 1
mgps = 0
mgps = 1
mgps = 2

B.


Probability of cancer-specific survival
0.00
0.25
0.50
0.75
1.00
0
12
24
36
48
60
time since radical nephroureterectomy
Logrank: mgps 0 vs 1 p=0.44
mgps 1 vs 2 p=0.01
mgps 0 vs 2 p<0.01
Number at risk
mgps = 0 216 176 140 112 92 72
mgps = 1 45 39 27 21 18 14
mgps = 2 12 7 4 4 3 2
mgps = 0
mgps = 1
mgps = 2

C.

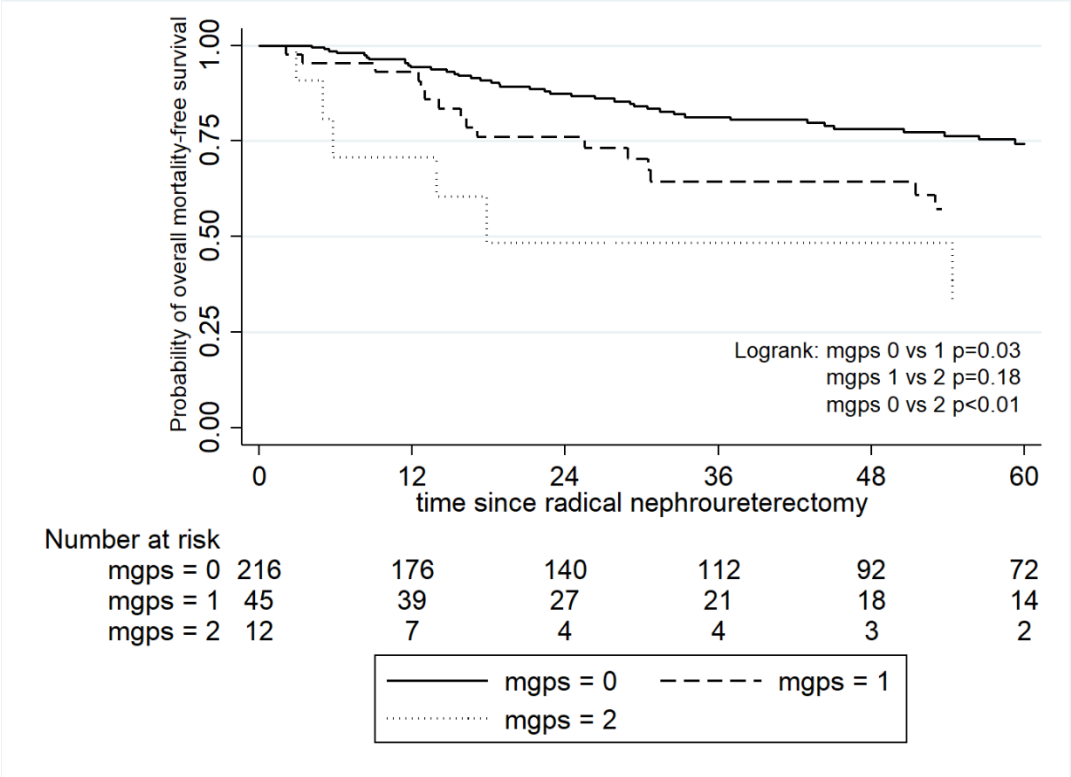


Figure1.Kaplan-Meier curves for recurrence-free survival (A), cancer-specific survival (B) and overall survival according to mGPS (modified Glasgow prognostic score) in 273 patients treated with radical nephrouretectomy for upper urinary tract urothelial carcinoma.