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Risk Stratification Model to Predict High-Risk Patients for Adjuvant Chemotherapy in Upper Urinary Tract Urothelial Cancer

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Abstract

Objective: Optimal patient selection for adjuvant chemotherapy has not been clarified in upper urinary tract urothelial cancer (UTUC). We aimed to develop a risk model to select candidates for adjuvant chemotherapy after radical nephroureterectomy (RNU).

Methods: A retrospective review of 936 patients with UTUC between 1995 and 2015 who received ≥ 2 cycles of platinum-based adjuvant chemotherapy after RNU (n=213) or surgery alone (n=723) was conducted in collaborative institutions. Risk factors for cancer-specific mortality were extracted using the proportional hazard model. The survival benefit in high-risk patients was compared between the groups.

Results: At a median follow-up of 1006 days (34 months), disease recurrence, cancer-specific mortality, and all-cause mortality were noted in 253 (27.5%), 206 (22.0%), and 285 (30.4%) patients, respectively. On multivariate analysis, baseline serum C-reactive protein (CRP) ≥ 0.32 mg/dL (HR: 1.74, 95% CI: 1.09–2.75, p=0.0201), pathologic T stage ≥ 3 (pT>3) (HR: 2.17, 95% CI: 1.28–3.76, (p=0.0033), cN+ (HR: 2.84, 95% CI: 1.50–5.01, p=0.0021), and lymphovascular invasion (LVI) (HR: 3.94, 95% CI: 2.23–7.17, p<0.0001) were independent predictors of cancer-specific mortality (CSM) in the training set. When they were used to categorize patients into low (0-1 factor) and high-risk groups (2-4 factors), high-risk patients had significantly worse CSM than those with low-risk. In the high-risk patients, 42.3% who received adjuvant chemotherapy had significantly better CSM and all-cause mortality than those who underwent surgery alone. In high-risk patients, multivariate analysis showed adjuvant chemotherapy as an independent prognostic factor for CSM (HR: 0.52) and all-cause mortality (HR: 0.57).

Conclusion: CRP, pT>3, cN+, and LVI was useful for identifying high-risk patients.

Keywords: Upper urinary tract; Urothelial cancer; Radical nephrouretectomy; Adjuvant chemotherapy; Lymphovascular invasion; Pathological T stage, C-reactive protein; Risk model

Introduction

Upper urinary tract urothelial cancer (UTUC) is a relatively rare malignancy accounting for 5% of all urological malignancies [1]. Prognosis of the patients varies from 5-year survival rates of more than 90% in patients with pTa/1 tumours to less than 20% in patients with pT4 disease after standard treatment with radical nephroureterectomy (RNU) with excision of the bladder cuff [2]. A substantial portion of localized UTUCs are stage T3 or more at the time of surgery, and up to 30% of patients with muscle-invasive UTUC already have lymph node involvement at diagnosis [3]. These circumstances clearly suggest the importance of perioperative chemotherapy for patients at high risk of cancer-specific death [4,5].

The treatment of UTUC is associated with several dilemmas due to the lack of randomized controlled trials because of the rarity of the disease, and distinct genetic and epigenetic differences from bladder urothelial carcinoma (UC) [6]. Thus, established indications for perioperative chemotherapy in bladder UC does not directly translate into the treatment of UTUC. Adjuvant chemotherapy has been reported to improve cancer-specific survival up to 50% [7], but inconsistent data have also been reported in UTUC [8]. A systematic review and meta-analysis indicated a prognostic benefit for both overall survival and disease-free survival for cisplatin-based adjuvant chemotherapy [9].

Adjuvant chemotherapy is recommended for high-risk patients but the definition of high-risk UTUC remains obscure. The European Association of Urology guidelines for UTUC defined high risk as cases having several factors including hydronephrosis, positive cytology, multifocal disease, pathological T3 stage, nodal involvement, or lymphovascular invasion (LVI) [1]. Two large multicentre cohort analyses confirmed the importance of LVI and tumour architecture as strong prognostic variables associated with aggressive UTUC [10,11]. Recent evidence has suggested C-reactive protein (CRP) as a

biomarker of survival in patients with UTUC treated with RNU [12-14].

In this study, we aimed to develop a risk stratification model to select candidates for adjuvant chemotherapy after RNU from a retrospective large cohort in a multicentre collaborative study.

Patients and Methods

Patient selection

We retrospectively reviewed our cohort of 1349 patients who had undergone RNU with pathologically diagnosed UTUC from 1994 to 2015 in our collaborative hospitals, and 936 patients were selected based on the data set necessary for the present analysis (213 who received adjuvant chemotherapy comprising at least two cycles of platinum-based adjuvant chemotherapy and 723 who underwent surgery alone) were included in this study. Patients who underwent radiation therapy or neoadjuvant chemotherapy, or those having active febrile infectious disease or chronic inflammatory or autoimmune diseases with steroid therapy were excluded from the analysis. This study was an institutional review board–approved multicentre study in our collaborative groups in the western section of Japan (Nara Uro-Oncology Research Group (n=279 adjuvant chemotherapy/surgery alone: 52/227), Osaka Medical University Hospital group (n=138; 16/122), Shimane University Hospital group (n=96; 43/53), and Yamaguchi Uro-Oncology Group (n=423; 102/321). Data obtained from the patients' records were patient data (age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), baseline serum C-reactive protein (CRP), tumour data (clinical T stage, clinical lymph node metastasis, location of tumour, concurrent bladder cancer, hydronephrosis of the affected site), treatment (lymphadenectomy performed, type and courses of adjuvant chemotherapy), pathology (preoperative urine cytology, pathologic T stage (Pt), pathologic lymph node metastases, lymphovascular invasion (LVI), carcinoma in situ (CIS), and multifocality), and survival (cancer-specific and all-cause mortality).

RNU was performed by a standard procedure consisting of whole dissection of the kidney, including perirenal fat, with the entire length of the ureter and adjacent segment of the bladder cuff. Regional lymph node dissection was performed in patients who were diagnosed as having enlarged nodes on preoperative radiographic evaluation or the surgeon's decision during intraoperative inspection. The median follow-up period of all cohorts was 1006 days (interquartile range (IQR): 518–1847).

Pathologic evaluation

All specimens were processed according to standard pathologic procedures at each institution, and histologically confirmed as UC. Tumours were staged according to the 2002 American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) TMN classification, and graded according to the 1973 World Health Organization classification. Clinical lymph node involvement (cN+) was defined as nodal swelling of hilar, para-aortic, inter-aortocaval, para- or retro-caval lesions by radiographic examination. LVI was defined as the presence of tumour cells within an endothelium-lined space without underlying muscular walls [11]. Tumour location was in the renal pelvis, ureter, or both, and categorized for the analysis. Multifocality was categorized as single or multiple, which was pathologically confirmed as two or more distinct lesions in the upper urinary tract.

Follow-up protocol

In general, patients were followed every 3-4 months for 2 years after RNU, every 6 months for the next 3 years, and annually thereafter. Routine checkups consisted of physical examination, routine blood test, urine cytology, chest radiography, and cystoscopic evaluation of the urinary bladder. Radiographic evaluations of the contralateral upper urinary tract using computed tomography (CT) were made every 6 months for the first 5 years and annually thereafter. Bone scintigraphy or magnetic resonance imaging was performed when clinically indicated.

Disease recurrence was defined as tumour relapse in the operative field, regional lymph nodes, and/or distant metastasis. Cause of death was determined by the treating physicians by chart review. All deceased patients were coded as cancer-specific mortality with prior disease recurrence or all-cause mortality regardless of the cause of death.

Adjuvant chemotherapy

Two or more courses of platinum-based adjuvant chemotherapy was performed for 213 patients (M-VAC: 88, GC: 54, other regimens: 71) with a mean of 2.37 courses. The M-VAC regimen (30 mg/m^2 methotrexate on days 1, 15, and 22; 3 mg/m^2 vinblastine on days 2, 15, and 22; 30 mg/m^2 adriamycin on day 2; and 70 mg/m^2 cisplatin on day 2) and the GC regimen (1,000 mg/m^2 gemcitabine on days 1, 8, and 15 and 70 mg/m^2 cisplatin on day 2) were given every 4 weeks. Most of other regimens consisted of either paclitaxel and carboplatin (CBDCA) regimens (175 mg/m^2 paclitaxel and area under the curve (AUC) 5 CBDCA on day 1) [15], or the gemcitabine and CBDCA regimen (1000 mg/m^2 gemcitabine on days 1 and 8 and AUC4-5 CBDCA on day 1) [16], and repeated every 3-4 weeks. Other regimens had been applied for patients with mild to moderate postoperative renal dysfunction. These regimens were started, as a rule, within 3 months after RNU.

Statistical analysis

The clinico-pathologic characteristics were compared using Student's t test or a chi-square test. Kaplan-Meier 7S plots were compared by the log-rank test. Baseline serum CRP (continuous variable) was dichotomized by the cut-off of 0.5 mg/dL. Univariate and multivariate Cox regression models addressed time to cancer-specific and all-cause death after RNU. Independent prognostic factors for cancer-specific mortality (CSM) were selected as risk factors in the training set (723 patients with surgery alone), and the dichotomized risk stratification model using the selected independent prognostic factors was adapted in the validation set (213 with surgery plus adjuvant chemotherapy). Predictive accuracy was quantified using Harrell's concordance index (c-index) [17]. All data were analysed using JMP software (SAS Institute, Cary, NC, US), with $P<0.05$ (two-sided) indicating statistical significance.

Results

Overview of the study

The descriptive and pathological characteristics of the 936 patients (surgery alone: 723, adjuvant chemotherapy: 213) are shown in Table 1. Median age at RNU was 72 years, and 70% of patients were men. Baseline median serum CRP level was 0.17 mg/dL. At the median follow-up of 1006 days (34 months), CSM and all-cause mortality were noted in 206 (22%) and 285 (30.5%) patients, respectively.

	No. of l Patients (%)				(b) High-risk patients No. of l Patients (%) No. of Patients (%)			
(a) Total patients	Total n=936	surgery, n=723	Adjuvant Chemotherapy y, n=213	P	Total n=355	Surgery, n=205	Adjuvant Chemotherapy y, n=150	P
Age: Median [IQR]	72 (13)	73.9 (13)	68.6 (11)	<0.001	72 (14)	75.2 (13.1)	74.3 (11)	<0.0001
CRP, Baseline Median [IQR] Serum Creatinine	0.17 (0.58)	0.15 (0.52)	0.2 (0.46)	0.1742	0.32 (1.1)	0.41 (1.1)	0.26 (1.1)	0.0092
Baseline , Median [IQR]	0.93 (0.39)	0.92 (0.39)	0.96 (0.32)	0.1158	1.0 (0.5)	1.0 (0.3)	1.0 (0.4)	0.0195
Postoperative, Median [IQR]	1.12 (0.35)	1.17 (0.44)	1.1 (0.34)	0.0939	1.15 (0.34)	1.1 (0.5)	1.15 (0.3)	0.1283
Sex				0.6699				0.0322
Female	278 (29.7)	213 (29.3)	68 (31.5)		122 (34.4)	80 (39.0)	42 (28)	
Male	659 (70.3)	514 (70.7)	148 (68.5)		233 (65.6)	125 (61.0)	108 (72)	
ECOG performance status				0.0055				0.0022
0,1	829 (95.4)	637 (94.4)	192 (99.0)		21 (6.4)	174 (90.2)	133 (98.5)	
2	40 (4.6)	38 (5.6)	2 (1.0)		307 (9.4)	19 (9.8)	2 (1.5)	
Concurrent bladder cancer				0.1675				0.2905
No	750 (80.5)	572 (79.4)	178 (84.0)		280 (79.1)	157 (77.0)	123 (82)	
Yes	182 (19.5)	148 (20.6)	34 (16.0)		74 (20.9)	47 (23.0)	27 (18)	
Multifocality				0.4568				0.5707
No	702 (82.0)	548 (82.5)	154 (80.2)		263 (80.7)	157 (81.8)	106 (79.1)	
Yes	154 (18.0)	116 (17.5)	38 (19.8)		63 (19.3)	35 (18.2)	28 (20.9)	
Hydronephrosis				0.0473				0.5633
No	378 (45.0)	304 (46.9)	74 (38.5)		120 (36.5)	72 (37.9)	48 (34.5)	
Yes	462 (55.0)	344 (53.1)	118 (61.5)		209 (63.5)	118 (62.2)	91 (65.5)	
Urine cytology				0.0049				0.4857
Negative, Equivocal	495 (63.8)	394 (66.6)	101 (54.9)		170 (44.1)	93 (54.1)	77 (58.3)	
Positive	281 (36.2)	198 (33.4)	83 (45.1)		170 (55.9)	79 (45.9)	55 (41.7)	
Clinical staging								
cT ≤2	670 (75.1)	561 (81.3)	109 (54.0)	<0.0001	170 (50.1)	111 (56.6)	59 (41.3)	0.006
cT ≥3	222 (24.9)	129 (18.7)	93(46.0)		169 (49.9)	85 (43.4)	84 (58.7)	
cN+	87 (9.3)	47 (6.5)	40 (18.8)	<0.0001	84 (23.7)	44 (21.5)	40 (26.7)	0.2585
Pathological staging								
pT ≤2	595 (63.6)	531 (73.4)	64 (30.0)	<0.0001	56 (15.8)	42 (20.5)	14 (9.3)	0.0049
pT ≥3	341 (36.4)	192 (26.6)	149 (70.0)		299 (84.2)	163 (79.5)	136 (90.7)	

pN+	75 (13.6)	39 (9.4)	36 (26.9)	<0.0001	55 (24.8)	26 (19.7)	29 (32.2)	0.0399
Tumor grade				<0.0001				0.2706
Grade 1,2	399 (44.2)	351 (50.4)	48 (23.3)		67 (19.6)	43 (21.8)	24 (16.7)	
Grade 3	504 (55.8)	346 (49.6)	158 (76.7)		274 (80.4)	154 (78.2)	120 (83.3)	
Lymphovascular invasion				<0.0001				0.1155
No	537 (60.0)	484 (70.2)	53 (25.7)		29 (8.6)	21 (19.8)	8 (5.6)	
Yes	358 (40.0)	205 (29.8)	153 (74.3)		309 (91.4)	173 (89.2)	136 (94.4)	
Carcinoma in situ				0.1977				1
No	638 (84.5)	486 (84.5)	152 (84.4)		255 (87.3)	137 (87.3)	118 (87.4)	
Yes	117 (15.5)	89 (15.5)	28 (15.6)		37 (12.7)	20 (12.7)	17 (12.6)	
Follow up period: Median, Day [IQR]	1006 (1329)	993 (1422)	1020 (1323)	0.1997	690 (947)	625 (829)	750 (1184)	0.0002
Cancer-specific Mortality 5-Year , %	72	75.1	62.4	0.0016	44.7	39.4	51.8	0.0104
Median, Day [IQR] All-Cause Mortality	Not Reached	Not Reached	Not Reached		1464	1145	2239	
5-Year (%)	64.7	66.6	58.5	0.2667	38.3	32.5	46.3	0.0011
Median, Day [IQR]	3576 (4371)	3576	3429 (4613)		1199 (4917)	907 (2461)	1710 (4762)	

Table 1: Differences in Patient and Tumor Characteristics Between Patients Who Did and Did Not Receive Adjuvant Chemotherapy:

		Univariate			Multivariate		
Factor	**Variables**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age	continuous	1.02	1.00-1.04	0.0136	1.01	0.99-1.04	0.9655
Baseline CRP	<0.32 *vs.* ≥ 0.32 ng/ml	2.64	1.92-3.63	<0.0001	1.89	1.24-2.88	0.0033
Sex	Male *vs.* Female	1.2	0.88-1.59	0.2345			
ECOG PS	0,1 *vs.* 2	2.94	1.75-4.64	0.0002	1.56	0.45-4.06	0.6058
Hydronephrosis	Yes *vs.* No	1.72	1.25-2.38	0.0007	1.52	0.97-2.43	0.0666
Concurrent BT	Yes *vs.* No	1.2	0.85-1.65	0.2877			
Urine cytology	Positive *vs,* Non-positive	2.02	1.48-2.77	<0.0001	1.14	0.75-1.73	0.5481
cT	≤2 *vs.* ≥3 ng/ml	3.95	2.98-5.24	<0.0001	1.36	0.85-2.19	0.2022
cN	cN+ *vs.* cN-	5.38	3.84-7.39	<0.0001	1.9	1.07-3.24	0.0289
pT	≤2 *vs.* ≥3	3.46	2.62-4.60	<0.0001	1.72	1.02-2.99	0.041
Tumor grade	Grade 1,2 *vs.* 3	4.21	3.00-6.05	<0.0001	1.53	0.92-2.68	0.1061
LVI	+ *vs.* -	5.91	4.30-8.24	<0.0001	4.49	2.46-8.66	<0.0001
CIS	Yes *vs.* No	1.27	0.78-2.23	0.3449			

Table 2: Proportional Hazard model for Cancer-Secific Mortality; BT: Bladder Tumor; LVI: Lymphovascular Invasion; CIS: Carcinoma in Situ.

Risk stratification model

Table 2 shows the univariate and multivariate Cox-regression models for the prediction of CSM in both training and validation sets. In the univariate analysis, age, sex (men), ECOG PS>2, hydronephrosis, positive urine cytology, grade 3 tumour, LVI, cN+, Pt>3, and baseline CRP elevation were significantly associated with CSM in the training set. On multivariable analysis, baseline CRP elevation (HR: 1.74, 95% CI: 1.09–2.75, p=0.0201), pT>3 (HR: 2.17, 95% CI: 1.28-3.76, p=0.0033), cN+ (HR: 2.84, 95% CI: 1.50–5.01, p=0.0021), and LVI (HR: 3.94, 95% CI: 2.23–7.17, p<0.0001) proved to be an independent predictor for CSM in the training set (Multivariate 1). When the risk score was equally allocated one to each risk factor, 578 patients were allocated to risk-score 0 (260 patients 45.0%), 1 (144, 24.9%), 2 (122, 21.1%), 3 (41, 7.1%), and 4 risk-scores (11, 1.9%) in the training set.

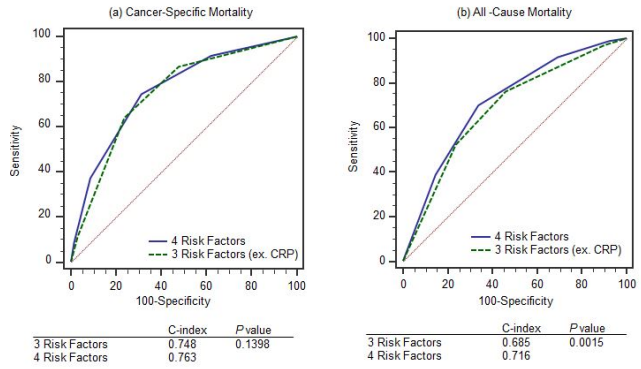

Figure1: Kaplan-Meier plots for cancer-specific survival stratified by risk score (a) and risk group (b) in the training set and the risk group in the validation set (c); A) Of 723 patients treated with surgery alone (training set), 578 (79.9%) were allocated to the risk score 0 (45.0%), 1 (24.9%), 2 (21.1%), 3 (7.1%), and 4 (1.9%). There was a significant difference in time to cancer-specific death among patients with scores, except for those with risk scores of 3 and 4 (p<0.0001); B) Of 723 patients treated with surgery alone (training set), 712 (98.5%) were allocated to the low-risk (71.6%) or high-risk (28.4%) groups. Patients allocated to the low-risk group had significantly better cancer-specific survival than those allocated to the high-risk group (p<0.0001); C) All (213) patients treated with surgery plus adjuvant chemotherapy (validation set) were allocated to the low-risk (30.5%) or high-risk group (69.5%). Patients allocated to the low-risk group had a significantly better cancer-specific survival than those allocated to the high-risk group (p<0.0001).

Figure 1a shows Kaplan-Meier plots for cancer-specific survival stratified by the risk score. A significant difference in time to CSM was observed between patients with 0 and 1 risk score (p=0.0041), 1 and 2 (p<0.0001), and 2 and 3 (p=0.0005). When cohorts were stratified by low (0–1 risk score) and high-risk (2–4 risk score), 712 patients were allocated to either the low-risk (510, 71.6%), or the high-risk (202, 28.4%) group with a significantly worse CSM in the high-risk as compared to the low-risk group (p<0.0001, Figure 1b). When the risk group was replaced with four independent variables (CRP elevation, pT>3, cN+, LVI) and re-analysed in the multivariate model, the high-risk group (HR: 6.87, 95% CI: 4.23–11.49, p<0.0001), positive urine cytology (HR: 1.66, 95% CI: 1.10–2.53, p=0.0168), and grade 3 tumour (HR: 1.86, 95% CI: 4.23–11.49, p=0.0129) were independent prognostic factors for CSM in the training set (Table 2, multivariate 2). The high-risk group had a significantly worse cancer-specific survival than the low-risk group Figure 1c, p<0.0001), and the high-risk group had independent prognostic factors for CSM (HR: 2.57, 95% CI: 1.38–5.27, p=0.0023) as well as grade 3 tumours (HR: 2.46, 95% CI: 1.22–5.66, p=0.0101) in the validation set (Table 2).

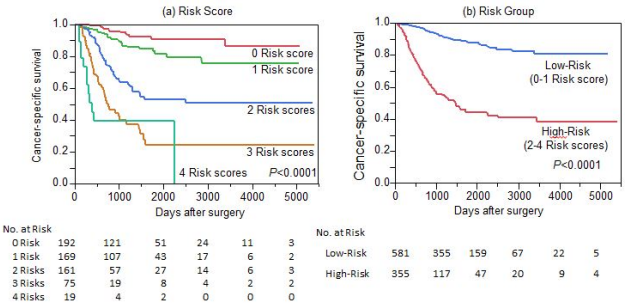

Figure 2: Comparison of predicting ability for cancer-specific mortality (a) and all-cause mortality (b) between 3 risk factors (cT ≥ 3, LVI, cN+) and 4 risk factors (cT ≥ 3, LVI, cN+, CRP elevation); The risk model with 4 risk factors had significantly better predicting ability for all-cause mortality than that with 3 risk factors (excluding baseline CRP ≥ 0.5 mg/dL, C-index: 0.716 *vs.* 0.685, p=0.0015).

Figure 2 compares the predicting ability between 3 (cT>3, LVI, cN+) and 4 risk factors (cT>3, LVI, cN+, CRP elevation). The predicting model for all-cause mortality using 4 risk factors had a significantly higher C-index than that using 3 risk factors Figure 2b, 0.716 *vs.* 0.685, p=0.0015), although there was no significant difference for CSM Figure 2a, 0.763 *vs.* 0.748, p=0.1398).

Survival benefit of adjuvant chemotherapy

Table 3 shows detailed data of the adjuvant chemotherapy. In total, 213 patients had received adjuvant chemotherapy with a mean 2.39 cycles. No statistical difference was observed among GC, M-VAC, and other regimens in terms of age, ECOG PS, and the number of cycles, while postoperative serum creatinine level was significantly higher in other regimes as compared to GC or M-VAC levels (Table 3a), p=0.0111). Out of 350 patients who were assigned to the high-risk group, 148 (42.3%) received adjuvant chemotherapy (GC: 44, M-VAC: 66, others: 38) at a mean 2.37 cycles.

Figure 3 depicts the cancer-specific survival of patients stratified by surgery with or without adjuvant chemotherapy. In the high-risk group, patients who had received adjuvant chemotherapy had significantly better cancer-specific survival than those who underwent surgery alone (Figure 3 b, p=0.0093). Patients in the high-risk group who received adjuvant chemotherapy also had a significantly better OS than those who did not receive chemotherapy (Figure 4b), p=0.0010). Out of the 584 low-risk patients, 65 (11.1%) had adjuvant chemotherapy. No survival advantage was observed in the low-risk

group in terms of cancer-specific survival or OS (Figure 3a), p=0.1556, Figure 4a, p=0.4152, respectively).

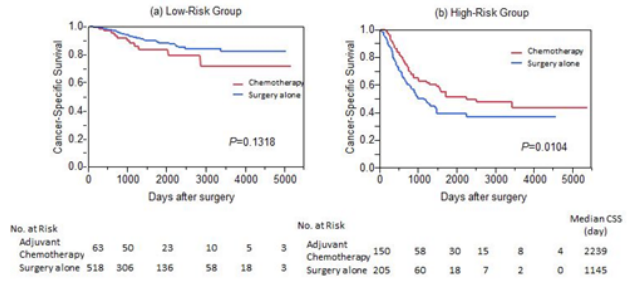

Figure 3: Cancer-specific survival of patients who underwent surgery alone or surgery plus adjuvant chemotherapy in the low-risk (a) and high-risk groups (b) Patients with adjuvant chemotherapy had significantly better cancer-specific survival than those who underwent surgery alone in the high-risk group (b) p=0.0093 with a median survival of 2239 and 975 days, respectively. No significant difference was noted in the low-risk group ((a) p=0.1556).

Table 4 and 5 shows univariate and multivariate analyses for CSM and all-cause mortality in high-risk patients, respectively. On multivariate analysis, adjuvant chemotherapy was an independent prognostic factor for CSM (HR: 0.52, 95% CI: 0.33–0.81, p=0.0037) as well as CRP elevation, pT>3, cN+, and LVI (Table 4). Chemotherapy was the independent prognostic factor for all-cause mortality (HR: 0.57, 95% CI: 0.36–0.89, p=0.0137) with a 43% risk reduction in high-risk patients (Table 5). No significant difference for either cancer-specific or overall survival was found among different chemotherapy regimens (Figure 5).

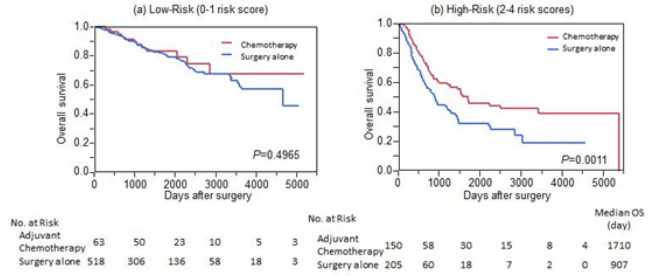

Figure 4: Overall survival of patients who underwent surgery alone or surgery plus adjuvant chemotherapy in the low-risk (a) and high-risk groups (b) Patients who had received adjuvant chemotherapy had significantly better OS than those who had undergone surgery alone in the high-risk group (b) p=0.0010) with a median OS of 1710 and 903 days, respectively. No significant difference was noted in the low-risk group ((a) p=0.4152).

(a) Total Patients						(b) High-Risk Patients				
	Total n=213	M-VAC n=88	GC n=54	Others n=71	p	Total n=150	M-VAC n=68	GC n=44	Others n=38	p
Age, Median (IQR)	68.6 (11)	68.5 (10.4)	68.1 (13.5)	69.9 (12.7)	0.251	69 (11.1)	69 (11.4)	67 (14.5)	70 (10.0)	0.4031
Serum Cr.(mg/dl) Postop.Median (IQR)	1.1 (0.34)	1.07 (0.29)	1.17 (0.38)	1.21 (0.37)	0.0111	1.15 (0.3)	1.1 (0.34)	1.18 (0.33)	1.2 (0.24)	0.1806
ECOG PS					0.5437					0.4515
0,1	192 (99.0)	78 (98.7)	50 (100)	64 (98.5)		98.5	98.4	100	97.1	
2	2 (1.0)	1 (1.2)	0 (0)	1 (1.5)		1.5	1.6	0	2.9	
No. Cycle					0.9756					0.9671
2	111	57	34	20		57.3	67.2	67.4	60	
3	57	28	17	12		26.7	29.9	30.2	35	
≥4	5	2	2	1		2.2	2.9	2.3	5	
Cycle number, Mean (SD)	2.39 (0.54)	2.37 (0.53)	2.4 (0.57)	2.42 (0.56)	0.8719	2.37 (0.54)	2.36 (0.54)	2.36 (0.53)	2.45	0.7709 (0.60)

Table 3: Adjuvant Chemotherapy.

Factor	Variables	Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p

Age	Continuous	1.01	0.99-1.03	0.1784			
CRP	<0.32 *vs.* ≥0.32	1.88	1.30-2.77	0.0008	2.15	1.32-3.55	0.0002
Sex	Male *vs.* Female	1.04	0.74-1.47	0.8399			
ECOG PS	0,1 *vs.* 2	2.65	1.64-4.04	0.0002	2.14	0.42-39.43	0.4205
Hydronephrosis	Yes *vs.* No	1.16	0.93-1.46	0.1889			
Concurrent BT	Yes *vs.* No	1.02	0.79-1.32	0.8545			
Urine Cytology	Posi. *vs,* Non-posi.	1.18	0.68-1.07	0.1658			
cT	≤2 *vs.* ≥3	1.19	0.96-1.48	0.1126			
cN	cN+ *vs.* cN-	1.56	1.21-1.98	0.0007	2	1.11-3.44	0.0213
pT	≤2 *vs.* ≥3	1.46	1.08-1.93	0.0136	2.37	1.11-5.91	0.0235
Tumor grade	Grade 1,2 *vs.* 3	2.23	1.39-3.79	0.0005			
LVI	LVI+ *vs.* -	2.1	1.06-4.97	0.0326	3.35	1.44-9.80	0.0035
CIS	Yes *vs.* No	1.64	1.15-2.35	0.0068	1.57	0.70-3.15	0.2569
Post-operative Serum Cr	Continuous	1.01	0.38-2.28	0.9864			
Adjuvant Chemotherapy	Yes *vs.* No	0.65	0.46-0.90	0.0099	0.53	1.15-3.09	0.0111
Chemotherapy Regimen	M-VAC	1					
	GC	1.07	0.49-2.19	0.8588			
	Others	1.36	0.74-2.44	0.316			

Table 4: Proportional Hazard Model for Cancer-Specific Mortality in 355 Patients with High Risk Group; BT: Bladder Tumor, LVI: Lymphovascular Invasion; CIS: Carcinoma in Situ; Cr: Creatinine.

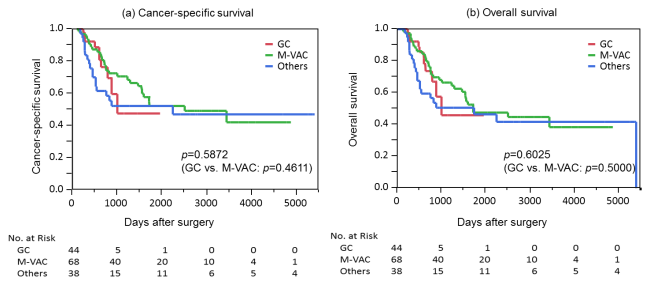

Figure 5: Kaplan-Meier plots for cancer-specific survival (a) and overall survival (b) in high-risk patients with adjuvant chemotherapy stratified by chemotherapy regimen; There was no significant difference for either cancer-specific survival (p=0.5873) or overall survival (p=0.6025) among chemotherapy regimens. Note no significant difference between the M-VAC and GC regimens (p=0.4611 and p = 0.5000, respectively).

Discussion

Serum CRP is an acute phase protein reflecting various inflammations including tumour-associated inflammatory response via the up-regulation of inflammatory mediator cytokines, in particular interleukin-6 [18]. The direct association of serum CRP elevation to upregulation of interleukin-6 has been reported in several malignancies [18], including bladder UC [19]. Baseline CRP level elevation is reportedly associated with poor outcome in various malignancies, including those in the colon [20] and liver [21]. Tanaka et al. demonstrated baseline CRP level elevation (>0.5 mg/dL), pathological T stage, nodal involvement, and LVI as an independent predictor for tumour progression [14]. Their results are in good agreement with our findings concerning the additional prognostic role of baseline CRP to conventional prognostic factors. We demonstrated that a 4 risk factor model (addition of baseline CRP to pT>3, LVI, and cN+) had significantly higher predictive ability for all-cause mortality than a 3 risk factor model. Failure to establish the additional benefit for cancer-specific mortality may result from the influence of comorbidities that inherently elevated CRP level. Based on the preliminary study, we assigned an equal risk score number to all risk factors despite an approximately two-fold higher hazard ratio of LVI than other risk factors. There was no significant difference in C-index between the equal risk score number of all risk factors and the risk score number 2 in LVI and 1 in the other 3 risk factors for all-cause mortality. Missing data on one or two risk factors is likely to occur in daily clinical practice. Although only 616 (65.8%) patients had completely available risk factor information, 98.8% (925/936 patients) of the patients could be stratified into either the low or high-risk group due to the equal risk score number as shown in (Figure 1).

Factor	Variables	Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p
Age	Continuous	4.47	1.54-13.34	0.0056	1.02	0.99-1.04	0.2148
CRP	<0.32 *vs.* ≥0.32	1.92	1.36-2.74	0.0002	1.68	1.10-2.57	0.0155
Sex	Male *vs.* Female	1.04	0.77-1.44	0.7807			
ECOG PS	0,1 *vs.* 2	3.94	2.32-6.29	<0.0001	1.78	0.66-4.00	0.2315
Hydronephrosis	Yes *vs.* No	1.06	0.76-1.49	0.7282			
Concurrent BT	Yes *vs.* No	1.02	0.72-1.49	0.9105			
Urine Cytology	Posi. *vs,* Non-posi.	1.56	1.13-2.18	0.0076	1.08	0.72-1.64	0.7102
cT	≤2 *vs.* ≥3	1.67	1.23-2.28	0.0011	1.34	0.86-2.10	0.1905
cN	cN+ *vs.* cN-	2.06	1.48-2.83	<0.0001	1.85	1.09-3.03	0.0223
pT	≤2 *vs.* ≥3	1.76	1.20-2.52	0.0048	1.56	0.88-2.95	0.136
Tumor grade	Grade 1,2 *vs.* 3	1.63	1.10-2.50	0.0142	1.48	0.90-2.53	0.1225
LVI	LVI+ *vs.* -	1.46	0.85-2.79	0.1835			
CIS	Yes *vs.* No	1.27	0.74-2.05	0.375			
Post-operative Serum Cr	Continuous	0.92	0.36-2.05	0.8487			
Adjuvant Chemotherapy	Yes *vs.* No	0.6	0.44-0.82	0.001	0.46	0.27-0.76	0.0021
Chemotherapy Regimen	M-VAC	1					
	GC	1.05	0.50-2.07	0.8908			
	Others	1.33	0.75-2.30	0.6149			

Table 5: Proportional Hazard Model for All-Cause Mortality in 355 Patients with High Risk Group; BT: Bladder Tumor, LVI: Lymphovascular Invasion; CIS: Carcinoma in Situ; Cr: Creatinine.

We defined lymph node involvement as preoperative regional lymph node swelling on radiological imaging. Although cN+ may have a discrepancy with pathological nodal involvement (pN+), a significant correlation was observed between cN+ and pN+ in 550 patients with an accuracy of 89.5% (sensitivity: 50.7%, specificity: 95.6%, PPV: 64.4%, data not shown). Since the anatomical dissected area of lymph node dissection has not been clearly defined, lymph node dissection appears to be unnecessary in cases of Ta-1 (2.2% of T1 *vs.* 16% of pT2-4 tumours) [22]. Based on the equivocal prognostic role of lymph node dissection in UTUC, application of lymph node dissection to all UTUC patients seems to be overtreatment, and cN+ could be a surrogate marker for pathological nodal involvement.

Not all patients can receive chemotherapy due to impaired renal function after radical surgery. Recent reports suggest that chemotherapy-related toxicity, particularly nephrotoxicity from platinum-based regimens, may significantly reduce survival in patients with post-operative renal dysfunction [23].

As shown in Table 3, patients in the total adjuvant chemotherapy group who were treated with other regimens, such as carboplatinum-based regimens, had statistically higher serum creatinine levels before starting adjuvant chemotherapy. Shirotake et al. concluded that the M-VAC regimen should be considered in standard adjuvant chemotherapy based on the significant superiority of the M-VAC regimen than GC regimen or without adjuvant chemotherapy [4]. Their results were in part in good agreement with our results concerning pT>3, positive LVI, and lymph node involvement as common risk factors, and a survival benefit from adjuvant chemotherapy for high-risk patients. However, our data demonstrated no significant difference in cancer-specific or overall survival among different regimens. The discrepancy may result from different patient backgrounds, cohort number, or definition of the risk group. Since only 55% of UTUC patients have more than 45 ml/min per 1.73 m2 of estimated glomerular filtration rate (eGFR) [23], carboplatin-based chemotherapy should be a pivotal regimen when considering chemotherapy in the adjuvant setting.

This study has several limitations, most of which are inherent to retrospective analyses, including missing data and inter-pathological heterogeneity of pathological diagnosis. Potential selection bias may result from post-operative impaired renal function. It is likely that there were a substantial number of high-risk patients for whom adjuvant chemotherapy could not be performed due to impaired renal function despite the physician' judgement that chemotherapy was needed. Other limitations may be based on the fact that the cohorts had been operated on by multiple surgeons, and data were collected over a wide length of time. Despite such limitations, the obtained results are straightforward and consistent with other investigators.

Most importantly, this multicentre collaboration study seems to reflect real-world practice patterns.

Conclusions

We developed a risk stratification model for the prediction of cancer-specific mortality following RNU by combining traditional clinical and pathological high-risk factors with a new biomarker, baseline serum CRP. This model may be useful for selecting patients who should be treated with adjuvant chemotherapy.

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