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Urothelial carcinoma of the upper urinary tract: preoperative pyuria is not correlated with bladder cancer recurrence and survival

Bogomir Milojevic[1,2] · Zoran Dzamic[1,2] · Nebojsa Bojanic[1,2] · Otas Durutovic[1,2] · Aleksandar Janicic[1,2] · Boris Kajmakovic[1,2] · Isidora Grozdic Milojevic[2,3] · Uros Bumbasirevic[1,2] · Nikola Grubor[4] · Sandra Sipetic Grujicic[5]

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Abstract

Objective To identify the impact of preoperative pyuria on the bladder cancer recurrence and survival of patients who were treated surgically for UTUC.

Patients and methods Study included 319 consecutive patients who were treated with RNU for UTUC. Cox proportional hazard regression models were used to evaluate the association of preoperative pyuria with outcome.

Results Eighty patients (25.1%) had pyuria. Preoperative pyuria was associated with sex ($P=0.01$), tumor focality ($P=0.01$), tumor size ($P=0.05$), tumor stage ($P=0.01$), lymph node metastasis ($P=0.01$), lymphovascular invasion ($P=0.02$), and chemotherapy ($P=0.04$). A total of 102 patients recurred, with a median time to bladder recurrence of 24.2 months. Bladder cancer recurrence-free survival rates for these 319 patients at 1, 3, 5, 7, and 10 years were 84.6, 72.4, 69.0, 68.3, and 68.0%, respectively. Preoperative pyuria was not independently associated with bladder cancer recurrence (HR 1.15; $p=0.5$). Preoperative pyuria was associated with OS (HR 1.57; $p=0.02$) and CSS (HR 1.65; $p=0.02$). However, preoperative pyuria was not independently associated with OS and CSS (HR 1.07; $p=0.79$).

Conclusions Preoperative pyuria is unable to predict outcomes in a single-centre series of consecutive patients who were treated with RNU.

Keywords Upper tract urothelial carcinoma · Survival · Recurrence · Radical nephroureterectomy · Bladder cancer

Introduction

Upper tract urothelial carcinoma (UTUC) are relatively rare, accounting for 5% of urothelial tumors [1]. Radical nephroureterectomy (RNU) with bladder cuff excision is the standard definitive therapy for patients with high-risk UTUC.

Previous studies showed that 15–50% of patients operated for UTUC have cancer development in the bladder during the follow-up [2, 3]. Considering this high incidence of subsequent bladder cancer formation after the management of UTUC, several investigators addressed possible risk factors for predicting bladder cancer recurrence.

Previous reports have showed that the presence of inflammation is associated with tumor progression [4, 5]. In recent years, several studies have shown that pyuria was a significant predictor of poor prognosis in patients with NMIBC and UTUC [6, 7]. While Satake et al. [8] showed that preoperative pyuria is independent predictor for intravesical recurrence, in patients with NMIBC, and, therefore, might be a potential indicator of tumor aggressiveness. Recently, Liang et al. [9] reported that preoperative pyuria was significantly associated with an advanced pathologic tumor stage and worse survival in 176 patients with UTUC after RNU.

Therefore, in the present study, we investigated the prognostic value of preoperative pyuria on bladder cancer recurrence, OS and CSS in patients with UTUC treated by RNU.

✉ Bogomir Milojevic
em2bogomir@yahoo.com

1 Clinic of Urology, Clinical Center of Serbia, Resavska 51, Belgrade 11000, Serbia

2 Faculty of Medicine, University of Belgrade, Belgrade, Serbia

3 Center of Nuclear Medicine, Clinical Center of Serbia, Belgrade, Serbia

4 Clinic for Digestive Surgery, Clinical Center of Serbia, Belgrade, Serbia

5 Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Materials and methods

Patient's selection

With the approval of our institutional review board, hospital medical records of patients with UTUC were retrospectively reviewed to assess the significance of several clinicopathologic factors stratified by preoperative pyuria (Table 1).

The present study cohort represents 373 patients who were surgically treated for UTUC with nephroureterectomy between January 1999 and December 2016. Patients who had a history of bladder tumor at a higher stage than the

Table 1 Demographic, clinical, and pathologic profiles of 319 patients with UTUC managed by RNU stratified by preoperative pyuria

Variable	Number of patients (%)	No pyuria (%)	Presence of pyuria (%)	*P**
All	319 (100)	239 (74.9)	80 (25.1)	–
Age (years), mean ± SD	66.6 ± 8.9	66.5 ± 8.7	66.9 ± 9.6	0.501†
Tumor side				0.307
Left	140 (43.8)	109 (77.8)	31 (22.2)	
Right	179 (56.2)	130 (72.6)	49 (27.4)	
Sex				0.013
Male	176 (55.2)	141 (80.1)	35 (19.9)	
Female	143 (44.8)	98 (68.5)	45 (31.5)	
Previous NMIBC				0.001
No	236 (73.9)	192 (81.3)	44 (18.7)	
Yes	83 (26.1)	47 (56.6)	36 (43.4)	
Anemia				0.17
Yes	100 (31.3)	71 (71.0)	29 (29.0)	
No	219 (68.7)	168 (76.7)	51 (23.3)	
Tumor location				0.13
Renal pelvis	188 (58.9)	136 (72.3)	52 (27.7)	
Ureter	131 (41.1)	103 (78.6)	28 (21.4)	
Tumor focality				0.01
Unifocal	214 (67.1)	169 (78.9)	45 (21.1)	
Multifocal	105 (32.9)	70 (66.6)	35 (33.4)	
Tumor size (cm)				0.048
≤ 3	139 (43.6)	111 (79.8)	28 (20.2)	
> 3	180 (56.4)	128 (71.1)	52 (28.9)	
Tumor grade				0.21
G1 or 2	158 (49.5)	122 (77.2)	36 (22.8)	
G3	161 (50.5)	117 (72.7)	44 (27.3)	
Tumor stage				0.01
pTa + pT1	33 (10.3)	30 (90.9)	3 (9.1)	
pT2	95 (29.8)	76 (80.0)	19 (20.0)	
pT3	167 (52.3)	121 (72.4)	46 (27.6)	
pT4	24 (7.6)	12 (50.0)	12 (50.0)	
Lymph node metastasis				0.01
pN*x*	254 (79.6)	199 (78.3)	55 (21.7)	
pN0	46 (14.4)	31 (67.4)	15 (32.6)	
pN+	19 (6.0)	9 (47.4)	10 (52.6)	
Lymphovascular invasion				0.02
Absent	124 (38.8)	102 (82.2)	22 (17.8)	
Present	195 (61.1)	137 (70.2)	58 (29.8)	
Adjuvant chemotherapy				0.04
Yes	75 (23.5)	50 (66.6)	25 (33.4)	
No	244 (76.5)	189 (77.5)	55 (22.5)	

*P value for χ^2 test

†P value for an unpaired t test

upper tract disease, preoperative chemotherapy, or previous contralateral UTUC were excluded. None of the patients included in this study had distant metastasis at diagnosis of UTUC. Patients with concomitant bladder cancer, active infections, and those with incomplete medical data were also excluded. In total, 319 patients (mean age, 66.6 years; range 36–85 years) were then available for evaluation.

No patients had any other significant inflammatory disease or an indwelling urinary catheter or stent before performing the urinalysis. The urinalysis and urinary culture results were performed before any procedures, such as cystoscopy, ureteroscopy, and RNU. Pyuria was defined as 10 white blood cells (WBCs) per high power field according to previous reports [6–9].

The diagnosis of UTUC was established by computed tomography, excretory urography, a retrograde ureteropyelogram, and/or ureteroscopy with tissue biopsies. The initial treatment of all patients was open RNU. Lymph node dissection (LND) was performed in 65 patients, while 254 patients did not receive LND (pNx). Whether LND would be performed or not as well as the extent of LND when performed were determined by each surgeon and not by strict prospective criteria. The extent of LND ranged from just the ipsilateral hilar lymph nodes (LNs) to all LNs around the ipsilateral great vessels with or without interaortocaval LNs.

Pathologic evaluation

Tumors were staged according to the tumor, node, and metastasis classification system [10] and graded using the 1998 World Health Organization classification [11]. Tumor location was defined as either renal pelvic or ureteral on the basis of the location of the dominant tumor. The dominant lesion was defined as that with the highest pathologic tumor stage (pT). For multifocal tumors at the same stage, the higher grade was selected for main tumor location. Tumor multifocality was defined as the synchronous presence of 2 or more pathologically confirmed tumors in any upper urinary tract location. No immunohistochemistry techniques were used to determine the presence of LVI.

Follow-up regimen

Routine follow-up consisted of physical examination and cystoscopy every 3 months during the first year and every 6–12 months thereafter. Chest radiography, abdominal ultrasonography, computed tomography, and excretory urography were performed annually, depending on the clinical stage of the cancer in the upper urinary tract. Most patients who were identified as having died from UTUC had progressive, widely disseminated metastases at the time of death. Cisplatin-based adjuvant chemotherapy was administered to some patients with pathologically confirmed lymph node metastasis (LNM) or with muscle-invasive disease (75 patients).

Statistical analysis

Demographic and clinicopathologic factors were analyzed using the Chi-square test or an unpaired *t* test. Recurrence-free probabilities (bladder cancer recurrence), overall survival (OS), and cancer-specific survival (CSS) were estimated by the Kaplan–Meier method, and the log-rank test was used for the statistical differences. We defined the time of surgery as time 0.

Univariate and multivariate Cox proportional hazard regression models were used to evaluate the association between various clinicopathologic factors and bladder cancer recurrence, OS, CSS after surgery. Only the significant factors were entered into multivariate Cox proportional hazard regression models. Hazard ratios (HRs) were estimated from the Cox analyses and are reported as relative risk with corresponding 95% confidence interval. In all tests, $P < 0.05$ (two sided) was considered statistically significant.

Results

The patients' clinical and pathological profiles are listed in Table 1. The median follow-up after surgery was 34.6 months (range 6–154 months). Among these 319 patients, 80 (25.1%) presented with preoperative pyuria, as defined by urine WBCs ≥ 10/high power field.

Preoperative pyuria was associated with sex ($P = 0.01$), tumor focality ($P = 0.01$), tumor size ($P = 0.05$), tumor stage ($P = 0.01$), lymph node metastasis ($P = 0.01$), lymphovascular invasion ($P = 0.02$), and adjuvant chemotherapy ($P = 0.04$). Previous NMIBC was significantly associated with preoperative pyuria (Table 1). Specifically, 43.4% of patients with the previous history of NMIBC had pyuria before RNU.

A total of 102 of the 319 (30.2%) cases recurred, with a median time to bladder recurrence of 24.2 months. Bladder cancer recurrence-free survival rates for these 319 patients at 1, 3, 5, 7, and 10 years were 84.6, 72.4, 69.0, 68.3, and 68.0%, respectively.

Using univariate analyses, history of bladder tumor (hazard ratio, HR 3.99; 95% confidence interval, CI 2.65–6.00; $p < 0.001$), tumor multifocality (HR 5.97; 95% CI 3.94–9.05; $p < 0.001$), lymph node status (HR 1.70; 95% CI 1.21–2.38; $p = 0.002$), preoperative anemia (HR 1.49; 95% CI 1.00–2.23; $p = 0.05$), and preoperative pyuria (HR 1.74; 95% CI 1.14–2.66; $p = 0.01$) were associated with bladder cancer recurrence. Using multivariate analysis, only history of bladder tumor (HR 1.95; 95% CI 1.20–3.15; $p = 0.007$) and tumor multifocality (HR

4.56; 95% CI 2.89–7.18; $p < 0.001$) was associated with urothelial recurrence (Table 2). Preoperative pyuria was not independently associated with bladder cancer recurrence (HR 1.15; 95% CI 0.72–1.82; $p = 0.5$) in multivariate Cox regression analyses (Table 2).

The Kaplan–Meier method showed that preoperative pyuria was significantly associated with worse bladder cancer recurrence-free survival ($P = 0.009$, log rank, mean bladder cancer RFS for patients with preoperative pyuria 44.9 ± 6.5 months versus mean bladder cancer RFS for patients without preoperative pyuria 81.6 ± 5.9 months) (Fig. 1). The 5-year bladder cancer RFS for patients with preoperative pyuria was 61.2% and for patients without preoperative pyuria was 71.5%.

During the follow-up, a total of 121 (37.9%) patients died, including 89 (27.9%) from UTUC. Overall rates at 3 year and 5 years in patients with preoperative pyuria were significantly lower than those in patients without preoperative pyuria (60.0% and 55.0% vs. 72.8% and 68.2%, respectively; $p = 0.019$) (Fig. 2). In addition, CSS rates at 3 year and 5 years in patients with preoperative pyuria were significantly lower than those in patients without preoperative pyuria (67.5% and 63.7% vs. 79.5% and 75.7%, respectively; $p = 0.023$) (Fig. 3). Using univariate analyses preoperative pyuria was associated with OS (HR 1.57; 95% CI 1.07–2.31; $p = 0.02$), and CSS (HR 1.65; 95% CI 1.06–2.58; $p = 0.02$). However, preoperative pyuria was not independently associated with OS and CSS (HR 1.07; 95% CI 0.66–1.72; $p = 0.79$) in multivariate Cox regression analyses (Table 2).

Discussion

The incidence of bladder cancer recurrence after surgical treatment for UTUC has been shown to be approximately 15–50% [2, 3, 12, and 13]. In this study, bladder cancer recurrence after RNU developed in 30.2% of patients. The reasons for bladder cancer recurrence are not completely understood; implantation from UTUC and the field change theory are predominant hypotheses [14, 15].

In the present study, we failed to detect a difference in bladder cancer recurrence or survival when stratifying patients by preoperative pyuria. We showed that 80 of 319 (25.1%) had pyuria, and that was higher than a previous study by Liang et al. [9]. However, our study had twice as many patients compared to the previous study. Satake et al. [8] reported that 116 of 237 (48.9%) had pyuria and that was relatively higher than our results. It might be because of the cut-off point of pyuria. We defined pyuria as having 10 or more white blood cells per high power field. In contrast, five or more is considered as having pyuria in the study of Satake et al. [8]. The appropriate cut-off point for detection of inflammation as a result of cancer cells should be investigated in the future.

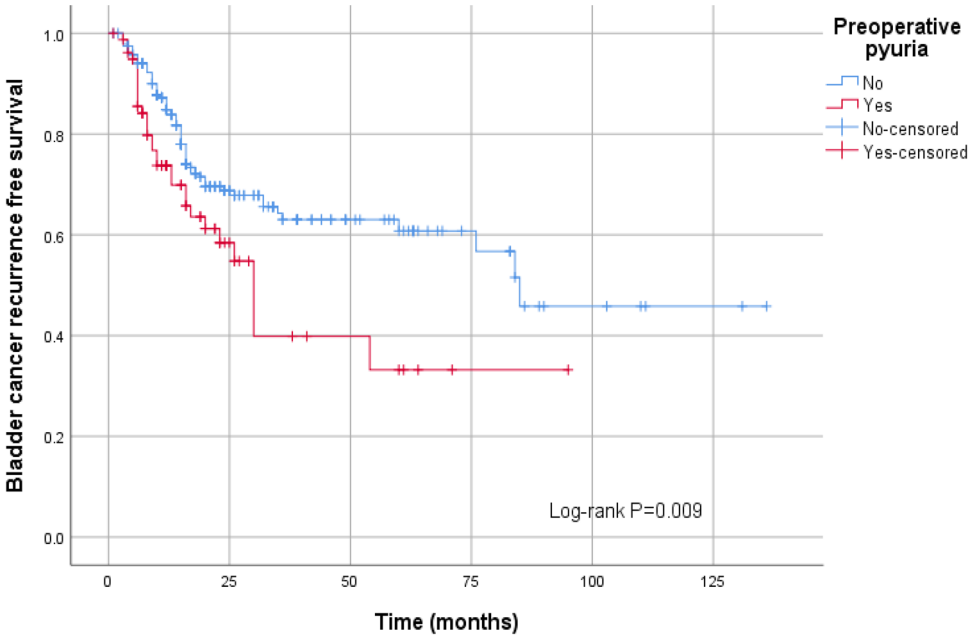
Studies Liang et al. [9] and Yoshida and al. [7] are the only two studies, to our knowledge, to assess the prognostic value of preoperative pyuria in patients with UTUC treated with RNU. They found that preoperative pyuria was significantly associated with poor RFS, CSS, and OS and that it was an independent prognostic factor in the multivariate

Table 2 Univariate and multivariate Cox regression models predicting bladder cancer recurrence-free survival and cancer-specific survival in 319 patients after radical nephroureterectomy for UTUC

Variable	Bladder cancer recurrence-free survival						Cancer-specific survival					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Sex (male vs. female)	1.33	0.90–1.96	0.15				0.87	0.57–1.34	0.55			
Age (years) (≤60 vs. > 60)	0.89	0.57–1.39	0.62				1.52	0.88–2.62	0.13			
Pyuria (no vs. yes)	1.74	1.14–2.66	0.01	1.15	0.72–1.82	0.56	1.65	1.06–2.58	0.02	1.07	0.66–1.72	0.79
Anemia (no vs. yes)	1.49	1.00–2.23	0.05	1.18	0.77–1.82	0.44	0.73	0.48–1.13	0.16			
History of BC (no vs. yes)	3.99	2.65–6.00	0.001	1.95	1.20–3.15	0.007	1.75	1.13–2.73	0.01	1.30	0.81–2.09	0.28
Renal pelvis vs. ureter	1.25	0.85–1.85	0.26				0.86	0.56–1.32	0.48			
Unifocal vs. multifocal	5.97	3.94–9.05	0.001	4.56	2.89–7.18	0.001	1.36	0.89–2.08	0.15			
Tumor size (≤3 cm vs. > 3 cm)	0.77	0.52–1.14	0.19				1.65	1.07–2.54	0.02	1.11	0.71–1.74	0.65
G1 or G2 vs. G3	0.86	0.58–1.27	0.45				1.72	1.11–2.67	0.02	0.63	0.39–1.00	0.06
≤ pT2 vs. ≥ pT3	1.29	0.86–1.95	0.21				14.4	6.2–33.3	0.001	17.1	6.84–42.6	0.001
pNx vs. pN+	1.70	1.21–2.38	0.002	1.25	0.88–1.77	0.21	5.68	3.28–9.84	0.001	2.92	1.65–5.19	0.001
LVI (absent vs. present)	1.06	0.71–1.58	0.76				1.56	1.01–2.43	0.05	0.68	0.43–1.11	0.12
Chemotherapy (no vs. yes)	1.31	0.82–2.08	0.26				1.67	1.06–2.62	0.03	1.33	0.84–2.13	0.23

P values are for the log-rank test

CI confidence interval, *HR* hazard ratio, *BC* bladder cancer, *LVI* lymphovascular invasion



No of patients at risk						
Time (months)	0	25	50	75	100	125
Patients without pyuria	239	77	33	14	4	1
Patients with pyuria	80	16	5	1	0	0

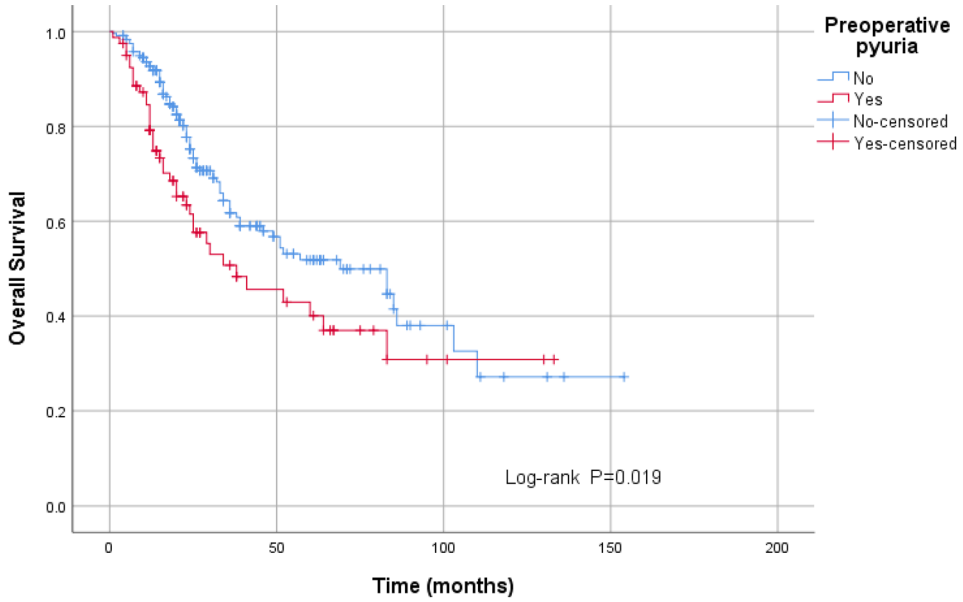
Fig. 1 Kaplan–Meier estimates for bladder cancer recurrence-free survival stratified according to preoperative pyuria in 319 patients after RNU for UTUC

analyses. Preoperative pyuria was also correlated with advanced surgical pathologies, including a high pathological T stage (pT3), high tumor Grade (G3), and lymphovascular invasion. They also claimed that preoperative pyuria is a potential surrogate prognostic marker that might guide the decision making process during postoperative clinical management of patients with UTUC after surgery with curative intent. These findings contradict our results. However, these results should be interpreted with caution, because it could be affected by a relatively small cohort of patients from a single center. Moreover, they might not completely eliminate factors associated with pyuria other than cancer. Which is thus one of the limitations of both studies.

Inflammation is recognized to pay important roles at different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis [16]. Pyuria (defined as the presence of leukocytes in the urine) is a nonspecific marker of urinary inflammation, most commonly caused by urinary infection, stones, obstruction, or cancer [17].

In accordance with our results, Liang et al. found no significant association between pyuria and bladder recurrence in patient with UTUC after RNU. This might be a reflection of different biological characteristics, or even tumorigenesis pathways between bladder and upper tract urothelial carcinoma [18, 19].

Azuma et al. have previously reported that pyuria is a significant predictor for recurrence and progression in patients with NMIBC [6]. Sataka et al. [8] showed that preoperative pyuria was significantly associated with intravesical recurrence in patients with NMIBC, and might be used as a predictor for efficacy of BCG induction therapy. Our study showed that preoperative pyuria was significantly associated with worse bladder cancer recurrence-free survival after RNU for UTUC. Also we showed that previous NMIBC was significantly associated with preoperative pyuria in patients with UTUC treated by RNU. However, preoperative pyuria was not independently associated with bladder cancer recurrence in multivariate analyses.



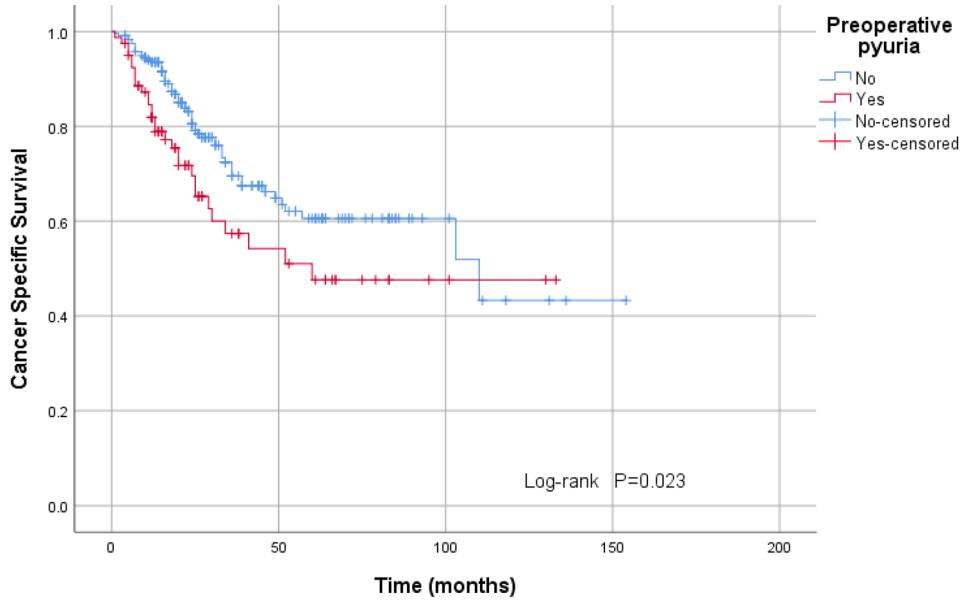
No of patients at risk						
Time (months)	0	25	50	75	100	125
Patients without pyuria	239	116	47	22	8	2
Patients with pyuria	80	31	16	7	2	0

Fig. 2 Kaplan–Meier estimates for overall survival stratified according to preoperative pyuria in 319 patients after RNU for UTUC

The 5-year cancer-specific survival for patients with preoperative pyuria was 67.5% and for patients without preoperative pyuria was 79.5%. In accordance with previous studies, we found that pathologic stage and lymph node metastasis are the strongest predictors of survival in UTUC cases [12, 13]. In this study, preoperative pyuria was identified as a significant predictor of overall and cancer-specific mortality in patients treated surgically for UTUC. However, our results showed that preoperative pyuria was not independently associated with OS and CSS.

This study is inherently limited by biases associated with its retrospective design. In addition, our results are subject to the inherent biases associated with high-volume tertiary care centres. Adjuvant treatments administered to patients with pT3 or pT4 disease could induce a bias, but these patients had the worst outcomes. In this cohort of patients, none had received neoadjuvant chemotherapy, which can be limitation of the study. We excluded from this analysis patients for whom we could not obtain complete information, possibly creating a selection bias. In addition, patients were not randomized to receive LND or not, and the extent of LND was decided by each surgeon. However, we consider that our observations provide further support for the therapeutic role of LND in the treatment of UTUC. Despite these limitations, our study has strengths, such as a centralized pathologic review and standardized follow-up.

In conclusion, preoperative pyuria is unable to predict outcomes in a single-centre series of consecutive patients who were treated with RNU for UTUC. Thus, UTUC patients with preoperative pyuria should not be given different consideration for follow-up compared to those with preoperative pyuria.



No of patients at risk						
Time (months)	0	25	50	75	100	125
Patients without pyuria	239	116	47	21	7	2
Patients with pyuria	80	31	17	7	2	0

Fig. 3 Kaplan–Meier estimates for cancer-specific survival stratified according to preoperative pyuria in 319 patients after RNU for UTUC

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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