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# Pyuria as an independent predictor of intravesical recurrence after radical nephroureterectomy in patients with upper tract urothelial carcinoma

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**Purpose:** About one-third of patients who undergo radical nephroureterectomy (RNUx) for upper tract urothelial carcinoma (UTUC) experience intravesical recurrence (IVR). This study investigated whether pyuria is a feasible predictor of IVR after RNUx in patients with UTUC.

**Materials and Methods:** Seven hundred forty-three patients with UTUC who underwent RNUx at a single institute were analyzed in this study. The participants were divided into two groups: those without pyuria (non-pyuria) and those with pyuria. Kaplan–Meier survival analysis was performed, and p-values were assessed using the log-rank test. Cox regression analyses were performed to identify the independent predictors of survival.

**Results:** The pyuria group had a shorter IVR-free survival period (p=0.009). The five-year IVR-free survival rate was 60.0% in the non-pyuria group vs. 49.7% in the pyuria group according to the Kaplan-Meier survival analysis. After the multivariate Cox regression analysis, pyuria (hazard ratio [HR]=1.368; p=0.041), a concurrent bladder tumor (HR=1.757; p=0.005), preoperative ureteroscopy (HR=1.476; p=0.013), laparoscopic surgery (HR=0.682; p=0.048), tumor multiplicity (HR=1.855; p=0.007), and a larger tumor (HR=1.041; p=0.050) were predictors of risk for IVR. There was no association between pyuria and recurrence-free survival (p=0.057) or cancer-specific survival (p=0.519) in the Kaplan–Meier survival analysis.

**Conclusions:** This study concluded that pyuria was an independent predictor of IVR in patients with UTUC after RNUx.

**Keywords:** Carcinoma; Pyuria; Transitional cell carcinoma; Urinary bladder



## INTRODUCTION

Upper tract urothelial carcinomas (UTUCs) are UCs originating from the upper urinary tract, which is the renal pelvocalyx and ureter. They are rare cancers, accounting for 5% to 10% of all UCs, and their estimated annual incidence is presumed to be 2 cases per 100,000 people in Western countries [1]. Radical nephroureterectomy (RNUx) with bladder cuff excision is the standard treatment for nonmetastatic UTUCs, and lymph node dissection is recommended for high-grade and large tumors [2]. However, approximately 22% to 47% of patients with UTUC experience intravesical recurrence (IVR) after RNUx with bladder cuff excision [1].

IVR in patients with UTUC is important because it

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forces patients to undergo additional surgery and anesthesia. More importantly, IVR as muscle-invasive bladder cancer (MIBC) or IVR in organ-confined UTUC has a poor prognosis [3,4]. Many efforts have been made to determine the risk factors for IVR in patients with UTUC. According to a previous study, some patient-related factors (male sex, history of bladder cancer, and preoperative chronic kidney disease [CKD]), tumor-specific factors (preoperative urine cytology, ureteral location, multifocality, invasive pathologic T stage, and tumor necrosis), and treatment-specific factors (laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins) are risk factors for IVR after RNUx [5].

Pyuria can be easily defined using urinalysis, and many studies have attempted to determine whether pyuria is a feasible tool for predicting the prognosis of UCs. Pyuria has been associated with a poor prognosis in non-MIBC and bacillus Calmette-Guérin unresponsiveness and recurrence [6-8]. Efforts to clarify the association between pyuria and UTUCs are ongoing, but given the rarity of UTUCs, previous studies are scarce and the results are controversial, especially regarding IVR after RNUx [9,10]. Some studies assert that preoperative pyuria can predict worse IVR-free survival (IVRFS) after RNUx [11,12]. Other studies claim that pyuria is related to better IVRFS, while other studies contend that it cannot predict IVR [13,14]. This study aimed to research the value of preoperative pyuria in predicting IVR in patients with UTUC after RNUx.

## MATERIALS AND METHODS

### 1. Study population

The study protocol for this retrospective study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (approval number: 2210-084-1368). The written informed consent was waived by the IRB. A total of 1,127 patients who underwent surgery for an upper tract urothelial tumor from May 15, 2001, to September 15, 2022, were eligible for this study. Among them, patients with preoperative bacteriuria and metastatic disease who had undergone radical cystectomy in the past, who were treated with methods other than RNUx (segmental ureterectomy and laser ablation), whose pathology was other than urothelial carcinoma, or who had insufficient information were excluded. Basic demographics (age, sex, body mass index, American Society of Anesthesiologists physical status classification) and medical history (history of hypertension, diabetes mellitus, concurrent bladder tumor, and whether neoadjuvant chemotherapy was performed) were collected. The preoperative workup included serum estimated glomerular filtration rate (eGFR), urine examinations (urinalysis, urine culture, and urine cytology), and computed tomography (CT) of the abdominal pelvis. The tumor characteristics included tumor location, size, multiplicity, and the presence of hydronephrosis before surgery. Information regarding the operation included the type (open, laparoscopic, or robotic) and whether lymph node dissection or bladder cuff excision was performed. Pathologic information included pathologic tumor, necrosis, and metastases stages; World Health Organization histologic grade; histologic variant; concomitant carcinoma *in situ*; lymphovascular invasion; and condition of the surgical margin [15,16]. Pyuria was defined as five or more white blood cells per high-power field in centrifuged urine, in accordance with previous studies, and the urinalysis was done before the surgery [6,7,12,13]. Hydronephrosis was assessed with an abdomen-pelvis CT image. According to the Kidney Disease: Improving Global Outcomes guidelines, CKD stages were classified on the basis of the eGFR [17]. Patients were evaluated every 3 months for the first 2 years, every 6 months for the next 2 years, and once a year beginning with the fifth year after surgery. They were evaluated by blood examinations and urine laboratory testing, including urine cytology, cystoscopy, lung imaging, abdomen-pelvis CT, and a bone scan.

### 2. Statistical analysis

The patients were divided into two groups according to the presence of pyuria. The mean and standard deviation (SD) of continuous variables were compared using a Student's t-test, and the frequencies of categorical variables were compared using the chi-squared test. Survival analysis was performed using the Kaplan–Meier survival analysis, and p-values were assessed using the log-rank test. Univariate and multivariate Cox regression analyses were used to identify independent factors affecting survival. Variables with a p-value of <0.2 after univariate analysis were included in the multivariate analysis, and those with a p-value of <0.05 were interpreted as statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 26 (IBM SPSS Corp.).

## RESULTS

A total of 743 patients with UTUCs were included in this study. The mean±SD age of the study population was 66.2±10.2 years, with 352 (47.4%) and 391 (52.6%) patients in the non-pyuria and pyuria groups, respectively. The mean±SD follow-up periods were 58.5±51.6 months and



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52.7±44.5 months for the non-pyuria and pyuria groups, respectively. Comparisons of the characteristics of the two groups are shown in Table 1. There was a significant difference between the two groups in preoperative urine cytology results (p<0.001) and tumor location (p=0.011). More patients in the pyuria group had a history of bladder cancer (11.6% vs. 17.4%; p=0.027) or a history of concurrent bladder tumors (6.8% vs. 12.0%; p=0.016) and underwent lymph node dissection (19.9% vs. 29.7%; p=0.002). Tumors of the pyuria group had a higher frequency of high-grade histology (73.5%

**Table 1.** Characteristics of the study population

| Variable | Non-pyuria | Pyuria | p-value |
|---|---|---|---|
| Total | 352 (47.4) | 391 (52.6) | |
| Age (y) | 66.2±9.9 | 66.2±10.5 | 0.976 |
| Sex | | | 0.096 |
| Male | 284 (80.7) | 295 (75.4) | |
| Female | 68 (19.3) | 96 (24.6) | |
| BMI (kg/m$^2$) | 24.6±3.3 | 24.7±7.8 | 0.909 |
| ASA classification | | | 0.372 |
| 1 | 68 (19.3) | 89 (22.9) | |
| 2 | 248 (70.5) | 268 (68.9) | |
| 3 | 36 (10.2) | 32 (8.2) | |
| HTN | 186 (52.8) | 197 (50.4) | 0.503 |
| DM | 90 (25.6) | 85 (21.7) | 0.219 |
| CKD stage | | | 0.334 |
| I, II | 146 (60.8) | 151 (53.0) | |
| IIIA | 65 (27.1) | 89 (31.2) | |
| IIIB | 24 (10.0) | 37 (13.0) | |
| IV | 4 (1.7) | 4 (1.4) | |
| V | 1 (0.4) | 4 (1.4) | |
| History of bladder cancer | 41 (11.6) | 68 (17.4) | 0.027 |
| Concurrent bladder tumor | 24 (6.8) | 47 (12.0) | 0.016 |
| Preoperative ureteroscopy | 85 (24.1) | 95 (24.3) | 0.962 |
| Neoadjuvant chemotherapy | 8 (2.3) | 10 (2.6) | 0.801 |
| Urine cytology | | | <0.001 |
| Negative, benign | 212 (62.2) | 178 (47.7) | |
| Atypical, suspicious | 117 (34.3) | 168 (45.0) | |
| Malignant | 12 (3.5) | 27 (7.2) | |
| Hydronephrosis | 162 (46.0) | 181 (46.3) | 0.941 |
| Lower ureter mass | 91 (25.9) | 81 (20.7) | 0.097 |
| Tumor location | | | 0.011 |
| Renal pelvis | 149 (44.2) | 202 (54.0) | |
| Ureter | 162 (48.1) | 138 (36.9) | |
| Renal pelvis and ureter | 26 (7.7) | 34 (9.1) | |
| Multiplicity | 28 (8.0) | 33 (8.4) | 0.810 |
| Tumor size (cm) | 3.4±2.4 | 4.4±3.4 | <0.001 |
| Operation type | | | 0.494 |
| Open | 203 (57.7) | 240 (61.4) | |
| Laparoscopic | 85 (24.1) | 81 (20.7) | |
| Robotic | 64 (18.2) | 70 (17.9) | |
| Lymph node dissection | 70 (19.9) | 116 (29.7) | 0.002 |
| Without bladder cuffing | 33 (9.4) | 39 (10.0) | 0.783 |
| Histologic grade | | | 0.006 |
| Low grade | 93 (26.5) | 71 (18.2) | |
| High grade | 258 (73.5) | 320 (81.8) | |

Table 1. Continued

| Variable | Non-pyuria | Pyuria | p-value |
|---|---|---|---|
| Pathologic T stage | | | 0.153 |
| pTa, pT1, pTis | 177 (50.3) | 168 (43.0) | |
| pT2 | 54 (15.3) | 61 (15.6) | |
| pT3 | 113 (32.1) | 155 (39.6) | |
| pT4 | 8 (2.3) | 7 (1.8) | |
| Pathologic N stage | | | 0.025 |
| pNx, pN0 | 343 (97.4) | 366 (93.6) | |
| pN1 | 2 (0.6) | 13 (3.3) | |
| pN2 | 7 (2.0) | 10 (2.6) | |
| pN3 | 0 (0.0) | 2 (0.5) | |
| Histologic variant | 28 (8.0) | 35 (9.0) | 0.626 |
| Concomitant Cis | 91 (25.9) | 83 (21.2) | 0.137 |
| Lymphovascular invasion | 51 (14.5) | 77 (19.7) | 0.063 |
| Positive surgical margin | 12 (3.4) | 17 (4.3) | 0.514 |
| Adjuvant chemotherapy | 72 (20.5) | 87 (22.3) | 0.551 |
| Intravesical recurrence | 121 (34.4) | 169 (43.2) | 0.014 |
| Recurrence | 73 (20.7) | 104 (26.6) | 0.061 |
| Follow-up period (mo) | 58.5±51.6 | 52.7±44.5 | 0.003 |

Values are presented as number (%) or mean±standard deviation.
BMI, body mass index; ASA, American Society of Anesthesiologists; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; Cis, carcinoma *in situ*.

vs. 81.8%; p=0.006) and were larger (3.4±2.4 vs. 4.4±3.4 cm; p<0.001). The pathologic N stage was higher in the pyuria group (p=0.025), and more patients in the pyuria group had IVR (34.4% vs. 43.2%; p=0.014).

Fig. 1 shows the Kaplan–Meier survival curve of (A) IVRFS, (B) recurrence-free survival (RFS), and (C) cancer-specific survival (CSS) between the two groups. Table 2 shows the results of the multivariate Cox regression analyses of IVRFS, RFS, and CSS. Pyuria was an independent predictor of IVR in patients with UTUC after RNUx. The pyuria group showed a shorter IVRFS period (p=0.009), with a 5-year IVRFS rate of 60.0% vs. 49.7% (non-pyuria vs. pyuria groups). After univariate analysis, the risk factors of IVR were pyuria (hazard ratio [HR]=1.361; p=0.010), CKD stage V (HR=5.624; p=0.001; CKD stage I, II as reference), history of bladder cancer (HR=1.620; p=0.001), concurrent bladder tumor (HR=1.863; p<0.001), preoperative ureteroscopy (HR=1.435; p=0.005), atypical or suspicious urine cytology (HR=1.472; p=0.002, negative urine cytology as reference), tumor multiplicity (HR=2.237; p<0.001), and larger tumor (HR=1.056; p=0.001). But laparoscopic surgery (HR=0.699; p=0.016; open surgery as reference), robotic surgery (HR=0.637; p=0.018; open surgery as reference), and adjuvant chemotherapy (HR=0.730; p=0.043) lowered the risk of IVR. However, after multivariate analysis, pyuria (HR=1.368; p=0.041), concurrent bladder tumor (HR=1.757; p=0.005), preoperative ureteroscopy (HR=1.476; p=0.013), tumor multiplicity (HR=1.855; p=0.007), and larger tumor (HR=1.041; p=0.050) were independent risk factors of IVR, whereas laparoscopic surgery (HR=0.682; p=0.048) was associated with lower risk for IVR.

Pyuria was not associated with RFS or CSS. According to the Kaplan–Meier survival curves of RFS and CSS between the two groups, there were no statistically significant differences in RFS (p=0.057) or CSS (p=0.519). After multivariate analysis, CKD stage (CKD stage IIIB: HR=1.816, p=0.025; CKD stage V: HR=5.672, p=0.005; CKD stage I, II as reference), neoadjuvant chemotherapy (HR=3.407; p=0.003), tumor location (ureteral tumor: HR=2.131, p=0.001; tumor in both renal pelvis and ureter: HR=2.440, p=0.006; renal pelvis tumor as reference), high-grade histology (HR=3.528; p=0.041), advanced pathologic T stage (pT3: HR=4.011, p<0.001; pT4: HR=40.881, p<0.001; pTa, pT1, and pTis as references), pathologic N2 (HR=2.662, p=0.010; pNx and pN0 as references), and the presence of lymphovascular invasion (HR=2.305; p<0.001) were risk factors of tumor recurrence after RNUx. However, adjuvant chemotherapy reduced the risk for tumor recurrence (HR=0.504; p=0.005).

After multivariate analysis, atypical or suspicious urine cytology (HR=2.588, p=0.015; negative or benign urine cytology as references), preoperative hydronephrosis (HR=3.539; p=0.002), ureteral tumor location (HR=4.447, p=0.001; renal pelvis tumor as reference), no bladder cuffing during


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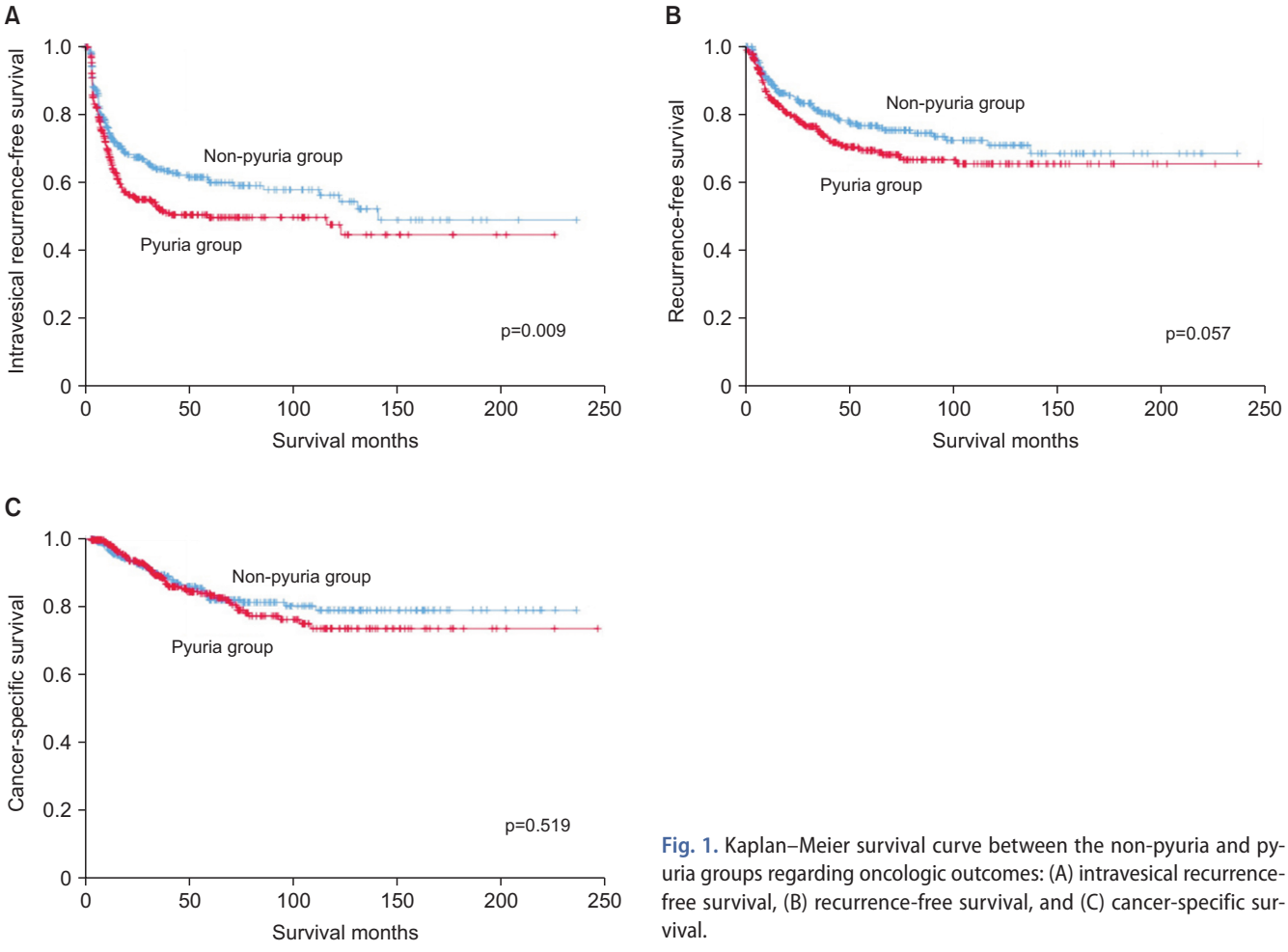


Fig. 1. Kaplan–Meier survival curve between the non-pyuria and pyuria groups regarding oncologic outcomes: (A) intravesical recurrence-free survival, (B) recurrence-free survival, and (C) cancer-specific survival.

RNUx (HR=5.120; p=0.001), advanced pathologic T stage (pT3: HR=5.642, p<0.001; pT4: HR=21.908, p=0.011; pTa, pT1, and pTis as references), and positive surgical margin (HR=10.673; p<0.001) were related with worse CSS. However, adjuvant chemotherapy improved CSS (HR=0.363; p=0.042).

## DISCUSSION

IVR is common in patients with UTUC after RNUx. IVR raises medical costs and is sometimes associated with a worse prognosis [1,3,4]. Thus, identifying the risk factors for IVR is important for predicting who will experience it. The noninvasiveness and convenience of defining pyuria make it tempting to determine whether it is feasible to use pyuria to predict disease prognosis, as pyuria is thought to be associated with various oncologic outcomes of UCs. Our study concluded that pyuria is an independent risk factor for IVR in patients with UTUC but is not related to RFS or CSS.

We assert that pyuria is a risk factor for IVR. The results of previous studies on the relationship between pyuria and IVR in patients with UTUC were controversial. Sato et al. [11] analyzed 268 patients with UTUC and found that preoperative pyuria was an independent risk factor for IVR. Jeon et al. [12] assessed 176 patients with UTUC and found that preoperative pyuria was associated with a higher risk for IVR. By contrast, Fukushima et al. [13] analyzed 97 patients and asserted that pyuria could lower the risk for IVR after RNUx. Moreover, Milojevic et al. [14] assessed 319 patients and suggested that preoperative pyuria was not correlated with IVR in patients with UTUC. Because of the rarity of UTUCs, the number of previous studies and the study population of each study were relatively small. We collected data from 743 patients with UTUC and found that pyuria was a feasible predictor of IVR in patients with UTUC after RNUx. Our findings provide a theoretical foundation for further research aimed at developing an IVR risk stratification model for patients with UTUC.

Patients with UTUC and pyuria should undergo a more thorough examination of the bladder to prevent IVR as early as possible. The modifiable risk factors for IVR based on our findings were preoperative ureteroscopy and type of surgery. According to Sharma et al. [18], preoperative

**Table 2.** Multivariate Cox regression analysis regarding intravesical recurrence-free survival, recurrence-free survival, and cancer-specific survival

| Variable | Intravesical recurrence-free survival | | Recurrence-free survival | | Cancer-specific survival | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Pyuria (yes vs. no) | 1.368 (1.012–1.849) | 0.041 | | | | |
| Age (continuous) | | | | | | |
| Sex | | | | | | |
| Male | | | Reference | | | |
| Female | | | 1.454 (0.955–2.213) | 0.081 | | |
| BMI (continuous) | | | | | | |
| ASA classification | | | | | | |
| 1 | | | | | Reference | |
| 2 | | | | | 1.897 (0.775–4.638) | 0.161 |
| 3 | | | | | 0.000 (0.000–) | 0.978 |
| HTN (yes vs. no) | | | | | | |
| DM (yes vs. no) | | | | | | |
| CKD stage | | | | | | |
| I, II | | | Reference | | | |
| IIIA | | | 1.215 (0.780–1.891) | 0.389 | | |
| IIIB | | | 1.816 (1.080–3.054) | 0.025 | | |
| IV | | | 0.000 (0.000–3.184E+186) | 0.954 | | |
| V | | | 5.672 (1.672–19.243) | 0.005 | | |
| History of bladder cancer (yes vs. no) | | | | | | |
| Concurrent bladder tumor (yes vs. no) | 1.757 (1.184–2.608) | 0.005 | | | | |
| Preoperative ureteroscopy (yes vs. no) | 1.476 (1.085–2.009) | 0.013 | | | | |
| Neoadjuvant chemotherapy (yes vs. no) | | | | | 4.824 (0.969–24.020) | 0.055 |
| Urine cytology | | | | | | |
| Negative, benign | | | | | Reference | |
| Atypical, suspicious | | | | | 2.588 (1.200–5.580) | 0.015 |
| Malignant | | | | | 2.819 (0.763–10.415) | 0.120 |
| Hydronephrosis (yes vs. no) | | | | | 3.539 (1.561–8.027) | 0.002 |
| Tumor location | | | | | | |
| Renal pelvis | | | Reference | | Reference | |
| Ureter | | | 2.131 (1.353–3.356) | 0.001 | 4.447 (1.885–10.492) | 0.001 |
| Renal pelvis and ureter | | | 2.440 (1.290–4.615) | 0.006 | 0.983 (0.258–3.750) | 0.980 |
| Multiplicity (yes vs. no) | 1.855 (1.186–2.902) | 0.007 | | | | |
| Tumor size (continuous) | 1.041 (1.000–1.085) | 0.050 | | | | |
| Operation type | | | | | | |
| Open | Reference | | Reference | | | |
| Laparoscopic | 0.682 (0.467–0.996) | 0.048 | 0.743 (0.424–1.302) | 0.300 | | |
| Robotic | 0.694 (0.466–1.034) | 0.073 | 1.515 (0.965–2.379) | 0.071 | | |
| Lymph node dissection (yes vs. no) | | | | | | |
| Without bladder cuffing (yes vs. no) | | | | | 5.120 (1.995–13.139) | 0.001 |
| Histologic grade | | | | | | |
| Low grade | | | Reference | | | |
| High grade | | | 3.528 (1.054–11.807) | 0.041 | | |
| Pathologic T stage | | | | | | |
| pTa, pT1, pTis | | | Reference | | Reference | |
| pT2 | | | 1.118 (0.563–2.220) | 0.751 | 0.793 (0.230–2.733) | 0.714 |
| pT3 | | | 4.011 (2.309–6.968) | <0.001 | 5.642 (2.284–13.938) | <0.001 |
| pT4 | | | 40.881 (8.118–205.875) | <0.001 | 21.908 (2.010–238.776) | 0.011 |



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Table 2. Continued

| Variable | Intravesical recurrence-free survival | | Recurrence-free survival | | Cancer-specific survival | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Pathologic N stage | | | | | | |
| pNx, pN0 | Reference | | Reference | | | |
| pN1 | 0.466 (0.111–1.954) | 0.296 | 0.461 (0.108–1.959) | 0.294 | | |
| pN2 | 0.173 (0.024–1.236) | 0.080 | 2.662 (1.265–5.603) | 0.010 | | |
| Histologic variant (yes vs. no) | | | | | | |
| Concomitant Cis (yes vs. no) | | | | | | |
| Lymphovascular invasion (yes vs. no) | | | 2.305 (1.494–3.556) | <0.001 | | |
| Positive surgical margin (yes vs. no) | | | | | 10.673 (3.140–36.278) | <0.001 |
| Adjuvant chemotherapy (yes vs. no) | 0.672 (0.444–1.019) | 0.061 | 0.504 (0.313–0.813) | 0.005 | 0.363 (0.137–0.964) | 0.042 |

HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; Cis, carcinoma *in situ*.

ureteroscopy without biopsy does not increase the risk for IVR, whereas ureteroscopic biopsy alone increases the risk. Increased manipulation of UTUCs, either during biopsy or by hand in open surgery, may cause tumor shedding and induce downstream dissemination of the tumor [18,19]. This idea is supported by Kamihira et al. [20], who claim that hand-assisted laparoscopic RNUx is a risk factor for IVR compared with pure laparoscopic surgery. Thus, ureteroscopic examination without biopsy or laparoscopic surgery in patients with UTUC and pyuria should be considered. In addition, intravesical chemotherapy after RNUx in patients with pyuria should be considered to reduce IVR [21]. These methods of preventing IVR by changing modifiable factors should be more seriously considered in older patients and in patients with many comorbidities who have a large burden of additional anesthesia.

Our study suggests that the inflammatory response is the key to explaining IVR in patients with UTUC; however, other mechanisms of action should be researched regarding the progression of UTUCs. Inflammation has been known to be important in carcinogenesis and disease progression, and increasing evidence suggests that leukocytes might play a role in cancer-related inflammation [7,22,23]. Pyuria in UCs is a manifestation of cancer-related inflammation. The association between pyuria and the prognosis of non-MIBC is explained by leukemic reactions and leukocyte production in bladder cancer. Bladder cancer cells produce granulocyte-colony stimulating factor (G-CSF), which induces a leukemic reaction and leukocyte production. This G-CSF loop increases the proliferation of bladder cancer cells [24,25]. However, the role of leukocytes and the G-CSF loop is not yet well explained in UTUC. According to our study, pyuria was a risk factor for IVR but was not related to RFS or CSS. We suggest that IVR in patients with UTUC might be related to inflammatory reactions associated with bladder cancer, whereas the progression of UTUCs might be due to other mechanisms. Some studies have found that UTUCs and bladder cancer share similarities but have some differences in their genomic profiles, which supports our idea that UTUCs might have a unique progression distinct from that of bladder cancer [26,27]. The progression mechanism of UTUCs needs further investigation, and we suggest that systemic therapy for UTUCs applied in different pathways than systemic therapy for bladder cancer might be more effective and improve the prognosis of patients with UTUC.

Our study has some limitations. First, this was a retrospective study with possible selection bias, and further well-designed studies are required to confirm these results. Second, the definition of pyuria varies among studies, and even if we exclude bacteriuria, there are conditions other than tumors, such as inflammation or autoimmune diseases, that can cause pyuria [6,7,9-14]. Third, the reason neoadjuvant chemotherapy increased the risk for tumor recurrence is most likely because the patients with a history of neoadjuvant chemotherapy had a biased advanced cancer profile (Supplementary Table 1). However, our study had some strengths. First, we suggest a promising predictive factor for IVR, which has not yet been discussed in detail. Second, the study population had a relatively long follow-up period. Third, owing to the rarity of the disease, the study population in previous studies was small, whereas our study had a relatively large study population.

## CONCLUSIONS

In conclusion, we investigated whether pyuria is an independent risk factor for IVR in patients with UTUC after RNUx. We suggest that patients with UTUC and preopera-

tive pyuria should be considered to have a higher risk for IVR after NUx and should undergo more meticulous bladder examinations. Furthermore, additional treatment plans for lowering IVR after NUx might help to improve the prognosis and lower the need for additional surgery or anesthesia in patients with UTUC. We believe that our research provides a basis for future studies establishing risk stratification models for IVR in patients with UTUC.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

## FUNDING

None.

## AUTHORS' CONTRIBUTIONS

Research conception and design: Jooho Lee and Ja Hyeon Ku. Data acquisition: Seung-hwan Jeong, Jang Hee Han, and Hyeong Dong Yuk. Statistical analysis: Jooho Lee. Data analysis and interpretation: Jooho Lee and Si Hyun Kim. Drafting of the manuscript: Jooho Lee. Critical revision of the manuscript: Si Hyun Kim and Ja Hyeon Ku. Administrative, technical, or material support: Chang Wook Jeong and Cheol Kwak. Supervision: Ja Hyeon Ku. Approval of the final manuscript: all authors.

## SUPPLEMENTARY MATERIAL

Supplementary material can be found via https://doi.org/10.4111/icu.20230066.

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## EDITORIAL COMMENT

I reviewed with great enthusiasm the article entitled "Pyuria as an independent predictor of intravesical recurrence [IVR] after radical nephroureterectomy [RNUx] in patients with upper tract urothelial carcinoma [UTUC]," which is being published in Investigative and Clinical Urology [1]. I congratulate the authors for this informative and comprehensive review. I have a few comments.

The study by Lee et al. [1] included 743 patients with UTUC who underwent RNUx and were divided into two groups: non-pyuria and pyuria. The researchers identified that the pyuria group had a shorter IVR-free survival period (p=0.009), and the 5-year IVR-free survival rate was 60.0% vs. 49.7% in the non-pyuria and pyuria groups, respectively (Fig. 1 in [1]). After the multivariate Cox regression analysis, pyuria (hazard ratio [HR]=1.368; p=0.041) was a predictor of risk for IVR (Table 2 in [1]). The authors concluded that pyuria was an independent predictor of IVR in patients with UTUC after RNUx.

Although the actual mechanisms of the association between preoperative pyuria and IVR have yet to be elucidated, urine leukocytes might play a key role in cancer-associated inflammation and carcinogenesis. I believe that patients with UTUC and pyuria should undergo a more meticulous examination of the bladder to prevent IVR as early as possible. Ureteroscopic examination without biopsy in patients with UTUC and pyuria should be considered. In addition, intravesical chemotherapy after RNUx in patients with pyuria should be considered to reduce IVR [2].

Without any reported significant downside to prophylactic intravesical chemotherapy and cystoscopic surveillance, I believe this practice should be the standard of care for patients with pyuria. My practice has been to place 40 mg/20 mL mitomycin C via surgical catheter as soon as the nephroureterectomy is begun with a maximum dwelling time of 2 hours. I then perform cystoscopy within the first 3 to 4 months postoperatively and every 6 to 12 months thereafter.

## CONFLICTS OF INTEREST

The author has nothing to disclose.

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Research conception and design: In Ho Chang. Drafting of the manuscript, Critical revision of the manuscript, and Approval of the final manuscript: In Ho Chang.

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