Effects of Previous or Synchronous Non-Muscle Invasive Bladder Cancer on Clinical Results after Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: A Multi-Institutional Study

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Purpose: To evaluate the effects of the presence of previous or synchronous non-muscle invasive bladder cancer (NMIBC) on the oncologic outcomes of radical nephroureterectomy in patients with upper tract urothelial carcinoma (UTUC).

Materials and Methods: In total, 505 patients with UTUC were enrolled from four different institutions. The clinicopathologic parameters of patients with and without previous or synchronous NMIBC were compared, and Kaplan-Meier estimates and multivariate Cox regression analyses were performed.

Results: The median follow-up period was 38.4 months. In all, 408 patients had primary UTUC, 45 (8.9%) had a history of NMIBC, 59 (11.7%) had concomitant bladder cancer, and seven (1.4%) had experienced both. Tumors in patients with associated NMIBC were more commonly multifocal (P = .001) and associated with surgical margin positivity (P = .001). Kaplan-Meier estimates revealed that previous or synchronous NMIBC was significantly associated with bladder recurrence (P < .001) and locoregional recurrence/distant metastasis (P = .008). A multivariate Cox regression model identified previous or synchronous NMIBC as an independent predictor of bladder recurrence (P < .001). However, the presence of previous or synchronous NMIBC was not a prognostic indicator of locoregional recurrence/distant metastasis.

Conclusion: In patients with UTUC, previous or synchronous NMIBC was significantly associated with an increased risk of cancer recurrences in the bladder after radical nephroureterectomy. The present findings suggest that a close monitoring should be required for the patients with previous or concomitant NMIBC.

Keywords: neoplasm recurrence; nephrectomy; urinary bladder neoplasms; treatment outcome; urologic surgical procedures; urothelium; pathology; urologic neoplasms.

INTRODUCTION

Both synchronous and metachronous multifocal development and frequent recurrences are common in bladder cancer (BC).[1,2] In fact, it is estimated that upper tract urothelial carcinomas (UTUCs) develop in 2-4% of patients with BC.[3-5] Conversely, the proportion of detected BC in patients with UTUC varies from 15 to 75%.[6-8] While experts attribute these phenomena to defect cancerization and clonal expansion,[9,10] no consensus has been reached in understanding the precise mechanisms underlying the proposed theories.[11-13] It has been reported that the chances of a recurrent urothelial carcinoma in normal-appearing urothelium with similar oncologic characteristics are about 50-80% after the initial resection of non-muscle-invasive BC (NMIBC) tumors.[1] Although several factors may play a role in this adverse prognosis in UTUC patients,[6,14,15] few studies have reported the effect of previous NMIBC on cancer recurrence and overall survival.[16] Here, we investigated whether previous or synchronous NMIBC were associated with poor oncologic outcomes for UTUC patients following radical nephroureterectomy (RNU).

MATERIALS AND METHODS

In total 505 UTUC patients who underwent either open (n = 183) or laparoscopic RNU (n = 322) at four academic institutions in Korea between March 2001 and December 2013 were included in our study and were retrospectively analyzed. Patients with previous or concurrent muscle-invasive BC (MIBC), those who received neoadjuvant chemotherapy, or those with the evidence of distant metastasis at the time of diagnosis were excluded in order to minimize the confounding errors in assessing survival estimates. After RNU, bladder

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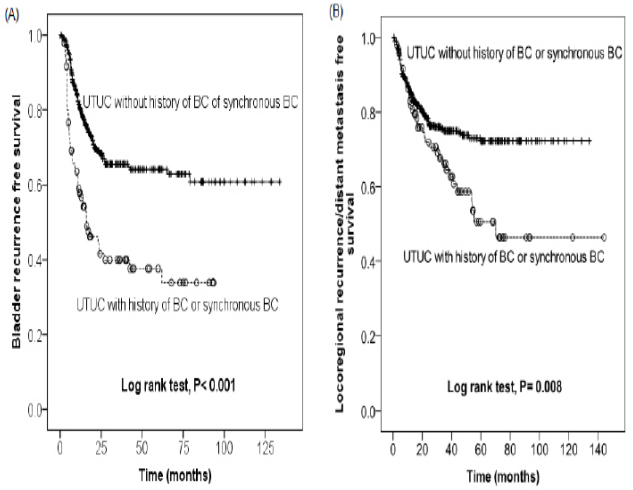

Figure 1. Effect of previous or concomitant non-muscle-invasive bladder cancer on bladder recurrence **(A)** and locoregional recurrence/distant metastasis **(B)** after radical nephroureterectomy.
Abbreviations: UTUC, upper tract urothelial carcinoma; BC, bladder cancer.

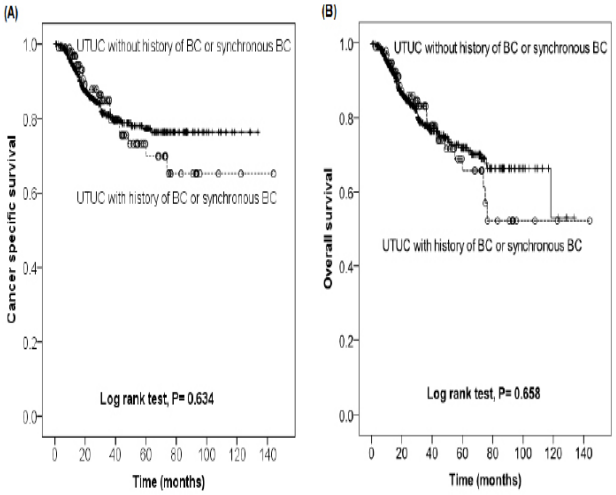

Figure 2. Effect of previous or concomitant non-muscle-invasive bladder cancer on cancer-specific survival **(A)** and overall survival **(B)** after radical nephroureterectomy.
Abbreviations: UTUC, upper tract urothelial carcinoma; BC, bladder cancer.

Table 1. Clinicopathological characteristics of patients with previous or synchronous NMIBC and those without.

Parameters	UTUC without Previous Synchronous NMIBC (n = 408)	UTUC with Previous or Synchronous NMIBC (n = 97)	*P* Value
Age, (mean ± SD), y	66.2 ± 10.5	66.6 ± 10.4	.719
BMI, kg/m²	23.7 ± 3.1	24.0 ± 2.9	.364
Gender, No. (%)			.224
Male	276 (67.6)	72 (74.2)	
Female	132 (32.4)	25 (25.8)	
Smoking status, No. (%)			.893
No	262 (64.3)	63 (65.3)	
Yes	146 (35.7)	34 (34.7)	
Laterality, No. (%)			1.000
Left	217 (53.2)	51 (52.6)	
Right	191 (46.8)	46 (47.4)	
Tumor size, (mean ± SD), mm	37.9 ± 22.7	41.8 ± 36.1	.316
Tumor location, No. (%)			<.001
Renal pelvis	161 (39.5)	24 (24.7)	
Ureter	206 (50.5)	46 (47.4)	
Both	41 (10.0)	27 (27.8)	
Bladder cuff resection, No. (%)			.485
No	46 (11.3)	14 (14.4)	
Yes	362 (88.7)	83 (85.6)	
Multifocality, No. (%)			.001
No	298 (72.5)	53 (54.6)	
Yes	112 (27.5)	44 (45.4)	
Pathologic T stage, No. (%)			.146
Ta, CIS, T1–2	232 (56.9)	63 (64.9)	
T3–4	176 (43.1)	34 (35.1)	
Pathologic N stage, No. (%)			.748
Nx	177 (43.4)	41 (42.3)	
N0	207 (50.7)	52 (53.6)	
N+	24 (5.9)	4 (4.1)	
Grade, No. (%)			.374
Low	141 (34.6)	39 (40.2)	
High	267 (65.4)	58 (59.8)	
Concomitant CIS, No. (%)			.148
No	383 (93.8)	86 (88.9)	
Yes	25 (6.2)	11 (11.1)	
Lymphovascular invasion, No. (%)			.468
No	335 (82.1)	76 (78.4)	
Yes	73 (17.9)	21 (21.6)	
Margin status, No. (%)			.001
Negative	394 (96.6)	85 (87.6)	
Positive	14 (3.4)	12 (12.4)	

Abbreviations: NMIBC, non-muscle-invasive bladder cancer; UTUC, upper tract urothelial carcinoma; CIS, carcinoma in situ; SD, standard deviation; BMI, body mass index.

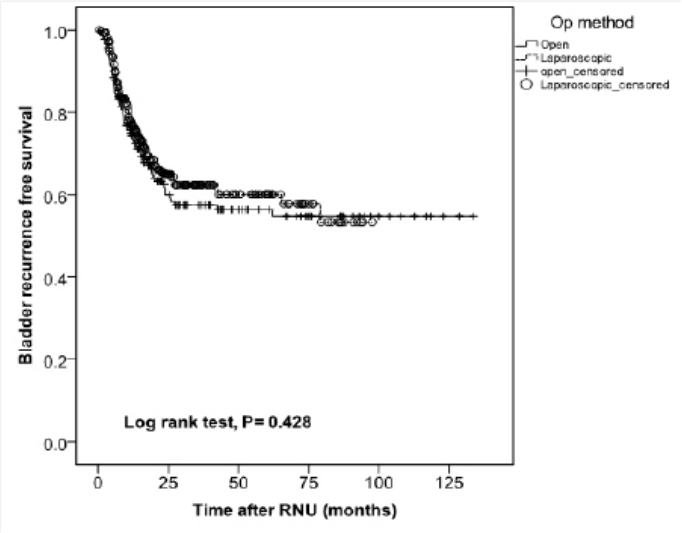

Figure 3. Bladder recurrence free survival between open and laparoscopic radical nephroureterectomy.
Abbreviations: OP, operative, RNU, radical nephroureterectomy.

cuff resection was performed using standard procedures (i.e., an extravesical approach via a Gibson incision) stipulated by each center. Lymph node dissection was indicated if lymphadenopathy was suspected upon preoperative imaging or observed during surgery. A majority of patients with non-organ-confined disease received cisplatin-based adjuvant chemotherapy. Tumors were staged according to the American Joint Committee on Cancer (6th edition) staging system.[17] Tumor grades were assessed according to the 1998 World Health Organization (WHO) classification system.[18] Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed tumors in any location (renal pelvis or ureter).[19]

Follow-up regimen included cystoscopy, urine cytology, chest X-ray, and computed tomography (CT) of the chest. Cystoscopy and urine cytology were performed at 3, 6 and 12 months post-surgery, and yearly thereafter. Imaging analyses (chest X-ray and CT of chest) were performed at 3, 6 and 12 months after RNU, and then at every 6 months from 1 to 5 years post-surgery. Scans were performed annually thereafter. Elective bone scans, chest CT, or positron emission tomography (PET) scans were performed when clinically indicated. The median follow-up period was 38.4 months (interquartile range, 15.6–56.5). One hundred and nine patients (21.6%) received adjuvant systemic chemotherapy and 287 patients (56.8%) underwent lymph node dissection during RNU. Four hundred-and-eight patients had primary UTUC (no history of previous NMIBC or concomitant NMIBC), 45 (8.9%) had previous NMIBC, 59 (11.7%) had concomitant NMIBC, and seven (1.4%) had experienced both. Thus, 97 patients (19.2%) had previous or concomitant NMIBC. The demographic and clinical characteristics of the 505 patients are listed in **Table 1**. UTUC without NMIBC was more likely to be associated with pathologic stage T3 or greater; however, the difference was not statistically significant. There were no significant differences between the two groups in terms of N stage, grade, lymphovascular invasion, and concomitant carcinoma in situ (CIS). Tumors with associated NMIBC were more

Table 2. Univariate and multivariate Cox regression analyses to identify predictors of bladder recurrence in patients with UTUC.

Parameters	Univariate Analysis		Multivariate Analysis	
	HR (95%, CI)	*P* Value	HR (95%, CI)	*P* Value
Age	1.000 (0.986–1.014)	.962	1.003 (0.984–1.023)	.748
Gender (male vs. female)	1.043 (0.757–1.436)	.797	1.199 (0.748–1.922)	.451
Smoking (no vs. yes)	0.771 (0.534–1.113)	.771	0.878 (0.547–1.407)	.587
Tumor size	1.002 (0.996–1.008)	.533	1.003 (0.996–1.011)	.360
Tumor location				
Renal pelvis	1	-----	1	-----
Ureter	1.599 (1.131–2.262)	.008	1.088 (0.669–1.767)	.735
Both	2.017 (1.272–3.201)	.003	0.804 (0.354–1.830)	.603
Bladder cuff resection (no vs. yes)	1.498 (0.867–2.588)	.147	1.535 (0.722–3.264)	.266
Multifocality (no vs. yes)	1.071 (0.779–1.472)	.675	1.318 (0.657–2.646)	.437
Pathologic T stage (Ta, CIS, T1–2 vs. T3–4)	1.035 (0.759–1.410)	.830	1.350 (0.836–2.181)	.219
Pathologic N stage (Nx, N0 vs. N+)	1.190 (0.607–2.332)	.612	1.670 (0.714–3.906)	.237
Grade (low vs. high)	1.274 (0.898–1.807)	.175	0.736 (0.435–1.245)	.253
Concomitant CIS (no vs. yes)	1.280 (0.709–2.312)	.413	0.866 (0.441–1.701)	.676
Lymphovascular invasion (no vs. yes)	1.027 (0.693–1.523)	.895	0.901 (0.530–1.532)	.700
Margin status (no vs. yes)	1.281 (0.676–2.428)	.448	0.586 (0.228–1.506)	.267
Previous or synchronous NMIBC (no vs. yes)	2.440 (1.768–3.367)	<.001	2.845 (1.811–4.470)	<.001

Abbreviations: UTUC, upper tract urothelial carcinoma; HR, hazard ratio; CI, confidence interval; CIS, carcinoma in situ; NMIBBC, non-muscle-invasive bladder cancer.

Table 3. Univariate and multivariate Cox regression analyses to identify predictors of locoregional recurrence/distant metastasis in patients with UTUC.

Parameters	Univariate Analysis		Multivariate Analysis	
	HR (95%, CI)	*P* Value	HR (95%, CI)	*P* Value
Age	1.020 (1.002−1.038)	.025	1.009 (0.983−1.036)	.506
Gender (male vs. female)	0.951 (0.653−1.385)	.795	0.791 (0.440−1.421)	.432
Smoking (no vs. yes)	0.952 (0.618−1.466)	.823	0.677 (0.385−1.192)	.177
Tumor size	1.007 (1.001−1.012)	.018	1.002 (0.995−1.009)	.64
Tumor location				
Renal pelvis	1	-----	1	-----
Ureter	1.176 (0.793−1.743)	.42	0.874 (0.488−1.567)	.652
Both	1.847 (1.123−3.038)	.016	0.840 (0.302−2.336)	.738
Bladder cuff resection (no vs. yes)	0.274 (0.195−0.917)	.019	0.475 (0.236−0.956)	.037
Multifocality (no vs. yes)	1.180 (0.821−1.695)	.371	1.284 (0.544−3.032)	.568
Pathologic T stage (Ta, CIS, T1–2 vs. T3–4)	3.274 (2.051−5.226)	<.001	2.221 (1.630−2.367)	.005
Pathologic N stage (Nx, N0 vs. N+)	5.845 (3.616−9.448)	<.001	3.908 (1.919−7.959)	<.001
Grade (low vs. high)	4.992 (2.686−9.278)	<.001	3.547 (1.305−9.639)	.013
Concomitant CIS (no vs. yes)	0.999 (0.481−2.031)	.975	1.135 (0.530−2.429)	.745
Lymphovascular invasion (no vs. yes)	4.069 (2.863−5.783)	<.001	1.877 (1.087−6.750)	.024
Margin status (no vs. yes)	4.979 (3.054−8.116)	<.001	3.045 (1.373−6.750)	.006
Previous or synchronous NMIBC (no vs. yes)	1.664 (1.136−2.483)	.009	1.571 (0.922−2.677)	.097

Abbreviations: UTUC, upper tract urothelial carcinoma; HR, hazard ratio; CI, confidence interval; CIS, carcinoma in situ; NMIBC, non-muscle-invasive bladder cancer.

often multifocal ($P = .001$), related to a positive surgical margin ($P = .001$), and localized to both the ureter and renal pelvis ($P < .001$).

To evaluate the outcomes, the enrolled UTUC were allocated into two groups: those with previous or synchronous NMIBC, and those without. The Student's *t* test and the Chi-square test were used to examine the association between variables between the two groups. Bladder recurrence-free survival, locoregional recurrence/distant metastasis-free survival, cancer-specific survival, and overall survival after RNU were estimated using the Kaplan-Meier method and the log rank test. Multivariate Cox regression analyses were performed to identify independent predictors of bladder recurrence and locoregional recurrence/distant metastasis. All statistical analyses were performed using Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 18.0. All reported *P* values were 2-sided and significance was set at $P < .05$.

RESULTS

In total, 173 patients (34.3%) experienced bladder recurrences after a median follow-up time of 17.0 months (interquartile range, 8.4-36.0). Bladder recurrence was significantly more common in patients with previous or concomitant NMIBC than in those with isolated UTUC (55.7% vs. 29.2%, respectively; $P < .001$). The Kaplan-Meier analysis revealed that bladder recurrence-free survival was significantly higher in men with a history of NMIBC (**Figure 1,** panel A, $P < .001$; log rank test). During the follow-up period, locoregional recurrence/distant metastasis were observed in129 patients (25.5%) after a median of 25.5 months (interquartile range, 12.0–51.4). Locoregional recurrence/distant metastasis was also more commonly seen in patients with previous or concomitant NMIBC than in those without (38.1% vs. 22.5%, respectively; $P = .002$). Locoregional recurrence/distant metastasis-free survival was significantly lower in patients with previous or concomitant NMIBC than in those without (**Figure 1,** panel B, $P = .008$; log rank test). There were no significant differences in cancer-specific survival (**Figure 2,** panel A, $P = .634$; log rank test) or overall survival (**Figure 2**, panel B; $P = .658$; log rank test) between patients with previous or concomitant NMIBC and those without.

Univariate Cox analyses identified tumor localization in areas other than the renal pelvis [ureter, hazard ratio (HR): 1.599, $P = .008$; both ureter and renal pelvis, HR: 2.017, $P = .003$] and previous or synchronous NMIBC (HR: 2.440; $P < .001$) as factors associated with bladder recurrence (**Table 2**). Multivariate Cox regression analysis identified previous or synchronous NMIBC as an independent predictor of bladder recurrence (HR: 2.845; $P < .001$; **Table 2**). Univariate analysis identified older age, larger tumor size, tumors located in both the ureter and renal pelvis, bladder cuff resection, worse pathologic T stage, pathologic N stage, grade, lymphovascular invasion, positive margin status, and previous or synchronous NMIBC as factors significantly associated with locoregional recurrence/distant metastasis (**Table 3**). Multivariate analysis identified bladder cuff resection, worse pathologic T stage, pathologic N stage, lymphovascular invasion, higher grade, and positive margin status as independent predictors of locoregional recurrence/distant metastasis. Previous or concurrent

NMIBC showed a marginal association with locoregional recurrence/distant metastasis (HR: 1.571; P = .097; **Table 3**).

DISCUSSION

To the best of our knowledge, the cohort of 505 patients with UTUC recruited from four academic centers in Korea represents the largest of its kind in East Asia to date. Our results revealed that previous or synchronous NMIBC was an independent predictor of bladder recurrence in patients with UTUC, but this was not associated with locoregional recurrence/distant metastasis, cancer-specific survival, or overall survival. These results were consistent with previously published reports.[16,20] A study performed in Serbia reported that a history of NMIBC was significantly associated with bladder recurrence, but not with non-bladder recurrence and cancer-specific survival.[16] A recent multi-institutional study performed in France[20] found that patients with previous or synchronous BC were more likely to experience bladder recurrence; this study also excluded the patients with previous or concomitant MIBC that was treated by cystectomy. The study also found that metastasis-free survival and cancer-specific survival rates were not significantly affected by the presence of associated BC. Hence, the more frequent incidence of bladder recurrence in patients with previous or synchronous NMIBC is likely attributed to the natural propensity of NMIBC to recur, but this association does not adversely affect the prognosis of patents with UTUC.

In this current study, patients with previous or synchronous NMIBC were more likely to show multifocality, and the tumors were localized in both the ureter and renal pelvis. Thus, our results were consistent with the earlier studies on tumor location and multifocality as predictors of bladder recurrence.[19,21,22] In addition, patients with NMIBC were also more likely to have a positive surgical margin than those with primary UTUC (12.4% vs. 3.4%, respectively; P = .001). Because positive margin status after RNU is associated with a poor prognosis and has a higher chance of developing metastasis,[23,24] it was likely that previous or synchronous NMIBC was also associated with locoregional recurrence/distant metastasis based on univariate analysis. The effect of operative methods between laparoscopic versus open RNU on bladder recurrence was controversial.[25] In this study, there were no significant differences in bladder recurrence-free survival between open and laparoscopic procedures (P = .428) (**Figure 3**).

In contrast to previous studies, our current study, which was performed exclusively in East Asia, displays several distinctive characteristics. In particular, the relatively low incidence of those with a history of NMIBC should be noted. For example, the incidence of previous NIMBC in the present study was 8.9%, compared to 12.5-28% reported in other prior studies.[16,20,26] Similarly, with the inclusion of concomitant NMIBC, we found that the rate of previous or synchronous NMIBC was 19.2% when Pignot and colleagues reported that 220 out of 662 patients (33.2%) had previous or synchronous NMIBC.[20] These findings collectively indicate that ethnicity may play a role concerning the discrepancies as our study population is uniformly composed of Koreans, as opposed to the earlier studies comprised of predominantly Caucasian study participants. Among the reported ethnic patterns in UTUC, it was shown that the incidence of UTUC was unusually high in Taiwanese patients. Also, the relative proportion of ureter tumors was higher among Korean patients with UTUC when compared to other ethnicities.[24,27] Indeed, our current study supported that ureter tumors were more commonly observed than tumors in the renal pelvis. As Matsumoto and colleagues highlighted some major differences in clinicopathological characteristics (gender distribution, pathologic stage, and grade) between Caucasian and Japanese patients,[28] race and ethnicity may account for the difference in the incidence rate of NMIBC between our current study and the previous reports.

Even though this is the largest cohort of UTUC patients in Asia, the present study is not without its limitations. First and foremost were the limitations inherent in retrospective analyses, which inevitably resulted in selection bias. Second, we were unable to obtain detailed clinicopathologic information on previous or concomitant NMIBC, including T stage, grade, and tumor size and number. Our data also lacked information on the clinical courses (e.g. number of recurrence and tumor progression) and types of treatments (e.g. intravesical therapy and radical cystectomy) in patients with bladder recurrence. Because the data were gathered from four different institutions, we were unable to combine a multiple set of complex information into a uniform database. Third, as we excluded patients with MIBC, we were not able to examine the potentially different oncologic patterns between MIBC and NMIBC. For example, several studies that included MIBC patients demonstrated that a history of BC has an adverse effect on the prognosis of UTUC patients.[26,29] However, the inclusion would go beyond the scope of our current study. Nonetheless, this may be an important investigation into which future prospective studies could possibly delve deeper.

The prevention of bladder recurrence after RNU is an important task for clinicians. As recent prospective randomized II study showed that a single intravesical instillation of anthracycline could reduce bladder recurrence after RNU,[30] our current study findings could provide useful information for clinicians to stratify patients and select patients who would most likely benefit from intravesical chemotherapy.

CONCLUSIONS

Our study findings demonstrated that the presence of a previous or synchronous NMIBC is associated with increased risk of developing bladder recurrence after RNU. These findings may assist physicians to estimate the risk of bladder recurrences in individual and establish, a risk-stratified surveillance strategy.

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CONFLICT OF INTEREST

None declared.

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