

Radical cystectomy versus bladder-preserving therapy in muscle-invasive bladder cancer patients after nephroureterectomy for upper tract urothelial carcinoma: a multicenter retrospective analysis

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Radical cystectomy versus bladder-preserving therapy in muscle-invasive bladder cancer patients after nephroureterectomy for upper tract urothelial carcinoma: a multicenter retrospective analysis

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#### ABSTRACT

### Radical cystectomy versus bladder-preserving therapy in muscle-invasive bladder cancer patients after nephroureterectomy for upper tract urothelial carcinoma: A multicenter retrospective analysis

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Purpose: Although radical cystectomy (RC) and concurrent chemoradiotherapy (CCRT) are curative options for muscle-invasive bladder cancer (MIBC), the optimal treatment strategy for MIBC patients with a history of nephroureterectomy for upper tract urothelial carcinoma (UTUC) remains unclear. This retrospective analysis was conducted to compare survival rates and evaluate prognostic factors related to treatment outcomes.

Material and Methods: We conducted a multi-institutional retrospective study of patients with MIBC after nephroureterectomy for UTUC between 2005 to 2023. Out of 75 patients, 30 underwent bladder-preserving therapy (BPT), including 22 patients who underwent radiation therapy (RT) and 8 patients who underwent CCRT, while 45 patients underwent RC. The overall survival (OS), cancer-specific survival (CSS), and progression-free survival (PFS) after BPT and RC were evaluated using Kaplan-Meier curves. Cox regression analysis was used to identify variables associated with OS, CSS, and PFS. Posttreatment changes in renal function were compared.

Results: At 3 years, the OS, CSS, and PFS rates in the BPT group were 52.4%, 71.7%, and 31.3%, respectively, with no significant difference compared to RC. In multivariate analysis, bladder cancer T stage was the only predictive factor for OS, CSS, and PFS. Similar results were also observed in the RT group compared to RC. A significant decrease in renal function was detected among patients in the RC group, while patients in the BPT group maintained preserved renal function. Patients in the BPT group



experienced a lower grade of toxicity after treatment compared to those in the RC group, and the rates of survival with functional bladder at 1 year, 3 years, and 5 years were 87.0%, 69.9%, and 69.9%, respectively.

Conclusions: Bladder-preserving therapy, including RT alone, may be a viable treatment option for patients with MIBC who have undergone nephroureterectomy, as it can achieve comparable oncologic outcomes to RC, while potentially preserving bladder and renal function.

Key words : Muscle-invasive bladder cancer, Cystectomy, Radiotherapy, Bladderpreserving therapy, Upper tract urothelial carcinoma



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#### I. INTRODUCTION

Radical cystectomy (RC) is still considered the standard treatment for patients with nonmetastatic muscle-invasive bladder cancer (MIBC). However, RC is associated with significant morbidity and diminished quality of life [1-3]. Recently, bladder preserving therapy (BPT) with maximal transurethral resection of bladder tumor (TURBT) and concurrent chemoradiotherapy has been recognized as an alternative to RC for selected patients in several international guidelines. Furthermore, BPT may provide relatively preserved renal function compared to RC after the treatment [4]. Radiation therapy (RT) alone can be considered if the patient is not a suitable candidate for RC or definitive chemoradiotherapy [5].

The recurrence rate in the bladder following treatment of primary upper urinary tract urothelial carcinoma (UTUC) has been found to range from 15% to 50%, and numerous studies have investigated the risk factors associated with bladder recurrence [6]. However, currently, there is limited knowledge regarding the development of MIBC after the treatment of UTUC [6, 7]. As the mechanism of carcinogenesis and the associated molecular pathways differ between patients with bladder cancer and UTUC [8, 9], it remains unclear whether the clinical behavior of recurrent MIBC after treatment of UTUC is similar to that of primary MIBC. Furthermore, special consideration should be given to



the treatment approach for patients with a solitary kidney. Given the lack of prospective studies comparing BPT to RC in patients with MIBC who have a previous history of nephroureterectomy for UTUC, we conducted a multi-center retrospective analysis to compare the treatment effects including survival and renal function between RC and BPT in this patients' population.

#### **II. MATERIALS AND METHODS**

This retrospective study was approved by the Institutional Review Board of Yonsei University Health System (4-2023-0474) for data collection of patients who underwent BPT or RC for MIBC after nephroureterectomy for UTUC between March 01, 2005, and March 31, 2023 in three hospitals: Severance Hospital, Gangnam Severance Hospital, and National Health Insurance Service Ilsan Hospital. Patients with distant metastasis or non-urothelial histology were excluded from the analysis.

#### Bladder preserving therapy

The BPT group included patients who received CCRT or RT alone due to medical and/or surgical contraindications for cystectomy or patients' intention to reject surgery. Diagnosis and staging involved TURBT and computed tomography (CT) scans of the chest and abdomen/pelvis, following the staging system of the American Joint Committee on Cancer (AJCC, 7th edition) [10].

Usually, external beam RT was delivered by three-dimensional conformal techniques, for 5 days each week over 6 weeks. The total radiation dose ranged from 38 to 64 Gy (Median 54) with 10 to 34 fractions (Median 27). The irradiated fields were defined according to common criteria in most patients, but there were instances where they were modified based on each physician's decision. Cisplatin was administered as a concurrent chemotherapeutic agent, with a dose of  $30 \text{mg/m}^2$  given every week on the first day of the chemotherapy cycle. Patients who were elderly, rejected chemotherapy, had a history of recent adjuvant chemotherapy, or were deemed by the physician to be unsuitable for



chemotherapy received RT alone.

#### Radical cystectomy

Diagnosis and staging prior to RC were similar to the diagnosis and staging conducted before BPT. All RC patients underwent pelvic lymph node dissection, and the type of urinary diversion was chosen, including ureterocutaneostomy, ileal conduit, or orthotopic neobladder, through the preoperative discussion with the patients (Supplementary Table 1).

#### Follow-up and salvage treatment

Follow-up for both patient groups included a yearly CT abdomen/pelvis and chest X-ray. After BPT, additional follow-up included cystoscopy with urine cytology at 3-month intervals for the first 2 years, followed by 6-month intervals thereafter. Bladder function after BPT was assessed through interviews. In cases where there was uncertainty regarding tumor recurrence, transurethral resection was performed. Non-muscle invasive bladder cancer (NMIBC) recurrences were treated with TURBT, with or without additional intravesical chemo- or immunotherapy. MIBC recurrences were treated with salvage cystectomy, provided that no systemic disease was found and the patient's general condition was sufficient.

#### Statistical analysis

Overall survival (OS) was defined as the time from treatment initiation to death from any cause. Cancer-specific survival (CSS) was defined as the time from treatment initiation to death specifically from bladder cancer. Progression-free survival (PFS) was defined as the time from treatment initiation to disease progression based on image study findings. NMIBC recurrences were not considered as disease progression. Survival with bladder preserved was defined as the interval between the date of radiotherapy and the date of cystectomy, grade>2 toxicity, or invasive bladder relapse and if no event the date of the



latest news or death. Early and late complications of BPT occurring within or after 3 months were graded according to the Radiation Therapy Oncology Group (RTOG) toxicity grading systems for radiation [11], and post-RC complications within 3 months were graded using the Clavien and Dindo Classification [12].

We compared the baseline characteristics and survival outcomes between the two groups using the chi-square test, student t-test, and Kaplan-Meier method with log-rank test. Univariate and multivariate Cox regression analysis was performed to identify independent predictors of OS, CSS and PFS. The paired-t test is used to compare estimated glomerular filtration rate (eGFR) between before and after each treatment. All statistical analyses were conducted using R software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria), and a p-value less than 0.05 was considered statistically significant.

#### III. RESULTS

Both the BPT and RC series have no significant differences in clinicopathological characteristics, except for a higher MIBC T stage (p=0.001) and higher UTUC T stage (p=0.009) in the BPT group. Similarly, there were no significant differences in clinicopathologic characteristics between patients in RT and RC groups, except for a higher MIBC T stage (p=0.002) in the RT group (Table 1).

Characteristic	BPT	(n=30)	RC (n=45)	p-value <sup>‡</sup>	
	RT (n=22)	CCRT (n=8)			
Age (yr)	68.9±11.4	64.6±4.9	68.8±7.9	0.635 (0.975)	
Sex				0.594 (0.806)	
Female	7 (31.8)	0 (0)	13 (28.9)		
Male	15 (68.2)	8 (100.0)	32 (71.1)		

#### Table 1. Clinicopathologic characteristics of patients



UTUC T stage				0.009 (0.052)
1	3 (13.6)	0 (0)	19 (42.2)	
2	7 (31.8)	3 (37.5)	12 (26.7)	
3	12 (54.5)	5 (62.5)	14 (31.1)	
UTUC N stage				0.520 (0.418)
0	20 (90.9)	8 (100)	43 (95.6)	
1	0 (0)	0 (0)	1 (2.2)	
2	1 (4.5)	0 (0)	1 (2.2)	
3	1 (4.5)	0 (0)	0 (0)	
UTUC location				0.163 (0.188)
Renal pelvis	8 (36.4)	4 (50.0)	26 (57.8)	
Ureter	7 (31.8)	3 (37.5)	7 (15.6)	
Both	7 (31.8)	1 (12.5)	12 (26.7)	
Time to MIBC diagnosis	24.8	25.9	19.8	0.725 (0.931)
(mo) <sup>+</sup> eGFR <sup>†</sup>	(8.6–42.5) 55.3±16.4	(8.6–43.2) 54.0±15.7	(9.2–38.6) 48.6±20.0	0.194 (0.148)
MIBC T				0.001 (0.002)
2	9 (40.9)	2 (25.0)	34 (75.6)	
3	11 (50.0)	4 (50.0)	5 (11.1)	
4	2 (9.1)	2 (25.0)	6 (13.3)	
MIBC N				0.226 (0.537)
0	17 (77.3)	5 (62.5)	40 (88.9)	
1	1 (4.5)	1 (12.5)	1 (2.2)	
2	3 (13.6)	2 (25.0)	2 (4.4)	
3	1 (4.5)	0 (0)	2 (4.4)	

Variables are presented as mean  $\pm$  standard deviation, median [1<sup>st</sup> quartile – 3<sup>rd</sup> quartile] or number (%)

\* It means the time to diagnosis of muscle-invasive bladder cancer after nephroureterectomy

† eGFR before the treatment for muscle-invasive bladder cancer

‡ p-value from comparison between radiation therapy and radical cystectomy

BPT, bladder preserving therapy; RT, radiation therapy; CCRT, concurrent

chemoradiotherapy; RC, radical cystectomy; eGFR, estimated glomerular filtration rate; UTUC, upper tract urothelial carcinoma; MIBC, muscle invasive bladder cancer.



During the follow-up period, a total of 26 patients died, with 17 deaths occurring in the RC group and 9 deaths in the BPT group. The 1-year, 3-year, and 5-year OS rates for patients in the RC group were 88.3%, 60.1%, and 60.1%, respectively. In comparison, the corresponding rates for patients in the BPT group were 92.2%, 52.4%, and 52.4%, respectively. However, there were no statistically significant differences in OS between the two groups (p=0.811) (Figure 1).

A total of 10 patients died due to bladder cancer during the follow-up period, with 5 deaths occurring in both the RC and BPT groups. The 1-year, 3-year, and 5-year CSS rates for patients in the RC group were 95.6%, 81.8%, and 81.8%, respectively, while for patients in the BPT group, the corresponding rates were 96.6%, 71.7%, and 71.7%, respectively. Again, there were no statistically significant differences in CSS between the two groups (p=0.218) (Figure 2). Disease progression was observed in 42 patients, with 24 cases in the RC group and 18 cases in the BPT group. The 1-year, 3-year, and 5-year PFS rates for patients in the RC group were 63.9%, 46.2%, and 34.7%, respectively, while for patients in the BPT group, the rates were 57.3%, 31.3%, and 31.3%, respectively. Similar to OS and CSS, there were no statistically significant differences in PFS between the two groups (p=0.208) (Figure 3). Among the patients in the BPT group, 24 individuals had preserved bladder function. One patient experienced gross hematuria that required transfusion, and five patients had MIBC recurrence, with four of them undergoing salvage RC. The 1-year, 3-year, and 5-year survival with bladder preserved rates for patients in the BPT group were 87.0%, 69.9%, and 69.9%, respectively.





**Figure 1-3**. Kaplan-Meier curve for overall survival, cancer-specific survival, progression-free survival; BPT, bladder preserving therapy; RC, radical cystectomy

The univariate analysis showed that whether patients underwent RC or BPT did not have a significant impact on OS (p=0.812), CSS (p=0.229), and PFS (p=0.211, Supplementary



Table 2). The multivariate analysis revealed that advanced stage of MIBC is a significant factor associated with worse OS, CSS, and PFS. Additionally, female gender was found to be associated with poorer OS and PFS outcomes (Table 2). Similar results were also observed among patients in the RT and RC group (Supplementary Table 3, 4).

**Table 2.** Multivariate Cox regression analysis for overall survival, cancer-specific survival, and progression-free survival after bladder preserving therapy or radical cystectomy

Variable	Overall sur	vival	Cancer-specific survival		Progression surviva	-free 1
	HR (95% CI)	p- value	HR (95% CI)	p- value	HR (95% CI)	p- value
Sex						
Female	Reference		-		Reference	
Male	0.17 (0.06– 0.47)	< 0.001	-		0.18 (0.08 - 0.40)	< 0.001
T stage	,				,	
2	Reference		Reference		Reference	
3	1.07 (0.37 - 3.08)	0.895	2.64 (0.45– 15.48)	0.283	1.46 (0.62– 3.42)	0.386
4	9.29 (2.52– 34.17)	0.001	15.90 (2.95– 85.64)	0.001	6.90 (2.39– 19.96)	< 0.001
N stage						
0	Reference		Reference		Reference	
1	1.99 (0.22– 18.37)	0.543	3.71 (0.32– 43.72)	0.298	1.75 (0.37– 8.27)	0.480
2	2.41 (0.45– 12.82)	0.303	NA	NA	7.11 (2.07– 24.54)	0.002
3	22.11 (4.53– 107.86)	< 0.001	14.10 (1.00– 199.43)	0.050	5.74 (1.50– 21.96)	0.011
UTUC T						
stage					-	
1	-		-		Reference	
2	-		-		0.99 (0.39– 2.53)	0.989



HR, hazard ratio; CI, confidence interval; UTUC, upper tract urothelial carcinoma; NA, not available.

Renal function exhibited a notable decline among patients in the RC group, whereas the BPT group demonstrated preserved renal function. We observed a significant decrease of eGFR in the RC group at 1 month (p<0.001), 3 months (p=0.001), and 12 months (p<0.001) after treatment (Table 3). In contrast, patients in the BPT and RT group did not exhibit a significant decrease in eGFR at any time point.

 Table 3. Differences between the pretreatment and posttreatment eGFR

Variable	Pretreatment eGFR	1-Month posttreatment		3-Month posttreatment		12-Month posttreatment	
		eGFR	p-value	eGFR	p-value	eGFR	p-value
BPT	54.0±15.7	55.0±16.7	0.491	56.2±16.1	0.083	56.8±16.2	0.268
RT	55.3±16.4	56.5±17.0	0.485	57.6±16.2	0.138	58.5±15.4	0.322
RC	48.6±20.0	40.3±18.6	< 0.001	40.2±21.3	0.001	34.0±18.0	< 0.001

Variables are presented as mean±standard deviation.

eGFR, estimated glomerular filtration rate (mL/min/1.73 m<sup>2</sup>); BPT, bladder-preserving therapy; RT, radiation therapy; RC, radical cystectomy.

Supplementary Table 5 presents the side effects of the treatments. The most common side effect for the BPT group was urinary symptoms and there were only four and five cases of grade 3+ toxicity for urinary symptoms and renal function. However, 77.7% of patients in the RC group had grade 3+ side effects and most of them were ureteral stent related problems.



#### IV. DISCUSSION

In situations where it is unclear whether the clinical behavior of recurrent MIBC after nephroureterectomy for UTUC is similar to that of primary MIBC, special consideration should be given to the fact that these patients have a solitary kidney. Due to the unique circumstances and potential complications associated with managing MIBC in individuals with a solitary kidney, more careful evaluation and treatment options are warranted. Our results demonstrated that there were no significant differences in OS, CSS, and PFS between the BPT and RC groups. Furthermore, the BPT group demonstrated preserved renal function, while the RC group exhibited a significant decrease in renal function. These results suggest that BPT, including RT alone, can be an effective treatment option for patients with MIBC who have previously undergone nephroureterectomy. This approach offers comparable outcomes to RC while potentially preserving bladder and renal function.

A recent report by the RTOG demonstrated a 5-year OS rate of 57% and a 5-year CSS rate of 71% for BPT [13]. In our study specifically focused on patients with a history of prior nephroureterectomy, we observed a 5-year OS rate of 52.4% and a 5-year CSS rate of 71.7%. Notably, our study achieved similar survival rates compared to the RTOG study, despite the differences in patient selection. The RTOG study did not specifically include patients with a history of prior UTUC and excluded patients with node metastasis.

The incidence of MIBC after nephroureterectomy is approximately 5%, and it typically occurs with a median interval of 17 months [6]. Previous research suggests that patients with advanced UTUC T stage ( $\geq$ pT3) and tumors located in the renal pelvis have an increased risk of developing MIBC [6]. In our study, we did not find any significant differences in oncologic outcomes between the RC and BPT groups, even though patients in the BPT group had slightly higher T stage tumors. This finding held true regardless of the stage and location of the previous UTUC. The effects of UTUC location on oncologic outcomes remain controversial [14, 15], and a shorter interval between UTUC and the



detection of MIBC has been associated with worse prognosis [7]. The intraluminal seeding theory helps explain the heterogeneity of intravesical recurrence and its correlation with the aggressiveness and prognosis of UTUC [16]. Therefore, close monitoring of patients with a history of higher stage UTUC is crucial for detecting intravesical recurrence before it progresses to MIBC. Once MIBC is diagnosed following nephroureterectomy, BPT can be considered a viable alternative, offering comparable oncologic outcomes to RC while potentially preserving bladder and renal function.

Our results indicate that female patients have a higher risk compared to male patients in terms of OS and PFS, and the stage of bladder cancer significantly impacts OS, CSS, and PFS. Previous studies investigating the association between female sex and survival outcomes in patients with MIBC have indeed shown conflicting results. Some studies have confirmed that female sex is associated with worse CSS outcomes, indicating a potentially poorer prognosis for women with MIBC [17, 18]. Another study has suggested that female gender is associated with a higher rate of local-regional cancer control failure in high-stage bladder cancer patients after RC [19]. One hypothesis proposed in a study is that altered androgen levels in females may contribute to earlier tumor progression and higher metastatic potential, leading to inferior survival outcomes compared to males [17]. However, further studies with larger patient populations are needed to thoroughly investigate the relationship between female gender and survival outcomes after BPT for MIBC.

BPT have benefit in preserving renal function compared to RC in our study. It is wellestablished that CCRT with maximal TURBT leads to better survival outcomes compared to RT alone [20]. However, the use of platinum-based chemotherapy in clinical practice has been limited due to potential kidney toxicities [21]. Although median follow-up period is relatively short in our study, in line with a previous study [22], our findings demonstrate a significant decrease in renal function in the RC group compared to the BPT and RT group after treatment. This decline in renal function following RC is of concern, particularly for patients with a single functioning kidney, as they are more susceptible to



renal function deterioration compared to patients with two functioning kidneys [3]. The decline in renal function following RC may increase the risk of chronic kidney disease and have a negative impact on long-term OS.

Furthermore, the utilization of CCRT can be employed without concerns regarding a decrease in renal function in selected patients. In this context, BPT, including RT alone, for MIBC in patients with a history of nephroureterectomy for UTUC, may offer potential benefits for OS without compromising renal function. It allows for satisfactory local cancer control while preserving renal function. The importance of careful patient selection and close monitoring of renal function after BPT is also emphasized.

Functional bladder preservation without high-grade toxicity and invasive cancer recurrence is a crucial consideration in the management of patients with MIBC, as it significantly impacts their quality of life. Our study demonstrated that BPT can achieve comparable oncologic outcomes to RC, while potentially preserving bladder function. We also observed a similar rate of functional bladder preservation compared to previous studies. Previous studies have reported overall 5-year bladder preservation rates ranging from 43% to 82% [23, 24], and a recent study showed that functional bladder was maintained in 89.2%, 75.0%, and 70.2% of patients at 1, 3, and 5 years, respectively [2]. In our study, despite all patients having a prior surgical history of nephroureterectomy, we observed a 1-year functional bladder survival rate of 87.0% and 3- and 5-year rates of 69.9% without high-grade toxicity, which is comparable to the recent report.

It is important to note that approximately 10% to 15% of MIBC patients treated with BPT may require salvage cystectomy due to recurrence [25]. In our study, four out of 30 patients treated with BPT underwent salvage cystectomy. However, these potential drawbacks of BPT can be mitigated by implementing strategies such as regular cystoscopy for early detection of intravesical recurrence, early TURBT, and intravesical Bacillus Calmette-Guérin (BCG) instillation [26]. By adopting these approaches, the challenges associated with BPT, including the need for salvage cystectomy, can be effectively addressed. Overall, our findings highlight the feasibility of functional bladder preservation



through BPT, with the key factors for success being early detection and management of intravesical recurrence.

Quality of life is indeed a crucial aspect to consider in the management of patients with MIBC. Our study findings demonstrated that patients in the BPT group reported a lower grade of toxicity compared to the RC group. Previous research supports our findings by indicating that patients who received BPT experienced improvements in mean global health status and social functioning after 12 months of treatment, while these aspects declined in the RC group [27]. Additionally, a study comparing long-term quality of life in MIBC patients treated with RC or BPT highlighted that although urinary symptom scores were similar between the groups, patients in the BPT group exhibited better sexual function, body image, and less concern about the negative effects of cancer. They also demonstrated greater scores related to informed decision-making [28]. Although we did not directly measure quality of life or cost-effectiveness before and after the treatment, the potential benefit of functional bladder preservation with rapidly developing BPT techniques could translate into improved quality of life for these patients, which is consistent with previous studies.

Our study had several limitations. Firstly, the retrospective design introduced a potential selection bias, as patients were not randomized to the treatment groups. Secondly, the patients were treated by different urologists and radiologists, leading to possible variations in surgical and imaging approaches. Thirdly, the sample size was relatively small, which could have limited the statistical power of our analysis. Lastly, we did not evaluate the quality of life or cost-effectiveness of the two treatment modalities, which are important factors in decision-making for patients with bladder cancer. Despite these limitations, our study provides valuable information on the treatment effects of RC and BPT in MIBC patients with a history of nephroureterectomy. Further studies with longer follow-up period are needed to identify the best candidates for BPT and to investigate the long-term oncologic outcomes of this treatment modality.



#### V. CONCLUSION

Our study suggests that BPT, including RT alone, is a viable treatment option for patients with MIBC who have undergone nephroureterectomy for UTUC. It can achieve comparable oncologic outcomes to RC while potentially preserving kidney function, bladder function, and quality of life. BPT should be considered as a treatment option for selected patients, and close monitoring and careful patient selection are necessary to ensure the best possible outcomes.

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## APPENDICES

The authors declare no conflict of interest

Supplem	entary	<b>Table</b>	1. Type of	f urinary	diversion	in radica	l cystectomy	patients

Number of patients (%)
40 (88.9%)
3 (6.7%)
2 (4.4%)



	Overall survival		Cancer-specific		Progression-free	
			survi	val	surviv	val
	Hazard	p-value	Hazard	p-value	Hazard	p-value
	ratio	-	ratio	-	ratio	-
Treatment						
BPT	ref.		ref.		ref.	
RC	0.91	0.812	0.46	0.229	0.67	0.211
Age	1.04	0.137	0.99	0.788	1.01	0.755
Sex						
Female	ref.		ref.		ref.	
Male	0.32	0.007	0.48	0.309	0.28	< 0.001
eGFR	0.99	0.384	1.02	0.384	0.99	0.099
T stage						
2	ref.		ref.		ref.	
3	2.12	0.099	3.39	0.145	2.19	0.024
4	4.90	0.004	16.24	0.001	4.47	0.001
N stage						
0	ref.		ref.		ref.	
1	4.22	0.177	12.90	0.037	2.23	0.276
2	4.35	058	NA	NA	8.51	< 0.001
3	9.72	0.001	11.68	0.045	4.15	0.021
UTUC T						
stage						
1	ref.		ref.		ref.	
2	1.60	0.400	4.14	0.219	2.48	0.036
3	2.24	0.105	6.35	0.088	2.08	0.073
UTUC N						
stage						
0	ref.		ref.		ref.	
1	NA	NA	NA	NA	7.06	0.063
2	1.40	0.743	NA	NA	0.62	0.634
3	4.53	0.148	NA	NA	4.48	0.148
UTUC						
location						
Ureter	ref.		ref.		ref.	
Renal pelvis	0.85	0.738	0.75	0.686	1.04	0.930
Both	0.79	0.679	0.29	0.286	0.81	0.646

**Supplementary Table 2**. Univariate Cox regression analysis for overall survival, cancerspecific survival, and progression-free survival after bladder preserving therapy or radical cystectomy

BPT, bladder preserving therapy; RC, radical cystectomy; eGFR, estimated glomerular filtration rate; UTUC, upper tract urothelial carcinoma



cystectomy						
	Overall survival		Cancer-specific		Progression-free	
			survival		survival	
	Hazard	p-value	Hazard	p-value	Hazard	p-value
	ratio		ratio		ratio	
Treatment						
RT	ref.		ref.		ref.	
RC	0.88	0.762	0.4	0.147	0.71	0.336
Age	1.04	0.133	0.99	0.747	1.01	0.506
Sex						
Female	ref.		ref.		ref.	
Male	0.31	0.007	0.52	0.373	0.25	< 0.001
eGFR	0.99	0.384	1.02	0.422	0.99	0.099
T stage						
2	ref.		ref.		ref.	
3	2.12	0.109	3.73	0.114	2.33	0.024
4	5.54	0.002	17.66	< 0.001	5.15	0.001
N stage						
0	ref.		ref.		ref.	
1	6.73	0.075	21.95	0.012	2.99	0.290
2	2.49	0.385	NA	NA	5.50	0.012
3	9.40	0.001	10.80	0.052	4.03	0.024
UTUC T						
stage						
1	ref.		ref.		ref.	
2	1.73	0.324	4.48	0.195	2.57	0.032
3	2.20	0.117	6.74	0.078	1.90	0.129
UTUC N						
stage						
0	ref.		ref.		ref.	
1	NA	NA	NA	NA	7.03	0.065
2	1.40	0.746	NA	NA	0.65	0.674
3	4.57	0.147	NA	NA	4.65	0.140
UTUC						
location						
Ureter	ref.		ref.		ref.	
Renal pelvis	0.79	0.641	0.74	0.675	1.19	0.686
Both	0.76	0.630	0.27	0.261	0.99	0.985

**Supplementary Table 3.** Univariate Cox regression analysis for overall survival, cancerspecific survival, and progression-free survival after radiation therapy or radical cystectomy

RT, radiation therapy; RC, radical cystectomy; eGFR, estimated glomerular filtration rate; UTUC, upper tract urothelial carcinoma; BCR, bladder cuff resection.

Variable	Overall survival		Cancer-specific survival		Progression-free survival	
	HR (95% CI)	p- value	HR (95% CI)	p- value	HR (95% CI)	p- value
Sex						
	Reference		-		Reference	
Female						
Male	0.17 (0.06– 0.47)	< 0.001	-		0.18 (0.08– 0.40)	< 0.001
T stage						
2	Reference		Reference		Reference	
3	1.07 (0.37 - 3.08)	0.895	2.64 (0.45– 15.48)	0.283	1.46 (0.62– 3.42)	0.386
4	9.29 (2.52– 34.17)	0.001	15.90 (2.95– 85.64)	0.001	6.90 (2.39– 19.96)	< 0.001
N stage	,		,			
0	Reference		Reference		Reference	
1	1.99 (0.22– 18.37)	0.543	3.71 (0.32– 43.72)	0.298	1.75 (0.37– 8.27)	0.480
2	2.41 (0.45– 12.82)	0.303	NA	NA	7.11 (2.07– 24.54)	0.002
3	22.11 (4.53– 107.86)	< 0.001	14.10 (1.00– 199.43)	0.050	5.74 (1.50– 21.96)	0.011
UTUC T						
1	-		-		Reference	
2	-		-		0.99 (0.39– 2.53)	0.989
3	-		-		1.18 (0.48– 2.95)	0.718

**Supplementary Table 4.** Multivariate Cox regression analysis for overall survival, cancer-specific survival, and progression-free survival after radiation therapy or radical cystectomy

HR, hazard ratio; CI, confidence interval; UTUC, upper tract urothelial carcinoma; NA, not available.



Grade	Bladder-preserving therapy						Radical Cystectomy
	Urinary		Gastrointestinal		Renal function		
	Early	Late	Early	Late	Early	Late	
0	14 (46.7)	7 (23.3)	28 (93.3)	26 (86.7)	27 (90.0)	21 (70.0)	4 (8.9)
1	14 (46.7)	13 (43.3)	2 (6.7)	2 (6.7)	3 (10.0)	2 (6.7)	3 (6.7)
2	2 (6.7)	6 (20.0)	0	2 (6.7)	0	2 (6.7)	3 (6.7)
3	0	2 (6.7)	0	0	0	3 (10.0)	31 (68.9)
4	0	2 (6.7)	0	0	0	2 (6.7)	2 (4.4)
5	0	0	0	0	0	0	2 (4.4)

**Supplementary Table 5**. Side effects of patients in bladder-preserving therapy (RTOG toxicity grading system) and radical cystectomy (Calvien-Dindo) group

Values are presented as number (%) RTOG, Radiation Therapy Oncology Group



#### ABSTRACT(IN KOREAN)

## 상부 요로상피암의 근치적 수술 후 발생한 근침윤성 방광암 환자에서의 근치적 방광절제술과 방광보존술의 치료 효과 비교: 다기관 분석

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#### 조 영 흔

목적: 근침윤성 방광암의 치료로 근치적 방광절제술과 동시항암방사선요법이 치료 방법으로 제시되고 있으나, 상부 요로상피암에 대해 신우요관절제술을 받은 환자들을 대상으로 한 치료 방법에 대한 연구는 부족한 상황이다. 본 후향적 연구는 두 치료 방법에 따른 생존율을 분석하고자 하였다.

방법: 2005년부터 2023년까지 상부 요로상피암에 대해 신우요관절제술을 받은 이후 근침윤성 방광암이 발생한 환자들을 대상으로 다기관 후향적 분석을 시행하였다. 75명 중 30명은 방광보존술, 그 중 22명은 방사선치료, 8명은 동시항암방사선요법을 시행받았고, 45명은 근치적 방광절제술을 받았다. 전체생존기간(OS), 암특이생존기간(CSS), 무진행생존기간(PFS)을 카플란-마이어 곡선을 이용해 구하였다. 콕스 회귀분석을 통해 각 생존기간에 영향을 미치는 변수들을 확인하였으며, 치료 전후 신장기능의 변화를 구하였다.

결과: 방광보존술을 받은 환자들의 3년째 OS, CSS, PFS은 각각 52.4%, 71.7%, 31.3%였으며, 두 치료법 사이 유의미한 차이는 없었다. 다변량 회귀분석에서 방광암의 T stage만이 생존기간에 영향을 주는 유일한 변수였다. 근치적 방광절제술을 받은 환자군에서 치료 후 신장기능이 유의미하게 감소하였으나, 방광보존술에서는 유지되었으며 치료 후 부작용 등급도 낮았다.

결론: 방광보존술은 신우요관절제술을 받은 과거력이 있는 근침윤성 방광암 환자에게 근치적 방광절제술과 비슷한 치료효과를 볼 수 있으며, 신장기능과 방광기능의 보존에도 우월하다.

핵심되는 말 : 근침윤성 방광암, 방광절제술, 방사선요법, 방광보존술, 상부 요로상피암



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