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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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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.

Materials 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, Bladder-preserving therapy, Upper tract urothelial carcinoma

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]. In recent years, several international guidelines have recognized bladder-preserving therapy (BPT) with maximal transurethral resection of bladder tumor (TURBT) and concurrent chemoradiotherapy as an alternative to RC for selected patients. Furthermore, BPT may preserve renal function to a greater extent than RC after treatment [4]. Radiation therapy (RT) alone can be considered in patients who are not suitable candidates 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, current knowledge is limited 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 multicenter retrospective analysis to compare the treatment effects, including survival and renal function, between RC and BPT in this patient population.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of the Yonsei University Health System (4-2023-0474) for data collection on patients who underwent BPT or RC for MIBC after nephroureterectomy for UTUC between March 1, 2005 and March 31, 2023 at 3 hospitals: Severance Hospital, Gangnam Severance Hospital, and National Health Insurance Service Ilsan Hospital. Patients with distant metastasis or nonurothelial histology were excluded from the analysis.

1. 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 (seventh edition) [10].

Usually, external-beam RT was delivered using the 3-dimensional conformal technique for 5 days each week over 6 weeks. The total radiation dose ranged from 38 to 64 Gy (median, 54 Gy) with 10 to 34 fractions (median, 27 fractions). The irradiated fields were defined according to common criteria in most patients, but there were instances where they were modified based on the physician's decision. Cisplatin was administered as a concurrent chemotherapeutic agent, with a dose of 30 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.

2. 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 an orthotopic neobladder, through a preoperative discussion with the patients (Supplementary Table 1).

3. Follow-up and Salvage Treatment

Follow-up for both patient groups included a yearly abdominopelvic CT scan 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

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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 adequate.

4. 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 imaging findings. NMIBC recurrences were not considered as disease progression. Survival with a preserved bladder was defined as the interval between the date of RT and the date of cystectomy, grade>2 toxicity, or invasive bladder relapse and if no event occurred, 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 system for radiation [11], and post-RC complications within 3 months were graded using the Clavien-Dindo classification [12].

We compared the baseline characteristics and survival outcomes between the 2 groups using the chi-square test, Student t-test, and Kaplan-Meier method with the log-rank test. Univariate and multivariate Cox regression analysis was performed to identify independent predictors of OS, CSS, and PFS. The paired t-test was used to compare the estimated glomerular filtration rate (eGFR) before and after each treatment. All statistical analyses were conducted using R ver. 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria), and a p-value less than 0.05 was considered to indicate statistical significance.

RESULTS

The patients who underwent BPT and RC had 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 the patients in RT and RC groups, except for a higher MIBC T stage (p=0.002) in the RT group (Table 1).

During the follow-up period, 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 2 groups (p=0.811) (Fig. 1).

Ten 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 2 groups (p=0.218) (Fig. 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 2 groups (p=0.208) (Fig. 3). Among the patients in the BPT group, 24 had preserved bladder function. One patient experienced gross hematuria that required transfusion, and 2 patients had MIBC recurrence, with 4 of them undergoing salvage RC. The 1-year, 3-year, and 5-year rates of survival with a preserved bladder for patients in the BPT group were 87.0%, 69.9%, and 69.9%, respectively.

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 MIBC was a significant factor associated with worse OS, CSS, and PFS. Additionally, female sex was found to be associated with poorer OS and PFS outcomes

Table 1. Clinicopathologic characteristics of patients

Characteristic	BPT (n=30)		RC (n=45)	p-value‡
	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)	
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 (mo)*	24.8 (8.6–42.5)	25.9 (8.6–43.2)	19.8 (9.2–38.6)	0.725 (0.931)
eGFR†	55.3±16.4	54.0±15.7	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±standard deviation, number (%), or median (interquartile range).

BPT, bladder-preserving therapy; RT, radiation therapy; CCRT, concurrent chemoradiotherapy; RC, radical cystectomy; UTUC, upper tract urothelial carcinoma; MIBC, muscle-invasive bladder cancer; eGFR, estimated glomerular filtration rate.

*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.

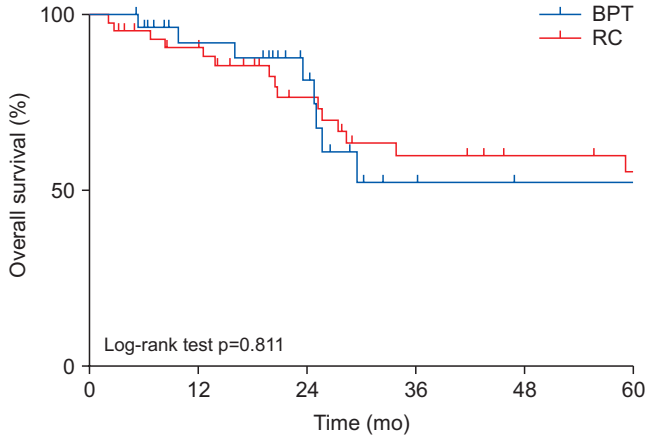

Fig. 1. Kaplan-Meier curve for overall survival. BPT, bladder-preserving therapy; RC, radical cystectomy.

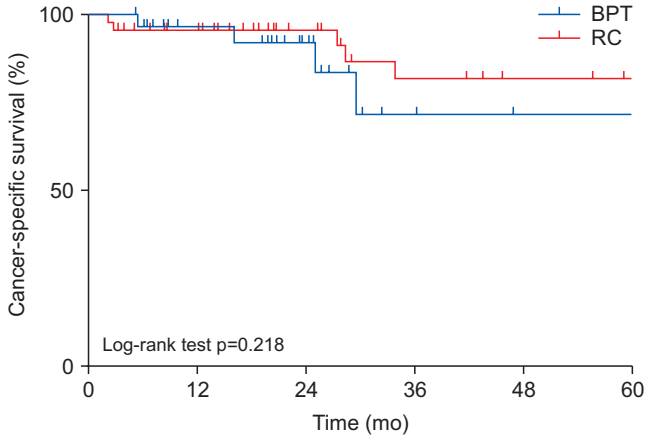

Fig. 2. Kaplan-Meier curve for cancer-specific survival. BPT, bladder-preserving therapy; RC, radical cystectomy.

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(Table 2). Similar results were also observed among patients in the RT and RC groups (Supplementary Tables 3, 4).

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 in the 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 groups did not exhibit a significant decrease in eGFR at any time point.

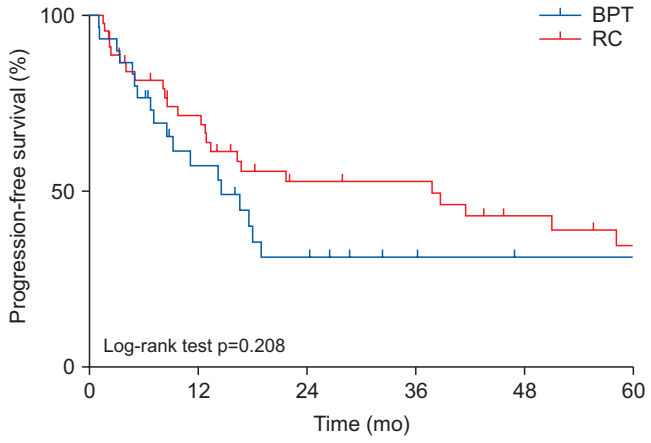

Fig. 3. Kaplan-Meier curve for progression-free survival. BPT, bladder-preserving therapy; RC, radical cystectomy.

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 5 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, most of which were ureteral stent-related problems.

DISCUSSION

In situations where it is unclear whether the clinical

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 survival		Cancer-specific survival		Progression-free survival	
	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
3	-		-		1.18 (0.48–2.95)	0.718

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

Table 3. Differences between the pretreatment and posttreatment eGFR

Variable	Pretreatment eGFR	1-Month posttreatment		3-Month posttreatment		12-Month posttreatment	
		eGFR (mL/min/1.73 m^2)	p-value	eGFR (mL/min/1.73 m^2)	p-value	eGFR (mL/min/1.73 m^2)	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; BPT, bladder-preserving therapy; RT, radiation therapy; RC, radical cystectomy.

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, which 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 to those of 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 at a median interval of 17 months [6]. Previous research has suggested that patients with advanced UTUC T stage (≥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 a matter of debate [14, 15], and a shorter interval between UTUC and the detection of MIBC has been associated with a 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 had higher risk than male patients in terms of OS and PFS, and the stage of bladder cancer significantly impacted 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 sex is associated with a higher rate of local-regional cancer control failure in high-stage bladder cancer patients after RC [19]. One hypothesis is that altered androgen levels in women may contribute to earlier tumor progression and higher metastatic potential, leading to inferior survival outcomes compared to men [17]. However, further studies with larger patient populations are needed to thoroughly investigate the relationship between female sex and survival outcomes after BPT for MIBC.

BPT had benefits in preserving renal function compared to RC in our study. It is well-established that CCRT with maximal TURBT leads to better survival outcomes than RT alone [20]. However, the use of platinum-based chemotherapy in clinical practice has been limited due to potential kidney toxicity [21]. Although the median follow-up period was 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 concerning, particularly for patients with a single functioning kidney, as they are more susceptible to renal function deterioration than patients with 2 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, 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

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with a history of nephroureterectomy for UTUC may offer potential benefits for OS without compromising renal function. It allows 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, 4 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 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 consideration in the management of patients with MIBC. Our study found a lower degree of toxicity in the BPT group than in the RC group. Previous research supports our findings, since 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 the 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 had higher scores for 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 the analysis. Lastly, we did not evaluate the quality of life or cost-effectiveness of the 2 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 periods are needed to identify the best candidates for BPT and to investigate the long-term oncologic outcomes of this treatment modality.

CONCLUSIONS

Our study suggests that BPT, including RT alone, is a viable treatment option for patients with MIBC who have undergone nephroureterectomy for UTUC. This modality can achieve comparable oncologic outcomes to RC while potentially preserving kidney and bladder function. 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.

NOTES

- Supplementary Materials: Supplementary Tables 1-5 can be found via https://doi.org/10.22465/juo.234600280014.
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