

Bladder Preservation With Transurethral Tumor Resection and Intravesical BCG Instillation in Superficial Muscle-Invasive Bladder Cancer: A 10-Year Follow-up

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Purpose: The aim of this study was to evaluate the 10-year oncological outcomes of bladder preservation with transurethral resection of bladder tumor (TURBT) and intravesical bacillus Calmette-Guérin (BCG) instillation in selected patients with superficial muscle-invasive bladder cancer (MIBC).

Materials and Methods: Patients diagnosed with superficial MIBC (stage T2a) by TURBT between 2001 and 2009 were included. Cystectomy-free survival, recurrence-free survival (RFS), progression-free survival (PFS), and cancer-specific survival (CSS) were estimated using the Kaplan-Meier method. Cox regression analysis was used to identify predictors of each type of survival.

Results: Of 145 patients, 135 underwent bladder preservation and 10 underwent immediate radical cystectomy (RC). Among the latter, 9 patients showed downstaging. During a median follow-up of 132 months (interquartile range, 96–161 months), 13 patients underwent RC, with a 10-year cystectomy-free survival rate of 83.9%. Seventy patients (48.3%) had recurrence, and the 10-year RFS rate was 48.9%. Progression occurred in 12 patients (8.3%), with a 10-year PFS rate of 90.1%. Death occurred only in patients who exhibited progression; 5 patients (3.4%) died of bladder cancer, and the 10-year CSS rate was 96.5%. Tumors greater than 3 cm were associated with RC, and a high tumor grade predicted recurrence. RC was related to progression and cancer-specific mortality.

Conclusions: Although high-grade tumors require careful follow-up, bladder preservation with TURBT and intravesical BCG instillation can enable the successful management of selected patients with stage T2a MIBC less than 3 cm, without carcinoma *in situ* or tumor-associated hydronephrosis, in a nonmetastatic setting.

Key Words: BCG vaccine, Organ preservation, Survival, Transurethral resection of bladder, Urinary bladder neoplasms

INTRODUCTION

Radical cystectomy (RC) has been regarded as the standard treatment for muscle-invasive bladder cancer (MIBC).

However, it is associated with high morbidity and diminished quality of life [1, 2]. Various bladder-preserving strategies have been introduced as alternatives for patients unfit for surgery and those unwilling to undergo RC without compromising



the oncological outcomes [3, 4]. The most representative method of bladder preservation is multimodal therapy (MMT), which includes radical transurethral resection of bladder tumor (TURBT) followed by radiation therapy (RT) with concurrent radiosensitizing chemotherapy. This bladder preservation strategy can provide a better quality of life with acceptable outcomes and may be considered a reasonable alternative to RC in properly selected patients [5].

Another bladder-preserving method is radical TURBT alone. The rationale behind performing TURBT alone lies in the possibility of pathologic absence of tumor (pT0) at RC. Recent RC series reported that the expected incidence of pT0 without neoadjuvant chemotherapy ranged from 6% to 20% [6-8]. RC is indisputably the best approach, even in patients with bladder cancer with pT0 disease, but patients may have missed the opportunity for bladder preservation. This rationale can be opposed by the following considerations: the risk of recurrence in pT0 disease is not zero, clinical and pathological stage discrepancies can occur, and lymphadenectomy can only be performed if RC is performed [9, 10]. Nevertheless, some surgeons have reported favorable outcomes of TURBT alone in selected patients with MIBC. Herr [11] reported a series of 99 patients with a 10-year disease-specific survival of 76%. Solsona et al. [12] reported a similar disease-specific survival of 76.7% at 15 years for 133 selected patients.

Currently, the overall consensus is that radical TURBT alone is a suboptimal treatment for MIBC. However, TURBT alone might provide comparable oncological outcomes to those of RC if candidates are selected more carefully [1, 2]. Superficial MIBC is an essential precondition for bladder preservation, but there is no effective imaging modality for discriminating the depth of proper muscle invasion (superficial vs. deep) [1, 13]. Thus, we diagnosed stage T2a MIBC based on TURBT, and bladder preservation was offered as a treatment option in these patients.

Bacillus Calmette-Guérin (BCG) instillation may have beneficial systemic effects in stage T2a MIBC patients receiving bladder-sparing therapy [14]. Therefore, we performed intravesical BCG instillation in all patients who received radical TURBT. This study aimed to evaluate the 10-year oncological outcomes of bladder preservation with TURBT and intravesical BCG instillation in highly selected

patients with stage T2a MIBC.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Yonsei University Severance Hospital (IRB number: 4-2020-0457) for data collection of patients who underwent TURBT for bladder cancer between 2001 and 2009. All procedures were performed by a single surgeon (YDC).

The schematic concept of diagnosing stage T2a based on TURBT is shown in Fig. 1. After a meticulous cystoscopic examination, the gross tumor was completely removed. Next, the tumor base was resected, including the superficial muscle layer. Two consecutive muscle layers below the tumor base were additionally resected until the adipose tissue was exposed and the tumor periphery was included in the resected section. In this procedure, we obtained specimens of the tumor base, deep muscle layer, and deeper muscle layer separately from the main mass. After the resection was complete, the resected surface was fully electrocauterized. We termed this procedure “transurethral layer-section” of the bladder tumor.

Pathological analysis of the specimens was performed at our institution by an experienced uropathologist (NHC) (Fig.

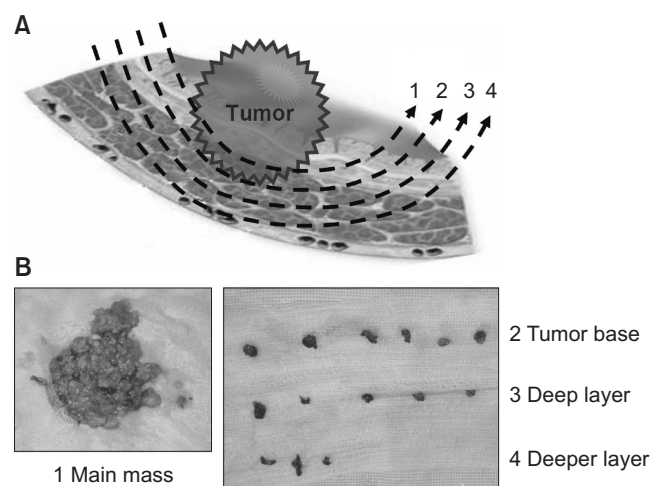


Fig. 1. Muscle layer specimen obtained during transurethral resection of a bladder tumor. (A) Schematic diagram of the concept. Lines 1–4 are resection lines for the main mass, tumor base, deep layer, and deeper layer of muscle, respectively. (B) An example of specimen preparation.

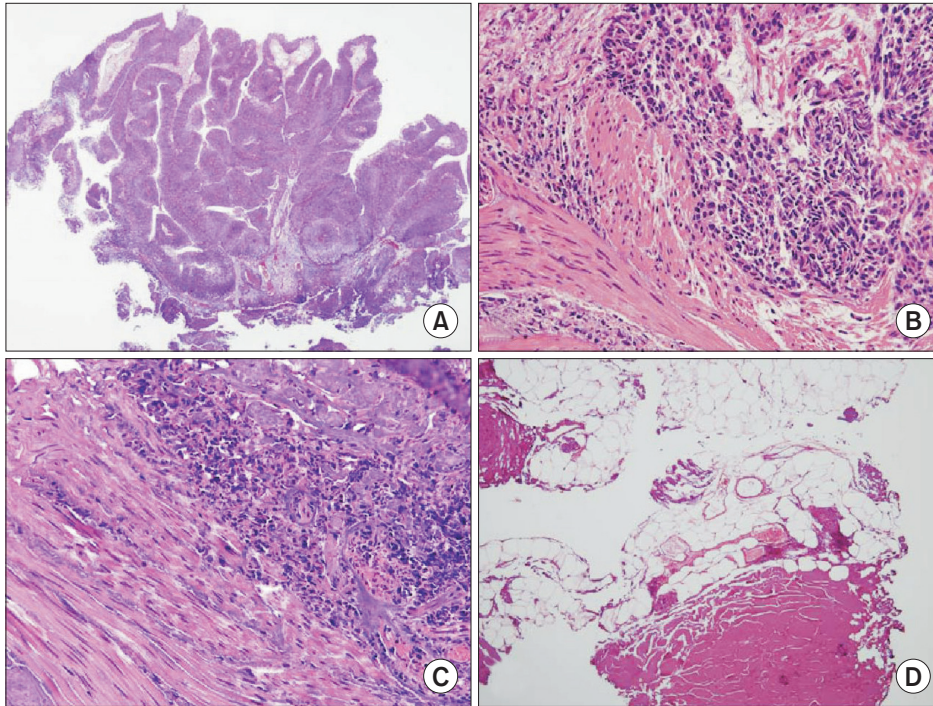


Fig. 2. Histologic findings (hematoxylin and eosin stain). (A) The main mass shows high-grade papillary urothelial carcinoma (magnification, $\times 40$). (B) The tumor base shows muscle-infiltrating carcinoma (magnification, $\times 400$). (C) The deep muscle layer shows muscle tissue without tissue infiltration (magnification, $\times 400$). (D) The deeper muscle layer shows muscle tissue including perivesical fat without tumor invasion (magnification, $\times 100$).

2). The pathological stage and tumor grade were assigned in accordance with the American Joint Committee on Cancer staging system and the World Health Organization classification of bladder tumors, respectively [15, 16]. All specimens were pure urothelial carcinoma, and we excluded variants of urothelial carcinoma. If a tumor was identified in the superficial muscle layer without tumor presence in 2 consecutive layers of deep and deeper muscles, it was considered as stage T2a MIBC without a residual tumor. Radical TURBT was performed in those cases. Preoperative imaging (computed tomography or magnetic resonance imaging [MRI]) was performed in all patients for staging. A Foley catheter was maintained for 7–14 days after surgery.

Bladder preservation without concurrent chemotherapy or RT was considered as an option for patients with stage T2a MIBC. We excluded patients with lymph node or distant metastasis at diagnosis, urothelial carcinoma of the upper urinary tract or prostate, tumor-associated hydronephrosis, or carcinoma *in situ* (CIS), as well as those in whom the largest tumor lesion was greater than 4 cm. Previous studies have indicated that the presence of CIS is not a contraindication for bladder preservation when intravesical BCG therapy is performed [17, 18]. However, we excluded patients with CIS, as the initial presence of CIS is a predictor of

cancer progression [17]. A previous study showed that the complication rate of TURBT was significantly higher in masses larger than 4 cm. Therefore, this study only included masses smaller than 4 cm, which are expected to have fewer complications of TURBT [19].

Patients were offered either standard RC or bladder preservation. To confirm the completeness of radical TURBT, repeated TURBT within 6 weeks after the initial operation was suggested. The planned procedures were discussed with each patient and performed after informed consent was obtained.

Intravesical BCG therapy was performed in all patients who selected bladder preservation. All patients received BCG induction 1 month after TURBT and received BCG instillation once a week for 6 weeks. BCG maintenance was not performed. These patients were evaluated regularly with cystoscopy, urine cytology, abdominopelvic computed tomography, bladder MRI, whole-body bone scan, and chest radiography every 3 months for 2 years, every 6 months for the subsequent 3 years, and annually thereafter. The same follow-up plan, except for cystoscopy and bladder MRI, was implemented for patients who underwent RC.

Recurrence was defined as superficial bladder cancer after TURBT or cancer within the soft tissue field of exenteration

after RC. Progression was considered as deeper tumor invasion of the muscle layer or the presence of lymph node or distant metastasis. If local recurrence after RC or metastasis occurred, patients received chemotherapy and/or RT. Data on mortality and cause of death were collected from the medical records in the Cancer Registry Center database at our institution. Recurrence-free survival (RFS), progression-free survival (PFS), cancer-specific survival (CSS), and cystectomy-free survival were determined from the time of the initial diagnosis of MIBC to the corresponding events or the last follow-up.

Continuous variables are expressed as medians (interquartile ranges [IQRs]), whereas categorical variables are reported as the number of occurrences and frequency (percentage). Survival was estimated using the Kaplan-Meier method and parameters were assessed by Cox regression analysis to identify the predictors. All statistical analyses were performed using IBM SPSS Statistics ver. 26.0 (IBM Co., Armonk, NY, USA).

RESULTS

The patients' baseline characteristics are summarized in Table 1. In total, 145 patients were diagnosed with stage T2a disease. The median age was 64 years (IQR, 56–71 years). High-grade tumors were found in 128 patients (88.3%) and multiple tumor lesions in 83 patients (57.2%). In 74 patients (51.0%), the largest tumor lesion was greater than 3 cm. Complications, such as bladder perforation, urine leakage, or bleeding, were not observed after TURBT. Of the 145 patients, 135 selected bladder preservation and 10 selected immediate RC. In the latter group, 5 patients had pT0 and 4 patients had non-MIBC. Repeated TURBT was performed in 42 patients (13 had T0 and 29 had T1) among those who underwent bladder preservation (Fig. 3).

During a median follow-up of 132 months (IQR, 96–161 months; maximum, 210 months), patients underwent a median of 2 TURBT procedures (IQR, 1–3 procedures; maximum, 13 procedures), and 13 patients eventually underwent RC. The 1-, 5-, and 10-year cystectomy-free survival rates were 89.6%, 85.9%, and 83.9%, respectively. Recurrence was observed in 70 patients (48.3%), and the 1-, 5-, and 10-year RFS rates were 80.1%, 51.6%, and 48.9%,

respectively. Progression occurred in 12 (8.3%) patients and the 1-, 5-, and 10-year PFS rates were 100%, 96.3%, and 90.1%, respectively. Death occurred only in patients with disease progression, and 5 patients (3.4%) died of bladder cancer; the 1-, 5-, and 10-year CSS rates were 100%, 98.5%, and 96.5%, respectively (Figs. 3, 4).

In the Cox regression analysis, a tumor lesion size greater than 3 cm was associated with RC (hazard ratio [HR], 2.531; 95% confidence interval [CI], 1.041–6.153; $p=0.041$). A high tumor grade was the only predictor of recurrence (HR, 6.183; 95% CI, 1.513–25.265; $p=0.011$). RC (HR, 12.118; 95% CI, 3.645–40.285; $p<0.001$) and recurrence (HR, 11.494; 95% CI, 1.484–89.037; $p=0.019$) were associated with progression. This association persisted in the multivariate analysis (RC: HR, 13.233; 95% CI, 3.943–44.413; $p<0.001$; recurrence: HR, 12.881; 95% CI, 1.642–101.036; $p=0.015$). RC was also a significant predictor of cancer-specific mortality (HR, 22.972; 95% CI, 2.566–205.662; $p=0.005$) (Table 2).

Table 1. Patient characteristics (n=145)

Characteristic	Value
Age (yr)	64 (56–71)
Sex	
Male	118 (81.4)
Female	27 (18.6)
Tumor grade	
Low	17 (11.7)
High	128 (88.3)
No. of tumors	
Single	62 (42.8)
Multiple	83 (57.2)
Size of tumor (cm)	
<3	71 (49.0)
≥3	74 (51.0)
Subsequent treatment	
Bladder preservation	122 (84.1)
Radical cystectomy	23 (15.9)
Repeat TURBT	
Performed	42 (29.0)
T1	29 (69.0)
T0	13 (31.0)
Not performed	103 (71.0)
No. of TURBTs	2 (1–3)
Recurrence	70 (48.3)
Progression	12 (8.3)
Cancer-specific mortality	5 (3.4)
Follow-up duration (mo)	132 (96–161)

Values are presented as median (interquartile range) or number (%).

TURBT, transurethral resection of bladder tumor.

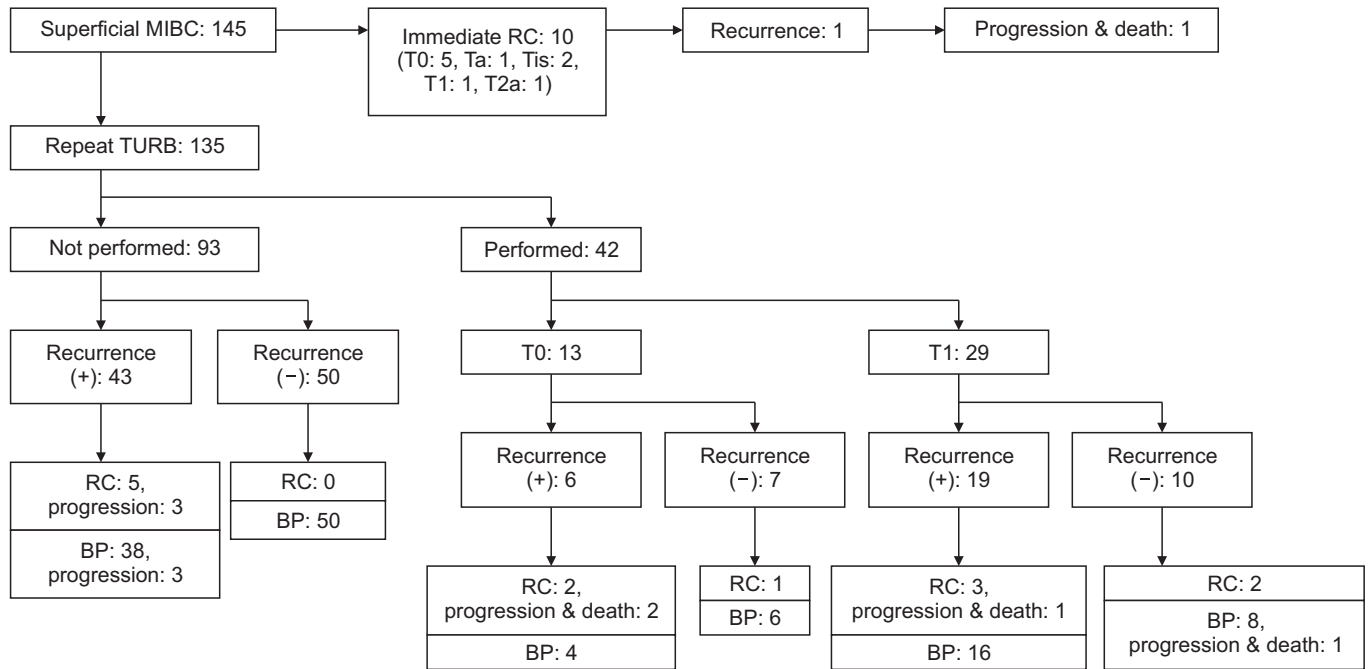


Fig. 3. Flowchart of 145 patients diagnosed with superficial MIBC. MIBC, muscle-invasive bladder cancer; RC, radical cystectomy; TURB, transurethral resection of bladder tumor; BP, bladder preservation.

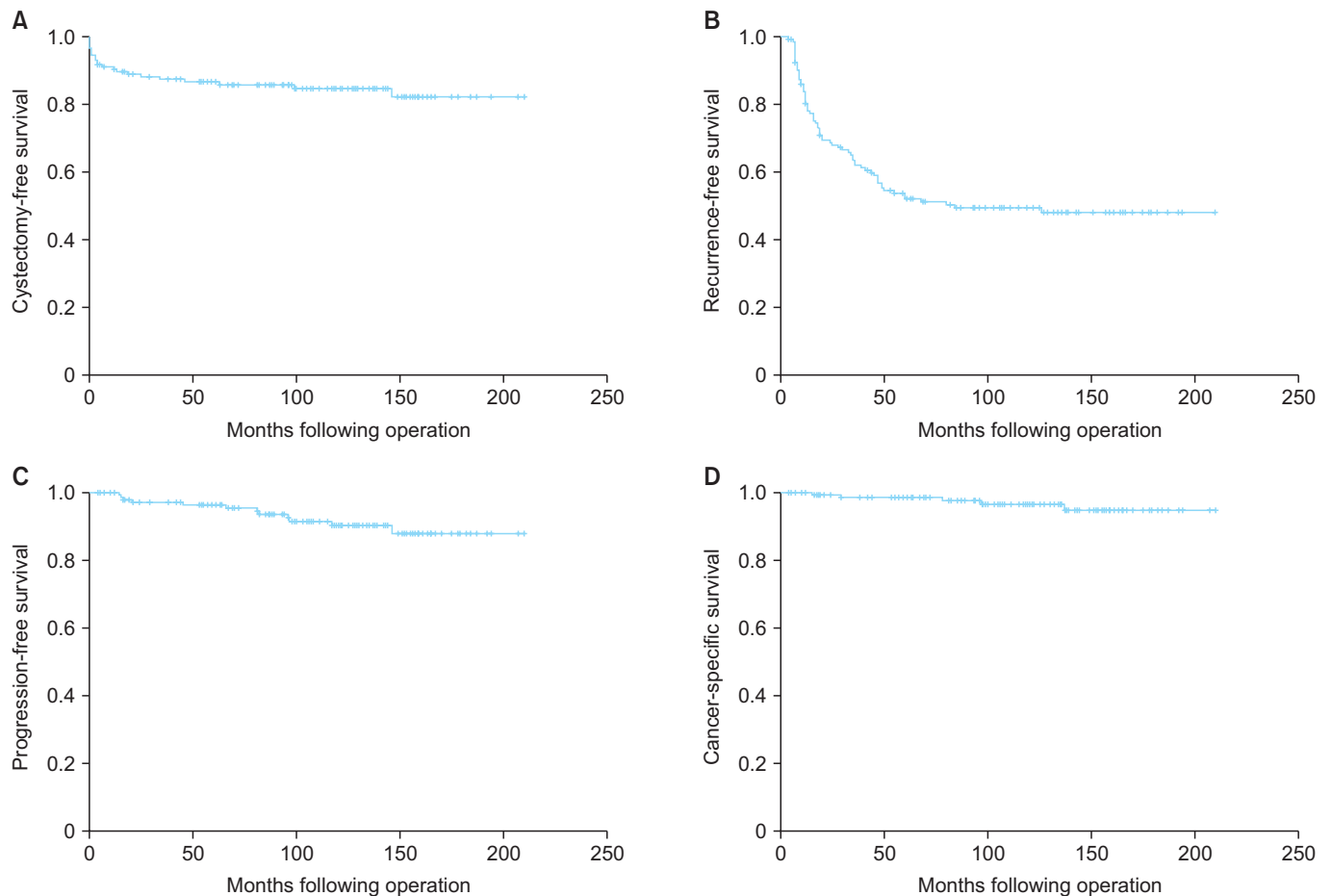


Fig. 4. Kaplan-Meier plots of cystectomy-free survival (A), recurrence-free survival (B), progression-free survival (C), and cancer-specific survival (D).

Table 2. Cox regression univariate analysis of survival

Variable	Cystectomy-free survival			Recurrence-free survival			Progression-free survival			Cancer-specific survival		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.001	0.967–1.036	0.968	1.016	0.995–1.038	0.144	1.050	0.992–1.111	0.092	1.086	0.988–1.192	0.086
Sex												
Male	1.000	Reference		1.000	Reference		1.000	Reference		1.000	Reference	
Female	0.614	0.182–2.070	0.431	0.799	0.420–1.521	0.494	0.796	0.174–3.641	0.768	0.921	0.102–8.297	0.942
Tumor grade												
Low	1.000	Reference		1.000	Reference		1.000	Reference		1.000	Reference	
High	3.267	0.440–24.253	0.247	6.183	1.513–25.265	0.011	25.316	0.020–3.226×10 ⁵	0.376	25.001	0–2.009×10 ⁶	0.576
No. of tumors												
Single	1.000	Reference		1.000	Reference		1.000	Reference		1.000	Reference	
Multiple	1.452	0.615–3.425	0.395	1.061	0.661–1.704	0.806	0.367	0.110–1.220	0.102	0.185	0.021–1.657	0.131
Size of tumor (cm)												
<3	1.000	Reference		1.000	Reference		1.000	Reference		1.000	Reference	
≥3	2.531	1.041–6.153	0.041	1.402	0.876–2.243	0.159	1.061	0.342–3.292	0.918	0.712	0.119–4.259	0.709
Subsequent treatment												
Bladder preservation		-		1.000	Reference		1.000	Reference		1.000	Reference	
Radical cystectomy		-		1.299	0.697–2.420	0.410	12.118	3.645–40.285	<0.001	22.972	2.566–205.662	0.005
Recurrence	1.076	0.474–2.439	0.861		-		11.494	1.484–89.037	0.019	4.064	0.454–36.377	0.210

HR, hazard ratio; CI, confidence interval.

DISCUSSION

This study found that bladder preservation with TURBT and intravesical BCG instillation enabled the successful management of selected patients with stage T2a MIBC. RC with bilateral pelvic lymphadenectomy provides excellent cancer control in patients with localized bladder cancer, with a contemporary series reporting 5-year overall survival rates of 40% to 60% [20]. However, despite improvements in surgical techniques, anesthetic delivery, and perioperative care, RC has a high morbidity rate [20]. Recent studies have reported that 30% to 77% of patients experienced adverse events of any grade, with a mortality rate of 1.7% to 5% at 90 days after RC [21–23]. Advanced age is a risk factor for complications and mortality, and preexisting comorbidities are also associated with high complication rates [2, 24]. Furthermore, any type of urinary diversion after RC has substantial implications for quality of life [25]. Thus, bladder preservation alternatives to RC are attractive to patients and clinicians alike.

The current guidelines recommend bladder preservation based on MMT, including radical TURBT with concurrent chemotherapy and RT, in limited patients with T2 tumors smaller than 6 cm without positive nodes or metastasis, hydronephrosis, or extensive or multifocal CIS [1, 2]. MMT

showed comparable outcomes to those of RC in well-selected patients, with 5-year CSS and overall survival rates of 50% to 82% and 36% to 74%, respectively [5]. However, for highly selected patients, radical TURBT alone can be sufficient to achieve favorable oncological outcomes. According to the National Comprehensive Cancer Network Guidelines, TURBT alone may be an option for patients with cT2 or higher stage who are not candidates for cystectomy [1]. Henry et al. [26] documented a 5-year CSS rate of 67% in 43 patients treated with TURBT alone, including 28 with superficial muscle invasion and 15 with deep muscle invasion, and concluded that TURBT was as successful as RC or RT in patients with MIBC. Some researchers have conducted prospective studies on the feasibility of TURBT alone for MIBC and its long-term outcomes. The results support the role of radical TURBT as a successful bladder-conserving treatment strategy in selected patients. Herr [11] demonstrated that MIBC recurred in 34% of 99 patients treated by TURBT alone and that the bladder preservation rate was 82% over more than 10 years of follow-up. Moreover, the cancer-specific mortality rate was 18% in 73 patients with T0 or Tis disease and 42% in 26 patients with T1 disease on restaging TURBT. These 99 patients with at least 10 years of follow-up had comparable outcomes to those who received RC [11]. Solsona et al. [12] reported

the outcomes in 133 patients (including 32 with CIS) with radical TURBT and negative restaging biopsies. Overall, 30% had recurrence and another 30% showed progression. The 5-, 10-, and 15-year PFS rates with bladder preservation were 75.5%, 64.9%, and 57.8%, respectively. The 5-, 10-, and 15-year CSS rates were 81.9%, 79.5%, and 76.7%, respectively.

Complete tumor removal is essential for successful bladder preservation by radical TURBT alone. However, approximately one-third of the lesions had a residual tumor in the tumor base and periphery, even after the surgeon resected all visible tumors [27]. In cases of radical TURBT, tumor negativity of the base and periphery of the resection bed is confirmed by biopsy [17, 20]. In this study, when performing radical TURBT, the tumor base and periphery were also resected to identify any residual tumors, as well as the depth of muscle invasion. When tumor negativity was identified sequentially in the deep and deeper muscle layers, the patient was considered to have stage T2a disease without a residual tumor, and was regarded to have undergone radical TURBT.

A previous prospective study showed encouraging results for TURBTs using intravesical BCG therapy in selected patients with stage T2a bladder cancer. A total of 22 patients with muscle-invasive transitional cell carcinoma of the bladder received 6 weekly BCG instillations after TURBT. The overall 5-year survival rate was 69.1%, while the disease-specific 5-year survival rate was 94% [14]. BCG instillation may reduce the risk of recurrent high-grade superficial transitional cell carcinoma, with a potential systemic effect on stage T2a MIBC.

This study evaluated the long-term oncological outcomes of TURBT and intravesical BCG instillation in selected patients with stage T2a MIBC. Bladder preservation was achieved in 84.1% of patients. The 10-year cystectomy-free survival and CSS rates were 83.9% and 96.5%, respectively. Although recurrence occurred more frequently than reported in previous research, the bladder preservation rate was comparable to previous studies and the CSS was better. These results could be compared to survival in patients who achieve pT0 disease after RC in the cT2 stage at TURBT. Several studies have investigated the oncologic outcomes of pT0 disease without neoadjuvant chemotherapy (i.e., tumor eradication by TURBT). May et al. [28] reported that 79

patients with the cT2/pT0 stage showed a 5-year CSS rate of 87%. Lee et al. [29] demonstrated a 10-year CSS rate of 100% in 11 patients with the cT2/pT0 stage. Focusing on stage T2a disease, Volkmer et al. [30] documented 5- and 10-year CSS rates of 96.2% and 92%, respectively, in 82 patients with the cT2a/pT0 stage. Thus, the survival outcomes in our study are acceptable compared with those in previous studies.

In our study, a tumor lesion size greater than 3 cm was associated with RC. The tumor grade was the only predictor for recurrence, whereas the size and number of tumors were not. Moreover, no pathologic factor was related to progression or survival, whereas RC was a significant risk factor for both. Recurrence itself was associated with progression, not with survival. These findings may appear to be the result of performing salvage RC when recurrence was not controlled by repeated TURBT. Integrating these findings, patients with stage T2a tumors less than 3 cm and without CIS or tumor-associated hydronephrosis in a nonmetastatic setting could be eligible for bladder preservation by radical TURBT and intravesical BCG instillation. However, high-grade tumors require more careful follow-up to recognize recurrence.

Our study has several limitations. First, the study cohort was small and our results may not be generalizable because all data were collected from a single institution. Second, we retrospectively reviewed records of patients without concurrent chemotherapy or RT despite the presence of MIBC. Notwithstanding these study limitations, patients were diagnosed with stage T2a MIBC after TURBT, and bladder preservation by radical TURBT and intravesical BCG instillation showed promising results in highly selected patients.

CONCLUSIONS

We found that following definite determination of muscle invasion by TURBT, patients diagnosed with stage T2a MIBC can be good candidates for bladder preservation. Although more careful follow-up is needed in high-grade tumors, patients with stage T2a tumors less than 3 cm and without CIS or tumor-associated hydronephrosis in a non-metastatic setting can successfully be managed by radical TURBT and intravesical BCG instillation without chemotherapy or RT.

NOTES

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