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Therapeutic benefit of second-look transurethral resection of bladder tumors for newly diagnosed T1 bladder cancer: a single-center experience

Wen-Hsin Tseng[1] · Chien-Liang Liu[1,2] · Steven K. Huang[1] · Alex Chien-Hwa Liao[1] · Jinn-Rung Kuo[3] · Shun-Hsing Hun[4] · Chun-Hao Chen[1] · Chia-Cheng Su[1] · Jhih-Cheng Wang[1] · Kau-Han Lee[1] · Kun-Hung Shen[1] · Chien-Feng Li[5]

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Abstract

Purpose In recent years, second-look transurethral resection of bladder tumors (TURBT) has been recommended for patients with stage T1 bladder cancer after the initial TURBT for restaging and deciding the subsequent treatment. However, we believe that second-look TURBT has therapeutic benefits, such as low incidence of recurrence and progression. Therefore, we compare the differences in long-term outcome between patients who did and did not accept second-look TURBT for stage T1 bladder cancer.

Methods We assessed 504 patients diagnosed with urothelial carcinoma who underwent initial TURBT between January 2012 and December 2016 at a single medical center; of these patients, 177 were diagnosed with T1 bladder cancer during the initial TURBT, and we excluded no muscle from the specimen in the initial TURBT. The patients were categorized into groups 1 and 2 based on the acceptance of second-look TURBT, which was performed within 4–14 weeks after the initial TURBT. Group 1 underwent second-look TURBT, but group 2 did not. Both groups were followed-up for recurrence-free survival (RFS) and progression-free survival (PFS), and the risk factors for recurrence and progression were analyzed.

Results In total, 93 (52.5%) patients in group 1 underwent second-look TURBT, and 84 (47.5%) in group 2 did not. The 2-year RFS rates were 74.6% and 60.0% and the PFS rates were 91.2% and 87.5% in groups 1 and 2, respectively.

Conclusion This study demonstrated higher recurrence-free and progression-free survival rates for patients who underwent second-look TURBT. This result emphasizes the importance of second-look TURBT in stage T1 bladder cancer not only for restaging but also for therapeutic benefit.

Keywords Second-look TURBT · Transurethral resection of bladder tumors · T1 bladder cancer · Therapeutic benefit

Introduction

In 2017, 79,030 patients were newly diagnosed with bladder cancer in the United States, and this type of cancer ranked sixth among all cancers [1]. Non-muscle invasive bladder cancer (NMIBC)accounts for approximately 75% of newly diagnosed bladder cancers [2]. For patients with NMIBC, transurethral resection of bladder tumor (TURBT) is the standard procedure for diagnosis and treatment [3]. The National Comprehensive Cancer Network (NCCN) guidelines and European Association of Urology (EAU) guidelines for NMIBC strongly recommend second-look TURBT for confirming residual tumor for correct staging, particularly of T1 stage bladder cancer [4, 5]. We must conduct a complete TURBT because some patients are referred from the clinic or regional hospital. Moreover, second-look

✉ Chien-Liang Liu
wyeun523@gmail.com; bearlau.tw@gmail.com

1 Division of Urology, Department of Surgery, Chi Mei Medical Center, Tainan, Taiwan

2 Division of Uro-Oncology, Department of Surgery, Chi Mei Medical Center, Tainan, Taiwan

3 Division of Neurosurgery, Department of Surgery, Chi Mei Medical Center, Tainan, Taiwan

4 Division of Urology, Department of Surgery, Chi Mei Hospital, Chiali, Tainan, Taiwan

5 Department of Pathology, Chi Mei Medical Center, Tainan, Taiwan

surgery is conducted because the initial TURBT did not include the muscle for accurate staging.

Numerous reviews have recently corroborated the restaging role of second-look TURBT [6, 7]. However, only few studies have assessed the therapeutic benefit of such a procedure based on recurrence and progression [8]. In addition, the EAU guidelines also showed that second resection improved the recurrence-free survival (RFS) and progression-free survival (PFS) only in patients without muscle in the specimen from the initial resection [5]. Therefore, some studies indentified second-look TURBT imply failure of initial surgery and have detected higher surgical morbidity and economic burden in two-thirds of patients [9, 10].

However, in our study, all patients received complete initial TURBT and were diagnosed with accurate T1 bladder cancer that we excluded no muscle in the initial specimen. In addition, all patients received single-dose intravesical chemotherapy within 24 h after the initial TURBT as well as subsequent intravesical chemotherapy or Bacillus Calmette–Guérin (BCG) therapy. Then, we compared the differences in RFS and PFS between patients who did and did not undergo second-look TURBT for newly diagnosed stage T1 bladder cancer at a single center. To the best of our knowledge, this is the first study to report the long-term outcome of second-look TURBT for T1 bladder cancer, which excluded without muscle in the specimen from the initial resection.

Patients and methods

In total, 504 patients who were pathologically diagnosed with urothelial carcinoma at Chi Mei Medical Center and underwent initial TURBT between January 2012 and December 2016 were enrolled in this retrospective study and their preoperative clinical evaluation, which includes assessment of medications, physical examination, and laboratory tests, was completed (Fig. 1). Of the patients, 240 had stage T1 urothelial bladder carcinoma, and 63 were excluded owing to a previous diagnosis of bladder cancer, presence of tumor not only in the bladder but also in the upper urinary tract or prostatic urethra, absence of the muscularis propria during the initial TURBT, loss to follow-up, identification of disease upstage or Tis during second-look TURBT. Because adequate staging required the inclusion of the muscularis propria in the initial TURBT specimen, patients were excluded from the study if staging could not be accurately determined.

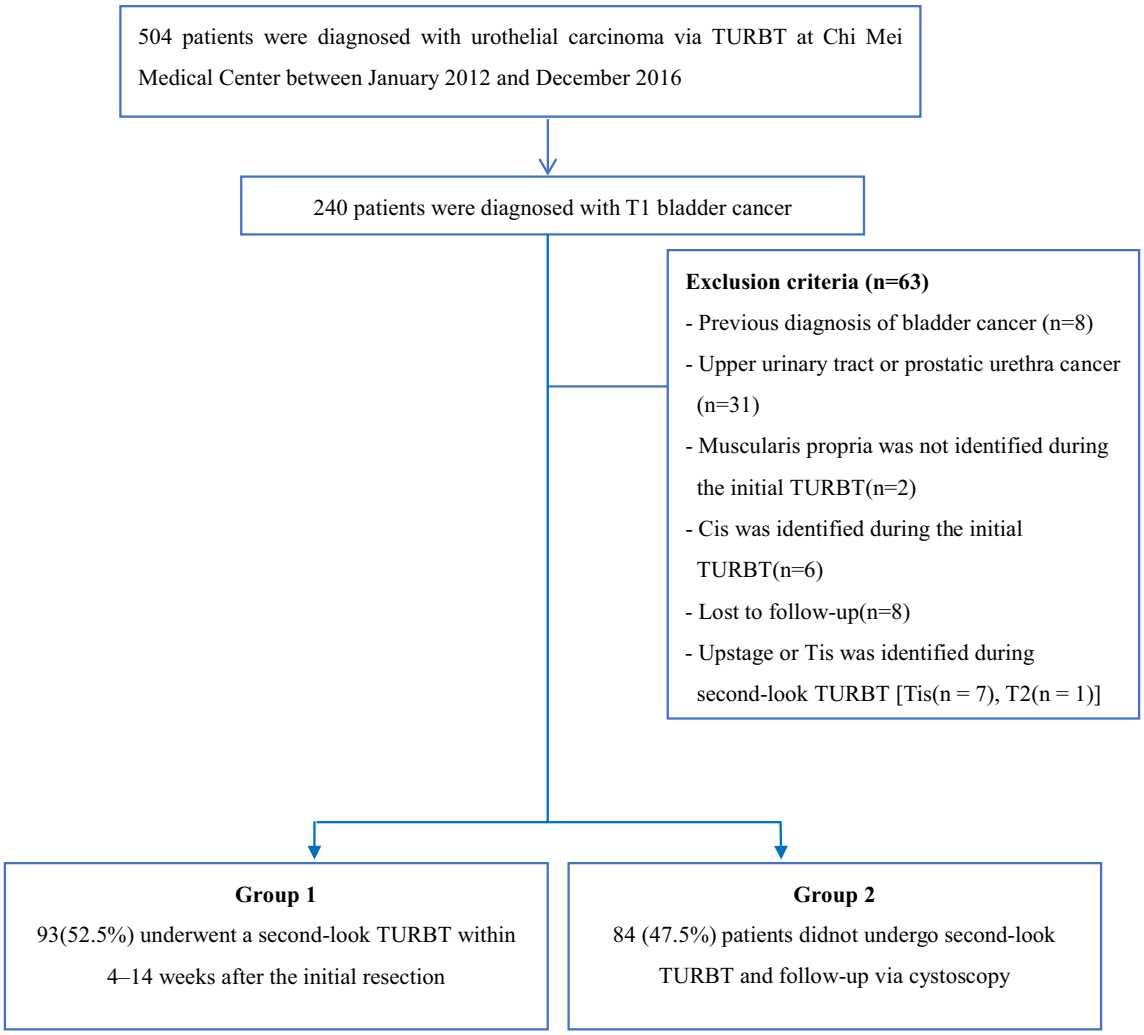
In our study, TURBT was performed using the bipolar loop electrode (Olympus WA22302D), which was connected to the Olympus Electrosurgical Generator ESG-400 with cutting, and coagulation power set at 200 and 120 W, respectively. In all initial TURBTs, visible tumors were resected with a safety margin of approximately 0.5–1 cm from the edges of the tumor; then, base resection was performed. All patients received immediate intravesical instillation therapy of 40 mg mitomycin or 40 mg epirubicin within 24 h after the initial resection. All patients who underwent intravesical instillation therapy received 40 mg BCG, 40 mg mitomycin, or 40 mg epirubicin once a week for 6–12 consecutive weeks. In addition, only patients who received intravesical instillation therapy of BCG received maintenance intravesical BCG, which was administered weekly instillation for 3 weeks at 3, 6, and 12 months.

Regardless of whether the patient underwent second-look TURBT, an experienced urologist identified the indication for surgery. The usual indications include tumor of size > 3 cm, multifocal lesion, or high-grade tumor. All second-look TURBT procedures included wide and deep resections over the initial TURBT site, and the specimens were sent for histopathological assessment according to the American Joint Committee on Cancer tumor–node–metastasis classification [4]. Of 93 patients (52.5%)who underwent second-look TURBT within 4–14 weeks after initial TURBT in group 1 and 84 patients (47.5%) who did not undergo second-look TURBT in group 2 (Fig. 1). The two groups followed all the protocols, and cystoscopy and urine cytology were performed at 3-month intervals for the first 2 years, at 6-month intervals until the fifth year, and annually thereafter. Abdominal echo or computed tomography was performed at 6-month intervals until the fifth year and annually thereafter.

The end points were used to assess long-term outcomes whether performing second-look TURBT for T1 bladder cancer that excluded no muscle in the specimen from the initial resection. RFS and PFS rates between the groups were assessed using the Kaplan–Meier curves. Using the Cox proportional hazards model, multivariate analysis of the risk factors for recurrence and progression was performed. A P value < 0.05 was considered to be statistically significant.

Results

Of the 101 patients who underwent second-look TURBT, 18 (18%) had residual tumors, as revealed on the pathologic report (one with stage pTa, seven with carcinoma in situ, nine with stage pT1, and one with stage pT2 disease; Table 1). Table 2 presents the clinical and pathological characteristics of the 93 patients in group 1 and 84 patients in group 2. The mean ages of the participants in groups 1 and 2 were 65.5 and 66.9 years, respectively. Analysis of the tumor characteristics between the two groups showed no significant difference in terms of tumor grade, size, or number. However, a significant difference was observed in the overall recurrence rate within 5 years



Abbreviation: TURBT, transurethral resection of bladder tumor

Fig. 1 Flow chart of patients who underwent second-look TURBT

Table 1 Pathological report of second-look TURBT in group 1

Pathologic stage	Number of patients
No residual tumors	83 (82%)
Total residual tumors	18 (18%)
Tis	7
Ta	1
T1	9
T2	1

TURBT transurethral resection of bladder tumor

of follow-up (21.5% and 40.5% between groups 1 and 2, respectively). The mean follow-up times for groups 1 and 2 were 42.9 and 40.6 months, respectively.

The RFS rates were 85.9, 74.6, and 66.7% in group 1 and 72.1, 60.0, and 50.8% in group 2 at 1, 2, and 3 years of follow-up, respectively (Table 3). The Kaplan–Meier curves of the RFS rates for the two groups are shown in Fig. 2 (log-rank test, 0.01). Moreover, the PFS rates were 95.7% and 88.7% in group 1 and 92.7% and 82.9% in group 2 at 1 and 3 years of follow-up, respectively (Table 3). The Kaplan–Meier curves of the PFS rates for the two groups are shown in Fig. 3 (log-rank test, 0.03).

In the multivariate analysis, patients with tumor number more than one or patients do not undergo second-look TURBT were at a high risk for recurrence (Table 4). However, no significant difference was observed in the risk of progression based on the multivariate analysis.

Table 2 Characteristics of patients with T1 bladder cancer

	Group 1 Second-look TURBT	Group 2 No second-look TURBT	Total	*P* value
Number of patients	93 (52.5%)	84 (47.5%)	177	
Mean age (years, range)	65.5 (26–84)	66.9 (32–88)	66.2	0.929
Sex (M:F)	69:24	68:16	137:40	0.283
Grade (low:high)	14:79	8:76	22:155	0.265
Size (< 3 cm: ≥ 3 cm)	60:33	63:21	123:54	0.130
Number of tumors (1: > 1)	60:33	52:32	112:65	0.719
Regimen of intravesical (epirubincin:mitomycin:BCG)	81:5:7	46:22:16	127:27:23	
Recurrence (yes:no)	20 (21.5%):73 (78.5%)	34 (40.5%):50 (59.5%)	54 (30.5%): 123 (69.5%)	0.038
Mean follow-up (months, ± SD)	42.9 ± 19.4	40.6 ± 24.0	41.9 ± 21.3	0.241
Mean recurrence (months, ± SD)	17.6 ± 12.9	17.0 ± 14.0	17.2 ± 13.3	0.869

TURBT transurethral resection of bladder tumor, *BCG* Bacillus Calmette–Guérin, *SD* standard deviation

Table 3 Comparison of the two groups according to recurrence and progression

	Recurrence-free survival rate		Progression-free survival rate	
	Second-look TURBT(+)	Second-look TURBT(−)	Second-look TURBT(+)	Second-look TURBT(−)
1 year	85.9% (79/92)	72.1% (60/83)	95.7% (87/93)	92.7% (72/86)
2 years	74.6% (67/91)	60.0% (48/80)	91.2% (83/91)	87.5% (70/80)
3 years	66.7% (58/87)	50.8% (39/77)	88.7% (79/89)	82.9% (63/76)

(Recurrence-free or progression-free survival patients/persist following patients)

TURBT transurethral resection of bladder tumor

Discussion

In the past decade, second-look TURBT was considered as a restaging tool particularly for incomplete resection or lack of muscle specimen during the initial TURBT. In our study, all patients underwent complete resection with the inclusion of the muscularis propria in the specimen for an accurate diagnosis of T1 bladder cancer after the initial TURBT. We reported a relatively lower incidence rate of residual tumor during second-look TURBT and higher RFS and PFS rates in patients who underwent second-look TURBT. This result emphasizes the importance of second-look TURBT in stage T1 bladder cancer for restaging and therapeutic benefit. This study revealed numerous interesting findings.

Recently, few systematic review articles have reported the outcome of second-look TURBT [6, 7]. Cumberbatch et al. [6] have shown that residual tumor was observed during second-look TURBT in approximately 20–71% of patients with T1 cancers, and the disease upstaged from T1 to T2 in approximately 0–32% of patients. This indicated that second-look TURBT is necessary for accurate staging and appropriate sequence therapy. In our experience at Chi Mei Medical Center, 177 patients presented with stage T1 bladder cancer with the inclusion of the detrusor muscle present in the initial TURBT, and 93 (52%) patients underwent second-look TURBT. The incidence rate of residual tumor during second-look TURBT was 18%, and the upstaging rate was only 1%. Some factors may affect the better outcome of second-look TURBT at Chi Mei Medical Center, one of which is the referral system. In most studies, patients underwent the initial TURBT for cancer diagnosis and were then transferred to a referral or academic center for second-look TURBT and further management [11]. Another reason is that the mean time interval between the initial and second-look TURBT procedures in our study was 7.4 weeks. Meanwhile, in other studies, the interval was approximately 2–6 weeks [6, 11–14]. Therefore, most patients underwent whole intravesical therapy, and we observed better outcomes following intravesical therapy. The third reason is that 60 (65%) patients in group 1 had a single tumor and tumor size < 1 cm during the initial TURBT and this rate was higher than that in other studies (approximately 35–53% and 35–66% for single tumor and tumor of size < 1 cm, respectively) [13–15]. This higher rate indicated that our patients were diagnosed earlier than those in other studies,

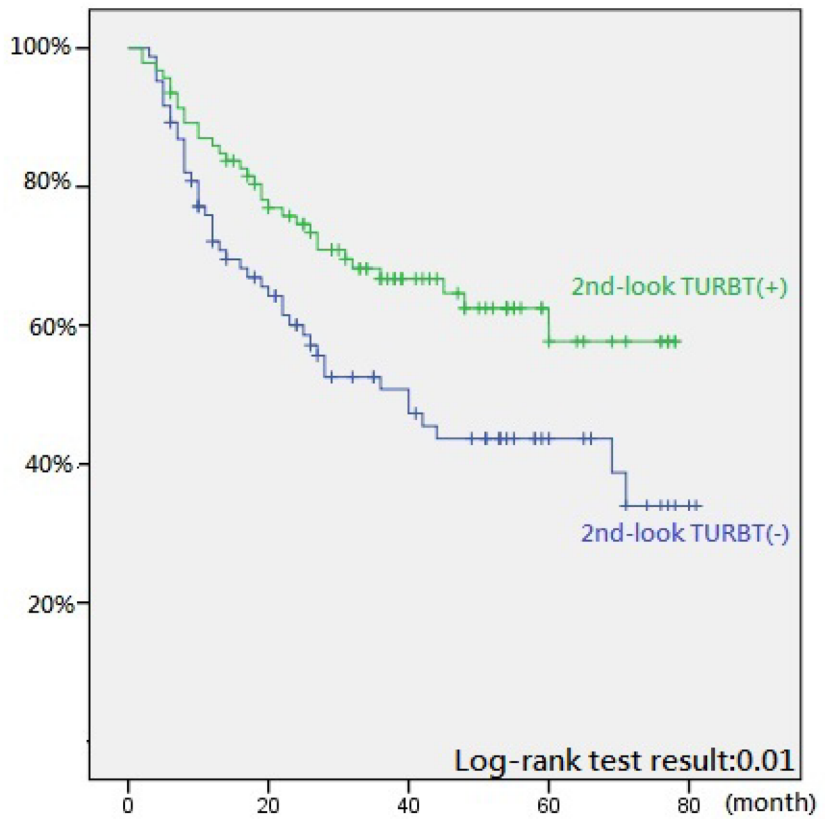


Fig. 2 Kaplan–Meier curves of the recurrence-free survival rates for the two groups

Abbreviation: 2nd-look TURBT, second-look transurethral resection of bladder tumor.

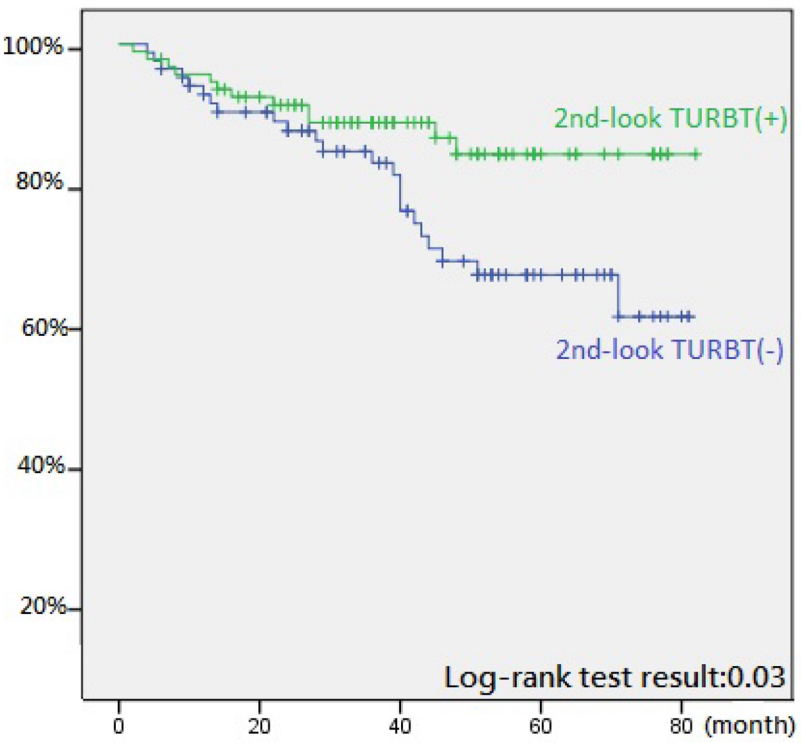


Fig. 3 Kaplan–Meier curves of the progression-free survival rates for the two groups

Abbreviation: 2nd-look TURBT, second-look transurethral resection of bladder tumor.

Table 4 Multivariate analysis according to recurrence and progression

	Recurrence		Progression	
	HR	*P* value	HR	*P* value
Age	1.015 (0.994–1.036)	0.170	1.012 (0.970–1.056)	0.567
Sex	0.959 (0.529–1.741)	0.892	1.261 (0.403–3.945)	0.690
Grade (low:high)	0.908 (0.404–2.039)	0.815	1.765 (0.784–2.213)	0.978
Size (< 3 cm: ≥ 3 cm)	1.152 (0.668–1.987)	0.610	1.802 (0.661–4.912)	0.250
Number of tumor (1: > 1)	2.045 (1.222–3.423)	0.006	1.421 (0.542–3.726)	0.474
Intravesical regimen (Epirubincin:mitomycin:BCG)	0.707 (0.284–1.758)	0.455	0.156 (0.019–1.300)	0.860
	0.688 (0.354–1.339)	0.271	0.309 (0.112–1.851)	0.230
	1	0.540	1	0.420
Second-look TURBT (no:yes)	0.553 (0.315–0.970)	0.039	0.455 (0.149–1.390)	0.167

HR hazard ratio, *BCG* Bacillus Calmette–Guérin, *TURBT* transurethral resection of bladder tumor

and all patients were newly diagnosed with T1 bladder cancer. The fourth reason is that all patients had muscle in the specimen during the initial TURBT, and it indicated a more complete resection of the tumor.

Second-look TURBT is not only considered a restaging tool but may also have therapeutic benefit [15]. As presented in Table 5, only three studies have compared the RFS and PFS rates between patients who did and did not undergo second-look TURBT to provide evidence for the therapeutic benefit of second-look TURBT [9, 14, 16]. Furthermore, only our study excluded cases in which the muscularis propria was not identified during the initial TURBT, and all patients were newly diagnosed with stage T1 bladder tumor and underwent intravesical therapy after the initial TURBT. With a mean follow-up time of 41.9 months, our 2-year RFS rates were 74.6% and 60.0% and the 2-year PFS rates were 91.2% and 87.5% with and without second-look TURBT, respectively. Recently, technical improvements in medical procedures, such as fluorescence imaging [18], narrow-band imaging [19], extensive TURBT [10], and en bloc resection with bipolar button electrode [20], may further improve the quality of NMIBC management and may replace the use of second-look TURBT as an accurate restaging tool. However, repeat TURBT is also believed to improve outcome in terms of tumor recurrence and progression rate.

The European Organisation for Research on Treatment of Cancer (EORTC) and Spanish Urological Club for Oncological Treatment risk models can help predict the prognosis of patients with NMIBC [21, 22]. Therefore, we also analyzed the RFS and PFS rates in high-risk patients (Table 4). Based on the results of our multivariate analysis, RFS was higher in patients with multifocal tumors ($P = 0.006$), and no significant observation was made regarding the recurrence rate in patients with tumors of high histological grade or those ≥ 3 cm in size. In addition, no significant difference was observed in terms of the progression rate. Second-look

Table 5 Analysis of the therapeutic benefit after second-look TURBT

	Number of patients	Mean follow-up (months)	Recurrence-free survival/year		Progression-free survival/year	
Divrik et al. [14]						
Second-look TURBT	98	66.4	65%/3	$P = 0.0001$	93%/3	$P = 0.001$
Single TURBT	93	17.2	45.8%/2		80.1%/2	
Kim et al. [9]						
Second-look TURBT	63	16.0	77.0%/2	$P = 0.025$	97.4%/2	$P > 0.05$
Single TURBT	63	17.2	45.8%/2		80.1%/2	
Sfakianos et al. [16]						
Second-look TURBT	894	> 60	38.4%/5	$P < 0.001$	81.7%/5	$P < 0.001$
Single TURBT	127		22.8%/5		67.2%/5	
Hashine et al. [15]						
Second-look TURBT	79	48.2	72.0%/5			
Single TURBT	92	84.4				
Herr et al. [17]						
Second-look TURBT	816	> 60	46.0%/5		32.0%/5	

TURBT transurethral resection of bladder tumor

TURBT was also considered as a significant prognostic factor for reduced recurrence rate ($P = 0.03$), and this result indicates that second TURBT may have therapeutic benefits.

This study had several limitations. First, this was a retrospective study with a small sample size, and this could have introduced bias; therefore, more randomized studies must be conducted to validate the outcome. Second, the indication for second-look TURBT was based on the intraoperative finding and experience of surgeons. Therefore, the association between the interval from the initial to second-look TURBT and tumor outcomes, such as recurrence, progression, or survival, should be investigated in the future. In our study, factors, such as smoking [23], obesity [24], and performance of monopolar or bipolar resection [25–28], were not assessed, and these factors are worthy of investigation.

Conclusion

Second-look TURBT can help in the early diagnosis of residual tumor, which can help in decision-making for subsequent treatment steps. Better outcomes in terms of the RFS and PFS rates were observed in patients who underwent second-look TURBT during a 2-year follow-up. Therefore, second-look TURBT has therapeutic benefits, and it may be further established as a standard procedure for stage T1 bladder cancer.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethics approval All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki.

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