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Original Article

Therapeutic and prognostic value of repeat transurethral resection for high-grade Ta bladder cancer: a propensity score matching analysis

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Abstract: High-grade Ta bladder cancer, although anatomically confined to the mucosa, exhibits aggressive biological behavior with high recurrence rate and progression risks. The role of repeat transurethral resection of bladder tumor (Re-TURBT) in this specific population remains controversial. This retrospective cohort study aimed to evaluate the therapeutic and prognostic value of Re-TURBT for high-grade Ta non-muscle-invasive bladder cancer (NMIBC) using propensity score matching (PSM) analysis. A total of 324 patients with pathologically confirmed high-grade Ta urothelial carcinoma who underwent initial TURBT from January 2014 to June 2023 were included in this study. Among them, 196 underwent Re-TURBT within 2-6 weeks, whereas 128 did not. PSM was performed in a 1:1 ratio using a caliper width of 0.10, resulting in 70 matched pairs with comparable baseline characteristics. Recurrence-free survival (RFS) was defined as primary outcome. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and the residual tumor detection rate. In the Re-TURBT group, residual tumor was detected in 29.6% of patients, with pathological upstaging observed in 8.6% of cases (7.1% to T1 and 1.5% to T2). The Re-TURBT group showed significantly lower recurrence rates (14.3% vs. 50.0%; P<0.001) and progression rates (4.3% vs. 15.7%; P=0.024). Cox regression identified Re-TURBT as an independent protective factor for RFS (HR=0.217, 95% CI: 0.107-0.439, P<0.001) and PFS (HR=0.253, 95% CI: 0.070-0.906, P=0.023); however, Re-TURBT was not significantly associated with OS (P=0.854). Subgroup analyses revealed that the benefits of Re-TURBT were particularly pronounced in patients with larger tumors (>3.2 cm) and those not receiving BCG maintenance therapy. The overall complication rate was 6.12%. All complications were mild to moderate and were managed conservatively. To sum up, in patients with high grade Ta bladder cancer, Re-TURBT significantly reduces the risks of recurrence and progression and should be considered an integral component of high-risk NMIBC management, particularly for patients with larger tumors or suboptimal BCG maintenance therapy.

Keywords: Bladder cancer, high-grade Ta, repeat transurethral resection, propensity score matching, prognosis

Introduction

Bladder cancer is one of the most common malignancies of the urinary tract. Upon initial diagnosis, about 70%-75% of patients present with non-muscle-invasive bladder cancer (NMIBC) [1]. Transurethral resection of bladder tumor (TURBT) remains the standard method for NMIBC. However, the biological behavior of these tumors varies considerably, and recurrence and progression rates differ significantly among patients [2]. According to the latest European Association of Urology (EAU) prognostic risk stratification model, tumor grade, size, multiplicity, and prior recurrence history are closely associated with NMIBC outcomes, highlighting the need for treatment intensification in high-risk patients [3].

Although anatomically confined to the mucosa, high-grade (HG) Ta bladder cancer demonstrates markedly different biological behavior compared with low-grade (LG) Ta bladder cancer. Previous studies have shown that patients

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with HG Ta tumors experience high recurrence rates, and in some cases, stage progression occurs, resulting in long-term prognosis comparable to other high-risk NMIBC subtypes [4]. Accumulating evidence suggests that all HG Ta tumors should be regarded as high-risk lesions [5]. Current international guidelines from the American Urological Association/Society of Urologic Oncology (AUA/SUO) and the EAU classify HG Ta tumor within the high-risk NMIBC category and recommend strict follow-up and consideration of intensified treatment strategies [2, 6].

The accuracy of pathological staging of TURBT is directly influenced by resection quality and clinical decision-making. The existence of detrusor muscle in the initial TURBT specimen signifies adequate resection quality, supported by significantly lower 5-year recurrence rates [7]. Furthermore, multicenter studies have demonstrated that standardized application of quality control indicators can significantly reduce TURBT-associated recurrence and progression [8]. In this context, repeat TURBT (Re-TURBT) has been proposed as an adjunct to a regular TURBT to remove residual tumor and correct potential understaging.

Recent systematic reviews and meta-analyses have re-evaluated the clinical utility of Re-TURBT in the era of modern surgical techniques. The adoption of photodynamic diagnosis and *en bloc* resection techniques has significantly reduced residual tumor rates [9]. Multicenter studies of HG Ta disease have further shown that Re-TURBT combined with standardized bacillus Calmette-Guérin (BCG) adjuvant therapy significantly improves recurrence-free and progression-free survival in high-risk patients [10]. Nevertheless, controversy remains regarding whether Re-TURBT should be routinely performed in all HG Ta cases, as some studies suggest that its long-term benefit may be limited in selected patient subgroups.

Intravesical BCG maintenance therapy has been shown to significantly reduce recurrence in high-risk NMIBC. Network meta-analysis indicate that BCG maintenance therapy for more than one year confers greater protection against recurrence than induction therapy alone. Alternative or combination intravesical chemotherapy have also been studied as substitutes for, or adjuncts to, BCG. Accordingly, inconsistent findings in previous studies may partly reflect interactions between Re-TURBT and BCG treatment strategies.

Due to lack of large randomized controlled trials (RCTs) for HG Ta bladder cancer, real-world data analysis using propensity score matching (PSM) can reduce baseline imbalance and selection bias across treatment groups. This approach enables a more objective assessment of the clinical value of Re-TURBT [13, 14]. Consequently, we conducted a PSM-based study to systematically evaluate the impact of Re-TURBT on recurrence, progression, and survival outcomes in patients with HG Ta bladder cancer, with the aim of determining whether routine Re-TURBT should be recommended for this population.

Materials and methods

Sample size calculation

The primary outcome, recurrence-free survival (RFS), was used to estimate the required sample size. Given that the main endpoint was a time-to-event outcome, the Schoenfeld method was used to calculate the required number of events and the total sample size. Based on a recent study by Lee et al. [15] specifically focusing on high-grade Ta bladder cancer patients, the 2-year RFS rates were 81.3% in the Re-TURBT group and 60.1% in the non-Re-TURBT groups, corresponding to a multivariable-adjusted hazard ratio (HR) of 0.41 (95% CI: 0.19-0.97). The Schoenfeld formula was applied as follows: $E=(Z_{\alpha/2}+Z_{\beta})^2/P_1\times P_2\times(\ln HR)^2$. The parameters were set as follows: $\alpha=0.05$ (two-sided; $Z\alpha/2=1.96$), $\beta=0.20$ (80% power; $Z\beta=0.84$), allocation ratio 1:1 ($P1=P2=0.5$), and HR=0.41. Assuming an average 2-year recurrence rate of 29.3% [(39.9%+18.7%)/2], the minimum sample size was calculated to be 137 patients [15]. Accounting for an anticipated 10% loss to follow-up, the adjusted minimum sample size was 152 patients. Our final cohort included 324 patients (PSM-matched cohort: 140 patients), exceeding the required threshold and providing adequate statistical power to detect the hypothesized effect size. Sensitivity analysis using a more conservative HR of 0.52 (univariate estimate from Lee et al.) yielded a required sample size of 277 patients, which was also satisfied by our cohort.

Study population and general information

This single-center retrospective cohort study reviewed clinical data from patients who underwent TURBT at Tianyou Hospital Affiliated to Wuhan University of Science and Technology between January 2014 and June 2023 and had pathologically confirmed high-grade Ta bladder cancer. A total of 324 patients were included, of whom 196 underwent Re-TURBT and 128 did not. The study protocol was approved by the Ethics Committee of Tianyou Hospital Affiliated to Wuhan University of Science and Technology and was conducted in accordance with the Declaration of Helsinki. Given the retrospective nature of the study, the requirement for written informed consent was waived (Figure S1).

Inclusion and exclusion criteria

Inclusion criteria: age ≥18 years; primary or recurrent bladder tumor with pathologically confirmed high-grade Ta urothelial carcinoma at initial TURBT; clinical decision to undergo or omit Re-TURBT after initial TURBT; availability of complete clinical, pathological, and follow-up data. Complete follow-up data were defined as at least one documented cystoscopic follow-up visit after initial TURBT, with available information on recurrence status, progression status, and vital status at last follow-up. Patients were considered to have incomplete data if they had no follow-up visits after discharge, or if critical outcome information was missing and could not be ascertained through telephone contact or medical record review.

Exclusion criteria: concurrent T1 or muscle-invasive bladder cancer (≥T2) [16]; non-urothelial carcinoma histology, or mixed tumors with predominantly non-urothelial components; prior radical cystectomy or pelvic radiotherapy; incomplete or lost follow-up data; or concurrent active malignancy at other sites. Concurrent active malignancy was defined as any histologically confirmed malignant tumor at a site other than the bladder diagnosed within 5 years prior to, or at the time of, the initial TURBT that required ongoing treatment or active surveillance. Exceptions included: (1) adequately treated non-melanoma skin cancer; (2) cervical carcinoma *in situ*; and (3) localized prostate cancer under active surveillance with stable prostate-specific antigen (PSA) levels. Patients with prior malignancy who had completed curative treatment for more than 5 years and remained disease-free were eligible.

Clinical data collection

Clinical, pathological, and treatment-related variables were systematically collected from the electronic medical record system. Demographic and baseline clinical characteristics included age, sex, body mass index (BMI), Charlson Comorbidity Index (CCI) [17], American Society of Anesthesiologists (ASA) classification [18], and smoking history. Tumor-related variables included largest tumor diameter, tumor multiplicity, tumor location (trigone/bladder neck, lateral wall, posterior wall, or dome/anterior wall), tumor morphology (papillary, sessile/solid, or mixed), presence of concomitant carcinoma in situ (CIS), preoperative urine cytology results (positive, negative, or not performed), and primary versus recurrent status.

Treatment-related variables included performance of Re-TURBT, presence of detrusor muscle in the initial TURBT specimen, performance of base or margin biopsies, administration of immediate postoperative intravesical chemotherapy (≤24 h), use of BCG induction and maintenance therapy, and surgical year period.

Measurement methods

All surgical specimens were fixed in 10% neutral-buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E). Pathological grading was performed according to the WHO/ISUP urothelial tumor grading system, and staging followed the AJCC TNM staging criteria. All pathological slides were independently reviewed by two experienced uropathologists, and discrepancies were resolved through joint consensus review. Prior to surgery, imaging of the urinary tract was routinely performed using ultrasonography, CT, or MRI to access tumor location and extent. These imaging findings informed clinical decision-making but were not included as primary analytical variables.

Follow-up protocol

In accordance with EAU guidelines for NMIBC [2], all patients were followed using a standardized protocol. Follow-up visits were scheduled at 3 months after the initiation of TURBT, every

3 months during the first 2 years, every 6 months during years 3-5, and annually thereafter. Follow-up assessments included cystoscopy, urine cytology, annual upper urinary tract imaging (or as clinically indicated), physical examination, and symptom evaluation.

Outcome measures

The primary outcome was recurrence-free survival (RFS), defined as the time from the initial TURBT to the first radiologically or pathologically confirmed tumor recurrence or the end of follow-up. Secondary outcomes included overall survival (OS), defined as the time from the initial TURBT to death from any cause or last follow-up, and PFS, defined as the time from initial TURBT to pathological stage progression to stage T1 or higher disease, including muscle-invasive progression, or last follow-up. Additional outcomes included residual tumor detection rate and the rate of pathological upstaging at Re-TURBT.

Statistical analysis

All statistical analyses were performed using SPSS software (version 27.0) and R software (version 4.5.1). Continuous variables were summarized as mean ± standard deviation or median (interquartile range), depending on distribution normality, and compared between groups using independent-sample t tests or Mann-Whitney U tests, as appropriate. Categorical variables were expressed as counts (percentages) and compared using χ^2 tests or Fisher's exact tests.

To reduce baseline differences between the Re-TURBT and non-Re-TURBT groups, a propensity score matching (PSM) was performed. Propensity scores was estimated using a multivariable logistic regression model incorporating relevant clinicopathological variables. One-to-one nearest-neighbor matching without replacement was employed using a caliper width of 0.10. Covariate balance before and after matching was assessed using standardized mean differences (SMDs), with SMD <0.10 indicating an adequate balance.

Survival outcomes, including RFS, PFS, and OS, were estimated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were applied to estimate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Variables with statistical significance in univariate analysis were entered into the multivariate model. Multicollinearity among covariates was assessed using variance inflation factors (VIFs) or generalized VIFs, as appropriate.

Based on tumor size, subgroup analyses were conducted. The optimal tumor-size cutpoint for recurrence risk was determined in the pre-PSM cohort using maximally selected log-rank statistics implemented via the *surv_cutpoint* function in the *survminer* R package. This cutpoint was subsequently applied unchanged to the post-PSM cohort to minimize overfitting and preserve analytical independence. Subgroup survival analyses were conducted using Kaplan-Meier methods and Cox regression models as appropriate. All statistical tests were two-sided, and a *P value* <0.05 was considered statistically significant.

Results

Baseline characteristics

Before PSM, significant differences were observed between the non-Re-TURBT and Re-TURBT groups in Charlson Comorbidity Index (CCI) score (P<0.001), largest tumor diameter (P<0.001), tumor number (P<0.001), primary/recurrent status (P=0.031), presence of detrusor muscle in the initial TURBT specimen (P<0.001), performance of base/margin biopsy (P=0.006), immediate postoperative intravesical chemotherapy (P=0.030), BCG induction therapy (P=0.001), BCG maintenance therapy (P<0.001), and surgical year period (P=0.020). In contrast, age (P=0.080), BMI (P=0.202), sex (P=0.182), ASA classification (P=0.087), smoking history (P=0.574), tumor location (P=0.725), tumor morphology (P=0.067), concomitant CIS (P=0.056), and preoperative urine cytology (P=0.135) did not differ significantly between groups.

Following 1:1 PSM with a caliper width of 0.10, 70 matched pairs were obtained. After matching, all baseline characteristics were well balanced between the two groups (all P>0.05), indicating effective covariate adjustment (**Table 1**; **Figure 1**). All SMD values were <0.1.

Table 1. Baseline characteristics of patients before and after propensity score matching

Variable	Before PSM			After PSM		
	Non-Re-TURBT (n=128)	Re-TURBT (n=196)	Statistics/P	Non-Re-TURBT (n=70)	Re-TURBT (n=70)	Statistics/P
Age (years)	67.09±10.03	65.11±9.81	1.755/0.080	65.66±9.99	65.97±8.92	0.196/0.845
BMI (kg/m^2)	24.25±3.00	23.81±3.01	1.277/0.202	23.88±2.96	23.89±3.23	0.025/0.980
CCI score	2.00 [1.00, 3.00]	2.00 [1.00, 2.00]	4.167/<0.001	2.00 [1.00, 3.00]	2.00 [2.00, 3.00]	0.217/0.828
Largest tumor diameter (cm)	2.95±1.41	3.94±1.51	5.917/<0.001	3.25±1.30	3.31±1.37	0.278/0.781
Tumor number	2.00 [1.00, 2.00]	2.00 [1.00, 4.00]	3.559/<0.001	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	0.790/0.430
Sex			1.785/0.182			0.041/0.839
Male	104 (81.25%)	170 (86.73%)		55 (78.57%)	54 (77.14%)	
Female	24 (18.75%)	26 (13.27%)		15 (21.43%)	16 (22.86%)	
ASA classification			2.932/0.087			0.179/0.673
I-II	95 (74.22%)	161 (82.14%)		57 (81.43%)	55 (78.57%)	
≥III	33 (25.78%)	35 (17.86%)		13 (18.57%)	15 (21.43%)	
Smoking history			0.317/0.574			0.490/0.484
Yes	49 (38.28%)	69 (35.20%)		28 (40.00%)	24 (34.29%)	
No	79 (61.72%)	127 (64.80%)		42 (60.00%)	46 (65.71%)	
Tumor location			1.319/0.725			2.639/0.451
Trigone/bladder neck	28 (21.88%)	36 (18.37%)		14 (20.00%)	16 (22.86%)	
Lateral wall	52 (40.62%)	86 (43.88%)		30 (42.86%)	31 (44.29%)	
Posterior wall	32 (25.00%)	44 (22.45%)		18 (25.71%)	11 (15.71%)	
Dome/anterior wall	16 (12.50%)	30 (15.31%)		8 (11.43%)	12 (17.14%)	
Tumor morphology			5.411/0.067			0.038/0.981
Papillary	88 (68.75%)	110 (56.12%)		42 (60.00%)	41 (58.57%)	
Sessile/solid	26 (20.31%)	52 (26.53%)		19 (27.14%)	20 (28.57%)	
Mixed	14 (10.94%)	34 (17.35%)		9 (12.86%)	9 (12.86%)	
Concomitant CIS			3.639/0.056			0.000/1.000
Yes	13 (10.16%)	35 (17.86%)		10 (14.29%)	10 (14.29%)	
No	115 (89.84%)	161 (82.14%)		60 (85.71%)	60 (85.71%)	
Preoperative urine cytology			4.004/0.135			0.333/0.847
Positive	30 (23.44%)	66 (33.67%)		17 (24.29%)	20 (28.57%)	
Negative	75 (58.59%)	97 (49.49%)		39 (55.71%)	37 (52.86%)	
Not performed	23 (17.97%)	33 (16.84%)		14 (20.00%)	13 (18.57%)	
Primary/recurrent			4.632/0.031			0.991/0.319
Primary	106 (82.81%)	142 (72.45%)		56 (80.00%)	51 (72.86%)	
Recurrent	22 (17.19%)	54 (27.55%)		14 (20.00%)	19 (27.14%)	

Detrusor muscle in initial TURBT			14.481/<0.001			0.034/0.853
Yes	77 (60.16%)	156 (79.59%)		50 (71.43%)	49 (70.00%)	
No	51 (39.84%)	40 (20.41%)		20 (28.57%)	21 (30.00%)	
Base/margin biopsy			7.679/0.006			0.726/0.394
Yes	44 (34.38%)	98 (50.00%)		28 (40.00%)	33 (47.14%)	
No	84 (65.62%)	98 (50.00%)		42 (60.00%)	37 (52.86%)	
Immediate intravesical chemotherapy (≤24 h)			4.733/0.030			0.264/0.608
Yes	62 (48.44%)	119 (60.71%)		42 (60.00%)	39 (55.71%)	
No	66 (51.56%)	77 (39.29%)		28 (40.00%)	31 (44.29%)	
BCG induction therapy			10.146/0.001			0.115/0.734
Yes	70 (54.69%)	141 (71.94%)		37 (52.86%)	39 (55.71%)	
No	58 (45.31%)	55 (28.06%)		33 (47.14%)	31 (44.29%)	
BCG maintenance therapy			12.574/<0.001			0.000/1.000
Yes	41 (32.03%)	102 (52.04%)		27 (38.57%)	27 (38.57%)	
No	87 (67.97%)	94 (47.96%)		43 (61.43%)	43 (61.43%)	
Surgical year period			5.391/0.020			0.030/0.863
2014-2018	63 (49.22%)	71 (36.22%)		28 (40.00%)	29 (41.43%)	
2019-2023	65 (50.78%)	125 (63.78%)		42 (60.00%)	41 (58.57%)	

Note: Re-TURBT, repeat transurethral resection of bladder tumor; BMI, body mass index; CCI, Charlson comorbidity index; ASA, American Society of Anesthesiologists; CIS, carcinoma in situ; TURBT, transurethral resection of bladder tumor; BCG, Bacillus Calmette-Guérin; PSM, propensity score matching. Continuous variables are presented as mean ± SD or median [IQR]. Categorical variables are presented as n (%).

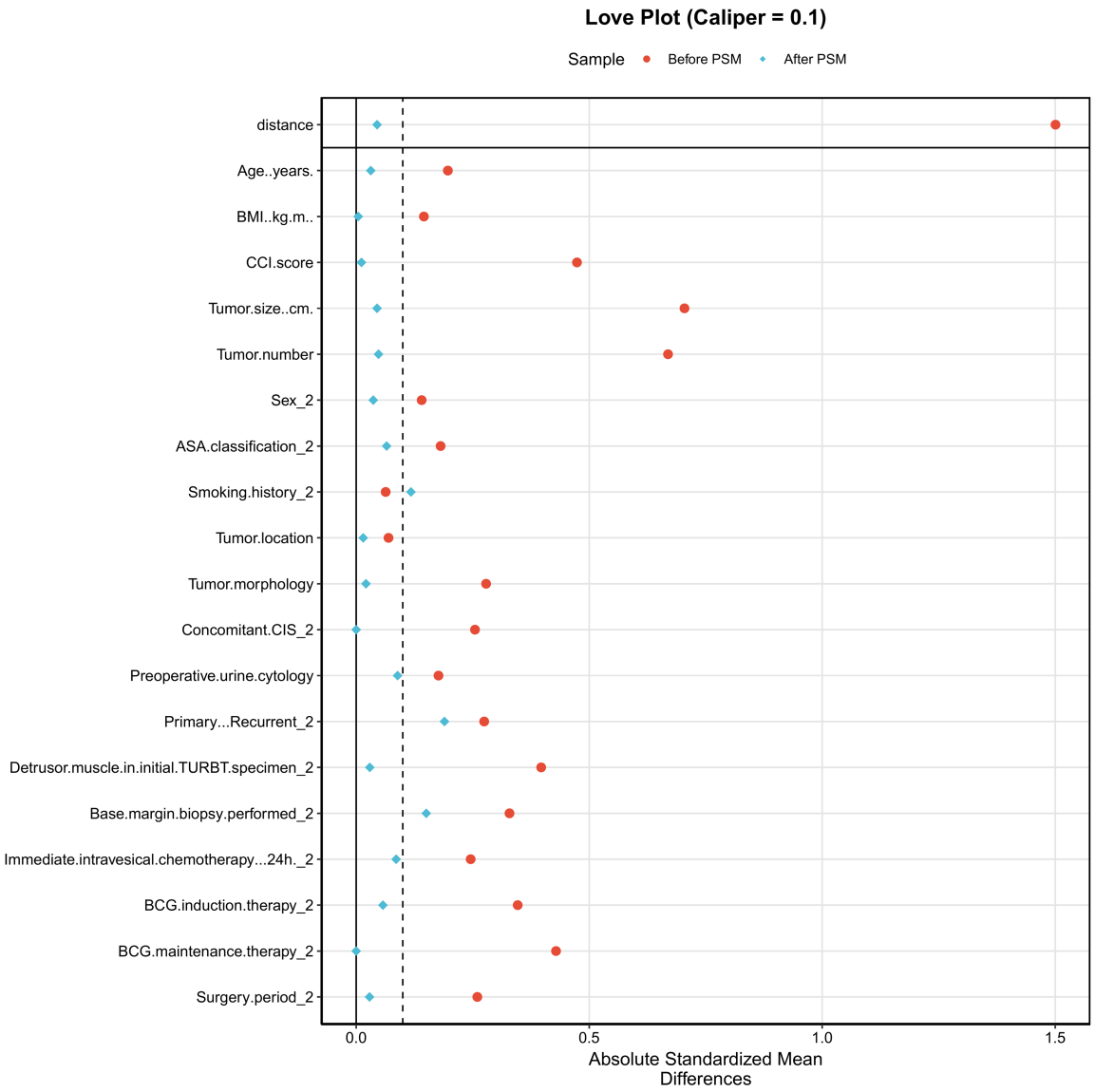

Figure 1. Love plot. Note: Re-TURBT: Repeat transurethral resection of bladder tumor, BMI: body mass index, CCI: Charlson comorbidity index, ASA: American Society of Anesthesiologists, CIS: carcinoma in situ, TURBT: transurethral resection of bladder tumor, BCG: Bacillus Calmette-Guérin, PSM: propensity score matching.

Surgical and pathological findings of Re-TURBT

Among patients who underwent Re-TURBT, residual tumor was detected in approximately one-third of cases, underscoring the limitations of initial TURBT in achieving complete tumor removal. **Figure 2A**, **2B** illustrate representative pathological findings of residual high-grade Ta urothelial carcinoma identified at Re-TURBT, characterized by typical papillary architecture, marked nuclear atypia, with tumor confined to the mucosa.

Furthermore, pathological upstaging was also observed in a subset of patients. Roughly 7% of cases were upstaged from Ta to T1/T2. These findings indicate that initial TURBT may underestimate pathological stage. **Figure 2C**, **2D** present a typical upstaging case in which the initial TURBT specimen showed high-grade Ta urothelial carcinoma confined to the epithelium, whereas the Re-TURBT specimen showed tumor cell breaching the basement membrane and invading the lamina propria in a nested or cord-like pattern consistent with T1 disease (**Table 2** and **Figure 2**).

After PSM, among the 70 matched patients in the Re-TURBT group, 14.3% had residual tumor detected, with a small number of patients

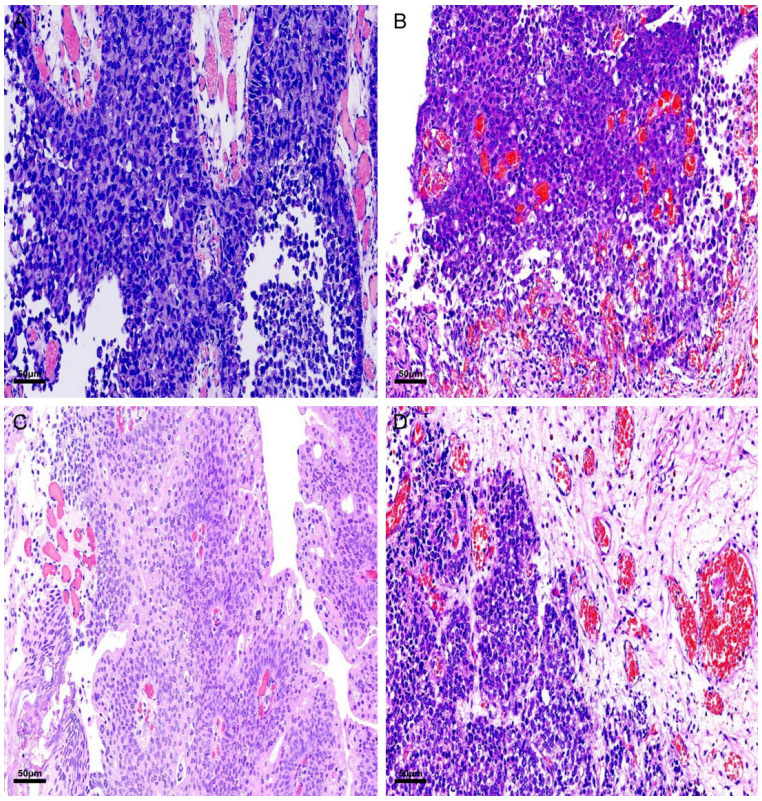

Figure 2. Representative histopathological findings of Re-TURBT specimens (H&E staining). (A, B) Residual high-grade Ta urothelial carcinoma detected at Re-TURBT: (A) Initial TURBT specimen showing high-grade papillary urothelial carcinoma confined to the mucosa (×200); (B) Re-TURBT specimen demonstrating residual high-grade Ta tumor with similar histological features (×200). (C, D) Pathological upstaging from Ta to T1: (C) Initial TURBT specimen showing high-grade Ta urothelial carcinoma limited to the epithelial layer without lamina propria invasion (×200); (D) Re-TURBT specimen revealing tumor invasion into the lamina propria (arrows) with nested growth pattern, confirming upstaging to T1 (×200). Note: Re-TURBT: Repeat transurethral resection of bladder tumor, TURBT: transurethral resection of bladder tumor, HE: hematoxylin and eosin (HE), PSM: propensity score matching.

Table 2. Pathological outcomes of repeat transurethral resection before and after propensity score matching

Variable	Re-TURBT before PSM (n=196)	Re-TURBT after PSM (n=70)
Residual tumor detected	58 (29.6%)	10 (14.3%)
Pathological upstaging		
Ta → T1	14 (7.1%)	2 (2.9%)
Ta → T2	3 (1.5%)	0 (0.0%)

Note: Re-TURBT, repeat transurethral resection of bladder tumor; PSM, propensity score matching.

showing upstaging from Ta to T1. These findings further support the value of Re-TURBT in detecting residual disease and correcting staging underestimation.

Follow-up and event rates

The median follow-up for the entire cohort was 42.5 months (IQR: 34-52 months). Before PSM, among the 324 patients, 102 experienced recurrence, 35 showed disease progression, and 37 died during follow-up. The non-Re-TURBT group demonstrated significantly higher recurrence and progression rates than the Re-TURBT group.

Before PSM, Kaplan-Meier analysis showed that the Re-TURBT group had significantly better RFS and PFS compared with the non-Re-TURBT group (both P<0.001), whereas OS did not differ significantly between groups (P>0.05) (**Figure 3A-C**).

After PSM, 140 patients (70 pairs) were included, with a median follow-up of 41.5 months (IQR: 33-49 months). During follow-up, 45 recurrence events, 14 progression events, and 14 deaths occurred. In the matched cohort, the Re-TURBT group had notably lower recurrence and progression rates than the non-Re-TURBT group, while mortality rates were similar (**Table 3**). Kaplan-Meier curves showed that the Re-TURBT group maintained significantly better RFS and PFS after matching (RFS: P<0.001; PFS: P=0.024), while OS curves largely overlapped with no significant difference (P=1.000) (**Figure 3D-F**).

Impact of Re-TURBT on recurrence-free survival

Kaplan-Meier survival analysis showed that, before PSM, the Re-TURBT group demonstrated significantly better RFS than the non-Re-TURBT group (Log-rank P<0.001) (**Figure 4A**). Univariate Cox regression demonstrated that Re-TURBT was associated with a significantly

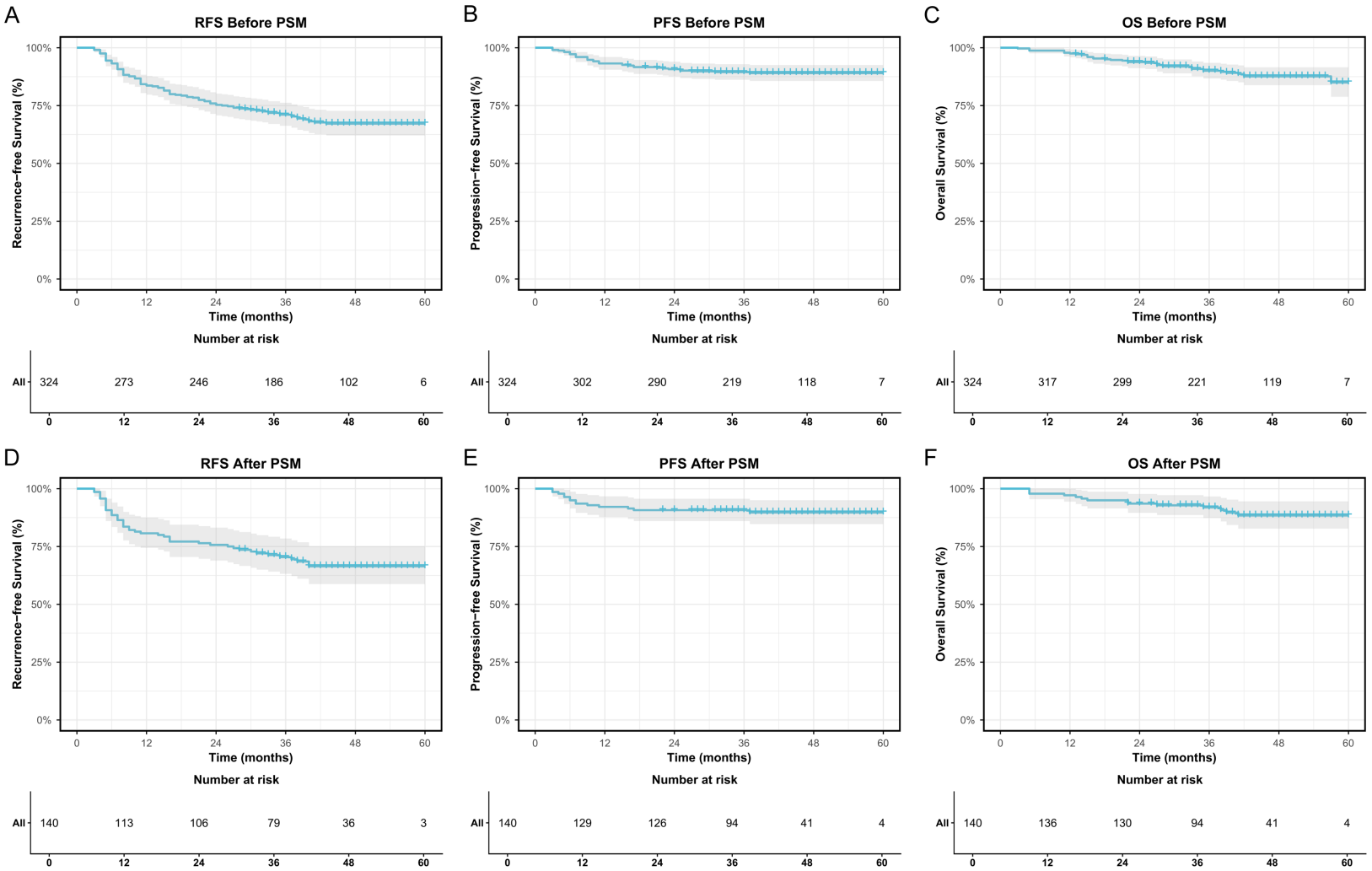

Figure 3. Kaplan-Meier survival curves comparing Re-TURBT and non-Re-TURBT groups before and after propensity score matching. A. Recurrence-free survival (RFS) before propensity score matching (PSM). B. Progression-free survival (PFS) before propensity score matching (PSM). C. Overall survival (OS) before propensity score matching (PSM). D. Recurrence-free survival (RFS) after propensity score matching (PSM). E. Progression-free survival (PFS) after propensity score matching (PSM). F. Overall survival (OS) after propensity score matching (PSM). Note: RFS, recurrence-free survival; PFS, progression-free survival; OS, overall survival; Re-TURBT, repeat transurethral resection of bladder tumor; PSM, propensity score matching.

Table 3. Outcome events before and after propensity score matching

Variable	Before PSM (n=324)				After PSM (n=140)			
	Total	Non-Re-TURBT (n=128)	Re-TURBT (n=196)	Statistics/P	Total	Non-Re-TURBT (n=70)	Re-TURBT (n=70)	Statistics/P
Recurrence, n (%)	102 (31.5)	59 (46.1)	43 (21.9)	20.945/<0.001	45 (32.1)	35 (50.0)	10 (14.3)	20.468/<0.001
Progression, n (%)	35 (10.8)	24 (18.8)	11 (5.6)	13.870/<0.001	14 (10.0)	11 (15.7)	3 (4.3)	5.079/0.024
Death, n (%)	37 (11.4)	17 (13.3)	20 (10.2)	0.725/0.395	14 (10.0)	7 (10.0)	7 (10.0)	0.000/1.000

Note: Re-TURBT, repeat transurethral resection of bladder tumor; PSM, propensity score matching.

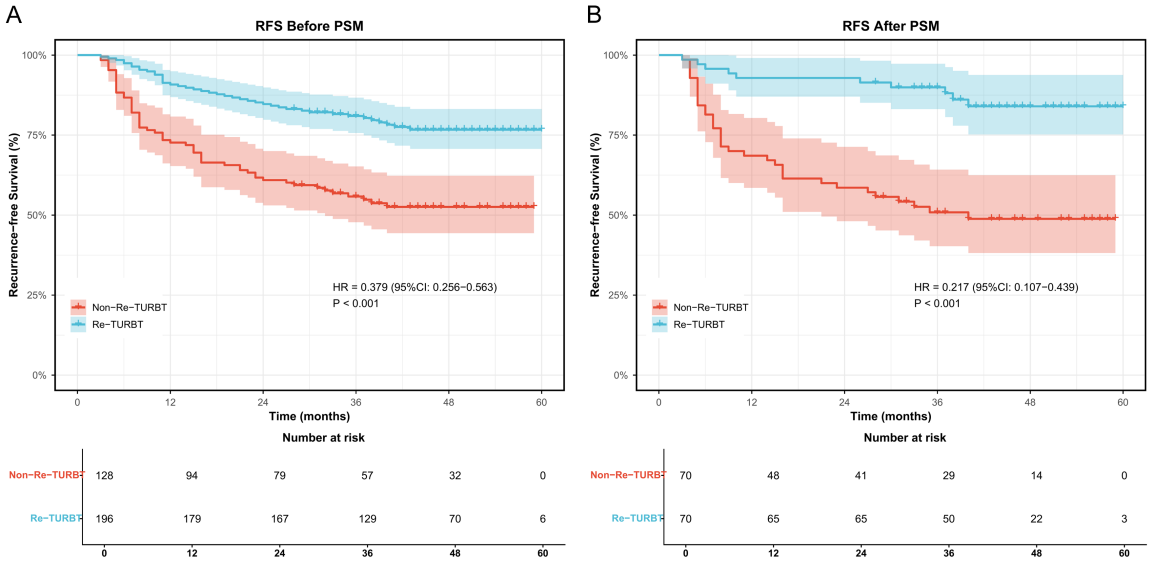

Figure 4. Effect of repeat transurethral resection of bladder tumor (Re-TURBT) on recurrence-free survival (RFS). A. Kaplan-Meier curves for recurrence-free survival (RFS) comparing Re-TURBT and non-Re-TURBT groups before propensity score matching (PSM). B. Kaplan-Meier curves for recurrence-free survival (RFS) comparing Re-TURBT and non-Re-TURBT groups after propensity score matching (PSM). Note: RFS, recurrence-free survival; Re-TURBT, repeat transurethral resection of bladder tumor; PSM, propensity score matching. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression. Survival curves were compared using the log-rank test.

reduced recurrence risk (HR=0.379, 95% CI: 0.256-0.563, P<0.001) (**Table 4**).

After PSM, the RFS benefit of Re-TURBT remained evident. Kaplan-Meier curves showed a significantly lower recurrence risk in the Re-TURBT group compared with the non-Re-TURBT group (Log-rank P<0.001) (**Figure 4B**). Cox regression further confirmed Re-TURBT as an independent protective factor against recurrence (HR=0.217, 95% CI: 0.107-0.439, P<0.001) (**Table 5**).

Impact of Re-TURBT on PFS

Kaplan-Meier analysis showed that before PSM, the Re-TURBT group had significantly better PFS than the non-Re-TURBT group (Log-rank P<0.001) (**Figure 5A**). Univariate Cox regression demonstrated that Re-TURBT significantly reduced progression risk (HR=0.272, 95% CI: 0.133-0.555, P<0.001).

After PSM, the PFS advantage for the Re-TURBT group persisted, with Kaplan-Meier curves showing significantly lower progression risk (Log-rank P=0.023) (**Figure 5B**). Cox regression confirmed the significant association between Re-TURBT and reduced progression risk (HR= 0.253, 95% CI: 0.070-0.906, P=0.023).

Impact of Re-TURBT on OS

Kaplan-Meier analysis showed that before PSM, OS curves for the Re-TURBT and non-Re-TURBT groups were similar, with no significant difference (P=0.218) (**Figure 6A**). Cox regres-

Table 4. Univariate and multivariate Cox regression analysis for recurrence-free survival before propensity score matching

Variable	Univariate			Multivariate		
	β	*P* value	HR (95% CI)	β	*P* value	HR (95% CI)
Re-TURBT						
No			1 (Ref)			1 (Ref)
Yes	-0.969	<0.001	0.379 (0.256-0.563)	-2.523	<0.001	0.080 (0.042-0.152)
Age (years)	0.001	0.890	1.001 (0.983-1.021)			
BMI (kg/m^2)	-0.039	0.222	0.962 (0.903-1.024)			
CCI score	0.226	0.006	1.254 (1.067-1.473)	0.127	0.181	1.135 (0.943-1.366)
Largest tumor diameter (cm)	0.332	<0.001	1.394 (1.228-1.582)	0.442	<0.001	1.556 (1.362-1.778)
Tumor number	0.453	<0.001	1.573 (1.404-1.762)	0.393	<0.001	1.481 (1.250-1.755)
Sex						
Male			1 (Ref)			
Female	0.317	0.212	1.373 (0.834-2.261)			
ASA classification						
I-II			1 (Ref)			
≥III	0.343	0.126	1.410 (0.908-2.189)			
Smoking history						
Yes			1 (Ref)			
No	0.041	0.843	1.042 (0.694-1.564)			
Tumor location						
Trigone/bladder neck			1 (Ref)			
Lateral wall	-0.240	0.353	0.787 (0.474-1.305)			
Posterior wall	-0.390	0.202	0.677 (0.372-1.232)			
Dome/anterior wall	-0.085	0.794	0.918 (0.485-1.738)			
Tumor morphology						
Papillary			1 (Ref)			1 (Ref)
Sessile/solid	0.506	0.042	1.659 (1.019-2.700)	0.462	0.072	1.586 (0.960-2.622)
Mixed	1.570	<0.001	4.805 (3.043-7.589)	0.883	0.005	2.417 (1.309-4.464)
Concomitant CIS						
Yes			1 (Ref)			1 (Ref)
No	-1.472	<0.001	0.229 (0.151-0.348)	-1.162	<0.001	0.313 (0.172-0.570)
Preoperative urine cytology						
Positive			1 (Ref)			
Negative	0.095	0.678	1.100 (0.702-1.725)			
Not performed	0.067	0.822	1.070 (0.594-1.926)			
Primary/recurrent						
Primary			1 (Ref)			1 (Ref)
Recurrent	1.418	<0.001	4.130 (2.795-6.101)	0.849	<0.001	2.338 (1.436-3.806)
Detrusor muscle in initial TURBT						
Yes			1 (Ref)			1 (Ref)
No	1.335	<0.001	3.801 (2.573-5.615)	0.857	<0.001	2.357 (1.559-3.562)
Base/margin biopsy						
Yes			1 (Ref)			
No	0.321	0.117	1.378 (0.923-2.059)			
Immediate intravesical chemotherapy (≤24 h)						
Yes			1 (Ref)			
No	-0.131	0.513	0.877 (0.592-1.300)			
BCG induction therapy						
Yes			1 (Ref)			
No	0.012	0.954	1.012 (0.672-1.523)			
BCG maintenance therapy						
Yes			1 (Ref)			1 (Ref)
No	1.513	<0.001	4.539 (2.755-7.479)	0.651	0.019	1.918 (1.112-3.306)

Surgical year period			
2014-2018			1 (Ref)
2019-2023	-0.076	0.706	0.927 (0.626-1.374)

Note: Re-TURBT, repeat transurethral resection of bladder tumor; BMI, body mass index; CCI, Charlson comorbidity index; ASA, American Society of Anesthesiologists; CIS, carcinoma in situ; TURBT, transurethral resection of bladder tumor; BCG, Bacillus Calmette-Guérin; HR, hazard ratio; CI, confidence interval; Ref, reference.

Table 5. Univariate and multivariate Cox regression analysis for recurrence-free survival after propensity score matching

Variable	Univariate			Multivariate		
	β	*P* value	HR (95% CI)	β	*P* value	HR (95% CI)
Re-TURBT						
No			1 (Ref)			1 (Ref)
Yes	-1.529	<0.001	0.217 (0.107-0.439)	-3.066	<0.001	0.047 (0.018-0.120)
Age (years)	0.004	0.806	1.004 (0.974-1.034)			
BMI (kg/m^2)	-0.082	0.072	0.921 (0.842-1.007)			
CCI score	0.179	0.150	1.195 (0.938-1.524)			
Largest tumor diameter (cm)	0.406	<0.001	1.501 (1.202-1.873)	0.307	0.011	1.360 (1.073-1.723)
Tumor number	0.700	<0.001	2.013 (1.594-2.544)	0.841	<0.001	2.318 (1.651-3.255)
Sex						
Male			1 (Ref)			
Female	0.412	0.210	1.510 (0.793-2.878)			
ASA classification						
I-II			1 (Ref)			
≥III	0.178	0.620	1.194 (0.591-2.412)			
Smoking history						
Yes			1 (Ref)			
No	-0.061	0.843	0.941 (0.515-1.719)			
Tumor location						
Trigone/bladder neck			1 (Ref)			
Lateral wall	0.158	0.687	1.172 (0.542-2.533)			
Posterior wall	-0.090	0.853	0.914 (0.352-2.369)			
Dome/anterior wall	-0.248	0.657	0.780 (0.261-2.329)			
Tumor morphology						
Papillary			1 (Ref)			1 (Ref)
Sessile/solid	0.716	0.043	2.046 (1.021-4.097)	0.587	0.124	1.798 (0.851-3.797)
Mixed	1.743	<0.001	5.714 (2.753-11.861)	1.395	0.003	4.036 (1.600-10.184)
Concomitant CIS						
Yes			1 (Ref)			1 (Ref)
No	-1.599	<0.001	0.202 (0.107-0.381)	-1.994	<0.001	0.136 (0.057-0.327)
Preoperative urine cytology						
Positive			1 (Ref)			
Negative	0.295	0.408	1.343 (0.668-2.697)			
Not performed	-0.316	0.534	0.729 (0.270-1.972)			
Primary/recurrent						
Primary			1 (Ref)			1 (Ref)
Recurrent	0.999	0.001	2.714 (1.484-4.965)	0.590	0.113	1.803 (0.870-3.737)
Detrusor muscle in initial TURBT						
Yes			1 (Ref)			1 (Ref)
No	0.973	0.001	2.645 (1.471-4.756)	0.544	0.156	1.722 (0.813-3.646)
Base/margin biopsy						
Yes			1 (Ref)			
No	0.162	0.594	1.176 (0.648-2.135)			
Immediate intravesical chemotherapy (≤24 h)						
Yes			1 (Ref)			
No	-0.516	0.103	0.597 (0.321-1.111)			

BCG induction therapy						
Yes			1 (Ref)			
No	0.038	0.898	1.039 (0.578-1.867)			
BCG maintenance therapy						
Yes			1 (Ref)			1 (Ref)
No	1.500	<0.001	4.483 (1.998-10.056)	1.085	0.027	2.958 (1.130-7.747)
Surgical year period						
2014-2018			1 (Ref)			
2019-2023	0.073	0.812	1.076 (0.589-1.966)			

Note: Re-TURBT, repeat transurethral resection of bladder tumor; BMI, body mass index; CCI, Charlson comorbidity index; ASA, American Society of Anesthesiologists; CIS, carcinoma in situ; TURBT, transurethral resection of bladder tumor; BCG, Bacillus Calmette-Guérin; HR, hazard ratio; CI, confidence interval; Ref, reference.

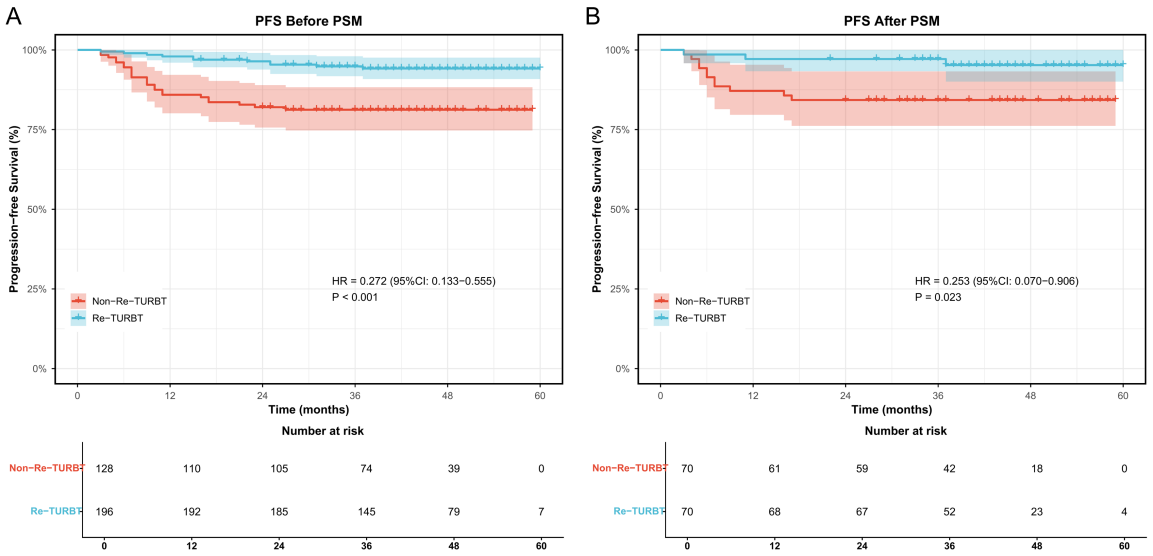

Figure 5. Effect of repeat transurethral resection of bladder tumor (Re-TURBT) on progression-free survival (PFS). A. Kaplan-Meier curves for progression-free survival (PFS) comparing Re-TURBT and non-Re-TURBT groups before propensity score matching (PSM). B. Kaplan-Meier curves for progression-free survival (PFS) comparing Re-TURBT and non-Re-TURBT groups after propensity score matching (PSM). Note: PFS, progression-free survival; Re-TURBT, repeat transurethral resection of bladder tumor; PSM, propensity score matching. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression. Survival curves were compared using the log-rank test.

sion also showed no significant association between Re-TURBT and OS (HR=0.668, 95% CI: 0.349-1.276, P=0.218).

After PSM, OS curves for both groups largely overlapped, and Log-rank testing again showed no significant difference (P=0.854) (**Figure 6B**). Cox regression confirmed that Re-TURBT had no significant impact on OS (HR=0.906, 95% CI: 0.317-2.585, P=0.854).

Efficacy of Re-TURBT by tumor size subgroups

Using optimal cutpoint analysis in the pre-PSM cohort with RFS as the endpoint, the optimal cutoff for largest tumor diameter was 3.19 cm (approximately 3.2 cm). In patients with tumors ≤3.2 cm, Kaplan-Meier analysis showed a significant RFS benefit of Re-TURBT before PSM (HR=0.251, 95% CI: 0.084-0.745, P=0.007), which remained observable after PSM (HR=0.134, 95% CI: 0.016-1.090, P=0.027) (**Figure 7A**, **7C**).

In patients with tumors >3.2 cm, the RFS benefit of Re-TURBT was more robust. Recurrence risk was significantly reduced both before PSM (HR=0.219, 95% CI: 0.141-0.341, P<0.001) and after PSM (HR=0.189, 95% CI: 0.088-0.405, P<0.001) (**Figure 7B**, **7D**).

For PFS, in the ≤3.2 cm subgroup, Re-TURBT did not significantly influence progression risk either before PSM (HR=0.420, 95% CI: 0.111-

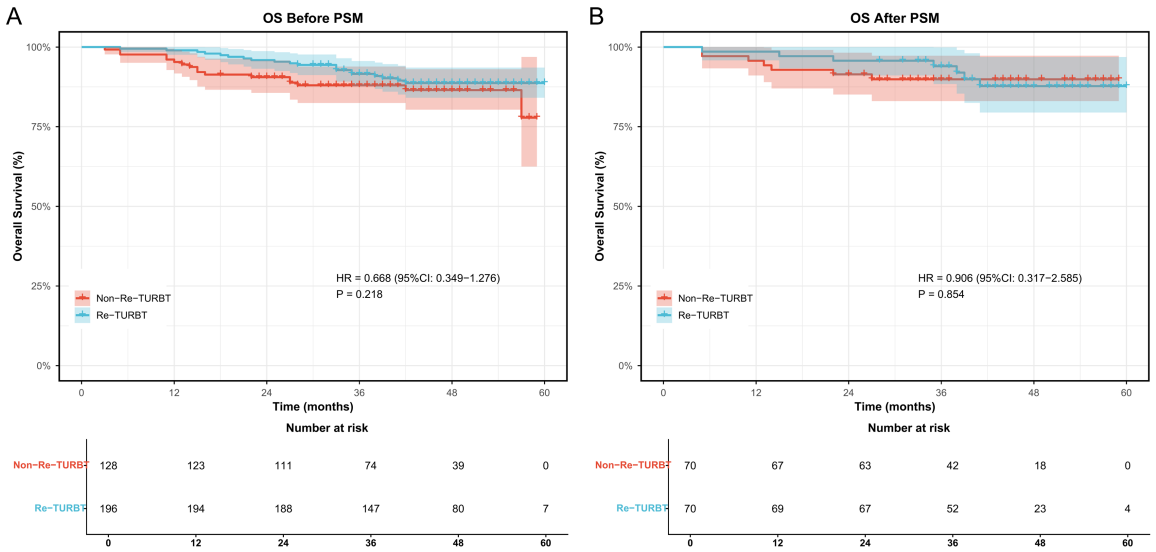

Figure 6. Effect of repeat transurethral resection of bladder tumor (Re-TURBT) on overall survival (OS). A. Kaplan-Meier curves for overall survival (OS) comparing Re-TURBT and non-Re-TURBT groups before propensity score matching (PSM). B. Kaplan-Meier curves for overall survival (OS) comparing Re-TURBT and non-Re-TURBT groups after propensity score matching (PSM). Note: OS, overall survival; Re-TURBT, repeat transurethral resection of bladder tumor; PSM, propensity score matching. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression. Survival curves were compared using the log-rank test.

1.583, P=0.186) or after PSM (HR=1.016, 95% CI: 0.064-16.245, P=0.991) (**Figure 8A**, **8C**). However, among patients with tumors >3.2 cm, Re-TURBT was associated with improved PFS both before PSM (HR=0.170, 95% CI: 0.073-0.398, P<0.001) and after PSM (HR=0.171, 95% CI: 0.037-0.780, P=0.010) (**Figure 8B**, **8D**).

Efficacy of Re-TURBT by BCG maintenance therapy subgroups

Stratified analyses were performed based on BCG maintenance therapy status. For RFS, among patients receiving BCG maintenance therapy, no significant reduction in recurrence risk was observed with Re-TURBT either before PSM (HR=0.642, 95% CI: 0.253-1.632, P=0.349) or after PSM (HR=0.350, 95% CI: 0.068-1.808, P=0.190) (**Figure 9A**, **9C**). In contrast, among patients not receiving BCG maintenance, Re-TURBT was significantly associated with reduced recurrence risk both before PSM (HR=0.421, 95% CI: 0.270-0.658, P<0.001) and after PSM (HR=0.174, 95% CI: 0.079-0.381, P<0.001) (**Figure 9B**, **9D**).

For PFS, among patients receiving BCG maintenance therapy, no significant difference was observed before PSM (HR=0.396, 95% CI: 0.056-2.810, P=0.337) (**Figure 10A**). After PSM, due to sparse events and possible complete separation, the Cox model produced unstable estimates with coefficients approaching infinity (HR=0.000, 95% CI: 0.000-Inf, P=0.317), requiring cautious interpretation (**Figure 10C**). Among patients without BCG maintenance, Re-TURBT was associated with improved PFS both before PSM (HR=0.334, 95% CI: 0.154-0.725, P=0.004) and after PSM (HR=0.271, 95% CI: 0.075-0.986, P=0.034) (**Figure 10B**, **10D**).

Univariate and multivariate cox regression for RFS before PSM

In the pre-PSM cohort, univariate Cox regression showed that Re-TURBT was significantly associated with reduced recurrence risk (HR=0.379, 95% CI: 0.256-0.563, P<0.001). Elevated CCI score (HR=1.254, 95% CI: 1.067-1.473, P=0.006), larger tumor diameter (HR=1.394, 95% CI: 1.228-1.582, P<0.001), and higher tumor number (HR=1.573, 95% CI: 1.404-1.762, P<0.001) were all associated with increased recurrence risk.

Regarding tumor morphology, compared with papillary tumors, sessile/solid tumors (HR=1.659, 95% CI: 1.019-2.700, P=0.042) and

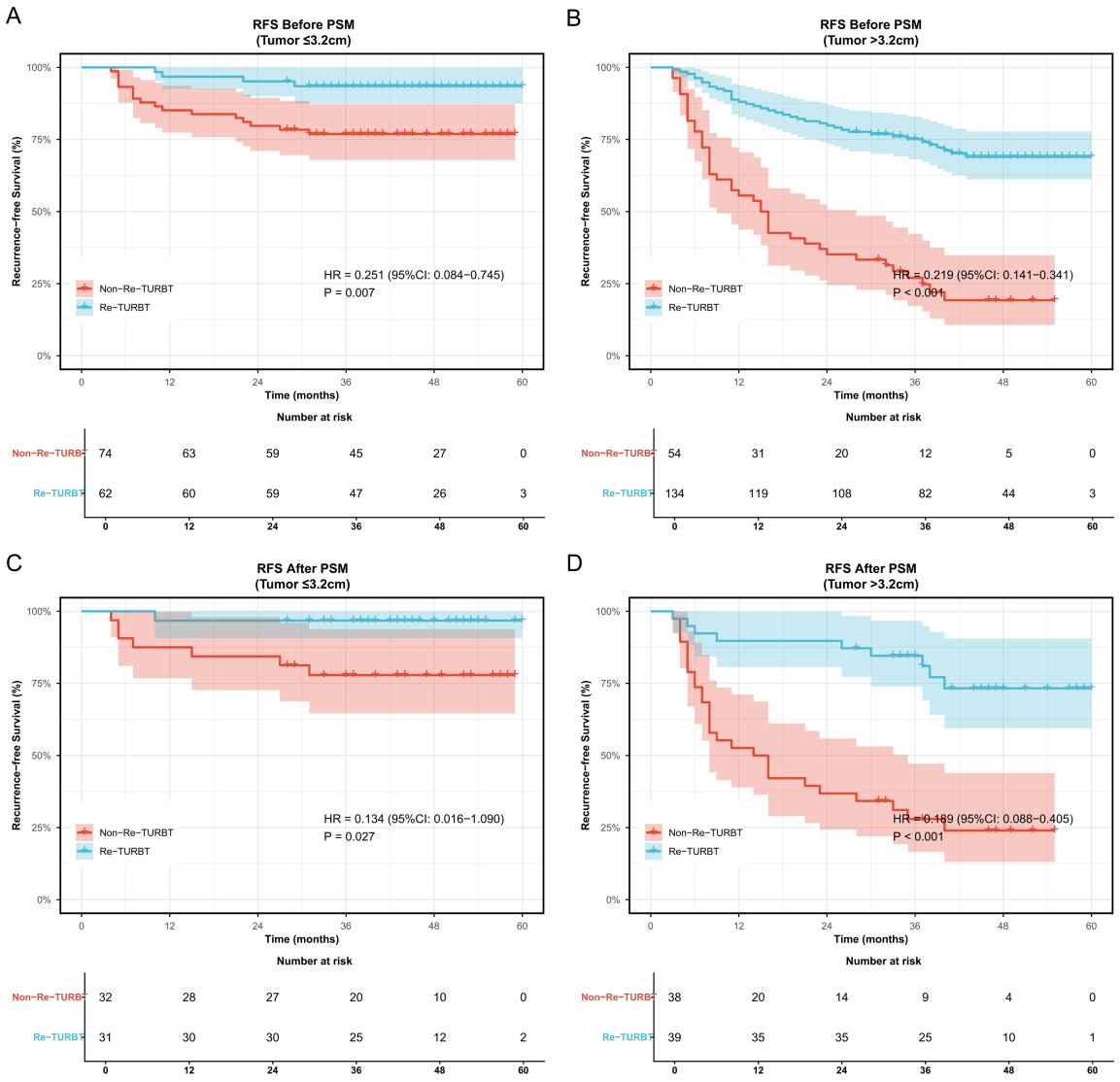

Figure 7. Kaplan-Meier analysis of recurrence-free survival (RFS) stratified by tumor size (cut-off 3.2 cm) before and after propensity score matching (PSM). A. RFS before PSM in patients with tumor size ≤3.2 cm. B. RFS before PSM in patients with tumor size >3.2 cm. C. RFS after PSM in patients with tumor size ≤3.2 cm. D. RFS after PSM in patients with tumor size >3.2 cm. Note: RFS, recurrence-free survival; Re-TURBT, repeat transurethral resection of bladder tumor; PSM, propensity score matching. The tumor-size cut-off (3.2 cm) was determined using maximally selected rank statistics based on the pre-PSM cohort. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression. Survival curves were compared using the log-rank test.

mixed-type tumors (HR=4.805, 95% CI: 3.043-7.589, P<0.001) carried higher recurrence risk. Recurrent tumors had higher recurrence risk than primary tumors (HR=4.130, 95% CI: 2.795-6.101, P<0.001). Absence of detrusor muscle in the initial TURBT specimen was associated with significantly increased recurrence risk (HR=3.801, 95% CI: 2.573-5.615, P< 0.001). For adjuvant therapy, absence of BCG maintenance therapy was associated with a higher recurrence risk (HR=4.539, 95% CI: 2.755-7.479, P<0.001).

In multivariate analysis, Re-TURBT remained an independent protective factor against recurrence (HR=0.080, 95% CI: 0.042-0.152, P< 0.001). Tumor diameter (HR=1.556, 95% CI: 1.362-1.778, P<0.001) and tumor number (HR=1.481, 95% CI: 1.250-1.755, P<0.001) remained independent risk factors. Mixed

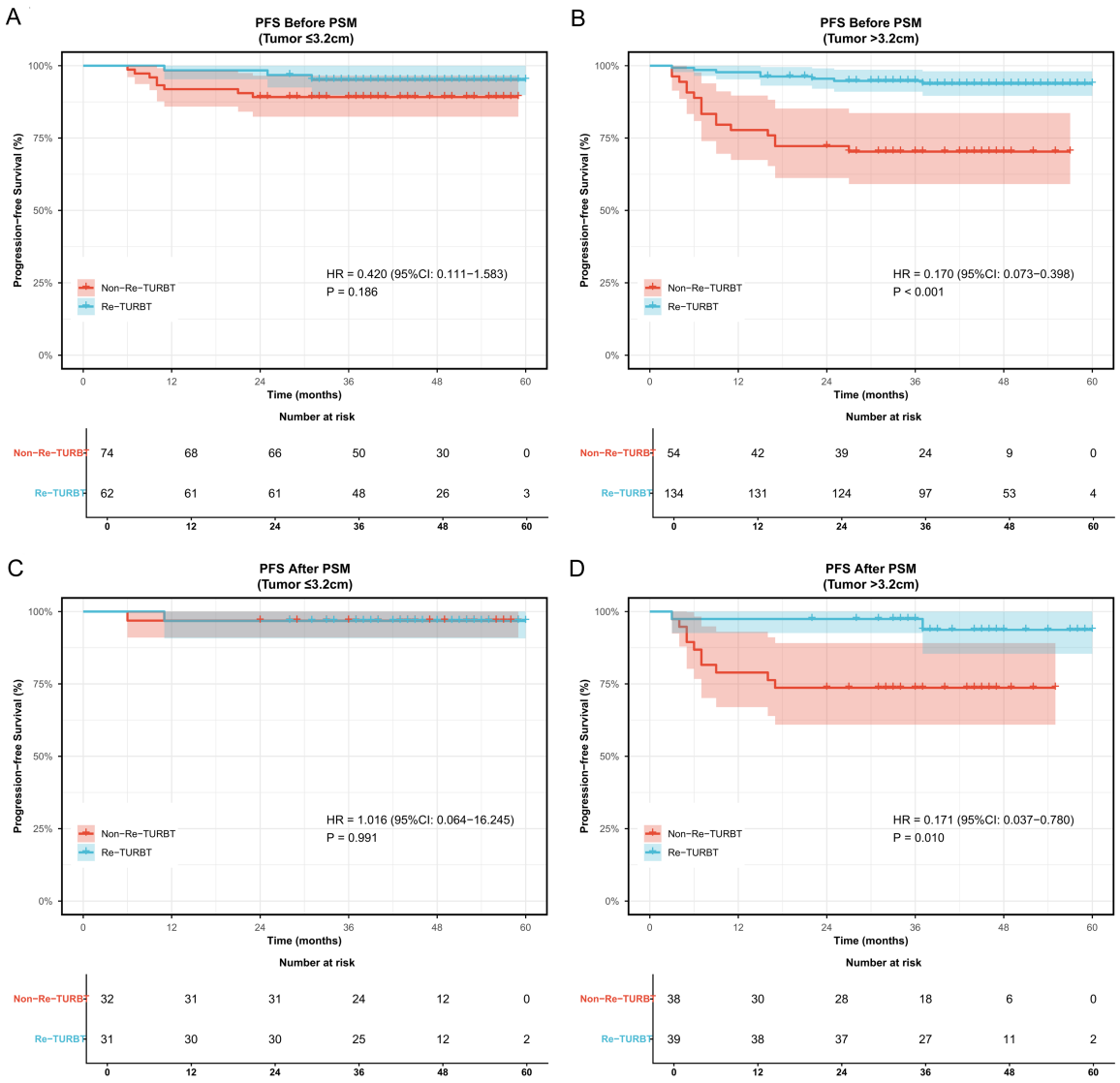

Figure 8. Kaplan-Meier analysis of progression-free survival (PFS) stratified by tumor size (cut-off 3.2 cm) before and after propensity score matching (PSM). A. PFS before PSM in patients with tumor size ≤3.2 cm. B. PFS before PSM in patients with tumor size >3.2 cm. C. PFS after PSM in patients with tumor size ≤3.2 cm. D. PFS after PSM in patients with tumor size >3.2 cm. Note: PFS, progression-free survival; Re-TURBT, repeat transurethral resection of bladder tumor; PSM, propensity score matching. The tumor-size cut-off (3.2 cm) was determined using maximally selected rank statistics based on the pre-PSM cohort. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression. Survival curves were compared using the log-rank test.

tumor morphology (HR=2.417, 95% CI: 1.309-4.464, P=0.005), recurrent tumors (HR=2.338, 95% CI: 1.436-3.806, P<0.001), absence of detrusor muscle in initial TURBT (HR=2.357, 95% CI: 1.559-3.562, P<0.001), and lack of BCG maintenance therapy (HR=1.918, 95% CI: 1.112-3.306, P=0.019) were also independent predictors of recurrence. Absence of concomitant CIS showed a protective association (no vs yes: HR=0.313, 95% CI: 0.172-0.570, P<0.001). CCI score and sessile/solid morphology did not reach statistical significance in multivariate analysis.

Univariate and multivariate cox regression for RFS after PSM

In the post-PSM cohort, univariate Cox regression showed that Re-TURBT was significantly associated with reduced recurrence risk (HR=0.217, 95% CI: 0.107-0.439, P<0.001). Larger tumor diameter (HR=1.501, 95% CI: 1.202-

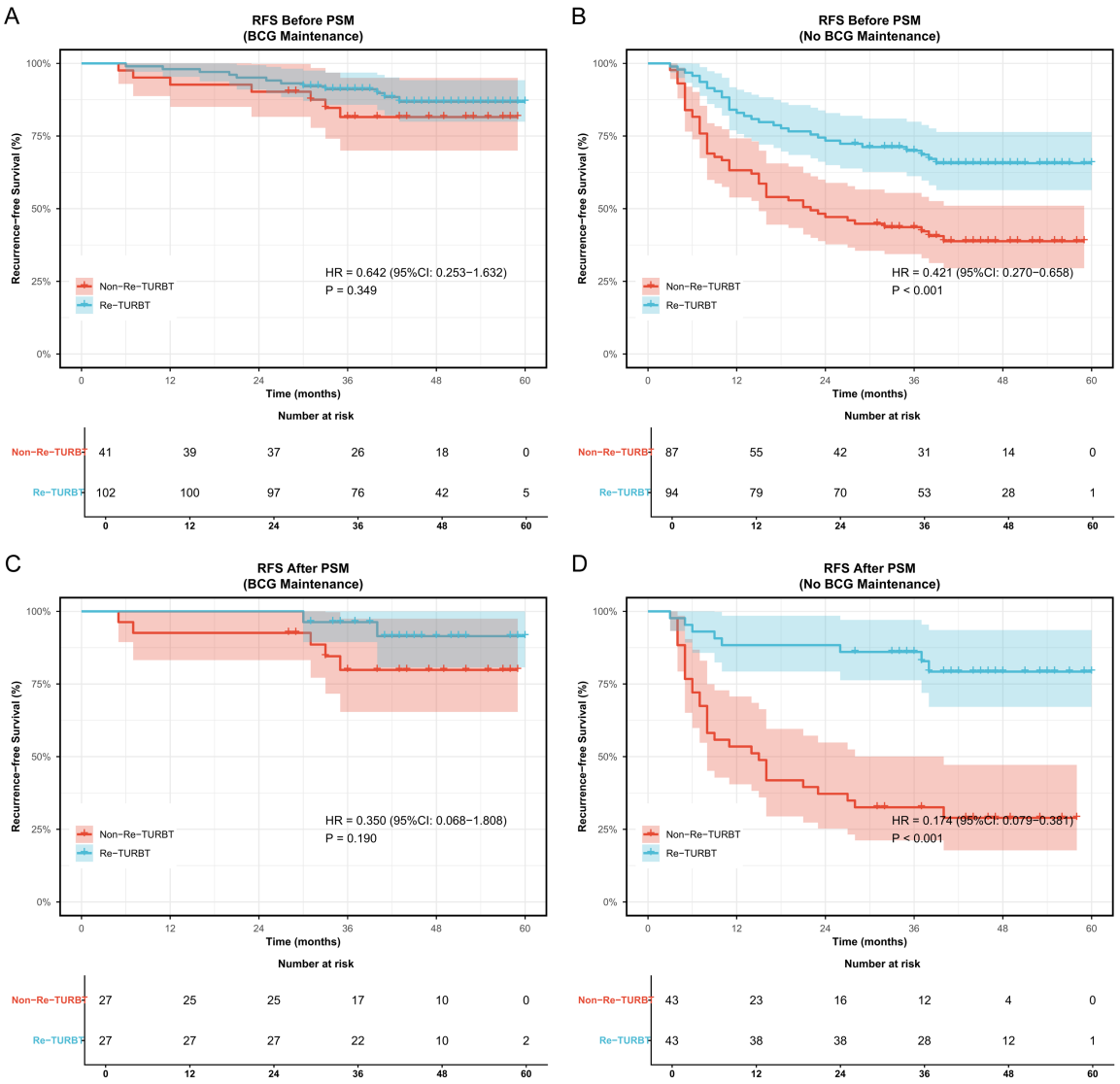

Figure 9. Kaplan-Meier analysis of recurrence-free survival (RFS) stratified by BCG maintenance therapy before and after propensity score matching (PSM). A. RFS before PSM in patients receiving BCG maintenance therapy. B. RFS before PSM in patients not receiving BCG maintenance therapy. C. RFS after PSM in patients receiving BCG maintenance therapy. D. RFS after PSM in patients not receiving BCG maintenance therapy. Note: RFS, recurrence-free survival; Re-TURBT, repeat transurethral resection of bladder tumor; PSM, propensity score matching; BCG, Bacillus Calmette-Guérin. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression. Survival curves were compared using the log-rank test.

1.873, P<0.001) and higher tumor number (HR=2.013, 95% CI: 1.594-2.544, P<0.001) were again associated with increased recurrence risk.

Regarding tumor morphology, sessile/solid tumors (HR=2.046, 95% CI: 1.021-4.097, P=0.043) and mixed-type tumors (HR=5.714, 95% CI: 2.753-11.861, P<0.001) carried higher recurrence risk. Absence of concomitant CIS was associated with a lower recurrence risk (no vs yes: HR=0.202, 95% CI: 0.107-0.381, P<0.001). Lack of BCG maintenance therapy (HR=4.483, 95% CI: 1.998-10.056, P<0.001), recurrent tumor status (HR=2.714, 95% CI: 1.484-4.965, P=0.001), and absence of detrusor muscle in initial TURBT (HR=2.645, 95% CI: 1.471-4.756, P=0.001) were also associated with elevated recurrence risk.

Multivariate Cox regression further demonstrated that Re-TURBT remained an indepen-

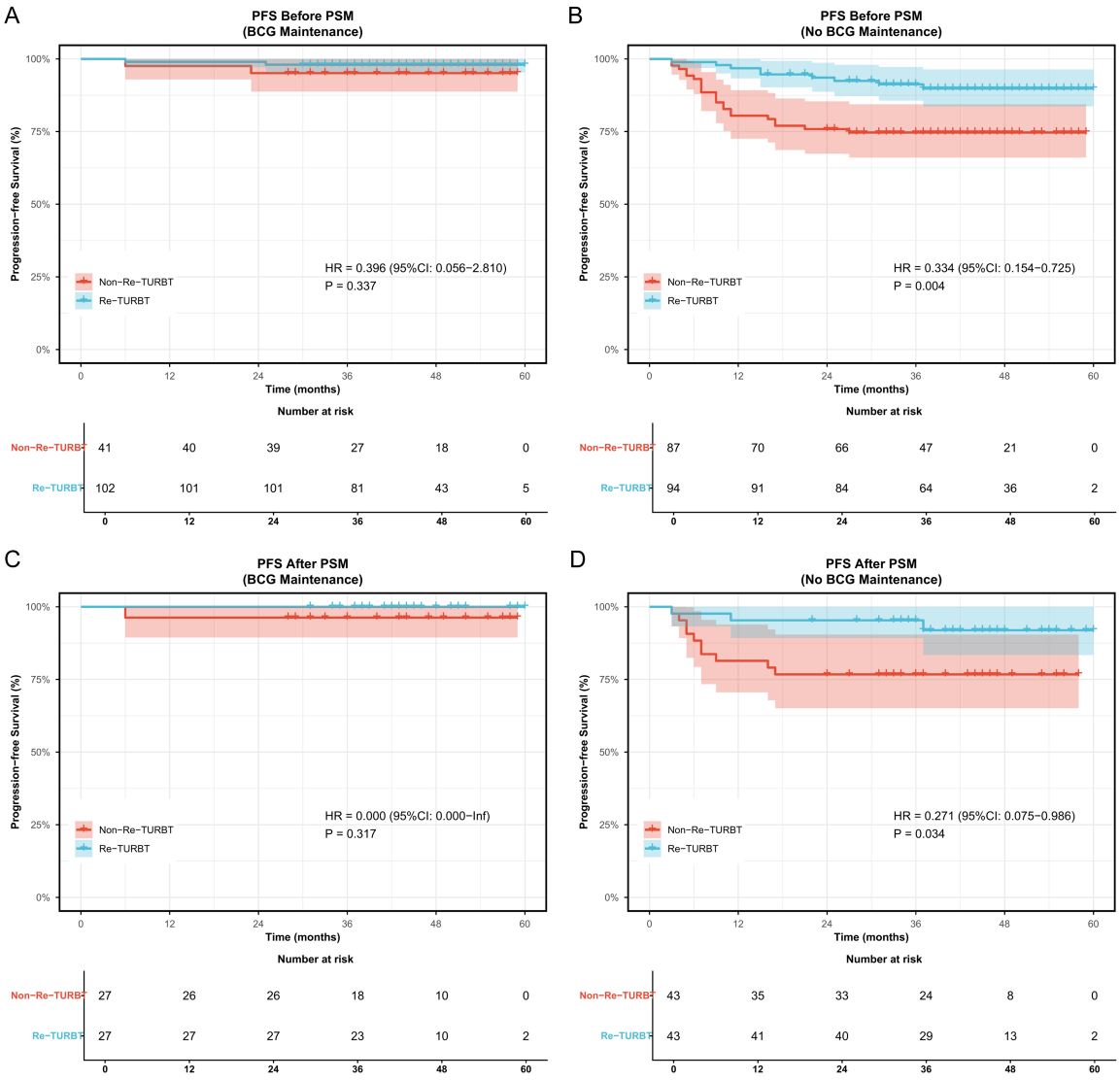

Figure 10. Kaplan-Meier analysis of progression-free survival (PFS) stratified by BCG maintenance therapy before and after propensity score matching (PSM). A. PFS before PSM in patients receiving BCG maintenance therapy. B. PFS before PSM in patients not receiving BCG maintenance therapy. C. PFS after PSM in patients receiving BCG maintenance therapy. D. PFS after PSM in patients not receiving BCG maintenance therapy. Note: PFS, progression-free survival; Re-TURBT, repeat transurethral resection of bladder tumor; PSM, propensity score matching; BCG, Bacillus Calmette-Guérin. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression. Survival curves were compared using the log-rank test. In the post-PSM BCG-maintenance subgroup, sparse events may lead to separation in the Cox model; results should be interpreted with caution.

dent protective factor (HR=0.047, 95% CI: 0.018-0.120, P<0.001). Tumor diameter (HR=1.360, 95% CI: 1.073-1.723, P=0.011) and tumor number (HR=2.318, 95% CI: 1.651-3.255, P<0.001) remained independent risk factors. Mixed tumor morphology (HR=4.036, 95% CI: 1.600-10.184, P=0.003), absence of concomitant CIS (no vs yes: HR=0.136, 95% CI: 0.057-0.327, P<0.001), and lack of BCG maintenance therapy (HR=2.958, 95% CI: 1.130-7.747, P=0.027) were also independently associated with recurrence risk. In contrast, primary/recurrent status and presence of detrusor muscle in the initial TURBT specimen did not reach statistical significance in the multivariate model after matching.

Interaction between Re-TURBT and BCG therapy on RFS and PFS

Figure 11 illustrates the impact of Re-TURBT versus Non-Re-TURBT on RFS and PFS, strati-

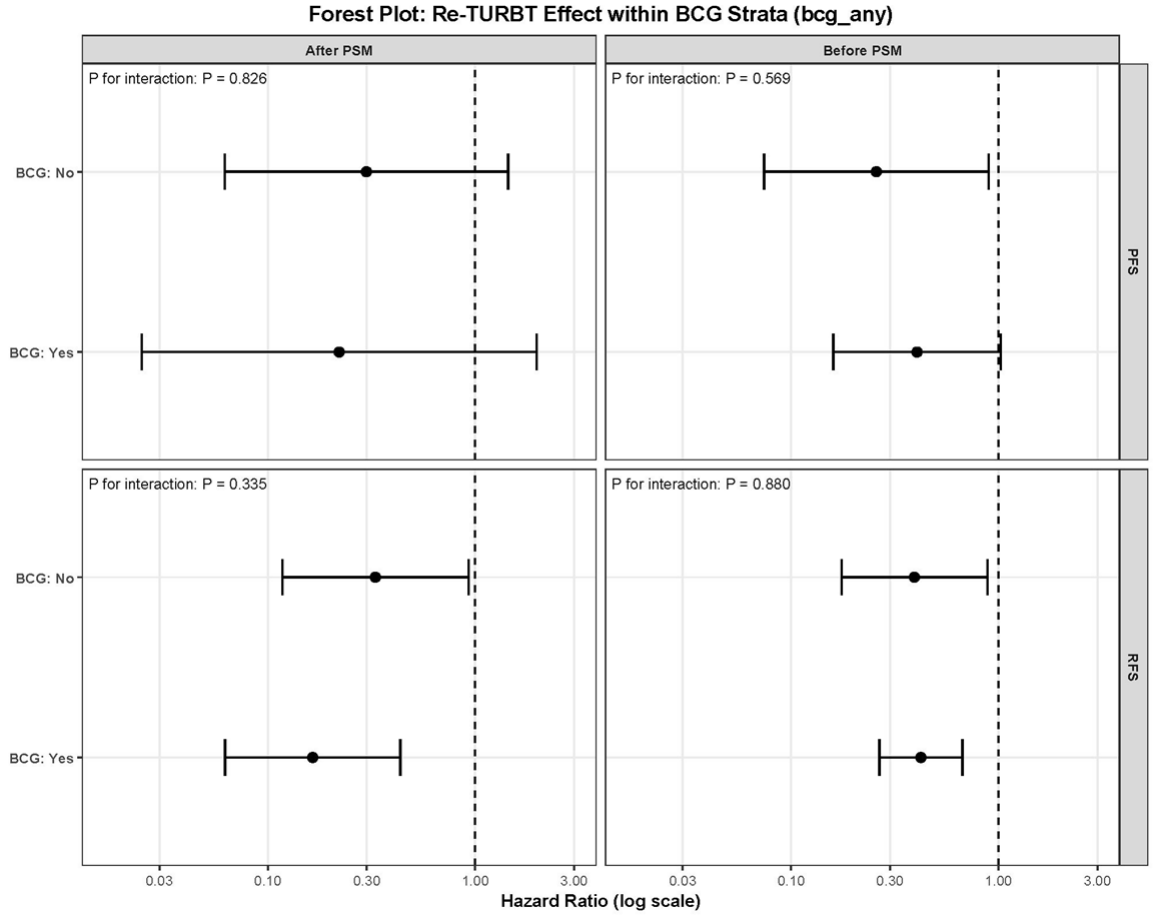

Figure 11. Interaction forest plot of Re-TURBT and any BCG therapy (bcg_any) for RFS and PFS before and after propensity score matching. Note: Re-TURBT, repeat transurethral resection of bladder tumor; BCG, Bacillus Calmette-Guérin; bcg_any, any BCG therapy (induction and/or maintenance); RFS, recurrence-free survival; PFS, progression-free survival; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval.

fied by receipt of any BCG therapy (bcg_any: Yes/No), both before and after PSM. Across all strata, the direction of the Re-TURBT effect was generally consistent (overall HRs <1), suggesting a comparable relative benefit regardless of BCG status. No statistically significant interaction was detected between Re-TURBT and bcg_any: before PSM, P for interaction was 0.880 for RFS and 0.569 for PFS; after PSM, the corresponding values were 0.335 and 0.826, respectively. Collectively, these findings indicate that BCG status did not significantly modify the association between Re-TURBT and RFS/PFS in this cohort.

Perioperative complications and management in the Re-TURBT group

In the Re-TURBT group (n=196), procedure-related perioperative complications occurred in 12 patients (12/196, 6.12%) and were predominantly mild-to-moderate events.

Bleeding-related complications were observed in 4 patients (4/196, 2.04%), most commonly presenting as postoperative gross hematuria or clot retention and were controlled with continuous bladder irrigation, extended catheterization, and, when necessary, endoscopic coagulation and/or clot evacuation. No patient required blood transfusion or major re-operation.

Infection, typically postoperative urinary tract infection (UTI) or fever, occurred in 6 patients (6/196, 3.06%). All cases improved with antimicrobial therapy, with culture-guided adjustment when indicated, and no severe infection (e.g., sepsis) was observed.

Bladder perforation was reported in 2 patients (2/196, 1.02%), mostly small extraperitoneal perforations managed conservatively with catheter drainage with or without antibiotics. All

patients recovered without the need for open or laparoscopic repair.

Discussion

This single-center real-world study assessed the therapeutic and prognostic impact of Re-TURBT in patients with high-grade Ta bladder cancer using PSM. Both unmatched and matched analyses showed that Re-TURBT was significantly associated with improved RFS and PFS, while no significant difference was observed in OS. These findings suggest that Re-TURBT confers meaningful clinical benefit in this high-risk population, extending beyond local tumor control to include improved staging accuracy and more informed therapeutic decision-making.

Core value of Re-TURBT: residual tumor clearance and stage correction

A key rationale for performing for Re-TURBT in high-risk NMIBC lies in the substantial probability of residual tumor and the risks of pathological understanding following the initial resection. In our cohort, nearly one-third of patients undergoing Re-TURBT harbored residual tumors before matching, and this promotion remained clinically relevant even after PSM. Furthermore, a subset of patients experienced pathological upstaging from Ta to T1. These findings are consistent with existing literature. For instance, Yanagisawa et al. [9] reported residual tumor rates ranging from 17% to 67% and upstaging rates of 0%-8% among high-risk NMIBC patients undergoing repeat resection. Earlier landmark studies similarly demonstrated that repeat resection improves detection of residual disease and reduces staging bias, establishing the clinical rationale for Re-TURBT [19].

Although high-grade Ta tumors are confined to the mucosa and lack lamina propria invasive, their biological behavior is considerably more aggressive than that of low-grade Ta tumors and may resemble T1 disease in recurrence and progression patterns. This supports the principle that “complete resection plus reliable staging” is particularly important in high-grade Ta disease. Bree et al. [5] emphasized that all high-grade Ta tumors should be managed as high-risk lesions, and systematic repeat resection has been shown to reduce residual disease and improve oncologic outcomes, especially when the quality of the index TURBT is uncertain [13]. Importantly, in our study, Re-TURBT retained a significant protective association with RFS and PFS after PSM. Meanwhile, the reduced significance for some covariates after PSM is not unexpected: variables that were imbalanced and entangled with treatment selection in the original cohort may lose apparent independent effects once balance is achieved, and confidence intervals may widen due to reduced effective sample size. The persistence of the Re-TURBT effect under improved covariate balance supports that the observed benefit is unlikely to be driven by confounding factors.

TURBT quality and detrusor muscle sampling: why recurrence still occurs and why Re-TURBT helps

The presence of detrusor muscle in the TURBT specimen is widely recognized as a surrogate marker of resection quality and staging reliability. According to Mariappan et al. [7], achieving adequate detrusor muscle sampling was associated with lower 5-year recurrence rates (38.9% vs 44.3%), highlighting the correlation between surgical quality and oncological control. In our pre-PSM cohort, differences in detrusor muscle sampling rates were observed between groups, suggesting that surgical quality and real-world case selection may jointly influence the decision to perform Re-TURBTs. Muilwijk et al. [8] consistently identified detrusor sampling rate, complete resection rate, and execution of immediate intravesical instillation as key quality indicators associated with recurrence and progression in a prospective registry.

Notably, Re-TURBT remained independently associated with improved outcomes after matching, implying that its benefit extends beyond merely compensating for inadequate initial resection. Repeat resection may reinforce the entire treatment chain by enabling a second pathological assessment, improving evaluation of margins/base, and facilitating more accurate risk re-stratification. Moreover, recurrence is not attributed solely to visible residual tumor: substantial inter-center variability in TURBT technique exists, and the implementation of standardization tools (e.g., checklists) can improve resection consistency and outcome reporting [20]. Thus, Re-TURBT may also reduce

the likelihood of missed lesions and eradicate microscopic residual disease via systematic re-examination and re-resection.

Consistency with prior studies: RFS/PFS benefits are more readily detected than OS differences

Our findings-clear benefits in RFS and PFS without a corresponding significant difference in OS-mirror the broader pattern observed in high-risk NMIBC. In this disease setting, endpoints reflecting local tumor control and delayed progression are more sensitive to treatment effects than OS, which is influenced by competing risks and subsequent therapies. Long-term randomized evidence in pT1 disease supports the role of repeat resection in improving durable tumor control. Eroglu et al. [21] reported significantly higher RFS at 5, 7, and 10 years in the re-resection group, along with improved PFS. In high-grade Ta specifically, contemporary studies suggest that Re-TURBT combined with structured intravesical therapy can improve long-term control. Ajami et al. [10] and Lee et al. [15] both reported meaningful improvements in 5-year RFS and PFS when Re-TURBT was incorporated into standardized BCG-based strategies.

In contrast, OS differences are often difficult to demonstrate in NMIBC because mortality is shaped by multiple competing factors, including age, comorbidity burden, treatment escalation, and non-cancer deaths [6]. Even when recurrence and progression are reduced, OS benefits may be diluted by limited follow-up and a relatively low number of death events. In addition, Re-TURBT may facilitate earlier recognition of upstaged or higher-risk pathology, leading to intensified BCG, earlier cystectomy, or other treatment escalation-creating a "treatment salvage" effect that narrows OS differences between treatment groups. Therefore, the absence of an OS difference in our cohort should be interpreted as "no difference observed" rather than definitive evidence of equivalence.

Interaction with BCG maintenance: why non-maintenance patients may benefit more

Our subgroup analyses suggest that Re-TURBT confers more pronounced benefit in patients who did not receive BCG maintenance therapy, whereas the effect was attenuated among those receiving maintenance therapy. Some post-PSM subgroup models also showed estimation instability due to sparse events. Clinically, this pattern is plausible: adequate BCG maintenance exerts a strong recurrence-suppressing effect, thereby reducing the incremental ("marginal") benefit that Re-TURBT may provide. Moon et al. [11] showed that maintenance therapy beyond one year significantly reduces recurrence risk compared with induction alone in high-risk NMIBC. However, real-world adherence to maintenance therapy remains suboptimal. Gaylis et al. [22] reported that although most patients completed induction, substantially fewer adhered to guideline-recommended maintenance schedules, potentially limiting treatment effectiveness in routine practice. Under such circumstances, the tumor-clearance and stage-correction effect of Re-TURBT may assume greater importance and partially compensate when maintenance therapy is interrupted or omitted. Additionally, for patients with inadequate or failed BCG, combination intravesical regimens (e.g., gemcitabine plus docetaxel) are increasingly used as alternatives [12].

Regarding sparse-event instability (including separation phenomena) in certain subgroups, this represents a recognized limitation of Cox modeling when event numbers are very small. Methodological literature supports the use of penalized regression approaches or competing-risk frameworks as potential solutions for future studies with larger sample sizes [23].

Tumor burden (diameter) and Re-TURBT benefit: from technical difficulty to biological risk

Using 3.2 cm as the cutpoint, the benefit of Re-TURBT appeared more stable and pronounced for tumors >3.2 cm, whereas the effect on PFS in the ≤3.2 cm subgroup was less evident. Larger tumors are more likely to be incompletely resected at the initial TURBT, more likely to harbor satellite lesions, and present greater technical challenges for hemostasis, visualization, and adequate sampling. They may also reflect more aggressive tumor biology, including a higher probability of occult lamina propria invasion. Fan et al. [24] proposed a practical risk-stratification framework incorporating detrusor muscle acquisition and other

surgical factors, demonstrating markedly higher residual tumor rates in high-risk groups, which helps identify patients most likely to benefit from Re-TURBT. Tumor size >3 cm is also an established criterion in AUA/SUO risk stratification [6], reinforcing tumor burden as a rational decision point.

Even with enhanced imaging, repeat resection may remain necessary. Alsyouf et al. [25] found no significant reduction in residual tumor rates when blue-light cystoscopy was used at the initial TURBT compared with white-light TURBT, supporting the continued role of Re-TURBT in high-risk disease. Our subgroup findings similarly support incorporating tumor burden into individualized decision-making regarding Re-TURBT.

Why RFS/PFS benefits may not translate into OS: integrating study-specific quantitative findings

Several study-specific observations help interpret the absence of OS difference despite improved RFS/PFS. First, competing mortality represents a major determinant of survival in NMIBC populations, which are typically older. Global epidemiological data emphasizes that bladder cancer disproportionately affects older adults [26], and competing-risk analyses demonstrate that non-cancer-related mortality can exceed bladder cancer-specific mortality in older NMIBC cohorts, particularly beyond age 70 [27]. Our cohort, with a mean age of approximately 66 years and heterogeneous comorbidity burden, is consistent with meaningful competing risks may dilute OS differences even when tumor control improves. Second, follow-up duration and event counts constrain the ability to detect OS differences. Although progression and cancer-specific death often occur within a limited window in high-risk NMIBC, the transition from recurrence to progression and ultimately to death often requires extended observation [28]. Our median follow-up of 42.5 months may therefore be insufficient to capture an OS separation, and prior work suggests that longer follow-up (often 5-10 years) is needed to detect survival differences in NMIBC populations [29]. Third, salvage therapies can substantially mitigate mortality differences. Early cystectomy in appropriately selected high-risk patients has been shown to yield favorable disease-specific survival compared with delayed surgery [30]. In our cohort, Re-TURBT may have facilitated earlier detection of higher-risk features and accelerated treatment escalation, potentially preserving OS in both groups and thereby diminishing observable between-group differences. Finally, the absolute number of deaths was low (37 deaths before PSM and 14 after PSM), limiting statistical power for OS comparisons and increasing uncertainty around effect estimates. This observation aligns with the generally favorable cancer-specific survival of NMIBC across risk strata [31]. Moreover, recurrence in NMIBC does not uniformly translate into mortality; population-based data show markedly different long-term cancer-specific mortality by stage/grade, with HG Ta disease exhibiting lower mortality than HG T1 tumors [32]. Collectively, these considerations support interpreting the absence of an OS difference in our study as reflecting limited statistical sensitivity rather than definitive evidence of therapeutic equivalence.

Integrated treatment chain: Re-TURBT should not be evaluated in isolation

NMIBC outcomes are determined by the continuity of care across the treatment chain, including the resection quality, the appropriate use of repeat resection, immediate intravesical instillation, adequate BCG induction/maintenance therapy, and structured surveillance. Guidelines emphasize integrated management rather than reliance on any single component [2]. Consequently, the incremental value of Re-TURBT may be more pronounced when other components (e.g., maintenance therapy or initial resection quality) are suboptimal, where repeat resection can provide both therapeutic clearance and staging correction. Conversely, in settings where care delivery is already highly standardized, the role of Re-TURBT may shift toward improving staging certainty and facilitating individualized risk stratification rather than producing large absolute gains in recurrence control. Observational analyses have suggested that, in selected high-grade Ta patients who complete structured intravesical therapy, the additional RFS benefit from Re-TURBT may be smaller, reinforcing the need to interpret Re-TURBT within an integrated treatment strategy [10].

Strengths, limitations, and clinical implications

This study leveraged PSM to improve baseline comparability and reported clinically relevant

endpoints, including residual tumor, upstaging, and long-term outcomes, reflecting real-world decision-making. Nonetheless, limitations should be acknowledged. First, although our a priori sample size planning was based on the overall cohort to ensure adequate power for RFS, 1:1 PSM necessarily reduced the effective sample size, which may have limited statistical power for less frequent endpoints such as OS. However, the observed post-PSM effect size for RFS exceeded that assumed in planning, and sufficient event numbers remained to support robust time-to-event inference for recurrence and progression. Second, as a single-center retrospective analysis, residual confounding is inevitable. Surgeon experience, resection technique, and adoption of enhanced visualization technologies may influence TURBT quality and outcomes [7, 8]. The decision to perform Re-TURBT may also be shaped by institutional practice patterns, introducing potential selection bias that cannot be fully eliminated even with PSM adjustment. Third, clinical practice evolved over the long study period (2014-2023) may have influenced outcomes. While surgical year was considered, the complexity of temporal changes in surgical approaches and technologies cannot be fully captured [9, 25]. Finally, the number of death events was limited, and cancer-specific survival was not separately assessed, which may further reduce sensitivity to detect survival differences. Future multicenter prospective studies with larger samples, standardized surgical documentation, longer follow-up, and refined risk stratification are warranted to define which subsets of high-grade Ta patients derive the greatest incremental benefit from Re-TURBT [9].

Conclusions

In patients with high-grade Ta bladder cancer, Re-TURBT was consistently associated with lower recurrence rates and reduced progression risk, with particularly clear benefits in patients with larger tumor burden or inadequate BCG maintenance therapy. The impact of Re-TURBT on OS should be interpreted cautiously, as longer follow-up, larger event numbers, and more specific endpoints (e.g., cancer-specific survival) are required to fully evaluate survival impact.

In clinical practice, Re-TURBT should be considered as an important component of the management of high-risk high-grade Ta tumors within an integrated treatment pathway that emphasizes TURBT quality, timely instillation, standardized BCG, and rigorous surveillance.

Disclosure of conflict of interest

None.

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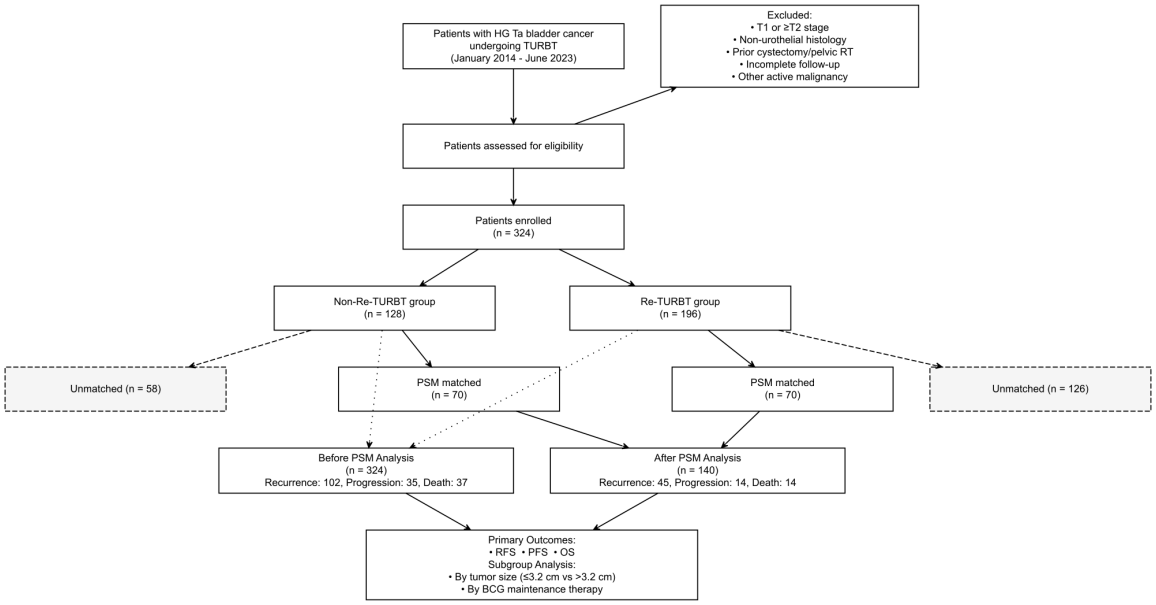

Figure S1. Research flowchart.