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Complete transurethral resection of bladder tumor before radical cystectomy is not a risk factor for organ-confined bladder cancer: A case-control study

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Abstract

Objectives: To investigate the role of complete transurethral resection of bladder tumor (TURBT) before radical cystectomy (RC) for organ-confined bladder cancer.

Materials and methods: Data of patients who underwent RC in our center from January 2008 to December 2018 were retrospectively reviewed. Patients with >T2N0M0 disease and positive surgical margins and those who received neoadjuvant/adjuvant chemotherapy or radiotherapy were excluded. Complete TURBT was defined as no visible lesion under endoscopic examination after TURBT or in the bladder specimen after RC. Kaplan-Meier curves and log-rank tests assessed disease-free survival (DFS). Logistic and Cox regression analyses were performed to identify potential predictors.

Results: A total of 236 patients were included in this review, including 207 males, with a median age of 61 years. The median tumor size was 3 cm, and a total of 94 patients had identified pathological T2 stage disease. Complete TURBT was correlated with tumor size ($p = 0.041$), histological variants ($p = 0.026$), and down-staging ($p < 0.001$). Tumor size, grade, and histological variants were independent predictors of complete TURBT. During a median follow-up of 42.7 months, 30 patients developed disease recurrence. Age and histological variants were independent predictors of DFS ($p = 0.022$ and 0.032, respectively), whereas complete TURBT was not an independent predictor of DFS ($p = 0.156$). Down-staging was not associated with survival outcome.

Conclusions: Complete TURBT was correlated with an increased rate of down-staging before RC. It was not associated with better oncologic outcomes for patients with organ-confined bladder cancer.

Keywords: Bladder cancer; Complete transurethral resection of bladder tumor; Down-staging; Radical cystectomy

1. Introduction

Transurethral resection of bladder tumor (TURBT) is often the initial treatment for bladder cancer. The extent and depth of TURBT, in addition to pathology results, play an important role in diagnosis and management, including intravesical instillation and neoadjuvant therapy followed by radical cystectomy (RC).[1–3] Clinical guidelines recommend RC as standard treatment for muscle-invasive bladder cancer and some high-risk non-muscle-invasive bladder cancer.[1,2] For locally advanced disease, neoadjuvant chemotherapy is recommended, and down-staging is associated with good prognosis.[4–9] However, the magnitude of benefit of neoadjuvant chemotherapy for T2N0M0 bladder cancer is still controversial.[10–13]

The role of down-staging from complete TURBT before RC is similarly controversial.[14–19] A few studies have demonstrated that complete TURBT was correlated with a higher rate of down-staging after RC and was associated with better oncological outcomes.[14–17,19] However, a recent study found that complete TURBT was not a significant predictor of oncological outcome, and incomplete TURBT was associated with pT stage, which in turn was a predictor of poor oncological outcome.[18]

In clinical practice, pT3/4 bladder cancer is linked to poor prognosis. Likewise, patients with positive lymph nodes or metastasis have worse outcomes. In addition, pT3/4 bladder cancer is unlikely to be completely resected through TURBT. Herein, we evaluated the role of complete TURBT before RC in patients with pathological stage ≤T2N0M0 bladder cancer for whom complete TURBT was possible.

2. Materials and methods

Patients with bladder cancer treated in our cancer center from January 2008 to December 2018 were retrospectively reviewed. Of these, 526 cases underwent RC and urinary diversion within 4 weeks after TURBT. A total of 287 cases were excluded because of stage >T2N0M0 disease, positive surgical margin in RC specimen, or neoadjuvant chemotherapy or radiotherapy. Three patients who died within 30 days after RC were excluded.

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Table 1

Correlation between complete TURBT and clinical pathologic factors in organ-confined bladder cancer.

		TURBT		
Characteristics	**n**	**Incomplete, n (%)**	**Complete, n (%)**	***p***
Sex				0.862
Male	207	82 (39.6)	125 (60.4)	
Female	29	11 (37.9)	18 (62.1)	
Age		62 (53–68)	59 (52–71)	0.760
≤60 yr	116	41 (35.3)	75 (64.7)	0.209
>60 yr	120	52 (43.3)	68 (56.7)	
Smoking				0.358
Yes	136	57 (41.9)	79 (58.1)	
No	100	36 (36)	64 (64)	
Multifocality				0.229
≤2	201	76 (37.8)	125 (62.2)	
>2	35	17 (48.6)	18 (51.4)	
Tumor size				0.041
≤3 cm	126	42 (33.3)	84 (66.7)	
>3 cm	110	51 (46.4)	59 (53.6)	
Recurrent tumor				0.309
Yes	43	14 (32.6)	29 (67.4)	
No	193	79 (40.9)	114 (59.1)	
Second TURBT				0.149
Yes	52	16 (30.8)	36 (69.2)	
No	184	77 (41.8)	107 (58.2)	
Grade				0.059
Low	31	17 (54.8)	14 (45.2)	
High	205	76 (37.1)	129 (62.9)	
Concomitant CIS				0.583
Yes	18	6 (33.3)	12 (66.7)	
No	218	87 (39.9)	131 (60.1)	
Variants				0.026
Yes	25	15 (60)	10 (40)	
No	211	78 (37.0)	133 (63.0)	
T stage				0.177
pTa–T1	142	51 (35.9)	91 (64.1)	
pT2	94	42 (44.7)	52 (55.3)	
LVI				0.068
Yes	44	12 (27.3)	32 (72.7)	
No	192	81 (42.2)	111 (57.8)	

CIS = cancer in situ; LVI = lymphovascular infiltration; TURBT = transurethral resection of bladder tumor.

Retrospective data including clinical characteristics, imaging, pathology, and follow-up were collected from our Bladder Cancer database.

Complete TURBT was defined as having no visible lesion under endoscopic examination after TURBT and no gross tumor in the bladder specimen after RC. Down-staging was defined as a T stage after TURBT that was greater than the stage after RC. Up-staging was defined as a T stage after RC that was greater than the stage after TURBT.

Disease-free survival (DFS) was the primary endpoint. Continuous and categorical variables were presented as medians (interquartile range) and numbers (%), and comparisons between variables were performed using the Mann-Whitney *U* test and chi-square test. Kaplan-Meier and log-rank tests were calculated for survival analysis. Multivariate logistic and Cox regression analyses were performed for all variables that were identified as potentially significant by univariate analysis. Data were analyzed using IBM SPSS Statistics®, version 24 (IBM Corp, Armonk, NY). All tests were 2-tailed; $p < 0.05$ was considered significant.

3. Results

In total, 236 patients were included, and 207 were male. The median age was 61 years. Median tumor number was 1 (range, 1–2), and median tumor size was 3 cm (range, 2–5 cm), respectively, and pathological T stage was T2 in 94 patients (39.8%). Complete TURBT was accomplished in 143 cases (60.6%), and down-staging in 25 cases (10.6%). Down-staging was accomplished in 24 cases (17%) in the complete TURBT group and 1 case (1%) in the incomplete TURBT group ($p < 0.001$) (Table 1). No adjuvant chemotherapy or radiotherapy was administrated for these organ-confined bladder cancer cases after RC.

Complete TURBT was related to tumor size ($p = 0.041$), down-staging ($p < 0.001$), up-staging ($p < 0.001$), and histologic variants ($p = 0.026$), a category of invasive urothelial carcinoma with divergent differentiation showing a component of usual-type urothelial carcinoma combined with other morphologies.[20] High-grade disease and lymphovascular infiltration were marginally associated with complete TURBT (Table 1). Univariate analysis indicated down-staging was significantly correlated with age, tumor recurrence, and second TURBT (Table 1S, http://links.lww.com/CURRUROL/A21). High-grade disease was marginally associated with down-staging

Table 2

Univariate and multivariate analyses of potential factors for disease-free survival in organ-confined bladder cancer.

		Univariate	Multivariate		
Factors	**Category**	***p***	**Wald value**	**Hazard ratio (95% CI)**	***p***
Sex	Female Male	0.144			
Age	>60 yr ≤60 yr	**0.027**	5.258	2.495 (1.142–5.451)	**0.022**
Smoking	Yes No	0.626			
Number	>2 ≤2	0.748			
Size	>3 cm ≤3 cm	0.629			
Recurrent tumor	Yes No	0.726			
Second TURBT	Yes No	0.683			
Grade	High Low	0.155			
Concomitant CIS	Yes No	0.395			
Variants	Yes No	**0.100**	4.581	2.695 (1.087–6.679)	**0.032**
T stage	T2 Ta–T1	0.120			
LVI	Yes No	0.626			
LND field	>Standard ≤Standard	0.234			
LN yield	>10 ≤10	0.539			
Complete TURBT	Yes No	0.119	2.014	1.775 (0.804–3.920)	0.156
Down-staging	Yes No	0.525			

Multivariate analyses revealed that age and histological variants are independent factors of disease-free survival, and complete TURBT is not.

CI = confidence interval; CIS = cancer in situ; LND = lymph node dissection; LN = lymph node; LVI = lymphovascular infiltration; TURBT = transurethral resection of bladder tumor.

rate (12% vs. 0%, $p = 0.053$). Multivariate logistic analysis revealed that tumor size, grade, and histological variants were independent predictors for complete TURBT (http://links.lww.com/CURRUROL/A22).

During a median follow-up of 42.7 months (range, 29.4–85.7 months), 13% (30/236) of patients suffered relapse. The median interval between RC and recurrence was 22.2 months (range, 3.2–131.3 months). The majority (28/30) of recurrences were detected within 4 years after RC, and 16 tumors recurred within 2 years.

A potential association was found between DFS and age, histologic variants, T stage, and complete TURBT in univariate analysis ($p < 0.13$). On multivariate analysis, age ($p = 0.022$) and histologic variants ($p = 0.032$) were independent predictors of DFS. Complete TURBT and down-staging were not found to be independent predictors of DFS (Table 2, Fig. 1).

4. Discussion

The role of complete TURBT for non-muscle-invasive bladder cancer before intravesical therapy and repeat TURBT has been confirmed by several studies.[1–3,21,22] However, its role before RC is controversial. The completeness of TURBT is affected by tumor burden, which is also associated with oncological outcome.[4,14,18] In several retrospective analyses, complete TURBT was associated with a higher rate of down-staging, which was related to better prognosis.[14,19,23] For locally advanced tumors, complete TURBT was not theoretically possible, and incomplete TURBT was often correlated with advanced stage disease (T3–T4), which was a predictor of poor prognosis.[18] Thus, further studies are needed to assess whether advanced stage or incomplete TURBT is a more significant predictor of prognosis. A recent study found that advanced stage was a greater predictor than incomplete TURBT, but confounding variables, including adjuvant therapy, positive surgical margin, and a relatively subjective definition of complete TURBT, limited the strength of conclusions.[18] Thus, for this study, we focused on organ-confined bladder cancer (Ta–T2), for which complete TURBT was possible, to investigate the role of complete TURBT in RC candidates with organ-confined bladder cancer. If complete TURBT did not result in improved outcomes for these patients, it should be performed with caution to avoid associated morbidity. If the opposite were true, complete TURBT should be performed before RC to improve oncological outcome.

Pak et al.[19] studied patients with pT3 bladder cancer, but only 43% (40/93) of patients underwent immediate RC after neoadjuvant chemotherapy. Furthermore, final cT stage before neoadjuvant chemotherapy in the complete TURBT group was much lower than that of the incomplete TURBT group. The difference between these cohorts may explain why their conclusions differed from ours.

In this study, complete TURBT was related to histologic variants, tumor size, down-staging, and up-staging. Using logistic regression analysis, we found that tumor grade, size, and histological variants were independent predictors for complete TURBT. These findings demonstrated that increased tumor size and variant histology were associated with lower rates of complete TURBT.

Survival analysis results demonstrated that age and histologic variants were independent predictors of DFS, and down-staging and complete TURBT were not associated with lower rates of recurrence. Our study revealed that RC candidates with organ-confined bladder cancer did not benefit from complete TURBT (Fig. 1). The down-staging rate of the complete TURBT group in this study was 16.8% (24/143), whereas 3.0% of patients with a complete TURBT achieved down-stage status in a study by Zamboni et al.[18] Both studies had much lower down-staging rates than other studies (22.3%–77.3%), which found that patients with complete TURBT and/or down-staging had better oncological outcomes.[14–17] This lower down-staging rate may have obscured a possible benefit of complete TURBT before RC.

Lee et al.[14] reported that 34 of 48 patients who underwent complete TURBT had a lower pathologic stage, whereas only 4 of 25 patients achieved down-staging status in the incomplete resection group. Graffeille et al.[23] conducted a multivariate analysis adjusting for multifocality, weight of endoscopic resection specimen, cT4 stage on preoperative imaging, interval between endoscopic

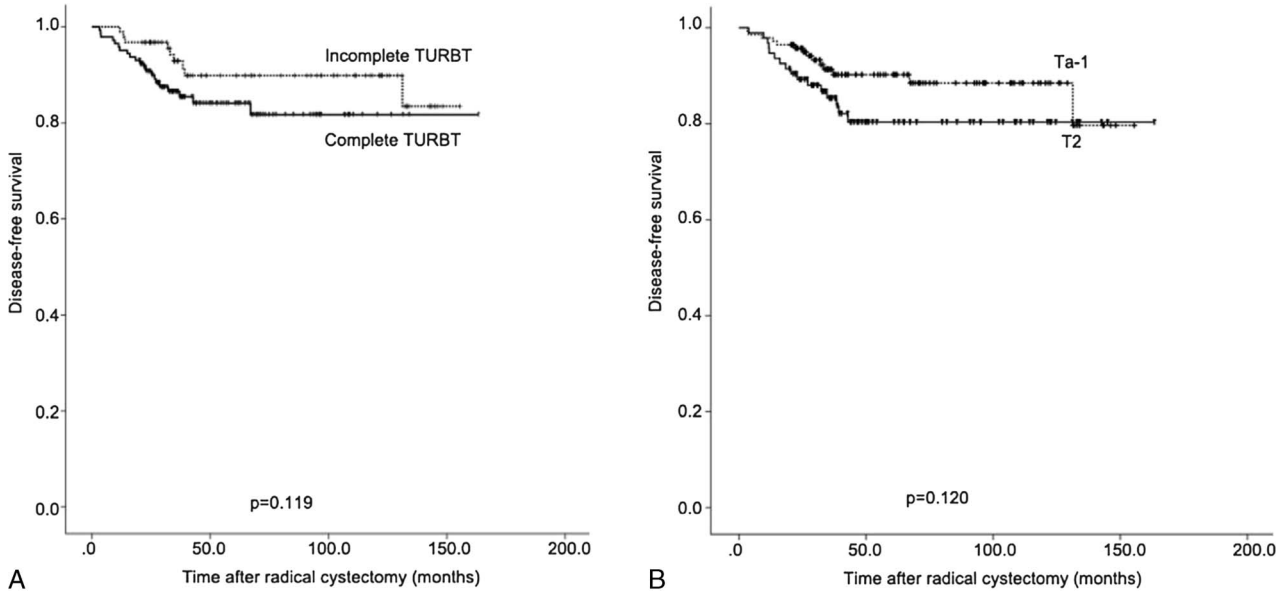

Figure 1. Disease-free survival analysis of different subgroups. (A) Disease-free survival stratified by complete TURBT status. (B) Disease-free survival stratified by maximal pathological T stage. TURBT = transurethral resection of bladder tumor.

resection and RC, neoadjuvant chemotherapy, pT stage, and associated carcinoma in situ, which demonstrated that macroscopically complete endoscopic resection remained the strongest predictor of both pT0 disease (odds ratio, 3.1; $p = 0.02$) and down-staging (odds ratio, 7.1; $p < 0.0001$) in RC specimens. Our results were similar to both of these previous studies, which revealed a significant correlation between complete TURBT and down-staging, whereas Zamboni et al.[18] reported that only 8 of 433 patients who underwent complete TURBT had lower pathologic stage, and 6 of 294 patients in the incomplete group had down-staging status ($p = 0.852$).

Theoretically, complete TURBT might reduce the possibility of field seeding by decreasing tumor exposure during the operation. As reported by Engilbertsson et al.,[24] circulating cancer cells increased during TURBT, and complete TURBT exhibited a potential to increase tumor cell spread, especially when bladder perforation occurred. However, complete TURBT was associated with early-stage disease and a lesser tumor burden, which is associated with better oncological outcomes. It is possible that the benefits of complete TURBT offset the harms; thus, no significant correlation between complete TURBT and improved oncological outcome was discovered in our study.

Strengths of this study include the fact that the confounding influences of neoadjuvant/adjuvant therapy, locally advanced tumor stage, and positive surgical margins were excluded, and a relatively long period of follow-up data was available for this cohort. Moreover, data were prospectively collected from our Bladder Cancer database, and follow-up was regularly updated. Finally, all recurrences were collected in this study, and local recurrence alone is rare. In terms of study limitations, all cases received care in a single cancer center, and TURBT and RC were performed by different surgeons, who were primarily residents, although quality was ensured through supervision by experienced surgeons. In addition, second TURBT was not performed according to consistent criteria. However, our study provided valuable information to evaluate the role of complete TURBT in RC candidates with organ-confined disease.

Based on our data, complete TURBT was correlated with a higher rate of down-staging before RC but did not improve oncological outcomes for patients with organ-confined bladder cancer. Thus, for cystectomy candidates, radical TURBT before RC might not be necessary.

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None.

Statement of ethics

Written informed consent was obtained from the patients, and approval of the research protocol was obtained from the Sun Yat-Sen University Cancer Center Institutional Review Board (approval no. GZR2018-053). All procedures performed in this study involving human participants were in accordance with institutional ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest statement

No conflict of interest has been declared by the authors.

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Author contributions

XY, MC and JY contributed equally. XY, MC and JY were responsible for data collection and analysis, interpretation of the results, and writing the manuscript. XY and YY were responsible for conducting the study design, data analysis and interpretation. All authors read and approved the final manuscript.

Availability of data and materials

The authenticity of this article has been validated by uploading key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn). The RDD approval number is RDDA2020001563.

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