

# Complete TURBT before Radical Cystectomy is not a Risk Factor for Organ-Confined Bladder Cancer: A Case Control Study

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## Research Article

**Keywords:** complete TURBT, radical cystectomy, downstaging, bladder cancer

**Posted Date:** February 19th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-231788/v1>

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# Abstract

## Background

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

## Patients and Methods

Patients who underwent radical cystectomy (RC) in our center from January 2008 to December 2018 were retrospectively reviewed. Those with disease  $>T2N0M0$  or positive surgical margin and those who were administered neoadjuvant/adjuvant chemotherapy or radiotherapy were excluded. Complete TURBT was defined as no visible lesion under endoscopic examination after TURBT or specimen of RC. Kaplan–Meier and log-rank tests assessed disease-free survival. Logistic and Cox regression analysis were performed to identify potential predictors.

## Results

In total, 236 patients were included, and 207 patients were male. The median age was 61 years old. The median number and size were 1 and 3cm respectively, and maximal pathological T stage was T2 in 94 patients. Complete TURBT was related to tumor size ( $p=0.041$ ), histological variants ( $p=0.026$ ) and downstaging ( $p<0.001$ ). Tumor size, grade and histological variants were independent predictors of complete TURBT. With a median follow-up of 42.7 months, 30 patients experienced recurrence. Age and histological variants were independent predictors of disease-free survival ( $p=0.022$  and  $0.032$ , respectively), and complete TURBT was not an independent predictor of disease-free survival ( $p=0.156$ ). Downstaging was not associated with survival outcome.

## Conclusions

Complete TURBT is related to an increased rate of downstaging before radical cystectomy, and it was not associated with better oncological outcomes for patients with organ-confined bladder cancer.

## Background

Transurethral resection of bladder tumor (TURBT) is often the initial treatment for bladder cancer. Given its role in treatment and diagnosis, the extent and depth of TURBT, as well as the pathological result are important for management via intravesical instillation, neoadjuvant therapy and radical cystectomy [1–3]. Radical cystectomy (RC) is the standard option for muscle invasive bladder cancer (MIBC) and some high-risk non-muscle invasive bladder cancer (NMIBC). For locally-advanced disease, neoadjuvant chemotherapy is recommended, and downstaging is associated with good prognosis [4–9]. For  $\leq pT2N0M0$  disease, complete TURBT was related to a higher rate of downstaging after RC, and it was associated with good outcomes [10–13]. However, in a recent study, the role of complete TURBT in oncological outcome was not significant, and incomplete TURBT was associated with a higher rate of

pT3/4, which was a greater predictor of worse outcome than incomplete TURBT [14, 15]. In clinical practice, advanced stage tied to poor prognosis, as well as incomplete TURBT. In contrast to pT3-4 bladder cancer,  $\leq$ pT2N0M0 disease could be potentially completely dissected through TURBT. However, whether these patients could benefit from complete TURBT before RC is controversial.

Hence, we evaluated the role of complete TURBT before radical cystectomy in patients with maximal pathological stage  $\leq$  T2N0M0 bladder cancer, in which radical TURBT was possible. Given that its role was most important for counseling prior radical cystectomy, TURBT parameters and the final pathological result after RC were taken into analysis. In addition,  $>$ T2N0M0 disease was not included in this study, because complete resection was not always achieved using TURBT in these patients. To avoid related biases, patients with neoadjuvant chemotherapy/radiotherapy were excluded, and the duration between last TURBT and RC was less than 6 weeks.

## Methods

Patients with bladder cancer treated in our cancer center from January 2008 to December 2018 were retrospectively reviewed. Of them, 526 cases underwent RC and urinary diversion in 4 weeks after last TURBT. In total, 287 cases were excluded for stage  $>$  T2N0M0, positive surgical margin, or neoadjuvant chemotherapy or radiotherapy. Three patients died in 30 days after RC were excluded. Clinical characteristics, imaging, pathology, and follow-up were retrospectively collected from our bladder cancer database.

Complete TURBT was defined as: no visible lesion under endoscope examination after TURBT, and no gross tumor in the bladder specimen after RC. Downstaging was defined as a T stage after TURBT that was greater than the stage after RC, and upstaging was defined as a T stage after RC that was greater than the stage after TURBT.

Disease-free survival was the primary endpoint. Continuous and categorical variables were presented as medians (interquartile range; IQR) and numbers (%), and the comparisons between these 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 two-tailed;  $p < 0.05$  was considered significant.

## Results

In total, 236 patients were included, and 207 were male. The median age was 61 (53–69) years old. Median tumor number and size were 1 (1–2) and 3 (2–5) cm, respectively, and the pathological T stage was T2 in 94 patients. Complete TURBT and downstaging were accomplished in 143 and 25 cases, respectively. The downstaging rate was 17% in complete TURBT group, and 1% in the incomplete TURBT

group ( $p < 0.001$ ) (Table 1). And no adjuvant chemotherapy or radiotherapy was administered for these organ-confined bladder cancer after radical cystectomy.

With Chi-square test, complete TURBT was related to tumor size ( $p = 0.041$ ), variants ( $p = 0.026$ ), downstaging ( $p < 0.001$ ) and upstaging ( $p < 0.001$ ), and high grade and LVI were marginally associated with complete TURBT (Table 1). Second TURBT was related to a higher rate of complete TURBT (69% vs. 58%,  $p = 0.149$ ), and this result was not significant. Second TURBT was significantly related to downstaging (14/184 vs. 11/52,  $p = 0.005$ ) (Table 1S).

With a median follow-up of 42.7 (29.4–85.7) months, 13% (30/236) patients suffered relapse, the duration between RC and recurrence was from 3.2-131.3 months, with a median time of 22.2 months. Most (28/30) recurrence was detected 4 years after RC, and 16 tumors recurred in 2 years.

Based on Table 1, logistic analysis revealed that tumor size, grade and histological variants were independent predictors of complete TURBT (Table 2S). In univariate analysis, age, histological variants, T stage and complete TURBT were potentially associated with disease-free survival (DFS) ( $p < 0.13$ ). In multivariate analysis, independent predictors of DFS were age, variants ( $p = 0.022$  and  $0.032$ , respectively), and complete TURBT was not an independent predictor of disease-free survival ( $p = 0.156$ ) (Table 2, Fig. 1).

## Discussion

The role of complete TURBT for NMIBC before intravesical therapy and repeat TURBT are confirmed by several studies [1–3, 16, 17]. However, its role before radical cystectomy (RC) is controversial. And the completeness of TURBT was affected by tumor burden, which was also associated with oncological outcome [9, 10, 14]. In several retrospective analyses, complete TURBT was associated with a higher rate of downstaging, which was related to good prognosis [10, 11]. For locally-advanced tumors, complete TURBT was not theoretically possible, and incomplete TURBT was often related to advanced stage (T3-4), which was a predictor of poor prognosis [14]. Thus, whether advanced stage or incomplete TURBT is a more effective predictor of prognosis was assessed. A recent study revealed that advanced stage was a greater predictor than incomplete TURBT, but some biases were inevitable, such as adjuvant therapy, positive surgical margin, and relatively subjective definition of complete TURBT [14]. Thus, we focused on organ-confined bladder cancer (Ta-T2), for which complete TURBT was available, to investigate the role of complete TURBT for RC candidates with organ-confined bladder cancer. For these patients, the primary tumor could be removed completely with RC, the role of complete TURBT would guide clinical practice for RC candidates. If complete TURBT did not improve outcome for these patients, it should be performed with caution to avoid related morbidities. In contrast, complete TURBT should be accomplished as much as possible before RC to improve oncological outcome.

In this study, complete TURBT was related to histological variants, tumor size, downstaging and upstaging. Using logistic analysis, we found that grade, size and histological variants were independent predictors of complete TURBT. These findings demonstrated that the increased tumor size and variant

histology were associated with reduced rates of complete TURBT. Second TURBT was not associated with complete TURBT, but was associated with downstaging. Survival analysis results demonstrated that age, complete TURBT and histological variants were independent predictor of disease-free survival (DFS), and downstaging was 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).

In studies of neoadjuvant chemotherapy for locally-advanced bladder cancer, downstaging and complete response were associated with good outcome. For those patients yielding downstaging, neoadjuvant chemotherapy was related to a better outcome than TURBT alone [5, 9]. These studies revealed that the response to chemotherapy and TURBT before RC led to better cancer control. But the role of complete TURBT was not significant in some cohorts in which early-stage disease was more effective predictor of prognosis than complete TURBT [14]. In addition to tumor stage, adjuvant therapy and surgical margin status also affected outcome. In this study, these factors were excluded, and we found that complete TURBT was associated with worse DFS, as well as age and T stage, though it was not statistically significant.

Theoretically, complete TURBT might reduce the possibility of field seeding by decreasing tumor exposure during the operation. Additionally, complete TURBT was associated with early-stage disease and less tumor burden, so the role of complete TURBT in oncological outcome was covered. As reported, the circulating cancer cells increased during TURBT, and complete TURBT exhibited potential to increase tumor cell spreading, especially when bladder perforation occurred [18]. Compared to TURBT, RC could remove bladder cancer radically for organ-confined disease and is considerably more reliable than complete TURBT [15, 19]. Based on this study, we had confirmed that complete TURBT did not improve survival for organ-confined bladder cancer patients before RC. And the bias between two groups, such as higher proportion of LVI, concomitant CIS and high-grade tumor, were substantially presented.

In most studies, downstaging had an important impact on survival, even neoadjuvant chemotherapy was not performed [4, 20, 6]. In this study, complete TURBT was related to a higher rate of downstaging, which was from T2/T1 to T1/Ta, and downstaging was not significantly associated with oncological outcome significantly. In Hautmann's research, a series of RC was performed without neoadjuvant chemotherapy, and patients with maximal tumor stage pT2aN0 had worse survival than patients with preoperative T2aN0 and downstaging by TURBT [20]. However, multivariable analysis was not available in this large population study to confirm the role of downstaging by TURBT, and tumor stage and size were associated with both downstaging and survival. In this study, it was possible that all tumors could be resected completely by RC regardless of downstaging, so the role of complete TURBT and downstaging was not significant to oncologic outcome.

Some advantages of this study included the fact that biases of neoadjuvant/adjuvant therapy, tumor stage and positive surgical margin were excluded, and a relative long-term follow-up was available in this cohort. In addition, the limitations of this retrospective analysis should be mentioned. All cases received care in a single cancer center, and TURBT and RC were performed by different surgeons, who were

primarily residents, but the quality was supervised by experienced surgeons. And second TURBT was not performed under consistent criteria. What's more, these 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. However, our study provided reliable information to evaluate the role of complete TURBT for RC candidates with organ-confined disease.

## Conclusions

Complete TURBT is related to a higher rate of downstaging before radical cystectomy, and don't improve oncological outcomes for patients with organ-confined bladder cancer. For cystectomy candidates, radical TURBT might not be necessary.

## Abbreviations

TURBT

transurethral resection of bladder tumor

RC

radical cystectomy

NMIBC

non-muscle invasive bladder cancer

MIBC

muscle invasive bladder cancer

IQR

inter-quartile range

DFS

disease-free survival

## Declarations

### Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Writing informed consent from the patients and approval from the Sun Yat-sen University Cancer Center Institute Research Ethics Committee (approval number: GZR2018-053) was obtained.

### Consent to publish

Not applicable.

### Availability of data and materials

The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform ([www.researchdata.org.cn](http://www.researchdata.org.cn)), with the approval RDD number as **RDDA2020001563**.

### Competing interests

The authors declare that they have no conflict of interests.

### Funding

This study was supported by the Fundamental Research Funds for the Central Universities (Grant NO. 20ykpy179) and Medical Science Funding of Guangdong province (A2020139).

### Authors' contributions

HTL, ZFC, ZPX and YLY were responsible for data collection and analysis, interpretation of the results, and writing the manuscript. YLY and ZKQ were responsible for conducting the study design, data analysis and interpretation. All authors have read and approved the final manuscript.

### Acknowledgments

Not applicable.

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# Tables

Due to technical limitations, table 1 and 2 is only available as a download in the Supplemental Files section.

# Figures

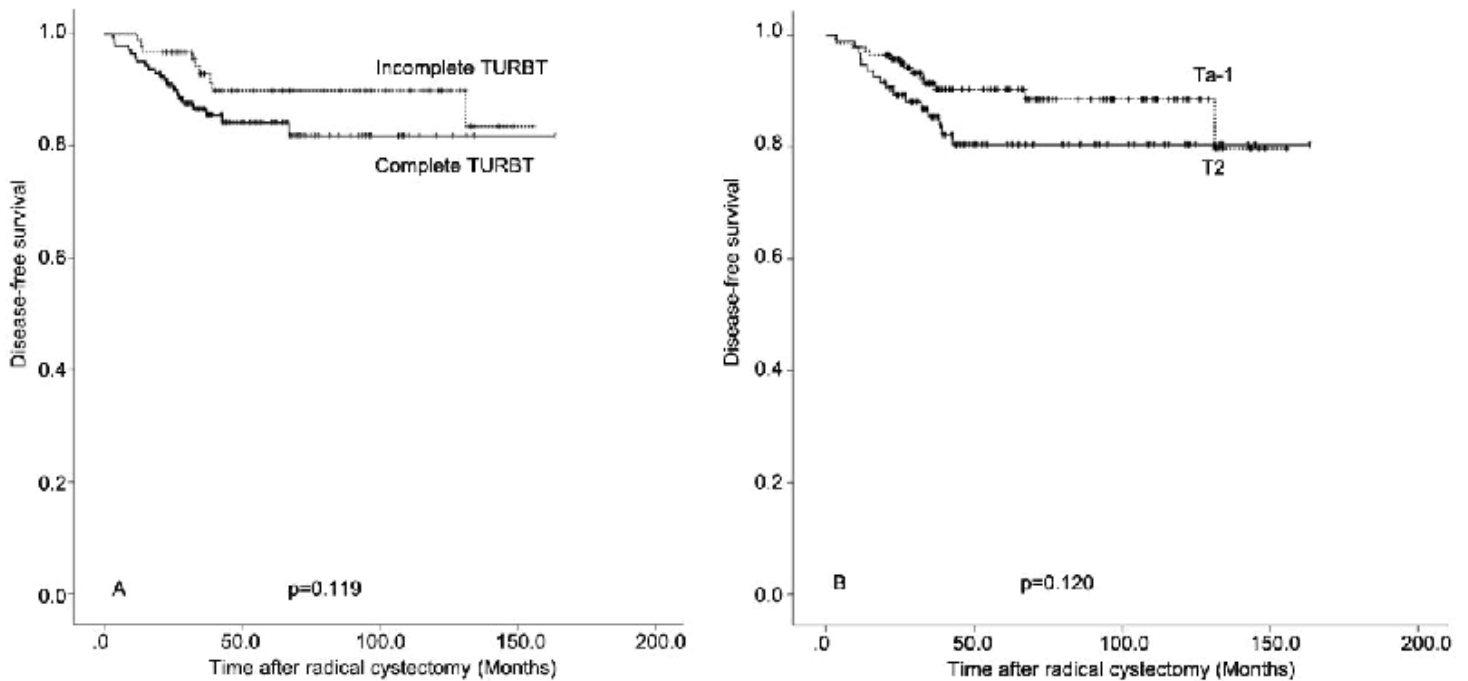


Figure 1

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.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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