Two-step transurethral resection of bladder tumor improves surgical quality and decreases disease recurrence: a retrospective study

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Research article

Keywords: Urinary Bladder Neoplasms, Bladder cancer, Cystoscopy, Cystoscopic Surgery, Recurrence

Posted Date: December 1st, 2019

DOI: <https://doi.org/10.21203/rs.2.17859/v1>

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Abstract

Background: Two-step transurethral resection of bladder tumor (TURBT) is a method of TURBT that is performed in two steps- exophytic tumors first and tumor bases second. The purpose is to improve tumor clearance. In current study, we evaluated outcomes of two-step TURBT in patients with non-muscle invasive bladder cancer (NMIBC).

Methods: We retrospectively reviewed a prospective database. Patients who had newly diagnosed NMIBC with at least a 2-year follow-up period during Jan. 1, 2012 and Dec. 31, 2017 were enrolled. Patients with concomitant or subsequent upper urinary tract urothelial carcinoma (UTUC) were excluded. Patients were categorized into the two-step TURBT (TR) group and the conventional TURBT (CR) group. The primary endpoints were the recurrence rate and the progression rate. The secondary endpoints were the recurrence-free survival (RFS), the progression-free survival (PFS), and the detrusor muscle sampling rate.

Results: A total of 205 patients were included, with 151 patients in the TR group and 54 patients in the CR group. The median follow-up period was 40.5 months. There were lower recurrence rate (29.8% vs 48.1%, $P = 0.015$), higher detrusor muscle sampling rate (70.7% vs 55.6%, $P = 0.043$), and longer RFS ($P = 0.007$) in the TR group. TR was also associated with longer RFS in both univariate ($HR=0.524$, $p=0.009$) and multivariate ($HR=0.426$, $p=0.003$) analysis.

Conclusions: Two-step TURBT results in lower recurrence rate and longer RFS for NMIBC, especially for Ta disease. Two-step TURBT also improves detrusor muscle sampling rate, which is essential for adequate resection and accurate staging.

Trial Registration:

The Institutional Review Board (IRB) of National Taiwan University Hospital has approved this study on (approval No: 201901119RINA). The date of registration in Nov.19th, 2019.

Introduction

Bladder cancer is the eleventh most common cancer in the world and the seventh most common cancer in man. Approximately 70% are non-muscle invasive at the first diagnosis, with 70% as stage Ta, 20% as T1, and 10% as carcinoma in situ (CIS)[1]. Among NMIBC, transurethral resection of bladder tumor (TURBT) is the standard treatment. Detrusor muscle sampling in surgical specimen is required for an adequate resection, which is representative of correct staging and better outcomes [2]. However, detrusor muscle sampling rates vary approximately between 50%-90% [2–11], resulting from plenty of factors, such as different methods of resection, different surgeons, or even different tumors. Different surgical protocols have been established to increase adequate resection. Extended transurethral resection consists of complete resections of the main tumor, bladder ground, and normal-appearing margins [12], which is time-consuming. In selected exophytic tumors, en bloc resection using monopolar or bipolar current, Thulium-YAG laser, or Holmium-YAG laser is also a feasible method [13]. However, en bloc

resection is skill-intensive and is also expensive if laser is used. In our medical center, we conduct two-step TURBT, which means complete resections of tumors are performed in two steps during the operation: exophytic tumors first and tumor bases second. In this study, we compared outcomes between two-step TURBT (TR) and conventional TURBT (CR) method as regards detrusor muscle sampling rate, cancer recurrence, and cancer progression.

Materials And Methods

Definition

TR was defined as that the exophytic part of the tumor and the underlying tumor base were resected and retrieved separately, which resulted in two specimen groups: the tumor and the tumor base (Fig. 1). CR was defined as that the tumor was resected without the intention of two-step management between the exophytic part of the tumor and the underlying tumor base. Recurrence was defined as gross tumors found by followed cystoscopy examination, in which tumors were resected or sampled and further confirmed as urothelial carcinoma by pathologists. Progression was defined base on the IBCG (International Bladder Cancer Group) definition as (1) increase in T stage from CIS or Ta to T1 (lamina propria invasion), (2) development of T2 or greater or lymph node (N+) disease or distant metastasis (M1), or (3) an increase in grade from low to high. Recurrence-free survival (RFS) was defined as the period from the date of the initial TURBT to the date of the operation in which the first cancer recurrence was found. Progression-free survival (PFS) was defined as the period from the date of the initial TURBT to the date of the operation or image study in which the first cancer progression was found.

Treatment and follow-up

In our hospital, TURBT was performed by well-trained senior resident doctors and using either two-step method or conventional method, depending on operators' preference and intraoperative condition. The second TURBT was conducted for all patients within 3 months after the first operation. Mapping biopsy was done to ensure there was no CIS. Follow-up strategies and therapies were based on current guidelines from American Urological Association (AUA) and European Association of Urology (EAU) if there were no contraindications.

Study design

We conducted a retrospective analysis from a prospective database. Patient profiles and disease characteristics were collected. Patient profiles included ages at the time of diagnosis, genders, BMI, history of smoking and comorbidities (DM, hypertension, elevated serum creatinine). Disease characteristics included tumor number, tumor size, pathologic stage (based on the 2009 TNM classification), grade (based on the 2004 WHO/ISUP classification), use of intravesical chemotherapy or Bacillus Calmette–Guérin (BCG), presence of concurrent CIS, and inclusion of detrusor muscle in TUR specimens. The primary endpoints were the recurrence rate and the progression rate. The secondary endpoints included the RFS, the PFS, and the detrusor muscle sampling rates.

Patient recruitment

Patients who received first-time TURBT and were subsequently diagnosed with NMIBC during January 2012 and December 2017 were enrolled. The inclusion criteria were: (1) histologically diagnosed with urothelial carcinoma, (2) newly diagnosed non-muscle invasive bladder cancer, and (3) a follow-up period of more than 2 years. The exclusion criteria were: (1) lack of the first operative or pathologic report, (2) upper tract urothelial carcinoma, which was diagnosed before, concurrently, or after the initial diagnosis of the bladder cancer, (3) muscle invasive bladder cancer, (4) advanced operation for the bladder cancer, e.g. cystectomy, (5) any metastatic cancer, or (6) histology other than urothelial carcinoma according to the pathology report.

Statistical analysis

Data were analyzed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). The distribution of patients' characteristics and clinicopathological covariates between the two groups were analyzed with the Chi-squared test for categorical variables. Univariate and multivariate logistic regression models were used for calculating odds ratios of recurrence. The RFS and PFS were analyzed with Kaplan-Meier analysis. Factors included in the univariate survival analysis using Cox proportional hazards model were ages, genders, history of smoking, BMI, hypertension, serum creatinine level, diabetes mellitus, clinical T1 stage, concurrent CIS, tumor number, tumor size, detrusor muscle sampling, and methods of TURBT. Multivariate regression analysis using Cox proportional hazards model (the stepwise forward procedure) was also performed to identify prognostic factors for the RFS and the PFS. In all cases, two-tailed $P < 0.05$ was considered statistically significant.

Results

Patient selection

During January 2012 and December 2017, 837 patients who had a diagnosis of bladder cancer were screened. There were 205 patients with pure NMIBC who had follow-up periods of more than 2 years (Fig. 2), including 151 (73.6%) patients who received two-step TURBT and 54 (26.4%) patients who received conventional TURBT.

Baseline characteristics

The mean age of all 205 patients was 67 years old. The median follow-up period was 40.5 months. The overall detrusor muscle sampling rate was 66.7%. The baseline characteristics were similar between two groups in terms of age, gender, history of smoke, BMI distribution, history of hypertension, baseline serum creatinine, initial T stage, initial tumor size, and initial tumor number. There were a lower rate of DM ($P = 0.049$), a lower rate of high-grade cancer ($P = 0.008$), and a higher rate of detrusor muscle sampling ($P = 0.043$) in the first operative specimens in the TR group (Table 1). Pathological details were reported in Supplementary Table 1.

Prognosis analysis

Outcome analysis revealed that the TR group was associated with lower recurrence rate ($P = 0.015$) (Table 2). The progression rates were not different between the two groups ($P = 0.913$). Unexpectedly, the detrusor muscle sampling was not associated with the recurrence rate and the progression rate (Supplementary Table 2). Univariate logistic regression model and multivariate logistic regression model controlling for potential confounders are presented in Table 3. TR was associated with lower odds of recurrence in both univariate ($OR = 0.457$, $P = 0.016$) and multivariate models (adjusted $OR = 0.472$, $P = 0.029$). The median RFS for the TR group was not reached, and the median RFS for the CR group was 51 months. The Kaplan-Meier analysis showed that TR was associated with longer RFS (Log Rank test, $P = 0.007$) but not the PFS (Log Rank test, $P = 0.886$) (Fig. 3a and 3b). The univariate Cox proportional hazards model also showed that TR was associated with longer RFS ($HR = 0.524$, 95% $CI = 0.323-0.851$, $P = 0.009$), whereas male gender ($HR = 2.225$, 95% $CI = 1.179-4.198$, $P = 0.014$), T1 stage ($HR = 1.340$, 95% $CI = 1.078-1.666$, $P = 0.008$), and tumor number ≥ 3 ($HR = 2.131$, 95% $CI = 1.254-3.621$, $P = 0.005$) were associated with shorter RFS (Table 4). The multivariate analysis using Cox proportional hazards model revealed that TR decreased the risk of recurrence ($HR = 0.426$, 95% $CI = 0.242-0.751$, $P = 0.003$), but tumor number ≥ 3 increased the risk of recurrence ($HR = 2.122$, 95% $CI = 1.214-3.708$, $P = 0.008$) (Table 4).

Subgroup analysis

We divided patients into subgroups according to clinical T stages. There were 133 patients diagnosed with Ta disease, including 104 (78.2%) patients in the TR group and 29 (21.8%) patients in the CR group. The detrusor muscle sampling rate was 67.7%. The recurrence rate was significantly lower in the TR group (24.0% vs 44.8%, $P = 0.028$) (Supplementary Table 3). The Kaplan-Meier analysis revealed significantly longer RFS in the TR group (Log Rank test, $P = 0.018$) (Fig. 4a). Detrusor muscle sampling was not associated with the recurrence rate (31.1% vs 23.2%, $P = 0.348$) and the RFS (Supplementary Table 3 and Supplementary Fig. 1a). There were 66 patients diagnosed with T1 disease, including 43 (65.2%) patients in the TR group and 23 (34.8%) patients in the CR group. The detrusor muscle sampling rate was 65.2%. However, the recurrence rate was not associated with methods of resection or detrusor muscle sampling (Fig. 4b, Supplementary Table 4 and Supplementary Fig. 1b).

Discussion

In our study, 151 out of the 205 patients received TR. The detrusor muscle sampling rate on the TR group was 70.7%, which was significantly higher than that of the CR group (55.6%). The recurrence rate on the TR group was 29.8%, which was significantly lower than that of the CR group (48.1%). Both univariate and multivariate logistic regression models showed that TR was associated with lower odds of recurrence. Besides, both univariate and multivariate Cox proportional hazards models also showed that TR was associated with longer RFS.

The NMIBC recurrence rates within 2 years, 5 years, and 10 years after the initial diagnosis were 61.1%, 69.5%, and 74.3% [14]. TURBT is the standard treatment for NMIBC. Current consensus has been made that an adequate TURBT must include detrusor muscle in the specimen, except for the Ta low-grade diseases. The lack of detrusor muscle in the specimen is also associated with higher risks of disease understaging, residual disease, and recurrence [2, 15–17]. Besides, Mariappan et al (2010) have reported that unskilled surgeries resulted in lower detrusor muscle sampling rate and higher recurrence rate (detrusor muscle sampling rate 56.8% vs 72.6%, early recurrence 39.3% vs 24.8%,) [2]. Therefore, finding out a method that can improve detrusor muscle sampling rate is important.

Complete resection either by fractioned or en bloc resection has been recommended in EAU guidelines. Detrusor muscle sampling rates for en bloc resection are nearly 96%-100% in past researches [6–8, 10, 18]. By contrast, detrusor muscle sampling rates varied between 54%-90% for conventional TURBT [3, 5, 9, 11]. As for oncological outcomes, Sureka et al (2014) have reported a lower recurrence rate in patients receiving en bloc resections, compared with patients receiving conventional TURBT (28.6% vs 62.5%) [19]. However, two larger RCTs showed no significant difference in terms of recurrence between two methods [4, 20]. Despite potential advantages from en bloc resection, there is no strong evidence proving its superiority to conventional TURBT. Moreover, en bloc technique is skill-intensive and is also expensive if the laser is used for resection.

Richterstetter et al. (2012) have reported an extended TURBT protocol, which consisted of complete resections in fractions of the main tumor, bladder ground, and normal-appearing margins[12]. It provides good information about the vertical and horizontal extents of the tumor and has no association with focality of the tumor and the experience of the surgeon. Surprisingly, the recurrence rate of all unifocal primary disease was only 14.4%. Nevertheless, no data regarding the detrusor muscle sampling rate has been reported. The drawbacks of extended TURBT protocol are time-consuming and skill-intensive.

For our two-step TURBT, surgeons only need to resect and retrieve tumors and tumor bases separately. This procedure is easier, more convenient, and more cost-effective than extended TURBT protocol and laser en block methods. The detrusor muscle sampling rate was also higher in the TR group, indicating a higher rate of adequate sampling. Patients who received TR were significantly associated with lower recurrence and longer RFS, compared with patients who received CR. Despite that the characteristics between the two groups were not similar in terms of DM and initially high-grade cancer, the multivariate regression analysis has confirmed that TR is an independent prognostic factor for lower recurrence. The detrusor muscle sampling in our study was not a predictor for the recurrence and progression. We speculate the reason to be the majority of Ta disease in our study population and the exclusion of MIBC, suggesting tumor eradication could be obtained even without a resection deep to the layer of detrusor muscle. Furthermore, better outcomes in the TR group might be due to deeper resections of tumor bases that conduced to better tumor eradication. The subgroup analyses of Ta diseases and T1 diseases (Supplementary data) also supported our assumption.

There were some limitations in our study. First, the sample size in the CR group was smaller, and the distribution of patient characteristics was not similar between the two groups. Second, the technique from different surgeons might have led to potential bias. Third, it was not possible to distinguish the residual disease from recurrent disease. There are several advantages of our study. First, we have a strict follow-up protocol, and all the data were collected prospectively. In addition, second TURBT procedures were performed routinely for all patients, and additional mapping biopsies were taken from patients with CIS. These managements reduced the chance of misdiagnosis and improved the detection of recurrence and progression. Second, as more than 80% of recurrences would occur within the first two years [14], we included patients with at least 2-year follow-up periods. Finally, multivariate analysis was used to adjust potential confounders between the TR and CR groups.

Conclusion

Two-step TURBT results in lower recurrence rate and longer RFS for NMIBC, especially for Ta disease. Two-step TURBT also improves detrusor muscle sampling rate, which is essential for adequate resection and accurate staging.

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Abbreviations

BCG
Bacillus Calmette–Guérin
CR
conventional TURBT
CIS
Carcinoma in situ
DM
Diabetes mellitus
IBCG
International Bladder Cancer Group
MIBC
muscle invasive bladder cancer
NMIBC
non-muscle invasive bladder cancer
PFS
progression-free survival
RFS
recurrence-free survival

TURBT

transurethral resection of bladder tumor

TUR

transurethral resection

TR

two-step TURBT

UTUC

upper urinary tract urothelial carcinoma

Declarations

Ethics approval and consent to participate

The present study protocol has been reviewed and approved by the Institutional Review Board (IRB) of National Taiwan University Hospital (approval No: 201901119RINA). The IRB have waived the informed consent requirement because of retrospective design of our study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

There is no funding for the current study.

Authors' contributions

Chow PM contributed to design of the study, interpretation of the data, and revision of the manuscript. Huang WL contributed to data acquisition, data analysis, data interpretation, and manuscript drafting. Huang CY, Huang KH, Pu YS, and Chang HC contributed to revision and supervision of the study. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank all of consultants and specialist registrars of the Department of Urology, National Taiwan University Hospital for their contribution in the database construction and study consultation. Likewise, we are also grateful for all help from medical staff in National Taiwan University Hospital.

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Tables

Due to technical limitations, tables are only available as a download in the supplemental files section

Figures

Fig 1

Bladder tumor

The resection of the
protruding tumor

The resection of the
tumor base

Figure 1

Steps of two-step TURBT. Legend: The first step is the resection of the protruding tumor. The second step is the resection of the tumor base. Specimens from two steps should be retrieved and analysis separately

Fig 2

Figure 2

The flowchart of patient selection. Legend: A total of 839 patients were screened during the study period. There were 356 patients classified as “pure NMIBC” with 205 patients who had follow-up periods more than 2 years.

Figure 3

Kaplan-Meier analysis for recurrence-free survival and progression-free survival Legend: Kaplan-Meier analysis for (a) recurrence-free survival. TR resulted in longer RFS than CR. Log Rank test (Mantel-Cox), $P= 0.007$ (b) progression-free survival. There is no difference between TR and CR in terms of PFS. Log Rank test (Mantel-Cox), $P= 0.886$.

Figure 4

Kaplan-Meier analysis for recurrence-free survival in subgroup analysis. Legend: (a) TR resulted in longer recurrence-free survival in the Ta subgroup ($n=133$). Log Rank test (Mantel-Cox), $P= 0.018$ (b) There is no difference between TR and CR in terms of RFS in the T1 subgroup ($n=66$). Log Rank test (Mantel-Cox), $P= 0.692$