Two-step transurethral resection of bladder tumor can result in a better surgical quality and lower recurrence in patients with non-muscle invasive bladder cancer: a retrospective study

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Research

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Abstract

Background Current protocols for transurethral resection of bladder tumor (TURBT) are still unstandardized, and outcomes are also uneven in different protocols. In our medical center, we performed two-step TURBT that the resection of bladder tumor is made in two steps- exophytic parts first and tumor bases second. The purpose is to improve tumor eradication and increase detrusor muscle sampling rates. The aim of current study is to evaluate clinical outcomes and detrusor muscle sampling rate of two-step TURBT in patients with non-muscle invasive bladder cancer (NMIBC). Methods We conducted a retrospective review from a prospective database. From January 2012 to December 2017, patients who had newly diagnosed NMIBC with a follow-up period of more than 2 years were enrolled. Patients with concomitant or subsequent upper urinary tract urothelial carcinoma (UTUC) were excluded. Patients were categorized into the two-step TURBT (TR) and the conventional TURBT (CR) groups. The primary endpoints were recurrence and progression rates. The secondary endpoints were recurrence-free survival (RFS), progression-free survival (PFS), and the detrusor muscle sampling rate. Results There were 205 patients included in our study, 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 (P = 0.015), higher detrusor muscle sampling rate (P = 0.043), and better RFS (Log-Rank P= 0.007) in the TR group. Two-step TURBT was also associated with better RFS in both univariate (P =0.009) and multivariate (P =0.003) Cox proportional hazards regression. Conclusions In patients with NMIBC, Two-step TURBT results in higher detrusor muscle sampling rate and better disease outcomes. The findings suggest that Two-step TURBT is a better surgical method for treating NMIBC.

Introduction

Bladder cancer is the eleventh most common cancer in the world and the seventh most common cancer in male population. 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). For non-muscle invasive bladder cancer (NMIBC), transurethral resection of bladder tumor (TURBT) is the standard treatment. Furthermore, detrusor muscle sampling in surgical specimens is required for an adequate surgery, which is representative of correct staging and leading to better outcomes (2). However, detrusor muscle sampling rates vary approximately between 50%-90% in different studies (2–11), resulting from plenty of factors, such as different methods of resection, different surgeons, or even different growth of tumors. Several surgical protocols have been established to increase adequate resection. One of the protocols is the extended transurethral resection, which consists of complete resections of the main tumor, bladder ground, and normal-appearing margins (12). However, the extended transurethral resection may be time-consuming and complicated. For selected exophytic tumors, en bloc resection using monopolar or bipolar current, Thulium-YAG laser, or Holmium-YAG laser is also a feasible method (13). Nevertheless, en bloc resection is skill-intensive and is also expensive if laser is used. In our medical center, we conduct two-step TURBT (TR), which means complete resections of tumors are performed in two steps during the operation: exophytic parts first and tumor bases second. In our experience, TR is easy and can also provide pathologic details of different

layers. In current study, we aim to compared TR with conventional TURBT (CR) on disease outcomes and detrusor muscle sampling rate.

Materials And Methods

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.

Definition

TR was defined as a method that the exophytic part of the tumor and the underlying tumor base were resected and retrieved separately, which resulted in two specimen groups: the exophytic tumor and the tumor base (Fig. 1). The two specimen groups were studied separately by the same pathologist. CR was defined as that the tumor was resected without the intention of staged management for the exophytic part and the underlying base. Recurrence was defined as gross tumors found by followed cystoscopy, 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. The second TURBT was routinely conducted within 3 months after the first operation or within 6 weeks in patients with incomplete initial resection, high-grade disease without muscle in original specimens, large or multi-focal lesions, and any T1 disease. Mapping biopsy was routinely performed for patients with CIS in followed cystoscopy to ensure there was no recurrence. 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 status, including ages at the time of diagnosis, sex, BMI, history of smoking, comorbidities, type of TURBT, cancer stage, histologic grade of urothelial carcinoma, tumor number, tumor size, inclusion of detrusor

muscle in the original specimens, intravesical therapy, date of diagnosis, date of recurrence, and date of progression were collected. We divided the patients into the TR and CR groups. Outcomes were recurrence, progression, RFS, PFS, and the detrusor muscle sampling rate.

Patient selection

We enrolled patients who received the first-time TURBT for bladder cancer from January 2012 and December 2017. Patients who had newly diagnosed NMIBC with a follow-up period of more than 2 years were included. We excluded patients who had following conditions: (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) bladder cancer other than urothelial carcinoma.

Statistical analysis

Data were analyzed using SPSS version 22(SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using Chi-squared test. Univariate and multivariate logistic regression were used for calculating odds ratios of recurrence. RFS and PFS were analyzed using Kaplan-Meier analysis. Factors including age, sex, history of smoking, BMI, hypertension, serum creatinine level, diabetes mellitus (DM), clinical T1 stage, grade of urothelial carcinoma, concurrent CIS, tumor number, tumor size, intravesical therapy, detrusor muscle sampling, and methods of TURBT were analyzed using univariate Cox proportional hazards regression to determine risk factors for recurrence. Factors with $P < 0.2$ in the univariate Cox proportional hazards regression were selected for multivariate analysis to determine independent risk factors for recurrence. In all cases, two-tailed $P < 0.05$ was considered statistically significant.

Results

Patient selection and baseline characteristics

From January 2012 to December 2017, 839 patients were screened. A total of 205 patients with newly diagnosed NMIBC who had a follow-up periods of more than 2 years were included. Among these patients, 151 patients (73.6%) received TR, and 54 patients (26.4%) received CR (Fig. 2).

The median age at the diagnosis of bladder cancer was 67 years. The median follow-up period was 40.5 months. The detrusor muscle sampling rate was 66.7%. Characteristics were similar between the two groups, except that the TR group had lower rates of DM ($P = 0.049$) and high-grade cancers ($P = 0.008$) and a higher rate of detrusor muscle sampling ($P = 0.043$) (Table 1). Recurrence and progression were observed after the initial diagnosis in 71 patients (34.6%) and 11 patients (5.3%), respectively. Pathological details were reported in Supplementary Table S1.

Prognosis analysis

The TR group had lower recurrence rate (P = 0.015). Progression rates of the two groups were not statistically different (P = 0.913) (Table 1). Detrusor muscle sampling was not associated with recurrence and progression (Supplementary Table S2). TR was associated with lower odds of recurrence in both univariate (odds ratio (OR) = 0.457, 95% CI 0.242–0.865, P = 0.016) and multivariate logistic regression (adjusted OR = 0.472, 95% CI 0.241–0.924, P = 0.029) (Table 2). The median RFS was not reached in the TR group and was 51 months in the CR group. Kaplan-Meier analysis showed that TR was associated with better RFS (Fig. 3a, log-rank P = 0.007); PFS was similar between the two groups (Fig. 3b, log-rank P = 0.886). Univariate Cox proportional hazards regression showed that TR was associated with better RFS (hazard ratio (HR) = 0.524, 95% CI = 0.323–0.851, P = 0.009), whereas male sex (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 worse RFS (Table 3). Multivariate Cox proportional hazards regression revealed that TR could independently decrease the risk of recurrence (HR = 0.444, 95% CI = 0.248–0.795, P = 0.006), whereas tumor number ≥ 3 was an independent risk factor for recurrence (HR = 2.300, 95% CI = 1.289–4.104, P = 0.005) (Table 3).

Subgroup analysis

We furtherly divided the patients into the Ta and T1 subgroups. Of all 205 patients, 133 patients had Ta diseases, including 104 patients (78.2%) received TR and 29 patients (21.8%) received CR. The recurrence rate was significantly lower in patients who received TR (24.0% vs 44.8%, P = 0.028) (Supplementary Table 3). Kaplan-Meier analysis revealed significantly better RFS in patients who received TR (Fig. 4a, log-rank P = 0.018). The detrusor muscle sampling rate was 67.7%. Detrusor muscle sampling was not associated with recurrence (31.1% vs 23.2%, P = 0.348) and RFS (Supplementary Table S3 and Supplementary Figure S1a). Of the other 66 patients who had T1 diseases, 43 patients (65.2%) received TR, and 23 patients (34.8%) received CR. The detrusor muscle sampling rate was 65.2%. Recurrence and RFS were not associated with methods of resection or detrusor muscle sampling in the T1 subgroup (Fig. 4b, Supplementary Table S4 and Supplementary Figure S1b).

Discussion

In our study, the detrusor muscle sampling rate of the TR group (70.7%) was significantly higher than that of the CR group (55.6%); the recurrence rate of the TR group (29.8%) was significantly lower than that of the CR group (48.1%). Both univariate and multivariate logistic regression showed that TR was associated with lower odds of recurrence. Besides, both univariate and multivariate Cox proportional hazards regression also showed that TR was associated with better RFS.

Recurrence rates of NMIBC within 2 years, 5 years, and 10 years after the initial diagnosis were 61.1%, 69.5%, and 74.3%, respectively (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 Ta low-grade diseases. The lack of detrusor muscle in the specimen is also associated with higher risks of disease understaging, residual tumor, and recurrence (2, 15–17). Besides, Mariappan et al (2010) have

reported that unskilled surgeries resulted in lower detrusor muscle sampling and higher recurrence rates (detrusor muscle sampling rates 56.8% vs 72.6%, early recurrence 39.3% vs 24.8%,) (2). Therefore, finding out a method to improve detrusor muscle sampling 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 the 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 can be 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 better quality of surgery. Patients who received TR were significantly associated with lower recurrence and better 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 Cox proportional hazards regression has confirmed that TR is an independent factor for lower recurrence. The detrusor muscle sampling in our study was not a predictor for outcomes. 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 without a resection to the 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, techniques from different surgeons might have led to potential bias. Third, it was not possible to distinguish residual diseases from recurrent diseases. On the other hand, there are several advantages of our study. First, we have a strict follow-up protocol, and all data were collected prospectively. In addition, second TURBT 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 a follow-up period of more than 2 years. Third, multivariate analysis was used to adjust potential confounders between the TR and CR groups.

Conclusion

TR results in lower recurrence and better RFS in patients with NMIBC, especially in patients with Ta diseases. TR can also improve detrusor muscle sampling rate, which is essential for adequate resection and accurate staging. The findings suggest that TR is a better surgical method for treating NMIBC.

List Of Abbreviations

BCG: Bacillus Calmette–Guérin

CIS: Carcinoma in situ

CR: conventional TURBT

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

TR: two-step TURBT

TUR: transurethral resection

TURBT: transurethral resection of bladder tumor

UTUC: upper urinary tract urothelial carcinoma

Declarations

Ethics approval and consent to participate

The present study followed all standards for ethics with regard to experimentation and research. The institutional review board of National Taiwan University Hospital approved our study (approval number:

201901119RINA) and waived the informed consent requirement due to the retrospective design of the 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

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Authors' contributions

Wei-Lun Huang performed data acquisition and analysis and manuscript drafting. Kuo-How Huang, Chao-Yuan Huang, Yeong-Shiau Pu, and Hong-Chiang Chang contributed in conception and consultation. Po-Ming Chow contributed in conception, interpretation of data, and manuscript revision.

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Tables

Due to technical limitations the Tables are available as a download in the Supplementary Files.

Figures

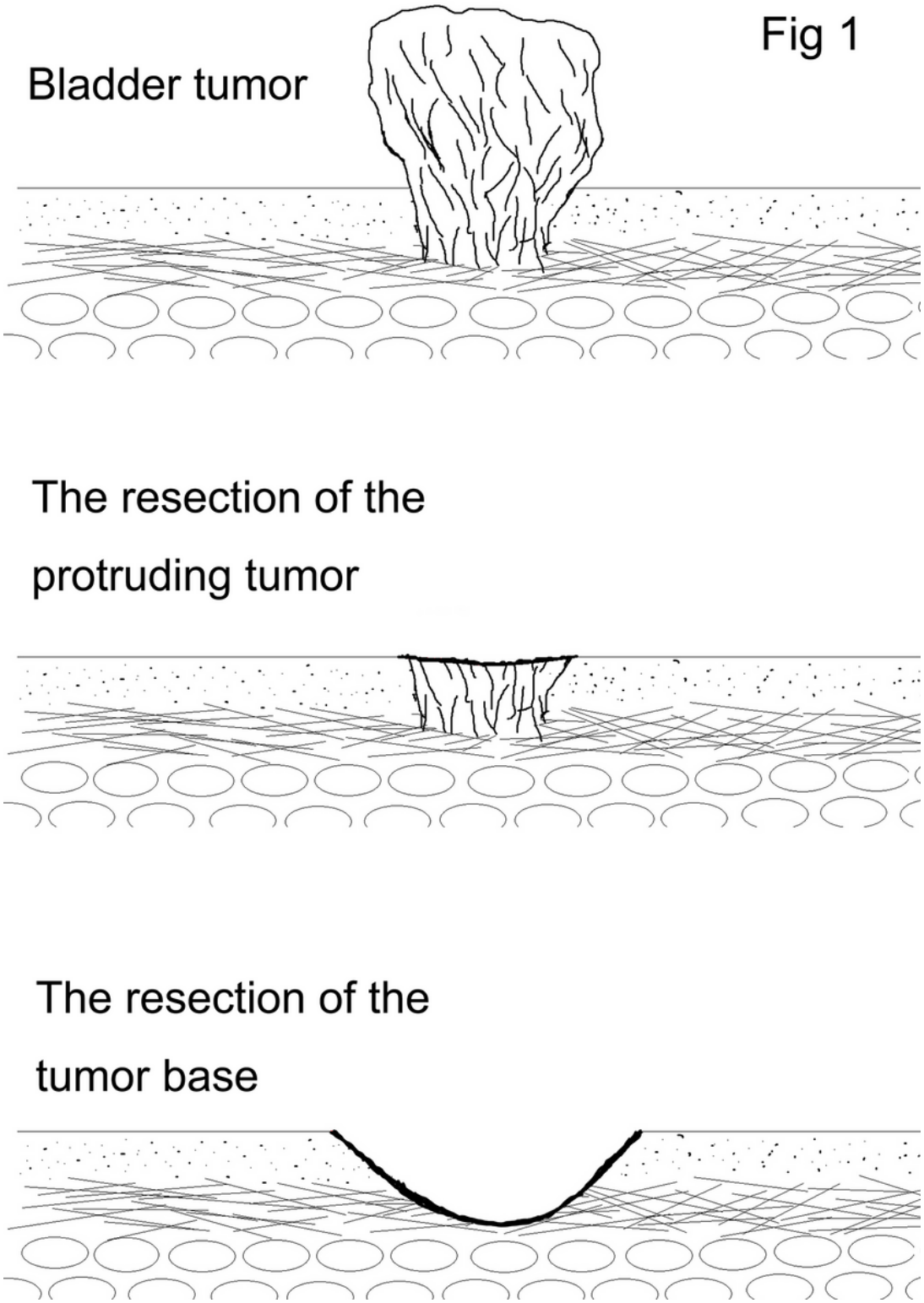


Figure 1

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

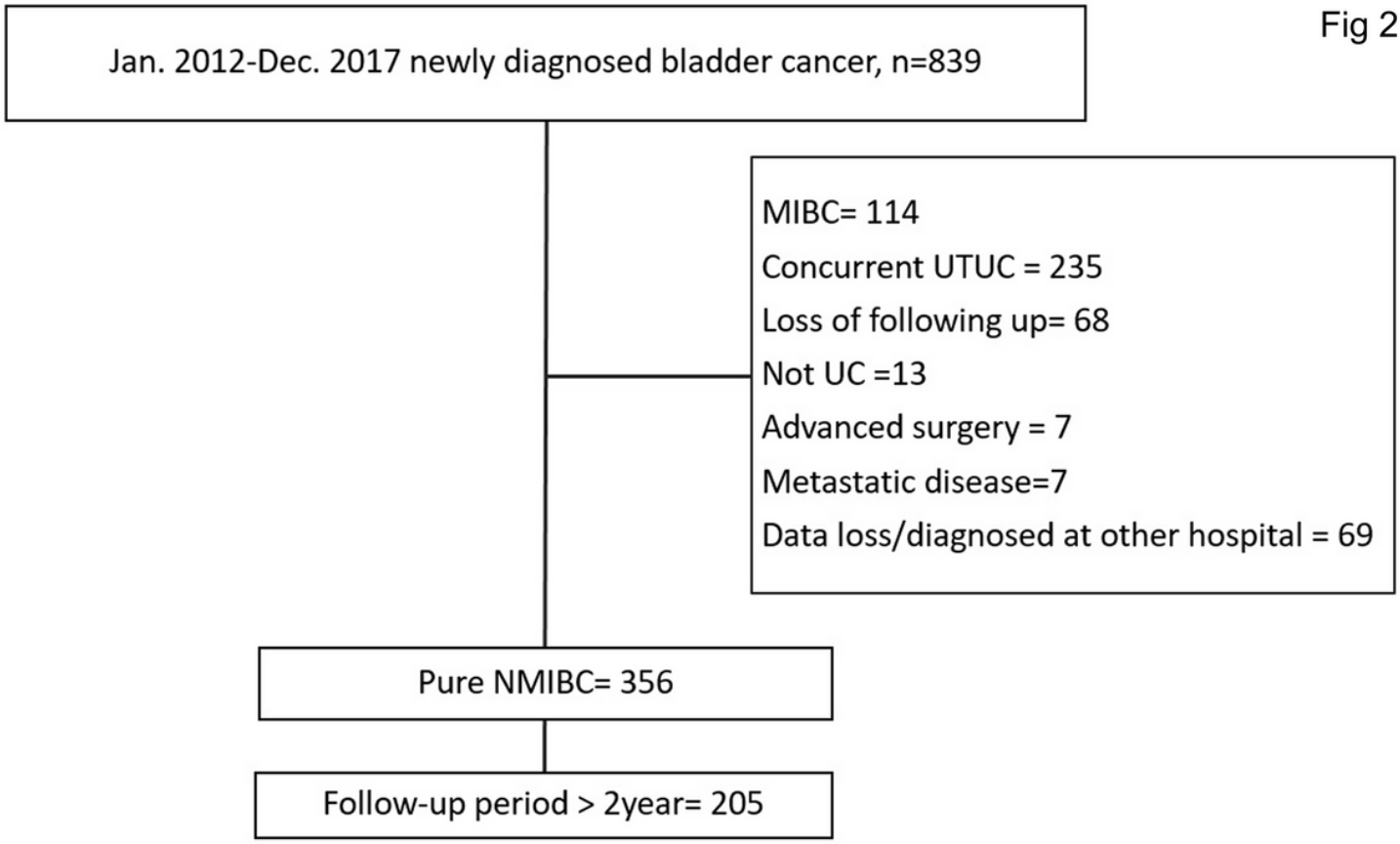
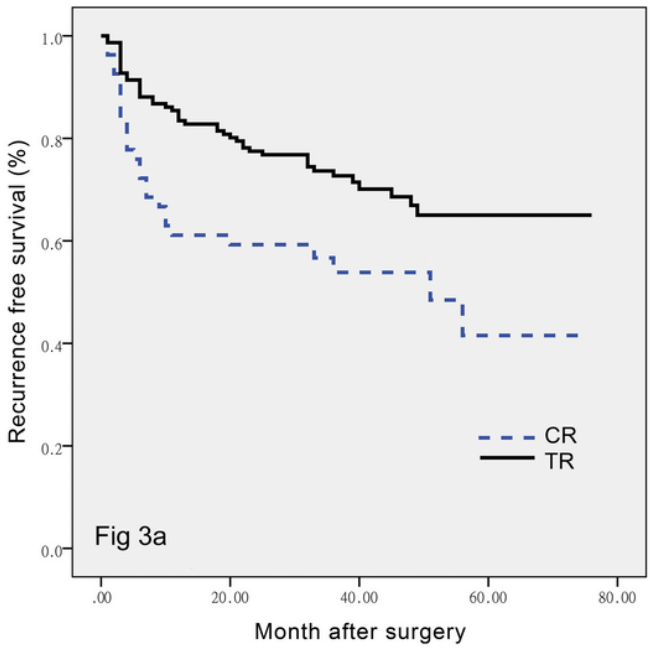


Figure 2

The flowchart of patient selection A total of 839 patients were screened during the study period. Of all patients, 356 patients were classified as “pure NMIBC“, with 205 patients who had a follow-up period of more than 2 years.



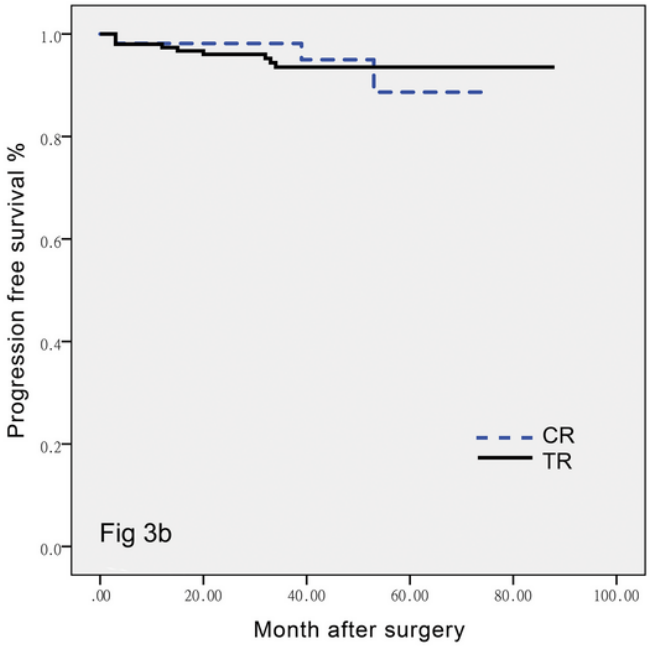


Figure 3

Kaplan-Meier analysis of RFS and PFS (a) TR resulted in better RFS than CR, log-rank P= 0.007 (b) No significant difference was found in PFS between the TR and CR groups, log-rank P= 0.886.

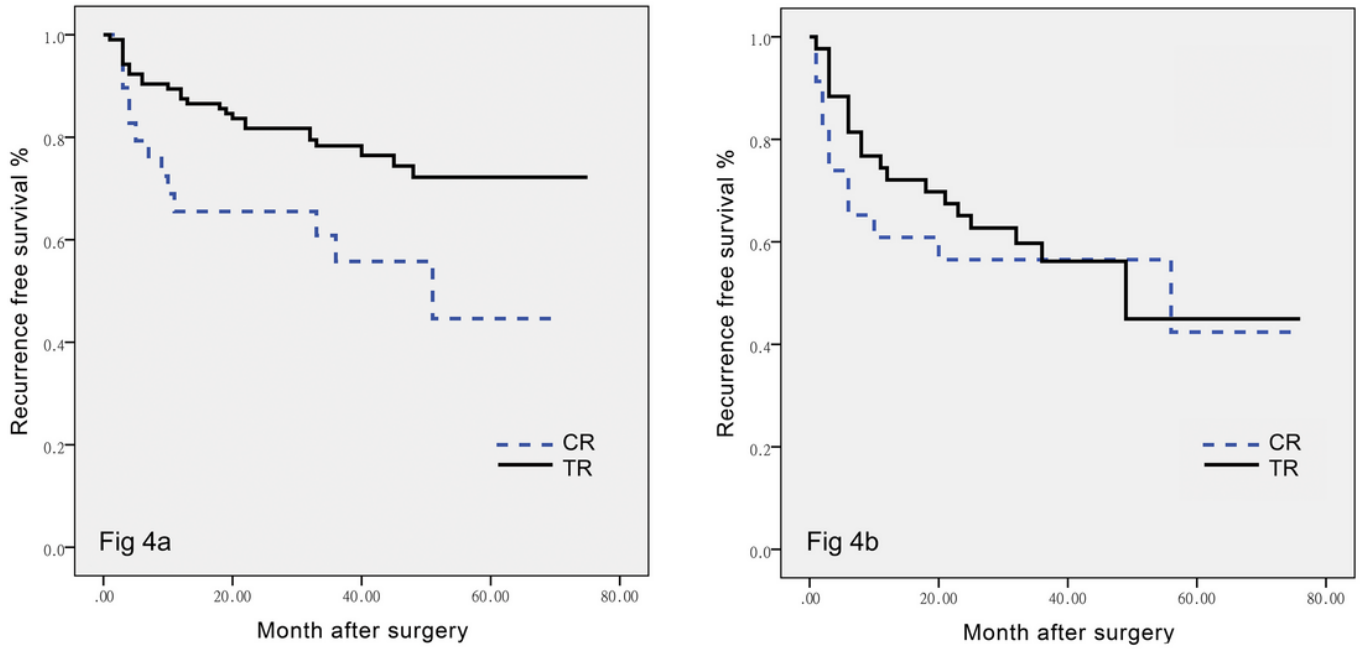


Figure 4

Kaplan-Meier analysis of RFS in the subgroup analysis (a) TR resulted in better RFS in the Ta subgroup (n=133), log-rank P= 0.018 (b) In the T1 subgroup, no significant difference was found in RFS between the TR and CR groups (n=66), log-rank P= 0.692.

Supplementary Files

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