Second transurethral resection for high-risk non-muscle invasive bladder cancer patients: a propensity score matched analysis

Title page

a) **Title**: Second transurethral resection for high-risk non-muscle invasive bladder cancer patients: a propensity score-matched analysis

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d) Running head: No prognostic effect of second TUR on high-risk NMIBC patients

ABSTRACT

Second transurethral resection (TUR) is recommended for patients diagnosed with high-risk non-muscle invasive bladder cancer (NMIBC); however, there have been several studies showing conflicting findings regarding the advantage of second TUR. The objective of this study was to investigate the prognostic significance of second TUR using propensity score-matched analysis. This study retrospectively included 164 consecutive patients who underwent initial TUR and were diagnosed with high-risk NMIBC. Of these, 56 subsequently received second TUR, and the remaining 108 underwent initial TUR alone. After adjusting patient variables by propensity score matching, 44 patients were included in each group. There was no significant difference in recurrence-free, progression-free, or overall survival between these two groups. These findings suggested no significant impact of second TUR on the prognosis of high-risk NMIBC patients; therefore, it may be necessary to perform a reassessment focusing on the indication for second TUR by conducting a large-scale prospective study.

MINI-ABSTRACT: We investigated the prognostic significance of second transurethral resection for patients with high-risk non-muscle invasive bladder cancer using propensity score-matched analysis. There were no significant impacts on oncological outcomes.

KEY WORDS: high-risk non-muscle invasive bladder cancer, second TUR, propensity score-matched analysis, prognosis

INTRODUCTION

Second transurethral resection (TUR) is currently recommended for patients diagnosed with high-risk non-muscle invasive bladder cancer (NMIBC) on initial TUR by major clinical guidelines. It has been shown to have various benefits, including the prevention of underdiagnosis of muscle invasive disease, improvement of postoperative recurrence rate, and enhancement of therapeutic effect on intravesical Bacillus Calmette-Guerin (BCG) therapy (1,2). However, there have been several studies showing no prognostic impact of second TUR, particularly for patients who underwent intensive tumor resection on initial TUR and subsequently received postoperative BCG therapy (3,4). The objective of this study was to investigate the prognostic significance of second TUR in patients with high-risk NMIBC using propensity score-matched analysis.

PATIENTS and METHODS

The design of the present study was approved by the research ethics committee of our institution (No.14-290), and the need to obtain informed consent from the included patients was waived because of its retrospective

design. However, an opportunity to opt out of this study was offered through our institution's website.

After excluding patients with an observation period < 3 months, this study included a total of 164 consecutive patients who underwent initial TUR and were pathologically diagnosed with high-grade pTa, low-grade pT1 or high-grade pT1 urothelial cancer between January 2007 and August 2018 at our institution. All clinicopathological data used in this study were obtained from the medical records for each patient.

All patients had cystoscopically confirmed tumors, and evidently visible tumors in these patients were completely removed by initial TUR. As a rule, cases who had specimens with pathologically confirmed muscle layer at the bottom of index tumor were regarded as receiving complete resection; however, a judgement on the proof of complete resection was also made in reference to the operator's record in each case. When the presence of concomitant carcinoma in situ (CIS) was suspected, random biopsy was added following tumor resection on initial TUR. Second TUR was then considered for patients who fulfilled the pathological criteria as described above; however, it was permitted to omit the second TUR depending on clinical features of each patient

such as age and performance status. Pathological examinations were conducted based on the 2002 American Joint Committee on Cancer TNM system and graded according to the 2004 World Health Organization/International Society of Urologic Pathology classification.

Follow-up schedules for patients included in this study were as follows: cystoscopy and urinary cytology were conducted every three to six months for two years, and then every six months from three to five years. Upon detection of visible tumor or hyperemic mucosa by cystoscopy and/or positive outcomes of urinary cytology, transurethral biopsy of the abnormal region and/or TUR of the tumor were carried out. In this study, recurrence-free survival (RFS), progression-free survival (PFS), and overall survival (OS) were defined as the length of time from performed TUR to pathologically diagnosed intravesical recurrence or death, that to diagnosed muscle invasive bladder and/or upper tract urothelial cancer or death, or that to death, respectively.

All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, ver. 1.40), and P-values < 0.05 were considered significant. Propensity score matching with a 1:1 ratio was applied to adjust for differences between the two groups. RFS, PFS, and OS rates were

calculated by the Kaplan–Meier method, and the log-rank test was performed to evaluate the differences between the two groups. The prognostic impact of second TUR was assessed by univariate analysis using the Cox proportional hazards regression model.

RESULTS

During the observation period of this study (median, 44.1 months), disease recurrence, disease progression, and overall death occurred in 49 (29.9%), 14 (8.5%), and 15 (9.1%) patients, respectively. The proportion of patients receiving detrusor muscle layer resection, random biopsy, and photodynamic diagnosis (PDD) on initial TUR was 97.0, 15.2, and 5.5%, respectively. Following initial TUR, 56 (34.1%) patients subsequently received second TUR (Group 1), and the remaining 108 (65.9%) underwent initial TUR alone (Group 2). In Group 1, residual tumor was detected in 20 patients (35.7%); however, only one patient (1.8%) was diagnosed as having muscle invasive tumor on second TUR.

Before propensity score matching, three factors were significantly different between Groups 1 and 2: tumor diameter (P = 0.031), T category (P

<0.001), and CIS (P = 0.019). To minimize the selection bias of second TUR between the two groups, the following variables were adjusted using 1:1 propensity score matching: age, sex, recurrent status, history of upper tract urinary cancer, number of tumors, tumor diameter, T category, concomitant CIS, subsequent BCG therapy, and combined use of PDD. After propensity score matching, 44 patients were assigned to each group, and no significant differences were noted in any parameters (Table 1).

After propensity score matching, the 5-year RFS, PFS, and OS rates in Group 1 were 62.8, 84.6, and 89.3%, respectively, and those in Group 2 were 58.6, 87.9, and 84.6%, respectively. As shown in Figure 1, there was no significant difference in the RFS, PFS or OS (P = 0.37, 0.53, or 0.72, respectively) between the two groups. Furthermore, the Cox proportional analyses revealed no significant impact of second TUR on RFS, PFS, or OS (P = 0.38, 0.53, and 0.72, respectively).

DISCUSSION

To date, based on the recommendations in the major clinical guidelines, second TUR has been the standard of care for NMIBC patients who fulfill the

following criteria: incomplete initial TUR, without muscle in the specimen on initial TUR with the exception of Ta low-grade tumors, and/or those with T1 tumors (1,2). Furthermore, a systematic review suggested the effects of second TUR on the prevention of progression and reduction of overall mortality in patients with high-risk NMIBC, including high-grade pTa, low-grade pT1 or high-grade pT1 tumor (3). Accordingly, second TUR has been widely accepted as an important procedure during the treatment of patients with NMIBC in routine clinical practice.

However, there have been several studies showing conflicting findings on the prognostic impact of second TUR (4,5). For example, Gontero et al. conducted a retrospective multi-center study that included 2,451 patients with high-grade T1 bladder cancer who received postoperative BCG therapy, and showed that second TUR in the presence of muscle in the primary specimen could not improve the outcome for any of the endpoints, including time to recurrence, progression, cancer-specific survival (CSS), and OS (4). Moreover, Calo et al. reported that there were no significant differences in RFS, PFS, or CSS between patients with completely resected high-grade T1 bladder cancer who had second TUR before starting BCG therapy and those who did not (5).

Collectively, these findings suggest that it may be necessary to reassess whether second TUR improves the prognosis of patients with high-risk NMIBC.

In this study, we retrospectively analyzed the prognostic outcomes in 164 patients who were diagnosed with high-grade pTa, low-grade pT1 or high-grade pT1 tumors on initial TUR, focusing on the significance of second TUR using a propensity score-matched analysis. After matching, there were no significant differences in major clinicopathological factors between the groups with and without second TUR, and no significant difference was documented in RFS, PFS, or OS between the two groups. The success of the initial TUR, characterized by a high proportion of patients containing muscle in resected specimens, may, at least in part, explain this outcome.

There were several limitations of this study. Firstly, this was a retrospective study consisting of a comparatively small sample size, particularly after propensity score matching; therefore, it is necessary to conduct a prospective study with a longer follow-up period including a larger number of patients to draw definitive conclusions regarding the prognostic significance of second TUR. Secondly, despite being assessed after adjusting for major patient variables, this study lacked the strict criteria with respect to the applications of

important therapeutic options, including second TUR and postoperative BCG instillation. In particular, a very strong impact of BCG instillation on the recurrence of high-risk NMIBC should be carefully recognized. Thirdly, due to a relatively long inclusion period in this series, this study involved different operators and pathologists, which could be a potential bias for the present findings. Lastly, several recent studies demonstrated insufficient ability to discriminate the probabilities of disease recurrence and progression in NMIBC patients, especially those classified into a high-risk group, by currently accepted risk classification systems (6,7). These findings should be considered when interpreting the outcomes of this study. Finally, the effects of recent advances in the field of treatment of patients with NMIBC, such as photodynamic diagnosis (8,9) and molecular biomarkers (10-13), should be taken into account when evaluating the significance of second TUR.

In conclusion, our retrospective comparative study using a propensity score-matched analysis showed no significant impact of second TUR on RFS, PFS, or OS in high-risk NMIBC patients undergoing initial TUR; therefore, the indication of second TUR for this category of patients should be investigated by

conducting a prospective study under strict criteria including a larger number of patients.

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None.

CONFLICT OF INTREST STATEMENT

The authors declare that they have no conflict of interest.

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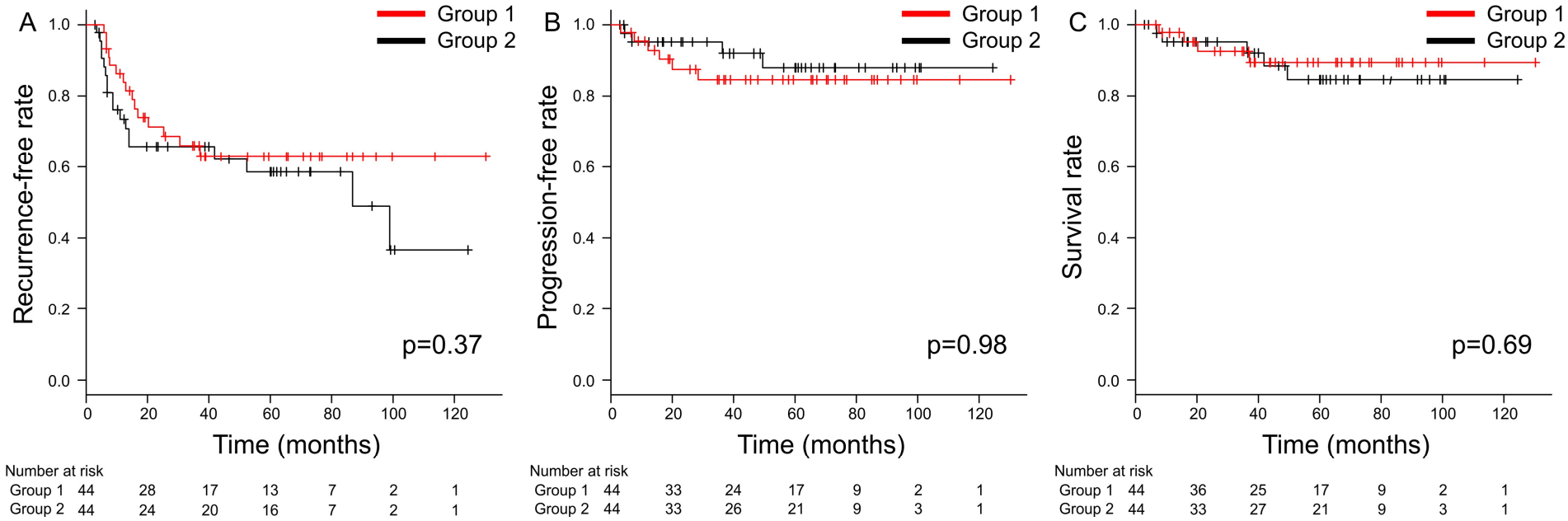
FIGURE LEGEND

Kapran-Meier curves. Comparison of recurrence-free survival (A), progression-free survival (B), and overall survival (C) between Group 1 and Group 2.

Table 1. Clinicopathological characteristics of propensity score-matched groups

	Group 1	Group 2	P
N	44	44	
Age (years)			1.00
≥70	25	24	
<70	19	20	
Sex			0.16
male	37	42	
female	7	2	
Recurrence status			1.00
primary	37	36	
recurrence	7	8	
History of upper tract urothelial cancer			1.00
Yes	5	4	
No	39	40	
Number of tumors			0.83
solitary	19	21	
multiple	25	23	
Tumor diameter			1.00
<3 cm	36	37	
≥3 cm	8	7	
T category			1.00
pTa	12	11	
pT1	32	33	
Concomitant CIS			1.00
negative	41	41	
positive	3	3	
BCG therapy			0.67
Yes	27	24	
No	17	20	
PDD-TURBT			1.00
Yes	2	2	
No	42	42	


A
Group 1
Group 2
Recurrence-free rate
1.0
0.8
0.6
0.4
0.2
0.0
p=0.37
0
20
40
60
80
100
120
Time (months)
Number at risk
Group 1 44 28 17 13 7 2 1
Group 2 44 24 20 16 7 2 1
B
Group 1
Group 2
Progression-free rate
1.0
0.8
0.6
0.4
0.2
0.0
p=0.98
0
20
40
60
80
100
120
Time (months)
Number at risk
Group 1 44 33 24 17 9 2 1
Group 2 44 33 26 21 9 3 1
C
Group 1
Group 2
Survival rate
1.0
0.8
0.6
0.4
0.2
0.0
p=0.69
0
20
40
60
80
100
120
Time (months)
Number at risk
Group 1 44 36 25 17 9 2 1
Group 2 44 33 27 21 9 3 1