Original Article

# Results of second transurethral resection for high-grade T1 bladder cancer

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## Abstract

**Background:** The aim of this study was to examine the histological outcome and potential therapeutic benefit of second transurethral resection (TUR) for high-grade T1 bladder cancer.

**Patients and Methods:** The subjects were 171 patients who underwent initial TUR between January 1993 and December 2013, and were diagnosed with high-grade T1 bladder cancer. Second TUR was performed within 4–6 weeks after the initial resection. Intravesical recurrence, invasive intravesical recurrence, and disease-free, progression-free, and overall survival were examined between second TUR group and no second TUR group.

**Results:** Of the 171 patients, 79 (46.2%) underwent second TUR. Histological findings from second TUR were no cancer in 33 (41.8%), carcinoma *in situ* in 18 (22.9%), Ta in 15 (19.0%), T1 in 12 (15.2%), and muscle invasive bladder cancer (T2) in 1 case (1.3%). The 5- and 10-year intravesical recurrence-free survival rates were 72.0% and 57.4%, respectively, and the disease-free survival rates at these times were 69.7% and 49.6%, respectively. Second TUR had no influence on intravesical recurrence, regardless of the use of Bacillus Calmette–Guerin (BCG) therapy. No BCG therapy and recurrent cancer were significantly associated with intravesical recurrence in multivariate analysis. Recurrent cancer was also a significant risk factor for invasive intravesical recurrence. BCG therapy significantly improved disease-free survival. Second TUR was a significant factor in overall survival. In the histological results for second TUR, no cancer and Tis cases had reduced intravesical recurrence compared to Ta and T1 cases.

**Conclusion:** Second TUR allows more accurate staging and pT0 cases in second TUR have a better outcome, indicating a possible therapeutic benefit of the procedure.

**Key Words:** Bacillus Calmette–Guérin, high-grade T1 bladder cancer, second transurethral resection

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## INTRODUCTION

Nonmuscle invasive bladder cancer (NMIBC) is treated by transurethral resection (TUR), with the aims of histological diagnosis (tumor stage and grade) and achieving complete removal of the tumor. Thus, TUR is a diagnostic and therapeutic procedure for NMIBC. High-grade T1 bladder

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cancer is difficult to treat and has a high malignant potential and a poor prognosis compared with other NMIBCs, with reported progression rates of 22–33.3% and cancer-specific mortality rates of 12–15%.[1,2]

The risk of recurrence and progression can be estimated for individual patients using the scoring system and risk tables in the European Association of Urology guidelines.[3,4] In these guidelines, high-risk cases such as those with high-grade T1 cancer are indicated for adjuvant treatment. Intravesical Bacillus Calmette–Guérin (BCG) therapy has been shown to improve the outcome of high-grade T1 bladder cancer in several meta-analyses of this therapy, compared with cases treated without BCG therapy.[3-6] However, BCG therapy alone may not be sufficient to improve the treatment outcome.[7-9]

Second TUR was introduced for high-grade T1 bladder cancer in the late 1990s,[10-13] with findings of residual cancer on second TUR at rates of 33.8–60% and muscle invasive cancer at 5–20%. These results suggest that many high-grade cancers are incompletely resected in initial TUR and that second TUR is needed for accurate staging and appropriate therapy. However, it is unclear if second TUR has a therapeutic benefit. Randomized clinical trials (RCTs) showed that second TUR reduced the recurrence rate compared with cases with no second TUR.[14,15] However, this study did not include BCG therapy. A retrospective study showed that second TUR contributes to recurrence- and progression-free survival, but other results have shown opposite findings.[8,11,16] Thus, the therapeutic effect of second TUR is uncertain. In this study, we examined the results of second TUR at our hospital.

## PATIENTS AND METHODS

The subjects were 171 patients who underwent TUR between January 1993 and December 2013 and were diagnosed with high-grade T1 bladder cancer. If the initial TUR was performed at other hospital, the patient was included if initial TUR specimens were reviewed at our institute and no macroscopic residual tumor was observed. Patients with recurrent invasive bladder cancer, the presence or past history of upper urinary tract cancer, BCG therapy, and micropapillary or nested variant cancer were excluded from the study. Patients with past history of high-grade T1 bladder cancer before 1993 were also excluded.

Second TUR was performed within 4–6 weeks after initial resection. All second TUR procedures were performed by experienced urologists and included deep and wide resection around the initial TUR site, with a collection of deep muscle specimens. The resection area in the second TUR included the previous resection scar lesion and edematous areas at the initial TUR site. Cold-cup biopsy including random biopsy was not performed routinely.

Instillation of BCG containing 80 mg of Tokyo strain or 81 mg of Connaught strain was performed 6–8 times (median 6) once a week. Maintenance instillation was not performed routinely. BCG therapy was performed routinely from 2002 for high-grade (Grade 3) T1 cancer without second TUR, and second TUR was performed routinely from late 2006. Before 2002, second TUR and BCG therapy was not performed routinely, and this technique was performed sometimes by the preference of the surgeon. Currently, we treat high-grade T1 bladder cancer with second TUR and BCG therapy.

Intravesical recurrence was defined as any type of recurrence in the bladder. Invasive intravesical recurrence was defined as histological bladder cancer without Ta and Tis. Disease-free survival was defined as the time (days) from initial TUR to first intravesical recurrence, death from any cause, distant metastasis, and cystectomy. Progression was defined as muscle invasion on TUR or development of metastatic disease and cystectomy. Urine cytology and follow-up cystoscopy were performed at 3-month intervals for the first 3-year, biannually up to 5-year, and annually thereafter. Computed tomography scans were performed 1-, 3-, and 5-year after the last TUR.

A Chi-square test was used to analyze associations between categorical variables and a Student's *t*-test was used for continuous variables. Survival curves were calculated using the Kaplan–Meier method. A Cox proportional hazards model was used to identify positive predictors for each type of survival. Patients with muscle invasion on second TUR were excluded from survival analysis. Differences were assessed using log-rank test. All statistical analyses were performed using SPSS ver. 20.0J.

## RESULTS

Among 171 patients with high-grade T1 bladder cancer, 79 underwent second TUR. Age, gender, primary (or recurrent), number of tumors, tumor diameter and presence of concomitant carcinoma *in situ* (CIS) did not differ significantly between the second TUR and nonsecond TUR groups, but the rate of BCG therapy was higher in the second TUR group. The median time to second TUR from initial TUR was 1.1 months. The mean follow-up periods were 48.2 months in the second TUR group and 84.4 months in the nonsecond TUR group [Table 1].

Histological results from the second TUR became as follows. No cancer was found in 33 patients (41.8%), CIS in 18 (22.9%), Ta in 15 (19.0%), T1 in 12 (15.2%), and muscle invasive T2 bladder cancer in 1 patient (1.3%). The

**Table 1: Background of cases of high-grade T1 bladder cancer**

| Variables | Total | Second TUR (+) | Second TUR (−) | *P* |
|---|---|---|---|---|
| Number of patients | 171 | 79 | 92 | |
| Age (range) | 69.0 (29-93) | 69.0 (47-93) | 70.0 (29-93) | 0.661 |
| Male: female | 130:41 | 59:20 | 71:21 | 0.723 |
| Primary: recurrence | 153:18 | 70:9 | 83:9 | 0.805 |
| Number of tumors | | | | |
| Single:multiple:unknown | 59:106:6 | 28:48:3 | 31:58:3 | 0.947 |
| Tumor diameter | | | | |
| <3 cm:≥3 cm:unknown | 115:50:6 | 52:24:3 | 63:26:3 | 0.930 |
| Concomitant CIS | 23 | 15 | 8 | 0.071 |
| Month to second TUR (range) | | 1.1 (0.2-4.5) | - | |
| Follow-up period (months) (range) | 60.2 (3.8-279.9) | 48.2 (4.9-161.3) | 84.4 (3.8-279.9) | <0.001 |
| BCG therapy | 108 | 70 | 38 | <0.001 |

TUR: Transurethral resection, CIS: Carcinoma in situ, BCG: Bacillus Calmette–Guérin

5- and 10-year intravesical recurrence-free survival rates were 72.0% and 57.4%, respectively, and the disease-free survival rates were 69.7% at 5-year and 49.6% at 10-year [Figure 1]. Intravesical recurrence-free survival did not differ significantly when stratified according to second TUR and BCG therapy [Figure 2]. However, BCG therapy had reduced intravesical recurrence among both second TUR group and no second TUR group.

Instillation of BCG and primary cancer were significant factors associated with reduced intravesical recurrence in multivariate analysis. Recurrent cancer was also a significant risk factor for invasive intravesical recurrence, and instillation of BCG was significantly associated with improved disease-free survival. Second TUR and age were significantly associated with overall survival in multivariate analysis. However, second TUR was not associated with other survival and recurrence. There was no significant factor associated with improved cause-specific survival or cystectomy-free survival, but recurrent cancer and no BCG therapy showed a tendency to be independent risk factors [Table 2].

Intravesical recurrence did not differ significantly among groups based on the histological results of second TUR. However, the rate of intravesical recurrence was significantly lower in patients with T0/Tis findings on second TUR compared with those with Ta/T1 findings [Figure 3].

## DISCUSSION

High-grade T1 bladder cancer has a high recurrence and progression rates. Chamie *et al.* reported 10-year recurrence, progression, and bladder cancer-related mortality rates of 74.3%, 33.3%, and 12.3%, respectively,[1] and van den Bosch and Witjes found a progression rate of 22% and a mortality due to disease of 15%.[2] In Japan, stage T1 and Grade 3 are risk factors for recurrence and progression.[17,18] These findings indicate the difficulty of treatment of high-grade T1 bladder cancer.

Intravesical BCG therapy and second TUR are used to improve the treatment outcome of high-grade T1 cancer. The efficacy of BCG therapy has been widely examined, and a meta-analysis has shown the effect of this therapy on intravesical recurrence.[5-7] A recent RCT demonstrated significantly reduced distant metastasis and better overall and disease-specific survival in patients treated with BCG compared with epirubicin.[6] The efficacy of BCG therapy on progression and cause-specific survival is still uncertain due to conflicting results for outcomes,[7-9] but intravesical BCG is recommended for high-grade T1 cancer.[3,4] We have performed BCG therapy for high-grade (Grade 3) T1 cancer from 2002, and the current study shows that intravesical BCG is significantly associated with reduced recurrence and improved disease-free survival. Thus, the outcomes of high-grade T1 cancer are improved by intravesical BCG, but these outcomes are still unsatisfactory.[7,9,19,20]

Second TUR was introduced in the late 1990s to improve outcomes of high-grade NMIBC. Many studies have reported a diagnosis of residual cancer and rates of muscle invasive cancer on second TUR.[10-13] In second TUR for 136 patients with T1 cancer, Schwaibold *et al.* found residual cancer in 52% and T2 cancer in 10%,[21] with the residual cancer found in the same lesion as that of initial TUR in 86% of cases. In a prospective examination of the outcome of second TUR in 80 patients, Divrik *et al.*[12] found residual cancer in 33.8% of cases, including 3 with muscle layer invasion, and concluded that second TUR was needed for optimal treatment. In the current study, residual cancer was discovered in 48% of cases and one patient had muscle invasion. Thus, second TUR is useful for diagnosis and accurate staging and we performed second TUR from 2006 routinely.

Second TUR may also have a therapeutic benefit, and Herr showed that second TUR improved the initial BCG response and reduced progression.[11] However, in an examination of the outcomes of 210 patients with T1G3 and without CIS who did not receive BCG therapy, Angulo *et al.* found that second TUR (performed in 62.4% of the cases) was not significantly associated with decreased progression.[16] Therefore, it is unclear

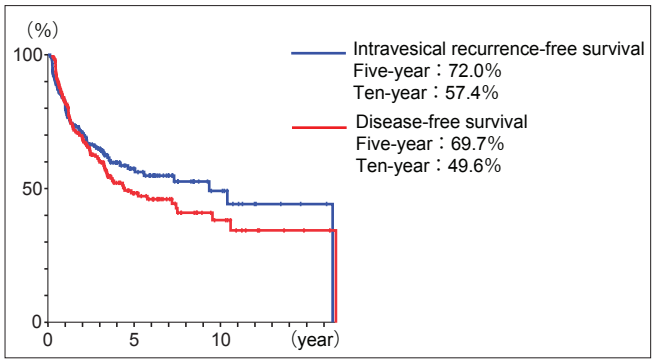


**Figure 1:** Intravesical recurrence- and disease-free survival curves

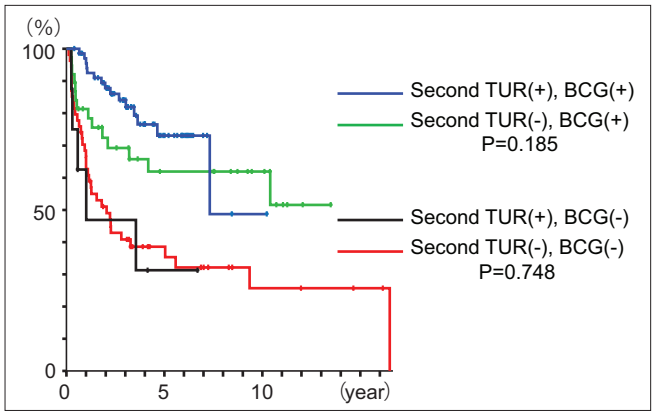


**Figure 2:** Intravesical recurrence-free survival curves for patients who did or did not undergo second transurethral resection or intravesical Bacillus Calmette–Guérin therapy

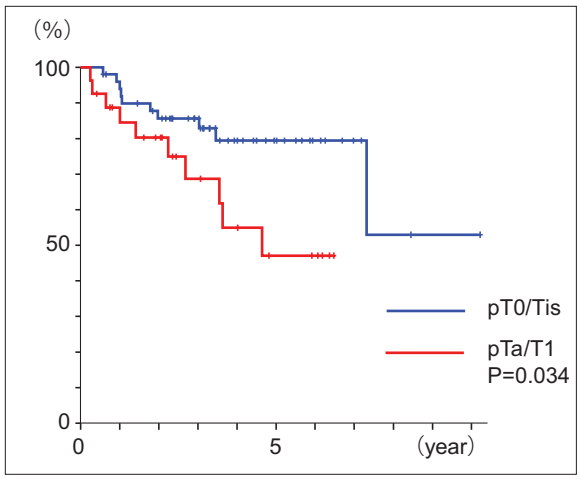


**Figure 3:** Intravesical recurrence-free survival curves based on histological findings from second transurethral resection

if second TUR has a therapeutic benefit, especially in the BCG era. In an evaluation of combination therapy with second TUR and BCG, Herr *et al.* found 2- and 5-year recurrence-free survival rates of 73% and 46%, respectively, in 816 patients with a response to BCG, a progression-free rate of 89%, and a 32% rate for requirement of additional BCG therapy.[19] Sfakianos *et al.* reported the outcomes of 1021 patients with

**Table 2: Multivariate analysis of risk factors for recurrence and survival**

| Risk factors | HR (95% CI) | *P* |
|---|---|---|
| Intravesical recurrence | | |
| BCG therapy | 3.1 (1.9-5.0) | <0.001 |
| Primary or recurrent | 1.9 (1.0-3.6) | 0.045 |
| Invasive intravesical recurrence | | |
| Primary or recurrent | 2.7 (1.2-6.3) | 0.018 |
| Disease-free survival | | |
| BCG therapy | 2.9 (1.8-4.4) | <0.001 |
| Overall survival | | |
| Age | 1.0 (1.0-1.1) | 0.018 |
| Second TUR | 3.0 (1.1-7.9) | 0.026 |
| Cause-specific survival | | |
| Primary or recurrent | 3.9 (1.0-15.7) | 0.056 |
| Cystectomy-free survival | | |
| BCG therapy | 4.4 (1.0-20.0) | 0.053 |

BCG: Bacillus Calmette–Guérin, TUR: Transurethral resection, CIS: Carcinoma *in situ*, CI: Confidence interval, HR: Hazard ratio

NMIBC (including 40% with T1 cancer) treated by intravesical BCG.[8] All patients were treated by BCG and 894 underwent second TUR, in which residual cancer was discovered in 55.5%. Second TUR was found to be a significant prognostic factor for reduced recurrence, and stage, grade and second TUR were significant prognostic factors for progression, indicating that second TUR may have a therapeutic benefit.

In the current study, second TUR combined with BCG therapy resulted in improved recurrence-free survival compared with cases with no second TUR, although the difference was not significant. Second TUR was also significantly associated with improved overall survival. However, some patients had a poor performance status that prevented the performance of second TUR, and this might have contributed to the lower overall survival rate among patients who did not undergo second TUR. Thus, second TUR may not have affected overall survival in the study. On the other hand, the small number of patients with no second TUR and no BCG therapy may cause the no difference. If the number of patients increases, a difference may appear in the recurrence rate and each survival according to second TUR. RCTs of second TUR[13-15] include that conducted by Divrik *et al.*, in which patients were randomly assigned to second TUR and nonsecond TUR groups.[15] Both groups received mitomycin-C and did not receive BCG. Recurrence and progression were significantly better in the second TUR group, but overall survival was similar in the two groups. The addition of further data did not alter the findings of any significant difference in overall survival, but mortality due to cancer was higher in the nonsecond TUR group.[14]

In our study, histological findings from second TUR affected the recurrence rate. Patients with T1/Ta on second TUR having lower recurrence-free survival, although overall survival was similar. Bishr *et al.* found that pT0 cases in second TUR had a good prognosis,[22] based on 31 pT0 cases among

94 patients who underwent second TUR. Other studies have shown that the histological outcome on second TUR is related to recurrence and progression, with pT0 cases on second TUR having a lower progression rate compared with non-pT0 cases.[10,23] Herr *et al.* performed second TUR in 352 T1 patients who received BCG therapy.[24] Among T1 cases on second TUR, 82% progressed to invasive cancer, whereas this progression rate was only 19% in patients without T1 cancer on second TUR, indicating that a finding of T1 on second TUR is a risk for early progression.

These results suggest that the prognosis is good if the histological result on second TUR is pT0, and this supports a therapeutic benefit of second TUR. Further evidence for this benefit is likely to emerge from an RCT comparing intravesical BCG therapy and no BCG therapy based on a finding of pT0 on second TUR, which is currently being conducted by the Japan Clinical Oncology Group.[25]

There were several limitations in the current study, including the retrospective design and the relatively small cohort. The background was similar in the groups with that did and did not undergo second TUR, but the follow-up period was shorter in the second TUR group, and further follow-up is needed. However, the results are informative with regard to the therapeutic benefit of second TUR and further establish this method as a standard procedure for high-grade T1 bladder cancer.

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## Conflicts of interest
There are no conflicts of interest.

## REFERENCES

1. Chamie K, Litwin MS, Bassett JC, Daskivich TJ, Lai J, Hanley JM, *et al.* Recurrence of high-risk bladder cancer: A population-based analysis. Cancer 2013;119:3219-27.
2. van den Bosch S, Alfred Witjes J. Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: A systematic review. Eur Urol 2011;60:493-500.
3. Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou-Redorta J; European Association of Urology (EAU). EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2008;54:303-14.
4. Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Compérat E, *et al.* EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2013. Eur Urol 2013;64:639-53.
5. Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, *et al.* Maintenance Bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma *in situ* transitional cell carcinoma of the bladder: A randomized Southwest Oncology Group Study. J Urol 2000;163:1124-9.
6. Sylvester RJ, Brausi MA, Kirkels WJ, Hoeltl W, Calais Da Silva F, Powell PH, *et al*. Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, Bacillus Calmette-Guérin, and Bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol 2010;57:766-73.
7. Gontero P, Sylvester R, Pisano F, Joniau S, Vander Eeckt K, Serretta V, *et al*. Prognostic factors and risk groups in T1G3 non-muscle-invasive bladder cancer patients initially treated with Bacillus Calmette-Guérin: Results of a retrospective multicenter study of 2451 patients. Eur Urol 2015;67:74-82.
8. Sfakianos JP, Kim PH, Hakimi AA, Herr HW. The effect of restaging transurethral resection on recurrence and progression rates in patients with nonmuscle invasive bladder cancer treated with intravesical Bacillus Calmette-Guérin. J Urol 2014;191:341-5.
9. Fernandez-Gomez J, Solsona E, Unda M, Martinez-Piñeiro L, Gonzalez M, Hernandez R, *et al*. Prognostic factors in patients with non-muscle-invasive bladder cancer treated with Bacillus Calmette-Guérin: Multivariate analysis of data from four randomized CUETO trials. Eur Urol 2008;53:992-1001.
10. Guevara A, Salomon L, Allory Y, Ploussard G, de la Taille A, Paul A, *et al.* The role of tumor-free status in repeat resection before intravesical Bacillus Calmette-Guerin for high grade Ta, T1 and CIS bladder cancer. J Urol 2010;183:2161-4.
11. Herr HW. Restaging transurethral resection of high risk superficial bladder cancer improves the initial response to Bacillus Calmette-Guerin therapy. J Urol 2005;174:2134-7.
12. Divrik T, Yildirim U, Eroglu AS, Zorlu F, Ozen H. Is a second transurethral resection necessary for newly diagnosed pT1 bladder cancer? J Urol 2006;175:1258-61.
13. Kim W, Song C, Park S, Kim J, Park J, Kim SC, *et al.* Value of immediate second resection of the tumor bed to improve the effectiveness of transurethral resection of bladder tumor. J Endourol 2012;26:1059-64.
14. Divrik RT, Sahin AF, Yildirim U, Altok M, Zorlu F. Impact of routine second transurethral resection on the long-term outcome of patients with newly diagnosed pT1 urothelial carcinoma with respect to recurrence, progression rate, and disease-specific survival: A prospective randomised clinical trial. Eur Urol 2010;58:185-90.
15. Divrik RT, Yildirim U, Zorlu F, Ozen H. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: A prospective, randomized clinical trial. J Urol 2006;175:1641-4.
16. Angulo JC, Palou J, García-Tello A, de Fata FR, Rodríguez O, Villavicencio H. Second transurethral resection and prognosis of high-grade non-muscle invasive bladder cancer in patients not receiving Bacillus Calmette-Guérin. Actas Urol Esp 2014;38:164-71.
17. Kikuchi E, Fujimoto H, Mizutani Y, Okajima E, Koga H, Hinotsu S, *et al.* Clinical outcome of tumor recurrence for Ta, T1 non-muscle invasive bladder cancer from the data on registered bladder cancer patients in Japan: 1999-2001 report from the Japanese Urological Association. Int J Urol 2009;16:279-86.
18. Kohjimoto Y, Kusumoto H, Nishizawa S, Kikkawa K, Kodama Y, Ko M, *et al*. External validation of European Organization for Research and Treatment of Cancer and Spanish Urological Club for Oncological Treatment scoring models to predict recurrence and progression in Japanese patients with non-muscle invasive bladder cancer treated with Bacillus Calmette-Guérin. Int J Urol 2014;21:1201-7.
19. Herr HW, Dalbagni G, Donat SM. Bacillus Calmette-Guérin without maintenance therapy for high-risk non-muscle-invasive bladder cancer. Eur Urol 2011;60:32-6.
20. Nishiyama N, Kitamura H, Hotta H, Takahashi A, Yanase M, Itoh N, *et al.* Construction of predictive models for cancer-specific survival of patients with non-muscle-invasive bladder cancer treated with Bacillus Calmette-Guérin: Results from a multicenter retrospective study. Jpn J Clin Oncol 2014;44:1101-8.
21. Schwaibold HE, Sivalingam S, May F, Hartung R. The value of a second transurethral resection for T1 bladder cancer. BJU Int 2006;97:1199-201.
22. Bishr M, Lattouf JB, Latour M, Saad F. Tumour stage on re-staging

transurethral resection predicts recurrence and progression-free survival of patients with high-risk non-muscle invasive bladder cancer. Can Urol Assoc J 2014;8:E306-10.
23. Takaoka E, Matsui Y, Inoue T, Miyazaki J, Nakashima M, Kimura T, *et al.* Risk factors for intravesical recurrence in patients with high-grade T1 bladder cancer in the second TUR era. Jpn J Clin Oncol 2013;43:404-9.
24. Herr HW, Donat SM, Dalbagni G. Can restaging transurethral resection of T1 bladder cancer select patients for immediate cystectomy? J Urol 2007;177:75-9.
25. Kunieda F, Kitamura H, Niwakawa M, Kuroiwa K, Shinohara N, Tobisu K, *et al.* Watchful waiting versus intravesical BCG therapy for high-grade pT1 bladder cancer with pT0 histology after second transurethral resection: Japan Clinical Oncology Group Study JCOG1019. Jpn J Clin Oncol 2012;42:1094-8.