ORIGINAL ARTICLE

Effect of Re-TUR time on recurrence and progression in high-risk non-muscle-invasive bladder cancer

Efecto del tiempo de Re-TUR en la recurrencia y progresión en cáncer de vejiga no músculo invasivo de alto riesgo

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Abstract

Objective: *We aimed to investigate the significance of time to re-staging transurethral resection (re-TUR) on recurrence and progression rates in patients with high-risk non-muscle-invasive bladder cancer as a prospective randomized study.* **Methods:** *The patients were randomly separated into three groups according to Re-TUR timing. In Groups 1, 2, and 3, the time interval between initial and re-TUR was 14-28 days, 29-42 days, and 43-56 days, respectively. Cox regression analysis was used to assess the effect of time from initial TUR to re-TUR on oncological outcomes.* **Results:** *Twenty patients in Group 1 (14-28 days), 22 patients in Group 2 (29-42 days), and 29 patients in Group 3 (43-56 days) completed the study. Kaplan–Meier plots showed no differences in recurrence-free survival (RFS) and progression-free survival (PFS) rates between the three groups. Cox regression analysis demonstrated that only tumor number was found to be a prognostic factor on RFS rates.* **Conclusion:** *Our prospective study demonstrated that time laps from initial TUR to re-TUR did not significantly affect on RFS and PFS rates.*

Keywords: *Non-muscle invasive bladder cancer. Restaging transurethral resection. High grade. Oncological outcomes.*

Resumen

Objetivo: *Nuestro objetivo fue investigar la importancia del tiempo para volver a estadificar la resección transuretral (re-RTU) en las tasas de recurrencia y progresión en pacientes con cáncer de vejiga no músculo invasivo de alto riesgo como un estudio prospectivo aleatorizado.* **Método:** *Los pacientes se separaron aleatoriamente en 3 grupos de acuerdo con el tiempo de Re-TUR. En el grupo 1, 2 y 3, el intervalo de tiempo entre la RTU inicial y la nueva fue de 14 a 28 días, 29 a 42 días y 43 a 56 días, respectivamente. Cox para evaluar el efecto del tiempo desde la RTU inicial hasta la nueva RTU sobre los resultados oncológicos.* **Resultados:** *Veinte pacientes del grupo 1, 22 pacientes del grupo 2, 29 pacientes del grupo 3 completaron el estudio. Los gráficos de Kaplan-Meier no mostraron diferencias en las tasas de SLR y SLP entre los tres grupos. El análisis de regresión de Cox demostró que solo se encontró que el número de tumores era un factor pronóstico en las tasas de RFS.* **Conclusión:** *Nuestro estudio prospectivo demostró que los lapsos de tiempo desde la RTU inicial hasta la nueva RTU no afectaron significativamente las tasas de SLR y SLP.*

Palabras clave: *Cáncer de vejiga no músculo invasivo. Reestablecimiento de la resección transuretral. Alto grado. Resultados oncológicos.*

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Introduction

Bladder cancer (BC) is the 11th most commonly diagnosed cancer worldwide[1]. Non-muscle invasive bladder cancer (NMIBC) accounts for approximately 75% of the cases. Despite advanced treatment methods, the recurrence and progression rates of NMIBC are still high (70-75% and 10%, respectively)[2]. To reduce the risk of recurrence and progression, re-staging transurethral resection (Re-TUR) of high risk bladder tumor and application of intravesical immunotherapy with Bacillus Calmette-Guerin (BCG) to that tumor are recommended by uro-oncology guidelines[1,3].

European Association of Urology (EAU) guidelines recommend that Re-TUR should be performed within 2-6 weeks after initial TUR[1,4]. Nevertheless, these recommendations are based on low levels of evidence[4]. To the best of our knowledge, there are no prospective studies in the literature addressing that issue. Therefore in this prospective, randomized controlled study, we aimed to investigate the significance of time to re-TUR on recurrence and progression rates in patients with high-risk non-muscle-invasive bladder cancer.

Materials and methods

This study was performed between August 2016 and December 2020 after obtaining the approval of local ethics committee (0651-5479). Clinical Trials Registration ID of the present study is NCT04768894. Patients diagnosed with primary high risk non-muscle-invasive bladder cancer at our clinic as well as the patients who were referred to our clinic with the same diagnosis were included to the study. All patients gave their written informed consent. The patients were randomly separated into three groups according to Re-TUR timing with the random number table envelope method. The names of the groups were written on small papers with the same size, they were folded, put in an envelope, and drawn by the doctors. In Groups 1, 2, and 3, the time interval between initial and re-TUR were 14-28 days, 29-42 days, and 43-56 days, respectively. Separate analysis was also performed for patients who had Re-TUR at ≤ 42 and > 42 days. All patients received six weekly instillations of BCG therapy, and at least 1 year of maintenance BCG therapy (3 weekly instillations administered at 3, 6, and 12 months).

Patients with a tumor pathology other than transitional cell carcinoma, incomplete resection at initial TUR, who cannot complete 1 year of maintenance BCG treatment, did not attend their regular cystoscopic control or wanted to leave from the study voluntarily and finally, with a diagnosis of muscle-invasive cancer on Re-TUR were excluded from the study. Inclusion criteria were having a high grade Ta or T1 transitional cell carcinoma with or without carcinoma *in situ* (CIS) after a complete initial TUR of bladder carcinoma, and receiving 6 weekly induction BCG therapy with at least 1 year maintenance.

Re-TUR contained resection of all visible tumor, deep resection of previously resected areas and adequate sampling of muscle layers. Cystoscopic control was performed according to EAU guideline recommendations for high-risk non-muscle-invasive bladder cancer[5,6]. Progression was defined as an increase in the pathological stage (Ta-T1 or T1-T2).

Demographic data of the patients such as age, gender, and parameters related to bladder cancer such as tumor grade, T stage, concomitant CIS, number of tumors, main tumor size, application of early single dose chemotherapy, recurrence, and progression were noted. Primary end point of the current study was recurrence and progression free survival rates. Pathologic investigations were made by single expert uropathologist at our hospital.

Statistical analysis

The data analyses were performed with PASW 18 (SPSS, IBM, Chicago, IL) software. Kolmogorov-Smirnov and P-P plot were used to verify the normality of the distribution of continuous variables. The results were reported as means standard deviations, or in situations in which the distributions were skewed, as the median (minimum-maximum). Categorical variables were given as percentages. For parameters that did not show normal distribution, the nonparametric Kruskal–Wallis One-Way analysis of variance and Mann–Whitney U test were used to compare them. Multivariable semi-parametric Cox regression analysis was used to evaluate predictors of recurrence-free survival (RFS) and progression-free survival (PFS) rates. Kaplan–Meier curves were constructed for RFS and PFS and groups were compared with the long-rank test. The study power and sample size were calculated with G power 3.1.9.7 version (A priori). When effect size is set to 0.33 (medium size) with 80% power, the total number of

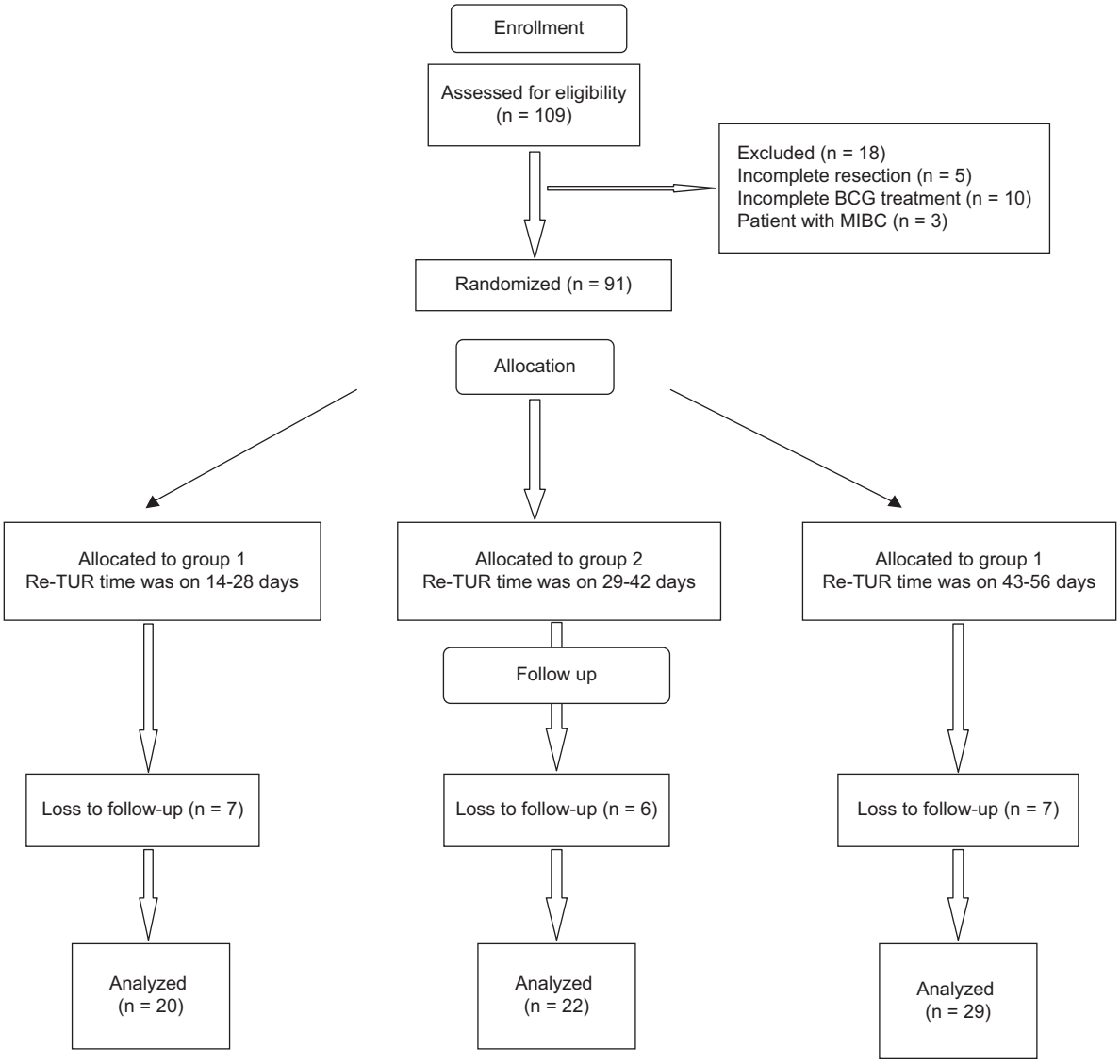

Figure 1. *Flow charts.*

patients required to be included in the study was 73. $p < 0.05$ was considered as statistically significant.

Results

A total of 109 patients with primary high risk non-muscle-invasive bladder cancer were randomly divided into three groups. Twenty patients were excluded because of loss to follow-up. Five patients with incomplete resection at initial TUR, ten patients who could not complete 1 year of maintenance BCG treatment, and three patients with a diagnosis of muscle-invasive cancer on re-TUR were excluded from the study. Twenty patients in Group 1 (14-28 days), 22 patients in Group 2 (29-42 days), and 29 patients in Group 3 (43-56 days) completed the study (Fig. 1).

The mean age of the study population was 64.5 ± 8.7 years and the mean follow-up was 20 ± 8.9 months. Of our patients 58 (81.7%) male and 13 (18.3%) were female. All tumors in this study were high grade. Stage Ta and T1 tumors were present in 14 (19.7%) and 57 (80.3%) patients, respectively. Concomitant CIS was present in 7 (9.9%) patients. Residual tumors were detected in 9 of 71 (12.6%) patients. No T2 tumor was detected in any patient after the re-TUR. There were no differences between the groups in age, sex, T stage, concomitant CIS, largest tumor diameter, tumor numbers, and instillation of immediate post-operative intravesical chemotherapy (Table 1). In the

Table 1. Baseline patients characteristics of groups

Variable	Group 1: 14-28 days, n (%)	Group 2: 29-42 days, n (%)	Group 3: 43-56 days, n (%)	p
Number of patients	20	22	29	
Age, median (minimum-maximum)	65 (49-86)	65 (44-83)	63 (46-77)	0.48
Gender				
Female	5 (25)	3 (13.6)	5 (17.2)	0.62
Male	15 (75)	19 (86.4)	24 (82.8)	
Stage				
Ta	6 (30)	4 (18.2)	4 (13.8)	0.36
T1	14 (70)	18 (81.8)	25 (86.2)	
Concomitant CIS	2 (10)	2 (9.1)	3 (10.3)	0.98
Tumor size (mm), median (minimum-maximum)	40 (15-100)	40 (20-100)	30 (15-75)	0.34
Number of initial tumors, median (minimum-maximum)	1 (1-5)	1 (1-5)	1 (1-5)	0.89
Immediate post-operative intravesical chemotherapy	17 (85)	20 (91)	27 (93)	0.63
Smoking	16 (80)	17 (77)	23 (79)	0.97
Progression rate	0	1 (4.5)	3 (10)	0.36

CIS: Carcinoma *in situ*

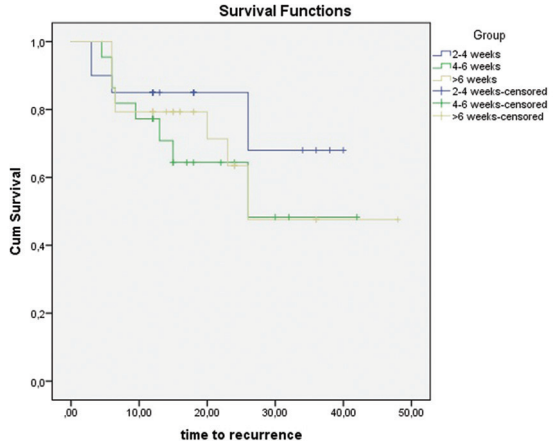

Figure 2. *Recurrence-free survival rates of the three groups at a mean follow-up of 20 months (14-28 days, 29-42 days, and 43-56 days).*

follow-up period, 4 (5.6%) patients underwent radical cystectomy. One patient had been administered radiation therapy with chemotherapy.

Recurrence-free survival rates of the patients were 80 %, 63.6%, and 69% in Groups 1, 2, and 3, respectively, at a mean follow-up of 20 months (p = 0.56). When we performed a separate analysis by dividing patients into two groups based on the interval between initial and Re-TUR (≤ 42 days and > 42 days), we did not also detect statistically different RFS rates (71.4% and 69%, respectively, p = 0.85) (Figs. 2 and 3). The progression rate in group > 42 days was similar to that of group ≤ 42 days (2.4% and 10.3% p = 0.20, respectively) (Table 2).

The progression was observed in 0, 1 (4.5%), 3 (10%) patients in groups 1, 2, and 3, respectively, at a mean follow-up of 20 months (p = 0.36). PFS was found as 100%, 95.5%, and 89.7% in Groups 1, 2, and 3 at a mean follow-up of 20 months (Fig. 4) (p = 0.36). According to the cox regression analysis, only number of tumors was found to be a prognostic factor on RFS rates (Table 3).

Discussion

A complete resection is vital to achieve a good prognosis in non-muscle invasive bladder cancer[7,8]. The goal of TUR of bladder cancer in NMIBC is to achieve the correct diagnosis and completely remove all visible lesions and it is an essential procedure in the management of NMIBC. The absence of muscularis propria in the specimen is associated with a significantly higher risk of residual tumor, early recurrence, and tumor understaging[9]. The significant risk of residual disease after initial TURB of NMIBC has been demonstrated[8,10]. Especially high-grade T1 bladder cancer has a high recurrence and progression rate.

A Re-TUR of bladder cancer can increase RFS, improve outcomes after BCG treatment and provide prognostic information[11-14]. Therefore, a Re-TUR is

Table 2. Baseline patients characteristics of groups according to ≤ 42 days and > 42 days

Variable	Group 1: ≤ 42 days, *n* (%)	Group 2: > 42 days, *n* (%)	p
Number of patients	42	29	
Age, median (minimum-maximum)	65 (44-86)	63 (46-77)	0.29
Gender			
Female	8 (19)	5 (17.2)	0.84
Male	34 (81)	24 (82.8)	
Stage			
Ta	10 (23.8)	4 (13.8)	0.3
T1	32 (76.2)	25 (86.2)	
Concomitant CIS	4 (9.5)	3 (10.3)	0.91
Tumor size (mm), median (minimum-maximum)	40 (15-100)	30 (15-75)	0.17
Number of initial tumors, median (minimum-maximum)	1 (1-5)	1 (1-5)	0.66
Immediate post-operative intravesical chemotherapy	37 (88.1)	27 (93.1)	0.49
Smoking	33 (78.6)	23 (79.3)	0.94
Progression rate	1 (2.4)	3 (10.3)	0.20

CIS: Carcinoma *in situ*

Table 3. Cox regression analysis of clinical factors potentially affecting oncological results

Covariate	Recurrence free survival		
	HR	95% CI	p
Age	1.05	0.99-1.1	0.07
Tumor size	1.1	0.26-4.72	0.87
Number of initial tumors	1.5	1.01-2.34	0.04
Concomitant CIS	0.47	0.08-2.5	0.38
Time to re-TUR (days)			
14-28	Ref		
29-42	0.98	0.26-3.6	0.97
43-56	1.96	0.64-5.9	0.23

HR: hazard ratio, CI: confidence interval, re-TUR: re-staging transurethral resection, CIS: carcinoma *in situ*

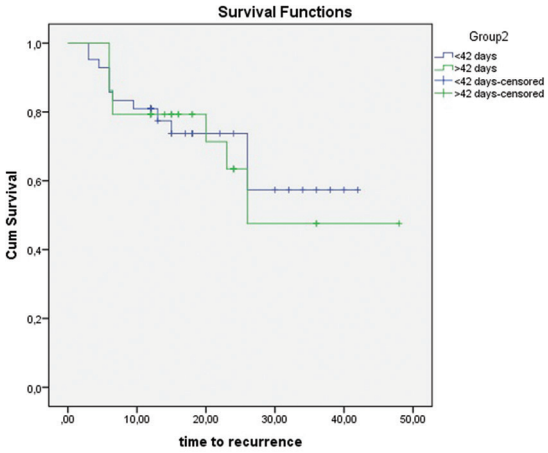

Figure 3. *Recurrence-free survival rates of the two groups at a mean follow-up of 20 months (≤ 42 and > 42 days).*

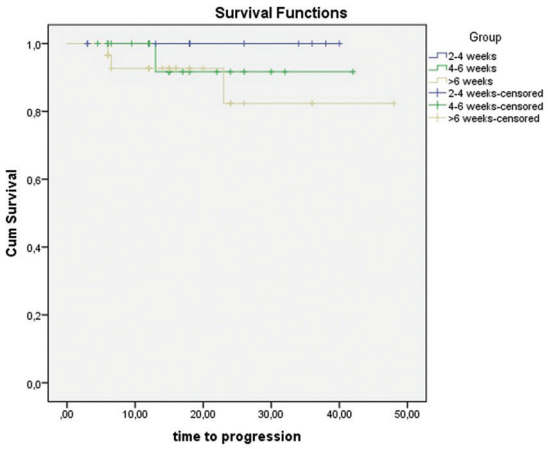

Figure 4. *Progression-free survival rates of the three groups at a mean follow-up of 20 months.*

recommended in patients with high risk NMIBC. Although Re-TUR is mostly recommended within 2-6 weeks after initial TUR in the recent EAU guideline, review of the literature regarding the timing of a Re-TUR arises a large range from an immediate second TUR to 3 months after the initial TUR[14,15]. This recommendation to perform Re-TUR 2-6 weeks after initial TUR is based on a retrospective study recently performed by Baltaci et al.[4]

To the best of our knowledge, the present study is the first prospective, randomized, and controlled study evaluating the time lapse from initial TUR to Re-TUR and its association with RFS rates and progression rates. Our results revealed that the RFS rates of the Groups 1, 2, and 3 were 80%, 63.6%, and 69%, respectively, at a mean follow-up of 20 months (p = 0.56). These rates were not statistically significant. Similarly, PFS was found as 100%, 95.5%, and 89.7% in Groups 1, 2, and 3 at a mean follow-up of 20 months, respectively, and these results were also not statistically significant. When we divide the patients into two groups, we found

that the progression rate in group > 42 days was also similar to that of group ≤ 42 days. To the best of our knowledge, there are three retrospective studies evaluating the role of time from initial TUR to Re-TUR[4,16,17]. Two of them are multicentric studies. Calo et al. investigated the timing from initial TUR to Re-TUR in patients with high grade NMIBC. The authors divided the patients into three groups (A, B, and C) based on time to Re-TUR in their study. In Group A, B, and C, Re-TUR times are determined as within 6 weeks, > 6-12 weeks, and > 12-18 weeks, respectively. They found that recurrence rate was 38.3%, 24.8%, and 28.3% in Groups A, B, and C, respectively. Kaplan–Meier plots showed that such differences were not statistically significant (p = 0.1). They also found that progression rates between the groups were also not statistically significant. The authors thought that biological tumor characteristics might be more relevant than the "traditional" clinical and pathological characteristics in predicting the oncological outcomes. Similarly, we could not detect any significant effect of time from initial TUR to Re-TUR on PFS and RFS rates. In the present study, residual tumor was detected in 9 of 71 (12.6%) patients after the Re-TUR. This finding is lower than the results of previous studies, as residual cancer can be found in 20-78% of cases on a Re-TUR[3,12,18]. Therefore, this may be one reason why we could not find any effect of time from initial TUR to Re-TUR on RFS and PFS rates in the current study.

Baltaci et al. showed that second TUR performed 14-42 days after initial resection yielded longer RFS and PFS rates compared to a second TUR performed after 43-90 days[4]. Specifically, the 3-year RFS rates were 73.6% versus 46.2% (p < 0.001) and the 3-year PFS rates were 89.1% versus 79.1% (p = 0.006) for those having a second TUR 14-42 days and 43-90 days after initial TUR, respectively. This study is a valuable study, but because of it is multi-centric, it is a disadvantage that the second TURs were performed by different surgeons and the pathology results were evaluated by different pathologists, which might have caused interobserver differences. At present, interobserver differences are common in reporting tumor grade and stage.

Another recently published study by Krajewski et al. demonstrated that a second TUR performed within 6 weeks was associated to better RFS, PFS and CSS rates[17]. There was a great heterogeneity in BCG treatment in this study as it included patients who received al least 7 BCG instillations. Studies have confirmed that BCG after TURB is superior to TURB alone or TURB plus chemotherapy for preventing the recurrence of NMIBC. Studies have also demonstrated that BCG therapy delays and potentially lowers the risk of tumor progression[19-22]. For this reason, it is important for such study that patients must receive BCG treatment for a similar time and similar dose to avoid bias.

The relatively low number of patients and the short follow-up period are the main limitations of the present study. However, to the best of our knowledge, this is the first prospective, randomized, and controlled study evaluating the time lapse from initial TUR to Re-TUR and its association with RFS rates and progression rates in a single tertiary center.

Conclusions

Our prospective study demonstrated that time lapse from initial TUR to Re-TUR did not significantly affect RFS and PFS rates. Further prospective randomized larger sample studies are needed to confirm these findings.

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Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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