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Predictive Factors for Residual Cancer in Second Transurethral Resection for Non-muscle-invasive Bladder Cancer

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Abstract. *Background/Aim: The significance of second transurethral resection (TUR), and identification of predictive factors for residual cancer remain unrevealed. This study aimed to find residual cancer and up-staging rates, as well as predictive factors for residual cancer, in patients who undergo second TUR for non-muscle-invasive bladder cancer (NMIBC). Patients and Methods: Patients who underwent second TURs for NMIBC between 2015 and 2017, were included in the study and their clinicopathological characteristics were analyzed for predictors of residual cancer. Results: Among 143 Japanese patients whose tumors were initially diagnosed as high-risk NMIBC, residual cancers detected at second TURs were, Tis: n=22 (15.4%), Ta: n=15 (10.5%) and T1: n=29 (20.3%). No patients showed up-staging from NMIBC to MIBC. The presence of carcinoma-in situ at initial TUR was an independent risk factor for any residual cancer (Tis, Ta and T1), non-flat residual cancer (Ta and T1), and flat residual cancer (Tis). Conclusion: The presence of carcinoma-in situ is suggested to be an independent predictor of residual cancer. This may help guide decisions to perform second TUR.*

Bladder cancer, which is usually pathologically characterized as urothelial carcinoma, is the ninth most common malignancy and 13th most common cause of cancer-related death in the world (1). Most bladder cancers present as non-muscle-invasive bladder cancer (NMIBC) and are usually managed by transurethral resection (TUR) and/or intravesical use of chemotherapeutic agents or bacillus Calmette–Guérin (BCG). Within 5 years, 15-61% of NMIBC recur as non-invasive cancers, and 1-45% recur as muscle-invasive bladder cancer (MIBC) (2). As high-grade and T1 NMIBCs are at high risk for recurrence and progression to MIBC, improvement in their medical management is greatly needed. Second TUR for high-risk NMIBCs have been suggested to decrease recurrence and progression by residual cancers (3).

The diagnostic role of second TUR is evident: at second TURs for T1 NMIBC, the reported rate for residual cancer is 20-71%, and for upstaged disease is 0%-32% (4). Meanwhile, second TUR has controversial therapeutic efficacy: recurrence-free, progression-free and overall survival are reportedly longer after second TUR (5-7). However, some studies report no improvement of recurrence-free survival or progression-free survival when muscle has been included on primary TUR specimens (8, 9). Residual cancer after second TUR leads to early recurrence and early progression, but prognosis may be improved by accurate diagnosis and curative therapy at the second TUR. Therefore, further investigation of the significance of second TUR, and identification of predictive factors for residual cancer are required. In this study, we analyzed rates of residual cancer and up-staging, and identified predictive clinicopathological factors for residual cancer at second TUR.

Patients and Methods

Patients. Patients who were diagnosed with high-risk NMIBC at their initial TUR and underwent second TUR at Kyushu University Hospital (Fukuoka, Japan) and Harasanshin General Hospital (Fukuoka, Japan) between 2015 and 2017, when routine second TURs for high-risk NMIBC were introduced in both institutions, were enrolled. High-risk NMIBC was defined as NMIBC of high-grade T1 or based on physician's judgement. This study was approved by the review boards of both institutions, and was performed in accordance with the principles described in the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research enacted by the Japanese Government.

Methods. Pathological evaluation of bladder cancer was performed according to 2004 WHO grading (10). Bladder cancer T-categories were determined in accordance with the unified TNM criteria based on the TUR pathological results (11). Random biopsies were

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performed to find concomitant carcinoma-*in situ* (CIS) when pre-operative cytological examination of urine was positive or MIBC was suspected. Almost all patients received single administrations of a chemotherapeutic agent within 24 h after their initial TUR. Second TUR was performed to remove all primary sites diagnosed as high risk, and any endoscopically visual tumors.

Statistical analysis. All statistical analyses were performed using JMP13 software (SAS Institute, Cary, NC, USA). Categorical and continuous data were analyzed by Pearson's chi square and Wilcoxon rank sum tests, respectively. Univariate and multivariable logistic regression models were used to calculate odds ratios (ORs). All *p*-values were two-sided. $p<0.05$ was considered significant.

Results

This study included 143 patients who underwent second TUR for high-risk NMIBC. Their clinicopathological characteristics are shown in Table I. Their median age was 73 years. Most cancers presented as primary bladder cancer and showed multiple tumors. All patients were pathologically diagnosed with urothelial carcinoma of the bladder; five patients also showed squamous cell carcinoma components, and 51 (35.7%) had concomitant CIS. Their second TUR was performed after a median of 1.2 months (interquartile range [IQR]: 1.1-1.6 months) after their initial TUR. Residual cancers (Tis, Ta and T1) on second TUR were detected in 66 of 143 cases (46.2%; Tis: n=22 [15.4%], Ta: n=15 [10.5%], T1: n=29 [20.3%]). No patients showed up-staging from NMIBC to MIBC. Primary CIS was newly detected in 7 patients (7.6%) on second TUR among the 92 patients who were not diagnosed with CIS on initial TUR.

Then predictive factors for residual cancer were explored. Univariate analysis showed that small tumors (OR=2.97, 95%CI=1.27-6.98, $p=0.012$) and the presence of CIS (OR=5.46, 95%CI=2.57-11.61, $p<0.0001$) were risk factors for residual cancer of any stage. However, multivariate analysis of tumor size and CIS found only CIS to be an independent risk factor for residual cancer (OR=4.83, 95%CI=2.24-10.41, $p<0.0001$), whereas small tumors (OR=2.12, 95%CI=0.86-5.25, $p=0.10$) were not (Table II).

Residual Tis cancers should be treated with BCG, whereas non-flat residual Ta and T1 cancers need removal by TUR. Resection of Ta and T1 tumors on second TUR thus supports the therapeutic significance of second TUR. Accordingly, factors predictive for non-flat residual Ta and T1 cancers were evaluated. In univariate analysis, only CIS (OR=2.41, 95%CI=1.16-5.02, $p=0.018$) was a risk factor for residual Ta and T1 cancers (Table II). Among patients who were not diagnosed with CIS on initial TUR, 22 (23.9%) were found to have non-flat residual Ta and T1 cancers on second TUR, compared with 22 patients (43.1%) diagnosed with CIS on initial TUR. Similarly, only CIS (OR=5.06, 95%CI=1.90-13.46, $p=0.0012$) was a risk factor for flat residual cancer (Table II).

Table I. *Patients' characteristics at initial TUR.*

Variable	n=143
Median age (IQR), years	73 (66-78)
Gender, n (%)	
Male	121 (84.6%)
Female	22 (15.4%)
Prior history, n (%)	
Primary	114 (79.7%)
Recurrent	29 (20.3%)
Pre-TUR urine cytology	
Negative	23 (16.1%)
False positive	49 (34.3%)
Positive	71 (49.7%)
Tumor count, n (%)	
Solitary	54 (37.8%)
Multiple	89 (62.2%)
Tumor size, n (%)	
<30 mm	110 (76.9%)
≥30 mm	33 (23.1%)
Grade, n (%)	
Low grade	4 (2.8%)
High grade	139 (97.2%)
T-stage, n (%)	
Ta	4 (2.8%)
T1	138 (97.2%)
Not determined	1
Carcinoma-*in situ*, n (%)	
Absence	92 (64.3%)
Presence	51 (35.7%)

TUR: Transurethral resection; IQR: interquartile range.

Discussion

The rate of residual cancer found on second TUR in T1 NMIBC has been reported to be 20-71% (4), which is consistent with our result of 46.2%. Similarly, the rates of residual Ta (4-40%) and T1 (9-31%) tumors in patients with T1 NMIBC were in line with the rates of 10.5% and 20.3% for residual Ta and T1 tumors in our study, respectively (4). These residual diseases are associated with early recurrence, and possible progression, of bladder cancer. Residual cancer with Tis was observed in 15.4%, and requires intravesical therapy. Up-staging was not observed in this study, although the reported rate of up-staging on second TUR for T1 NMIBC is 0-32% (4). Thus, this distribution of pathological stages on second TUR is identical to those in previous reports (4), and confirms the modest diagnostic and possible therapeutic significance of second TUR for high-risk NMIBC as of this study.

Several clinicopathological factors, such as the inclusion of muscle in resected specimens, recurrent disease, CIS, tumor size, and tumor multiplicity on initial TUR, were reported to be significant predictors of recurrence and progression before the era of second TUR (2), which suggests that some of these risk factors are associated with adverse prognosis *via* residual

Table II. *Univariate and multivariate analyses of predictors of residual cancer at second TUR.*

		Any residual cancer (Tis/Ta/T1) Univariate analysis (multivariate analysis)			Non-flat residual cancer (Ta/T1) Univariate analysis			Flat residual cancer (Tis) Univariate analysis		
Variable	n	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value	OR	95% CI	*p*-Value
Age, years										
<70	59	ref			ref			ref		
≥70	84	0.54	0.27-1.05	0.070	0.78	0.38-1.60	0.50	0.53	0.21-1.32	0.17
Gender										
Male	121	ref			ref			ref		
Female	22	1.44	0.58-3.59	0.43	1.35	0.52-3.50	0.54	1.27	0.39-4.19	0.69
Prior history										
Primary	114	ref			ref			ref		
Recurrent	29	0.76	0.33-1.73	0.51	1.02	0.42-2.45	0.97	0.58	0.16-2.10	0.40
Pre-TUR urine cytology										
Negative	23	ref			ref			ref		
False positive	49	1.29	0.46-3.62	0.62	1.02	0.33-3.16	0.97	1.75	0.33-9.17	0.51
Positive	71	2.29	0.86-6.07	0.097	1.54	0.54-4.40	0.42	2.35	0.49-11.31	0.29
Tumor count										
Solitary	54	ref			ref			ref		
Multiple	89	1.90	0.95-3.80	0.068	1.45	0.69-3.08	0.33	1.75	0.64-4.80	0.27
Tumor size										
<30 mm	110	ref			ref			ref		
≥30 mm	33	0.34 (0.47)	0.14-0.79 (0.19-1.16)	0.012* (0.10)	0.53	0.21-1.34	0.18	0.29	0.064-1.31	0.11
Grade										
Low grade	4	ref			ref			ref		
High grade	139	0.88	0.12-6.41	0.90	0.43	0.059-3.18	0.41	-	-	-
T-stage										
Ta	4	ref			ref			ref		
T1	138	0.29	0.029-2.84	0.29	0.44	0.060-3.21	0.42	0.54	0.053-5.43	0.60
Concomitant carcinoma-*in situ*										
Absence	92	ref			ref			ref		
Presence	51	5.46 (4.83)	2.57-11.61 (2.24-10.41)	<0.0001* (<0.0001*)	2.41	1.16-5.02	0.018*	5.06	1.90-13.46	0.0012*

*Statistically significant. TUR: Transurethral resection; OR: odds ratio; CI: confidence interval.

cancer after initial TUR. Our findings imply that the presence of CIS increases the likelihood of residual cancer after initial TUR, and thus the risks for recurrence and progression. Notably, concomitant CIS was a significant predictive factor for residual CIS, as well as non-flat residual Ta and T1 cancers. Intriguingly, it has been reported that the presence of CIS was a significant predictor of recurrence after BCG treatment in univariate analysis, but not in multivariate analysis with second TUR as one of parameters, which suggests that the detrimental effect of CIS may be diminished by second TUR, possibly by eliminating non-flat residual cancer (12). In addition, the presence of muscle on initial TUR specimens was identified as a predictor of residual cancer (13). Also, in a prospective trial, tumor grade, multiplicity and size were identified as risk factors for residual cancer (7). Surprisingly, larger tumors were associated with reduced risk of any-stage residual cancer on univariate analysis, but not on multivariate analysis; this may be attributed to the association between small tumors and the presence of CIS (data not shown). Intriguingly, the utility of a molecular marker panel in guiding decisions about second TURs has been reported (14). Although these parameters have been suggested as predictors of residual cancer on second TUR, they should be validated in a future study.

Because non-flat residual cancer would result in early bladder cancer recurrence, and possible progressive disease, second TUR is strongly recommended for patients at high risk for non-flat residual cancer. Conversely, patients in whom non-flat residual cancer was not detected on second TUR were considered to have undergone an unnecessary procedure. Therefore, patients at low risk for residual cancer may be candidates for omitting second TUR.

The present study had several limitations. The study design was retrospective, and the sample size was relatively small. In

addition, this study included patients from two institutions, between which details of clinical practice may have differed.

Conclusion

In conclusion, oncological outcomes of second TURs were consistent with previous reports, with a moderate residual cancer rate and a very low up-staging rate. This study indicated that the presence of CIS at the initial TUR is a predictor for residual cancer. Therefore, patients found to have CIS at initial TUR (possibly in combination with other parameters) may be recommended to undergo second TUR. This study requires further validation.

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Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

AY designed the study. MA analyzed the data. MS wrote the draft of the manuscript. All other Authors have contributed to data collection and interpretation, and critically reviewed the manuscript. EM supervised the study.

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