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ORIGINAL ARTICLE

Androgen Receptor Predicts First and Multiple Recurrences in Non-Muscle Invasive Urothelial Carcinoma of the Bladder

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Abstract

The aim of this study is to investigate the role of androgen receptor (AR) expression on clinicopathologic characteristics, first recurrence free survival (RFS), progression free survival (PFS) and multiple recurrences in non-muscle invasive bladder cancer (NMIBC). AR expression in 40 paraffin-embedded specimens of primarily diagnosed NMIBC after transurethral resection was examined by immunohistochemistry using a monoclonal AR antibody. Associations between AR expression and clinicopathologic features and prognosis were statistically assessed. Multivariate Cox proportional hazards model was applied for evaluating predictive factors on RFS and PFS. For multiple recurrences, we used the Andersen-Gill model. AR was positive in 20/40 (50%) cases. Twenty-three patients (57.5%) had no recurrence, 10 (25.0%) had one recurrence, and 7 (17.5%) experienced more than one recurrence. AR expression and clinicopathologic features were not significantly correlated ($P > 0.05$). Univariate analyses showed that AR expression was significantly associated with RFS and PFS ($P < 0.05$). Via multivariate analyses, positive AR expression was significantly associated with lower risk of first recurrence (hazard ratio (HR) = 0.265; 95% confidence interval (95% CI) = 0.084–0.829; $P = 0.022$). Multivariate analysis of PFS was not feasible in our cohort. Using the multivariate Andersen-Gill model, positive AR expression in the primary tumor was an independent factor predicting lower risk of multiple recurrences (HR = 0.387, 95% CI = 0.161–0.927, $P = 0.033$). Androgen receptor expression is associated with first and multiple recurrences in NMIBC.

Keywords Androgen receptor · Recurrence · Bladder cancer · Immunohistochemistry

Introduction

Bladder cancer is a malignant tumor that arises from urothelial epithelium. Bladder cancer is classified as either muscle-invasive or non-muscle-invasive. Patients with non-muscle invasive urothelial carcinoma of the bladder (NMIBC) experience a high rate of local recurrence within the bladder. The 5-year recurrence rate ranges from 31 to 78% in NMIBC [1]. Therefore, it is clinically important to identify risk factors for recurrence in NMIBC. In addition, bladder cancer has a gender-specific difference of incidence in Caucasians and African Americans [2], and in a Japanese population [3]. This gender-specificity indicates a potential association of sex steroid hormones, such as androgen, in bladder cancer [4].

Androgen is a sex hormone, and androgen receptors (AR) are expressed in the urethral and bladder epithelium [5]. Emerging reports have indicated relationship between AR signaling and bladder carcinogenesis [6–10]. However, in clinical settings, there has been no clear consensus on the role of AR expression on clinicopathologic features [7, 11–17] or prognosis [15–17] in bladder cancer. No study has investigated whether the AR expression is associated with NMIBC prognosis in a Japanese population to date. Moreover, there have been few studies investigating risk factors of multiple recurrences with extended Cox regression analysis [18–20] in NMIBC, although multiple recurrences are characteristic of NMIBC. To date, particularly, the prognostic significance of AR on the multiple recurrences has not been reported.

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We aimed to determine whether AR expression is important for clinicopathologic characteristics, first recurrence-free survival (RFS), progression-free survival (PFS) and multiple recurrences after the first transurethral resection of bladder tumors in non-muscle invasive urothelial carcinoma of the bladder in a Japanese population.

Materials and Methods

Patient Enrollment

The clinical data of 56 patients with bladder cancer treated at the Tochigi Medical Center Shimotsuga Hospital and their specimens obtained from transurethral resection of bladder tumor of urothelial carcinoma of the bladder in the period between April 2011 and December 2015 were retrospectively reviewed. We excluded 16 patients who had optimal supportive care without further cystoscopy and transurethral resection of bladder tumor after the first diagnosis of bladder cancer (one man and one woman), who had undergone radical cystectomy after the first transurethral resection of bladder tumor (two men), or whose follow-up period was <6 months (five men and three women). One patient had concomitant carcinoma *in situ* and waited for further cystectomy (one female). Three patients diagnosed microscopically with pT2 bladder cancer were excluded (three men). Forty participants were included in the final evaluation. We retrospectively assessed the participants' metadata including gender, age at first transurethral resection of bladder tumor, smoking status defined as ever-smoker (current or former) or never-smoker [21] and pathological factors of the tumor tissue including histological grade (papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade, or high-grade) [22], tumor multiplicity (single or multiple), tumor size (<3 cm or ≥3 cm) and tumor T stage (pTa, pTis, or pT1). We monitored patients every 3–6 months in the first few years after the first transurethral resection of a bladder tumor and every 6–12 months if any recurrence was not confirmed by cytology and cystoscopy. Biopsies were performed in the case of lesions suspicious of recurrence. We defined recurrence as histological confirmation of urothelial carcinoma occurring at any site inside the bladder. RFS was defined as the interval period between the first transurethral resection of bladder tumor and first intravesical recurrence.

Immunohistochemical Analysis

We immunostained formalin-fixed and paraffin embedded tissue sections (4 μm) with anti-AR antibody (Clone AR441, Dako, USA; 1:25 dilution) using a Histofine Histostainer (Nichirei Bioscience Inc., Tokyo, Japan) according to the manufacturer's instructions or amino acid polymer methods. One pathologist (S.Y), who was blinded to patient identities, manually scored all staining results using the German Immunoreactive Score (GIS), which was calculated by multiplying the percentage of immunoreactive cells (0% = 0; 1–10% = 1; 11–50% = 2; 51–80% = 3; 81–100% = 4) by staining intensity (0, negative; 1, weak; 2, moderate; 3, strong) [14]. AR expression was defined as positive when a patient had a score of GIS more than the median value of GIS. Sections of normal prostate glands were used as positive controls for AR.

Statistical Analysis

Fisher's exact test was used to assess categorized variables between participants with positive AR expression and those with negative expression. The Mann-Whitney U test was used to evaluate continuous variables between groups. The recurrence free survival rate for the first recurrence was calculated using the Kaplan-Meier method and compared using a log-rank test. In the univariate analysis, we used univariate Cox proportional hazard model to assess the prognostic value of categorical and continuous variables. To assess the effect of AR expression on first RFS and PFS, we performed multivariate Cox regression analyses including variables identified with a *P*-value less than 0.2 via univariate analyses. We used the Andersen-Gill model as an extended model of Cox regression analysis to evaluate risk factors on multiple events such as multiple recurrences in NMIBC [23]. All *P*-values were two-sided, and P-values ≤0.05 were considered statistically significant. We used GraphPad Prism 7.00 (GraphPad Software Inc., La Jolla, CA, USA) to generate all graphs. All statistical analyses were performed using R freeware (http://www.r-project.org).

Results

General Characteristics of Participants

Table 1 shows baseline characteristics of patients ($n = 40$). Median age of all participants was 73.0 years (range, 60.0–94.0 years), and the median observation period was 37.87 months (range, 8.43–72.13 months). Although 23 (57.5%) and 36 patients (90.0%) remained recurrence-free and progression-free, respectively, recurrences and progression developed in the remaining 17 and 4 patients during the observation period, respectively. During follow-up, ten patients (25.0%) had one recurrence and four (10.0%) had two recurrences whereas three (7.5%) had three recurrences. The median overall RFS was 24.62 months (range, 3.57–72.13 months), and the median overall PFS was 35.53 months (range, 4.20–72.13 months). Twenty-seven participants (67.5%) were male and 13 (32.5%) were female. Ever-

Table 1 Baseline patient characteristics ($N = 40$)

Variable	Total subjects
No. of patients	40
Observation period, months; median (range)	37.87 (8.43–72.13)
Recurrence	
Yes	17 (42.5%)
None	23 (57.5%)
Recurrence-free survival, months; median (range)	24.62 (3.57–72.13)
Total no. of recurrences	
0	23 (57.5%)
1	10 (25.0%)
2	4 (10.0%)
3	3 (7.5%)
Progression	
Yes	4 (10.0%)
No	36 (90.0%)
Progression-free survival, months; median (range)	35.53 (4.20–72.13)
Age, years; median (range)	73 (60–94)
Sex	
Male	27 (67.5%)
Female	13 (32.5%)
Smoking status	
Current/former	17 (42.5%)
Never	23 (57.5%)
Intravesical BCG	
Yes	3 (7.5%)
None	37 (92.5%)
Tumor multicentricity	
Yes	18 (45.0%)
No	22 (55.0%)
Tumor size	
≥ 3 cm	5 (12.5%)
< 3 cm	35 (87.5%)
Histologic grade	
PUNLMP	0 (0%)
Low	26 (65.0%)
High	14 (35.0%)
% of AR immunoreactive cells	
0%	19 (47.5%)
1–10%	1 (2.5%)
11–50%	16 (40.0%)
51–80%	4 (10.0%)
81–100%	0 (0%)
AR staining intensity	
Negative	19 (47.5%)
Weak	8 (20.0%)
Moderate	12 (30.0%)
Strong	1 (2.5%)
German Immunoreactive Score; median (range)	1.5 (0–6)

AR androgen receptor, *PUNLMP* papillary urothelial neoplasm of low malignant potential, *BCG* Bacille Calmette-Guerin

smokers (current or former) and never-smokers totaled 17 (42.5%) and 23 (57.5%), respectively. Most patients (37/40, 92.5%) had never received intravesical Bacillus Calmette-Guérin (BCG) instillation after transurethral resection of bladder tumors. Three patients (7.5%) had intravesical BCG after surgery. None of participants had androgen-deprivation therapy before or after surgery. Almost half of enrolled patients (18/40, 45.0%) had multiple tumors. Whereas five patients (12.5%) had growths greater than 3 cm, tumors in most instances (35/40, 87.5%) were small (<3 cm). No patient was diagnosed with PUNLMP (low-grade carcinoma: 26/40, 65.0%; high-grade carcinoma: 14/40, 35.0%). Twenty-nine patients (72.5%) were staged pTa and one (2.5%) as pTis. Hence, 30 patients (75.0%) had non-invasive tumors (pTa/pTis), and the remaining 10 (25%) exhibited superficial invasion (pT1). Almost half patients (19/40, 47.5%) had none of immunoreactive cells. One patient (2.5%) had 1–10%, 16 patients (40.0%) had 11–50%, 4 patients (10.0%) had 51–80%, and 0 patients had 81–100% of immunoreactive cells. Almost half of enrolled patients (19/40, 47.5%) had negative staining intensity of AR. Of all patients, 8 patients (20.0%) had weak intensity, 12 patients (30.0%) had moderate intensity, and 1 patient (2.5%) had strong intensity. Nineteen patients (47.5%) had a GIS of 0, 1 patients (2.5%) had a GIS of 1, 7 patients (17.5%) had a GIS of 2, 8 patients (20.0%) had a GIS of 4, and 5 patients (12.5%) had a GIS of 6. The median of GIS (range) was 1.5 (0–6) and a cut-off for positive AR expression was defined a GIS of 1.5. Thus, 20 patients (50.0%) were considered as AR positive expression (Fig. 1).

Univariate and Multivariate Analyses of Risk Factors for the First Recurrence and Progression of Bladder Cancer

Table 2 shows the clinicopathologic characteristics of patients with positive and negative AR expression. Clinicopathologic characteristics were well balanced between groups with regard to any categorical and continuous variable ($P > 0.05$). The Kaplan–Meier survival curves for first RFS and PFS according to AR expression are shown in Fig. 2. Via univariate analysis by log-rank test, AR expression was significantly associated with RFS and PFS ($P = 0.040$ and $P = 0.026$, respectively; Fig. 2). Multivariate Cox regression analysis revealed that positive AR and lower age were significantly associated with lower risk of first recurrence (HR = 0.265, 95% CI = 0.084–0.829, $P = 0.022$ and HR = 1.056, 95% CI = 1.003–1.111, $P = 0.039$, respectively; Table 3). Multivariate analysis of PFS was not feasible in our cohort, owing to few events ($n = 4$).

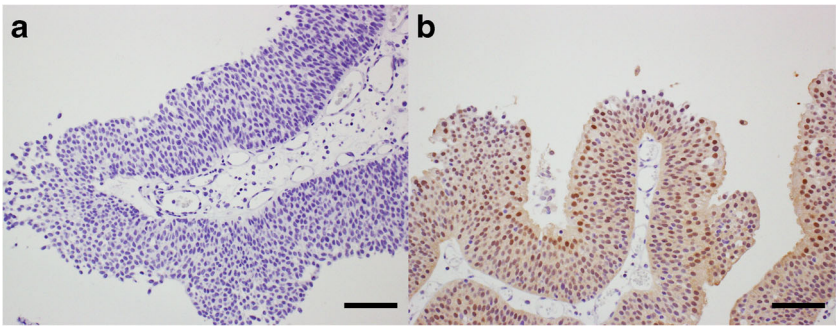

Fig. 1 Immunohistochemical staining for androgen receptor. **a** Negative staining in low-grade papillary urothelial carcinoma (100×). **b** Positive staining in low-grade papillary urothelial carcinoma (100×). All scale bars represent 100 μm

Table 2 Characteristics of patient population ($N = 40$) as shown by androgen receptor expression

Variables	AR (+)	AR (−)	*P* value
No. of patients (%)	20 (50%)	20 (50%)	
Observation period (months)			0.305
Median	34.93	40.82	
Range	17.87–63.63	8.43–72.13	
Total no. of recurrences			0.404
0	13	10	
1	5	5	
2	2	2	
3	0	3	
Age (years)			0.684
Median	71.50	73.5	
Range	60–94	61–89	
Sex			0.501
Male	15	12	
Female	5	8	
Smoking status			0.200
Current/former	11	6	
Never	9	14	
Intravesical BCG			0.231
Yes	3	0	
None	17	20	
Tumor multicentricity			0.341
Yes	11	7	
No	9	13	
Tumor size			1.000
≥ 3 cm	3	2	
< 3 cm	17	18	
Histologic grade			0.320
PUNLMP	0	0	
Low	11	15	
High	9	5	
T stage			0.273
pTis/pTa	13	17	
pT1	7	3	

AR androgen receptor, *PUNLMP* papillary urothelial neoplasm of low malignant potential, *BCG* Bacille Calmette-Guerin

Univariate and Multivariate Analyses of Risk Factors for Multiple Recurrences of Bladder Cancer using the Andersen-Gill Model

Via univariate analysis, AR expression in primary tumor tissue was a significant factor for multiple recurrences (HR = 0.406, 95% CI = 0.168–0.981, $P = 0.045$; Table 4). Advanced age at the initial surgery tended to confer an increased risk of multiple recurrences, but did not reach statistical significance (HR = 1.036, 95% CI = 0.998–1.076, $P = 0.064$; Table 4). The multivariate analysis showed that positive AR expression was significantly associated with lower risk of multiple recurrences (HR = 0.387, 95% CI = 0.161–0.927, $P = 0.033$; Table 4). Other significant factor was continuous age at the initial surgery (HR = 1.038, 95% CI = 1.010–1.070, $P = 0.018$; Table 4).

Discussion

The main objective of this study was to assess whether AR expression is associated with clinicopathologic characteristics and prognoses such as RFS in non-muscle invasive urothelial carcinoma of the bladder. Our findings provide evidence supporting the following conclusions: (i) positive AR expression is associated with longer RFS in NMIBC; and (ii) positive AR expression and younger age are associated with lower risk of multiple recurrences in NMIBC. To the best of our knowledge, this is the first study to provide evidence that AR expression predicts multiple recurrences in NMIBC.

Gender disparity is characteristic of bladder cancer. Environmental factors such as smoking have been thought to be associated with the difference between men and women [4]. However, there is a significant difference in incidence even after adjusting for potential environmental factors between genders, suggesting that innate sexual characteristics such as anatomic differences, urination habits, or hormonal factors may be involved [4]. Previous studies reported the role of AR on clinicopathologic characteristics [6, 7, 11–16] and prognosis including RFS [15–17] and PFS [15, 16]. There have been conflicting reports on the relationship between

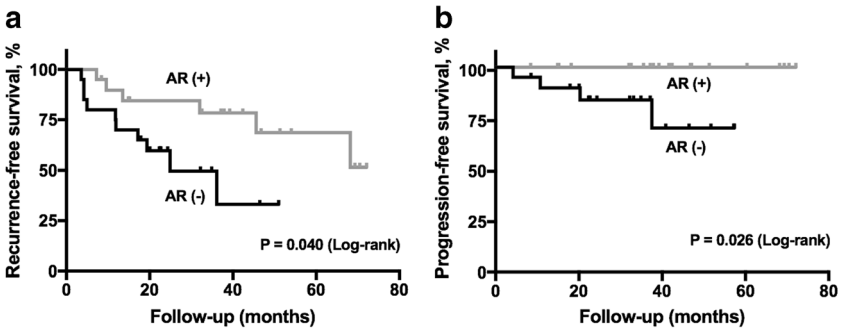

Fig. 2 Kaplan-Meier curves of recurrence-free (**a**) and progression-free survival (**b**) according to androgen receptor expression in non-muscle invasive bladder cancer

AR expression and clinicopathologic profile including gender difference [6, 11, 14–17], tumor grade [6, 11, 13–17], tumor stage [6, 14–17], and tumor multiplicity [7, 16, 17]. These differing results could be caused by different methods of signal detection, such as immunohistochemistry using different antibodies, antigen retrieval methods, or detection reagents [15]. One meta-analysis evaluating gender difference, tumor grade and tumor stage concluded that AR expression is associated with gender difference and tumor grade [24].

The present study failed to show an association between AR positivity and clinicopathologic characteristics. It is possible that the small cohort in our study did not allow us to detect weak correlations. Miyamoto et al. reported that AR expression in NMIBC was not significantly associated with RFS or PFS by log-rank test [15]. In contrast, Nam et al. demonstrated a significant association between AR expression and lower recurrence rates ($P = 0.011$) in NMIBC via multivariable analysis [17]. Tuygun et al. reported that AR

Table 3 Univariate and multivariate analyses of androgen receptor expression utility in predicting first recurrence

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value[a]	HR (95% CI)	*P* value
Continuous age (years)	1.046 (0.991–1.103)	0.102	1.056 (1.003–1.111)	0.039
Sex				
Male	2.130 (0.603–7.523)	0.240		
Female		–		
Smoking status				
Current/former	1.286 (0.495–3.341)	0.332		
Never		–		
Intravesical BCG				
Yes	0.857 (0.111–6.597)	0.882		
None		–		
Tumor multiplicity				
Multiple	1.887 (0.700–5.083)	0.209		
Single		–		
Tumor size				
≥ 3 cm	1.238 (0.277–5.53)	0.780		
< 3 cm		–		
T stage				
pT1	0.690 (0.194–2.462)	0.568		
pTa/pTis		–		
Tumor grade				
High-grade	1.538 (0.540–4.378)	0.420		
Low-grade		–		
AR				
Positive	0.330 (0.109–0.996)	0.049	0.265 (0.084–0.829)	0.022
Negative		–	Reference	–

HR hazard ratio, *CI* confidence interval, *BCG* Bacille Calmette-Guerin, *AR* androgen receptor

[a] Univariate Cox proportional hazard model

Table 4 Univariate and multivariate analyses of androgen receptor expression utility in predicting multiple recurrences using the Andersen-Gill model

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value[a]	HR (95% CI)	*P* value
Continuous age (years)	1.036 (0.998–1.076)	0.064	1.038 (1.010–1.070)	0.018
Sex				
Male	1.316 (0.482–3.590)	0.592		
Female	Reference	–		
Smoking status				
Current/former	0.965 (0.439–2.124)	0.930		
Never	Reference	–		
Intravesical BCG				
Yes	0.578 (0.128–2.616)	0.476		
None	Reference	–		
Tumor multiplicity				
Multiple	1.637 (0.722–3.710)	0.238		
Single	Reference	–		
Tumor size				
≥ 3 cm	1.996 (0.612–6.506)	0.252		
< 3 cm	Reference	–		
T stage				
pT1	0.562 (0.187–1.648)	0.303		
pTa/pTis	Reference	–		
Tumor grade				
High-grade	1.496 (0.614–3.649)	0.375		
Low-grade	Reference	–		
AR				
Positive	0.406 (0.168–0.981)	0.045	0.387 (0.161–0.927)	0.033
Negative	Reference	–	Reference	–

HR hazard ratio, *CI* confidence interval, *BCG* Bacille Calmette-Guerin, *AR* androgen receptor

[a] Univariate Andersen-Gill model

expression tended to be associated with longer RFS and PFS in NMIBC, but did not achieve statistical significance ($P = 0.059$ and $P = 0.167$, respectively) [16]. One meta-analysis that included these three studies concluded that AR positivity is associated with better RFS, but not PFS ($P = 0.006$ and $P = 0.223$, respectively) in NMIBC [24]. Our results on RFS were consistent with previous research [15–17, 24] and supported the conclusion that AR expression is important for RFS in NMIBC. Univariate analysis in the present study revealed that positive AR was associated with longer PFS ($P = 0.026$; Fig. 1), although earlier studies failed to show that AR expression was not significant in PFS [15, 16]. Unfortunately, multivariate analysis of PFS was not feasible in our cohort, due to few qualifying events ($n = 4$).

Only a few studies have reported data on multiple recurrences in bladder cancer, even though multiple recurrences are characteristic of NMIBC [18–20]. For instance, Takashi et al. showed multiple recurrences after initial BCG therapy were associated with number of tumors, a history of bladder cancer and pathological stage [18]. Yan et al. reported that p53 positivity in initial tumor tissue predicts higher risk of second recurrence [19]. Androgen-deprived therapy (ADT) for primary prostate cancer is associated with a lower risk of recurrences in patients with concomitant NMIBC [20]. To the best of our knowledge, this is the first study to demonstrate a significant association between AR expression in tumor tissue and multiple recurrences. Extended Cox regression model, such as the Andersen-Gill model, should be applied to identify risk factors for multiple endpoints, such as recurrence, in future studies.

AR promotes bladder cancer tumorigenesis [7, 8] and progression [7] in murine models. Several studies focused on AR-related pathways to explain the underlying mechanism [25]. One study showed that AR inhibits p53, which promotes apoptosis and cell cycle arrest [8]. Amirghofran Z et al. investigated apoptosis and the expressions of p53 and bcl-2 in transitional cell carcinoma of bladder [26]. Furthermore, bcl-2 and bcl-6 expression was confirmed in NMIBC [26]. Whereas AR expression was correlated with that of bcl-2 in prostate cancer [27], we failed to show any significant association between

AR expression and that of bcl-2 or bcl-6 in NMIBC specimens ($n = 39$; data not shown). Moreover, neither bcl-2 nor bcl-6 expression was significantly associated with clinicopathologic characteristics, RFS or PFS ($n = 39$; data not shown), although the small sample size may preclude identifying weak correlations. Further studies on the mechanism of AR-related signaling pathways and its effect on prognosis are warranted in NMIBC.

The AR signaling pathway can be a clinical target in NMIBC. The risk of developing bladder cancer was reduced by anti-androgen treatment, such as ADT for prostate cancer [28] or finasteride for reducing the size of the prostate or promoting hair growth [29]. ADT for prostate cancer prevented recurrences of concomitant bladder cancer [20]. Additionally, positive AR expression in concomitant NMIBC was associated with lower recurrence risk of NMIBC in prostate cancer patients who had received ADT [30]. Our results taken together with previous research [15–17, 24] indicate that positive AR expression in NMIBC appears to be a predictor of a lower risk of recurrences. However, this seems contradictory to the previous reports indicating that AR is necessary for tumorigenesis and progression in mice [7, 8]. This discrepancy can partly be explained by the hypothesis that both AR-related and other pathways affect bladder cancer recurrence [30]. Anti-androgen medication effectively prevented recurrence of AR-positive tumors because the AR-related pathway could affect AR-positive tumors more than other pathways [30]. However, positive AR expression in NMIBC patients without any anti-androgen therapy was also associated with better prognosis [15–17, 24]. Given that positive AR expression is associated with lower risk of first and multiple recurrences, closer follow-up after the first transurethral resection of bladder tumor can contribute to early detection of recurrence if the specimen was negative of AR by immunohistochemistry, regardless of anti-androgen treatment. In addition, it is of great importance to investigate mutations or amplification of AR gene or differences in the number of polyglutamine (CAG). These changes can affect the prognosis of patients who have androgen-deprivation therapy. In prostate cancer, most mutations of AR gene are located in ligand-binding domain, which provides the explanation on the resistance to anti-androgen therapy [31, 32]. In bladder cancer, several studies suggest that differences in the number of CAG repeats within exon 1 of the AR gene that are related to the transcription activity are associated with clinicopathological features in bladder cancer [33–35]. One study showed that there is no somatic missense mutation of AR gene by whole-exom sequencing analysis [36]. In the present study, we lack the information on AR gene status and no patients received androgen-deprivation therapy. Further studies on the relation between AR and prognosis in bladder cancer should examine genetic alteration of AR.

The present study has several acknowledged limitations: (i) the patient dataset was small and gathered by a single institution, potentially reflecting selection bias and underpowered detection of weak correlations between AR expression and clinicopathologic characteristics; and (ii) a lack of data including other sex steroid hormones such as ER α and ER β, which can be important for determining NMIBC prognosis [15, 16, 24].

In conclusion, AR expression is important in determining first recurrence-free survival and multiple recurrences in NMIBC. Closer follow-up after the initial transurethral resection of bladder tumor is meaningful if AR expression is negative by immunohistochemistry in the resected tumor. Further studies are warranted to determine the underlying mechanism between the AR signaling pathway and clinical outcomes in NMIBC.

Compliance with Ethical Standards

Conflict of Interest The authors declare that there are no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of Tochigi Medical Center Shimotsuga Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed Consent The requirement for written informed consent was waived by the institutional review board due to the retrospective nature of this study. All patient data were processed in anonymity and de-identified prior to analysis.

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