The Association of A Number of Predictive Factors for The Recurrence of Papillary Urothelial Neoplasm of Low Malignant Potential: Prognostic Analysis From Multiple Academic Centers

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Purpose: To identify clinically useful predictors for the recurrence of papillary urothelial neoplasm of low malignant potential (PUNLMP), we reviewed the clinical information of patients who were diagnosed and treated in multiple tertiary-care academic facilities.

Materials and Methods: Between February 2007 and April 2015, 95 patients diagnosed with PUNLMP after transurethral resection of bladder (TURB) were included in this study. Age, gender, body mass index, smoking history, the presence or absence of previous history of urothelial neoplasm, the presence or absence of gross hematuria, cytological results at the time of diagnosis, tumor diameter, and multiplicity of tumor were estimated as variables for analysis. Cox regression tests were used for identifying predictive factors for recurrence of PUNLMP.

Results: Sixty-nine cases of PUNLMP were de novo primary bladder PUNLMPs without known urothelial lesions in the urinary tract, and 26 PUNLMPs were identified on surveillance biopsies of patients with a previous history of urothelial neoplasm. During the follow-up period, recurrences developed in 13 patients (13.7%). Recurrence rates were 4.2% and 9.5% at 12 and 24 months, respectively. On univariate and multivariate Cox regression analyses, previous history of urothelial neoplasm [95% confidence interval (CI): 0.057-0.604, hazard ratio (HR) = 0.185, P = .005] and multiplicity of tumors [95% CI = 0.064-0.584, HR = 0.193, P = .004] were identified as independent predictors for recurrence-free survival of patients with PUNLMP.

Conclusion: Tumor multiplicity and previous history of urothelial neoplasm are independent prognostic factors for prediction of recurrence of PUNLMP. More careful and closer follow-up should be recommended for PULNMP patients with tumor multiplicity or a previous history of urothelial neoplasm.

Keywords: papillary urothelial neoplasm of low malignant potential; recurrence rate; prognosis; prediction factor

INTRODUCTION

The term ‘papillary urothelial neoplasm of low malignant potential’ (PUNLMP) was introduced at the 1998 World Health Organization/International Society of Urological Pathology (WHO/ISUP) meeting[(1)] In 2004, WHO/ISUP separated the noninvasive papillary neoplasms into four categories: urothelial papilloma, PUNLMP, low-grade urothelial carcinoma, and high-grade urothelial carcinoma.[(2)] These four categories replaced the 1973 WHO classification in which urothelial papilloma was categorized according to carcinoma grades 1 to 3,[(1,3)] and this system has been widely used in the clinical or pathologic fields.[(4-6)] Histologically, PUNLMP was defined as a ‘papillary urothelial lesion with an orderly arrangement of cells within papillae with minimal architectural abnormalities and minimal nuclear atypia irrespective of cell thickness.[(1)]

Several studies about PUNLMP demonstrate that the risk rate of recurrence ranges from 17.9% to 60%, and the histological progression rate is 1.9% to 29.0%.(4-8) Clinical predictors for recurrence of PUNLMP have been shown to include age, tumor size, and tumor multiplicity.[(4,6,7,9)] Histopathologic predictors include mitoses, chromatin organization state, global acetylation, methylation changes, and subtle architectural disorder.[(4,10-14)]

The histopathologic predictive factors that have been identified to date have the limitation that they cannot be applied easily in the clinical field. Additionally, previous studies about clinical predictors of PUNLMP have the limitation that they were relatively small-scale studies that were performed in single center. These limitations indicate that further efforts for identifying

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Table 1. Patient characteristics.

Number of patients	95
Gender	
Male	74
Female	21
Age at being diagnosed with PUNLMP, median (years old, IQR)	63.00 (53.00 – 71.00)
BMI, median (kg/m^2, IQR)	24.40 (22.30 – 26.10)
Smoking history	
Presence	45
Absence	41
Unknown	9
Previous history of urothelial neoplasm	
Presence	26
Absence	69
Gross hematuria	
Presence	56
Absence	39
Cytologic result	
Inadequate	1
Negative	66
Atypia, favor benign	10
Atypia, favor neoplastic	7
Suspicious malignancy	0
Malignancy	3
Not estimated	8
Tumor multifocality	
Presence	17
Absence	78
Tumor diameter, median (cm, IQR)	0.50 (0.50 – 1.00)

Abbreviations: PUNLMP, papillary urothelial neoplasm of low malignant potential; BMI, body mass index; IQR, interquartile range

prognostic factors of PUNLMP are needed. The current study was therefore conducted to investigate clinically useful predictors for the recurrence of PUNLMP in patients who were diagnosed and treated in multiple tertiary-care academic facilities.

PATIENTS AND METHODS

Patients

Five Korean institutions (Shinchon Severance Hospital, Yonsei University College of Medicine; Ajou University School of Medicine; Gangnam Severance Hospital, Yonsei University College of Medicine; Hallym University College of Medicine; Gangneung Asan Hospital, University of Ulsan College of Medicine) contributed data to this study. Between February 2007 and April 2015, 95 patients who were diagnosed with PUNLMP after transurethral resection of bladder (TURB) were included in this study. The patients were assessed by urine cytology and cystoscopy every 3 months for 2 years after TURB, every 6 months for the next 3 years, and yearly thereafter. The patients also had a computed tomography scan yearly. Recurrence was defined as the histopathologically proven reappearance of any urothelial neoplasm during the follow-up period, and progression was defined as recurrence to a higher-grade neoplasm. Histopathologic diagnosis was classified using the 2004 WHO/ISUP criteria.[1,15] The medical ethics committee of Severance Hospital,
Yonsei University Health Care System (Seoul, Korea) approved this retrospective study. After receiving institutional review board approval, we conducted a retrospective chart review of included patients.

Clinical data and statistical analysis

Age, gender, body mass index, smoking history, the presence or absence of previous history of urothelial neoplasm, the presence or absence of gross hematuria, cytological results at the time of diagnosis, tumor diameter, and multiplicity of tumor were estimated as variables for analysis. Gross hematuria was defined as the case in which the hematuria was visually confirmed, and tumor multiplicity was defined as the presence of tumors at 2 or more sites in the cystoscopy.
The end point of the study was recurrence-free survival (RFS), and RFS defined as the time interval between inital TURB and first recurrence. Statistical analyses to identify independent predictors for RFS of PUNLMP were performed using univariate and multivariate Cox's proportional hazard regression analyses. Variables that were significant in the univariate analysis ($p<0.05$) were entered into the multivariate model. All statistical analyses were performed using SPSS Statistics version 20.0.0 (IBM Corp., Armonk, NY, USA). For all analyses, a two-sided p-value of < 0.05 was considered to indicate statistical significance.

RESULTS

The median follow-up period after being diagnosed with PUNLMP after TURB was 25.3 months, and all included patients had tumors that were classified as noninvasive (Ta) PUNLMP. Baseline characteristics of included patients are outlined in **Table 1**. 69 patients had de novo primary bladder PUNLMPs without known urothelial lesions in the urinary tract. 26 PUNLMPs were diagnosed with surveillance biopsies on patients with a previous history of urothelial neoplasm. Of 26 patients, 5 and 21 patients were classified as T1 and Ta, respectively. All of 26 patients were diagnosed with low-grade urothelial carcinoma.
During the follow-up period, recurrences developed in 13 patients (13.7%). Recurrence rates were 4.2% and 9.5% at 12 and 24 months, respectively. Histologic grade progression developed in seven patients (7.4%), and none of the included patients developed stage progression (> pTa). All of patients who progressed in histologic grade were diagnosed as having low-grade urothelial carcinoma. Of recurred patients, there were none who progressed to high-grade or either to pT1. Five patients died during the follow-up period from dis-

Table 2. Predictors for recurrence free survival of PUNLMP

Variables	HR	95%CI	*P*
Univariate analysis			
Age at being diagnosed with PUNLMP	0.998	0.940-1.059	0.948
Gender relative to male			
Female	0.409	0.069-2.435	0.326
BMI	1.609	1.060-2.442	0.025
Smoking history relative to absence			
Presence	0.932	0.037-23.247	0.966
Gross hematuria relative to absence			
Presence	0.886	0.225-3.486	0.862
Previous history of urothelial neoplasm relative to absence			
Presence	0.050	0.009-0.294	0.001
Cytologic result relative to ≤atypia, favor benign			
≥atypia, favor neoplastic	1.726	0.224 – 13.293	0.600
Multifocality relative to absence			
presence	0.075	0.016-0.361	0.001
Tumor size	1.200	0.440-3.269	0.722
Multivariate analysis			
BMI	1.110	0.903-1.365	0.323
Previous history of urothelial neoplasm relative to absence			
Presence	0.185	0.057-0.604	0.005
Multifocality relative to absence			
Presence	0.193	0.064-0.584	0.004

Abbreviations: PUNLMP, papillary urothelial neoplasm of low malignant potential; HR, hazard ratio; CI, confidence interval; BMI, body mass index

eases other than an urothelial malignancy. Univariate and multivariate Cox regression analyses were conducted to identify independent predictive factors for RFS of patients with PUNLMP (**Table 2**). On univariate and multivariate Cox regression analyses, previous history of urothelial neoplasm [95% confidence interval (CI) = 0.057-0.604, HR = 0.185, *P* = .005] and multiplicity of tumors (95% CI = 0.064-0.584, HR = 0.193, *P* = .004) were identified as independent predictors for RFS of patients with PUNLMP.

The RFS of groups who were categorized by previous history of urothelial neoplasm and multiplicity were calculated using the Kaplan-Meier method (**Figure 1**). The differences in RFS between groups were statistically significant ($p < 0.001$) as determined by the log rank test.

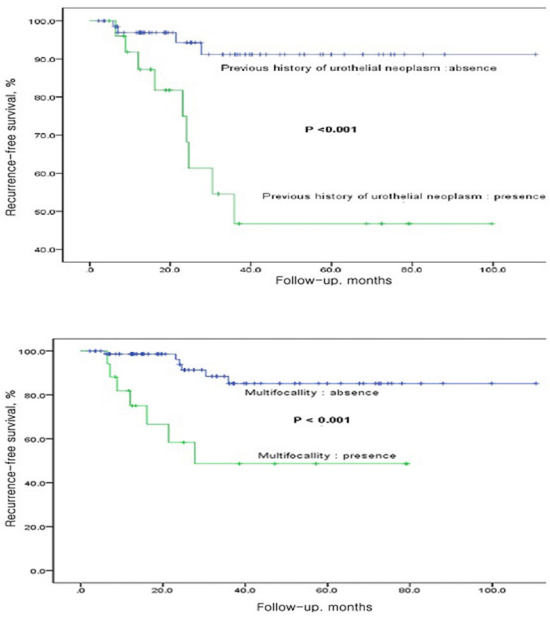

Figure 1. a) Kaplan-Meier curve for recurrence (%) in group with previous history of urothelial neoplasm and group without previous history of urothelial neoplasm.
b) Kaplan-Meier curve for recurrence (%) in group with tumor multiplicity and group without previous history of urothelial neoplasm.

DISCUSSION

PUNLMP has the histopathologic feature which requires clinical follow-up even though it has limited biologic aggressiveness, and it may seem evident that it is generally regarded as malignancy because of the character that the recurrence and the progression might develop in PUNLMP.[16] However, it has been not categorized as malignancy. Reducing the psychological and financial hardship of patients who were diagnosed as cancer is one of the reasons that clinicians and pathologists do not regard PUNLP as carcinoma.[16] For the reason, clinicians should recommend regular follow-up for patients who have PUNLMP because of its clinically ambiguous characteristics. Traditionally, most clinicians have had difficulty in planning follow-up because the obvious prognosis of PUNLMP has not yet been identified. Several studies for identifying the prognosis and histopathologic predictive factors for recurrence or progression of PUNLMP have been conducted to improve this situation.

Montironi et al. reported that chromatin organizational state is a predictive factor for the recurrence of PUNLMP,[10,11] and Mazzucchelli et al. reported that global acetylation and methylation changes predict the recurrence of PUNLMP.[12] It has also been reported that subtle architectural disorder detected by quantitative analysis in DAXX (death domain-associated protein)-immunostained tissue sections in recurrent cases of PUNLMP may play a role in recurrence of this disorder.[13] Pich et al. reported that proliferative activity is the most significant predictor of recurrence in nonin-

vasive PUNLMP and grade 1 papillary carcinomas of the bladder.[14] However, this study has the limitation that it combines patients with both noninvasive PUNLMP and grade 1 papillary carcinoma. Although these studies identified histopathologic predictive factors for recurrence of PUNLMP, the factors are not easily assessed and applied to predictions of recurrence in the most clinical fields.

Clinical data for identifying the prognosis and the prognostic factor of PUNLMP have also been reported. Fujii et al. studied the long-term outcome of bladder PUNLMP[8] and reported that the 2-, 5-, and 10-year recurrence free rates were 66%, 51%, and 36%, respectively. Maxwell et al. also reported results identified from long-term follow-up periods.[5] Although these clinical studies have the strength of long-term follow-up periods, they did not suggest any predictive factor for the recurrence of PUNLMP. Several authors reported that tumor multiplicity, tumor size, and prior recurrence rate are significant prognostic factors for prediction of recurrence in non-muscle-invasive urothelial neoplasm that contain PUNLMP.[7,9] However, again these studies have the limitation that they did not include cases of PUNLMP exclusively. It has also been reported that the size of the initial tumor in patients with recurrences was significantly higher compared with those from patients with no recurrence, but this factor was not confirmed in multivariate analysis.[6]

Recently, Zhang et al. identified age, tumor multiplicity, and mitosis as significant prognostic factors for the recurrence of PUNLMP through multivariate analysis.[4] Even though this report has a relatively small scale, it is important because the significant prognostic factors suggested in this study can be easily applied in clinical fields.

Tumor multiplicity has been known as one of the prognostic factors for RFS of superficial urothelial carcinoma that has developed in bladder.[17]) Patients with multiple tumors may have had increased risk because the probability of incomplete resection and microscopic tumor dissemination increase with the number of tumor.[18] The current study also indicates that tumor multiplicity is a prognostic predictor for recurrence of PUNLMP, like the result reported by Zhang et al. The fact that these two studies show tumor multiplicity as a predictor of recurrence of PUNLMP indicates that PUNLMP should not be clinically regarded as a purely benign neoplasm.

The prior recurrence rate has also been known as one of the predictive factors for the recurrence of stage Ta T1 bladder cancer.[17] Similarly, the current study results indicate that a previous history of urothelial neoplasm is one of the significant prognostic factors in PUNLMP. This similarity of results suggests PUNLMP is similar to a malignancy.

Although the proportion of PUNLMP cases with a previous history of urothelial neoplasm in most published studies has not been mentioned, PUNLMP cases with a previous history of urothelial neoplasm are not rare clinically. The study that was reported by Lee et al. showed that 29 of 63 patients with PUNLMP had a previous history of urothelial neoplasm.[6] A strength of the current study, in contrast with previous reported studies, is that the enrolled patients included patients with a previous history of urothelial neoplasm. These results suggest that more careful and closer follow-up should be recommended in patients with PULNMP who have a previous history of urothelial neoplasm. The results of the current study also show that tumor multiplicity and the previous history of urothelial neoplasm, which are prognostic factors of noninvasive urothelial carcinoma, can be applied as prognostic factors for the recurrence of PUNLMP.

The results reported in the current study need to be confirmed and validated by analyzing data from a larger prospective study because they may have been affected by the retrospective nature of the study and the small number of enrolled patients.

CONCLUSIONS

In the current study, we found that tumor multiplicity and previous history of urothelial neoplasm are independent prognostic factors for the prediction of recurrence of PUNLMP. Clinicians should recommend careful and close follow-up of PUNLMP patients who have tumor multiplicity or previous history of urothelial neoplasm.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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