Original Article
Bladder papillary urothelial neoplasm of low malignant potential in Chinese: a clinical and pathological analysis

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Abstract: Papillary urothelial neoplasm of low malignant potential (PUNLMP) had the incidence of low and definitive recurrence. Therefore, few studies showed that the relationship between pathological factors and the prognosis of patients with PUNLMP. The aim of this study assessed the linkage of pathological factors and prognosis of patients with PUNLMP including the presence or absence of mitoses and the thickness of urothelium. A retrospective analysis of 71 patients with PUNLMP was enrolled between January 2007 and June 2013. The clinicopathological factors consisting of tumor diameter, multifocality, the presence or absence of mitoses and cell thickness of urothelium were retrieved, Log-rank test and Cox proportional hazards regression models were used for univariate and multivariate analyses to evaluate the associations of these factors with recurrence-free survival (RFS) and progression-free survival (PFS).The incidence of recurrence and progression for PUNLMP was 19.7% and 16.9%, respectively. Patients with grade progression represented 85.7% in the recurrent patients. No patients had stage progression and no cases died from invasive urothelial carcinoma. Univariate analysis showed that the presence of mitoses, tumor diameter greater than or equal to 0.8 cm, multifocality were significantly correlated with worse RFS ($P < 0.05$) and PFS ($P < 0.05$). Multivariate analysis demonstrated that the presence of mitoses, tumor multifocality were significantly independent biomarkers for worse RFS ($P < 0.05$) and PFS ($P < 0.05$). Although the rare and infrequent mitoses were found for PUNLMP, the presence of mitoses and tumor multifocality were still the independent and poor predictors for the prognosis of PUNLMP. In addition, once the PUNLMP appeared to the recurrence, the inevitable grade progression could be determined, herein, long-term follow-up was necessary to be warranted, especially for patients with multiple lesions and the presence of mitoses.

Keywords: PUNLMP, recurrence, progression, mitoses, multifocality

Introduction

Non-invasive papillary urothelial neoplasms represented appropriately 45% of all the urinary tumors [1]. For the grade of papillary urothelial neoplasms, the WHO 1973 classification scheme was primarily accepted by partial urologists and pathologists, and it categorized these urothelial neoplasms into the 4 groups consisting of papilloma, and grading 1 to 3 carcinomas [2]. However, a degree of poorly diagnostic reproducibility was served as one of the some limitations for pathologists in the clinical practice for WHO 1973 classification system. Therefore, the WHO 2004/ISUP classification

system was more extensively applied due to the description of clear histological features of urothelial neoplasms and decreases of the diagnostic subjectivity of WHO 1973 scheme, and improved the grading system of non-invasive papillary urothelial neoplasms [1]. The WHO 2004/ISUP 1998 classification system grouped non-invasive papillary urothelial tumors into papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), low and high grade papillary urothelial carcinoma [3]. The definition of PUNLMP was initially recommended as a papillary urothelial lesion in this classification system, which was histologically characterized with an orderly arrangement of cells in

Table 1. Clinical outcome of 71 patients with papillary urothelial neoplasm of low malignant potential

Clinical outcomes	Number of cases
Recurrence	14 (19.7%)
1 times	5
2 times	9
Higher grade progression	12 (16.9%)
Low grade	9
High grade	3
Stage progression (> pTa)	0 (0%)
Died of bladder cancers	0 (0%)

papillae with greater than cell thickness of normal urothelium, mild architectural abnormalities and nuclear atypia, and rare mitoses of the basal cell layer.

According to the above mentioned, the PUNLMP could be considered as a borderline tumor varying from the benign papilloma and the urothelial carcinoma. Some studies demonstrated that the risk rate of recurrence ranged from 21.6% to 60% and the progression rate was 2.4%, 8% and 29%, respectively for the patients with PUNLMP, but the pathological stage progressed was not found [4-8], suggesting that in general, this neoplasm had a minimal risk of grading progression and recurrence, therefore, long-term observation was necessary to prevent the patients with PUNLMP from disease development. In addition, some prognostic factors associated with patients' survival for non-invasive papillary urothelial neoplasms were identified including tumor size, tumor grade, recurrence and multifocality [1]. Many literatures have reported that clinical outcome of the recurrence and progression for patients with PUNLMP [8-10], however, few studies showed that the relationship between pathological factors and the prognosis of patients with PUNLMP. The aim of this study assessed the linkage of pathological factors and prognosis of patients with PUNLMP including the presence or absence of mitoses and the cell thickness of urothelium.

Materials and methods

Patients

A cohort of retrospective study data of patients with PUNLMP came from Sun Yat-Sen University

Cancer Center; and 71 specimens of PUNLMP were achieved between January 2007 and June 2013. The clinicopathological data of these specimens were collected from medical records in the Department of Urology and pathology reports from the Department of Pathology, including patients' age, gender, tumor diameter, multifocality, the presence or absence of mitoses and cell thickness of urothelium by microscopy. The clinical data was also comprised of recurrence-free survival (RFS) and progression-free survival (PFS). The selection of patients necessitated to fit these requirements: the PUNLMP as pathological diagnosis; without other preoperative malignant tumors; without chemotherapy and radiotherapy history; consecutively follow-up. The 71 patients were observed by urine analysis, cystoscopy every 3 months within the post-operative first 3 years, every 3-6 months in the next year and every 6-12 mouths from the fifth year, and annually thereafter.

Statistical analysis

Statistical analysis was made with the SPSS software, version 16.0 (SPSS, Chicago, USA). The association of the number of recurrence with tumor grade progression was calculated by chi-square test. The survival curves for clinical and pathological factors were plotted by Kaplan-Meier method and calculated with log-rank test. Univariate and multivariate regression analysis were performed with the Cox proportional hazards regression model to identify the impact of the significant factors on prognosis, Hazard ratios (HRs) estimated from the Cox analysis were recorded as relative risks with corresponding 95% confidence intervals (CIs). $P < 0.05$ was regarded as significantly statistical significance.

Results

Patients' features

The clinicopathological features of patients with PUNLMP were demonstrated. The mean age of the 71 patients was 51.4 years old, ranging from 22 to 74 years. For all the patients included 52 (73.2%) male patients and 19 (26.8%) female patients (male to female ratio, 2.7:1). The average follow-up interval was 50.0 months, with a range from 3 to 89 months, 14 of 71 patients had bladder tumor recurrence,

Table 2. Univariate and multivariate analyses of recurrence-free survival

Variable	Univariate analysis			Multivariate analysis	
	All cases	HR (95% CI)	P value	HR (95% CI)	P value
Gender			0.161		
Female	19	Reference			
Male	52	34.014 (0.246-4.712E3)			
Age (years)			0.023	7.381 (1.275-42.735)	0.026
≤ 52	36	Reference			
> 52	35	4.413 (1.228-15.856)			
Tumor multifocality			< 0.001	17.024 (4.160-69.665)	< 0.001
No	54	Reference			
Yes	17	17.105 (4.739-61.737)			
Tumor diameter (cm)			0.019	3.732 (0.373-37.343)	0.262
≤ 0.8	31	Reference			
> 0.8	40	11.391 (1.487-87.249)			
Mitoses			< 0.001	9.930 (2.594-38.006)	0.001
Absent	54	Reference			
Present	17	8.311 (2.773-24.906)			
Urothelial cell layers			0.983		
≤ 12	37	Reference			
> 12	34	1.012 (0.355-2.885)			

and 12 of 14 patients progressed to non-invasive higher grading neoplasms (9 patients with low grade papillary urothelial carcinoma and 3 patients with high grade papillary urothelial carcinoma). Patients with grade progression represented 85.7% (12/14) in the recurrent patients. No cases progressed to the invasive carcinoma and no patients died of bladder cancers (**Table 1**). The number of tumor recurrence was significantly associated with tumor progression (2 recurrence vs. 1 recurrence, 100% vs. 60%, P = 0.04). The RFS rates at the 5th and 10th years were 81% and 76%, respectively. The median RFS was 40.0 months. The PFS rates at the 5th and 10th years were 85% and 40%, respectively. The median PFS was 42.0 months.

Relationship of clinicopathological factors and the prognosis for patients with PUNLMP

Univariate analysis revealed that the clinical factors consisting of tumor size, multifocality and age at diagnosis were closely impacted on RFS and PFS of patients with PUNLMP (P < 0.05, **Tables 2** and **3**). Prognostic evaluation of patients with PUNLMP demonstrated that the presence of mitoses was associated significantly with poor RFS (P < 0.001, **Figure 1A**) and PFS (P < 0.001, **Figure 2A**). Whereas patients

with urothelial cell layers greater than 12 of PUNLMP in microscopy had no significantly different prognosis compared with that of urothelial cell layers less than or equal to 12 (P > 0.05). Univariate analysis found that the presence of mitoses, tumor multifocality, tumor diameter (≥ 0.8 cm) and age at diagnosis were significantly associated with the prognosis of PUNLMP (P < 0.05). Multivariate analysis showed that the presence of mitoses, tumor multifocality and age at diagnosis were independent predictive factors for RFS (**Table 2**) and the presence of mitoses, tumor multifocality also were served as the independent predictive factors for PFS (**Table 3**).

Discussion

Our study found that the patients with PUNLMP had the risk of recurrence and progression. Therefore, we considered either the PUNLMP was a benign neoplasm or the tumor had a really low malignant potential. However, the WHO 2004/ISUP classification system had confirmed that PUNLMP was regarded as a separate neoplasm distinguishable from urothelial papilloma, low and high grade papillary urothelial neoplasms [4]. In this study, 19.7% of patients with PUNLMP were found in the locore-
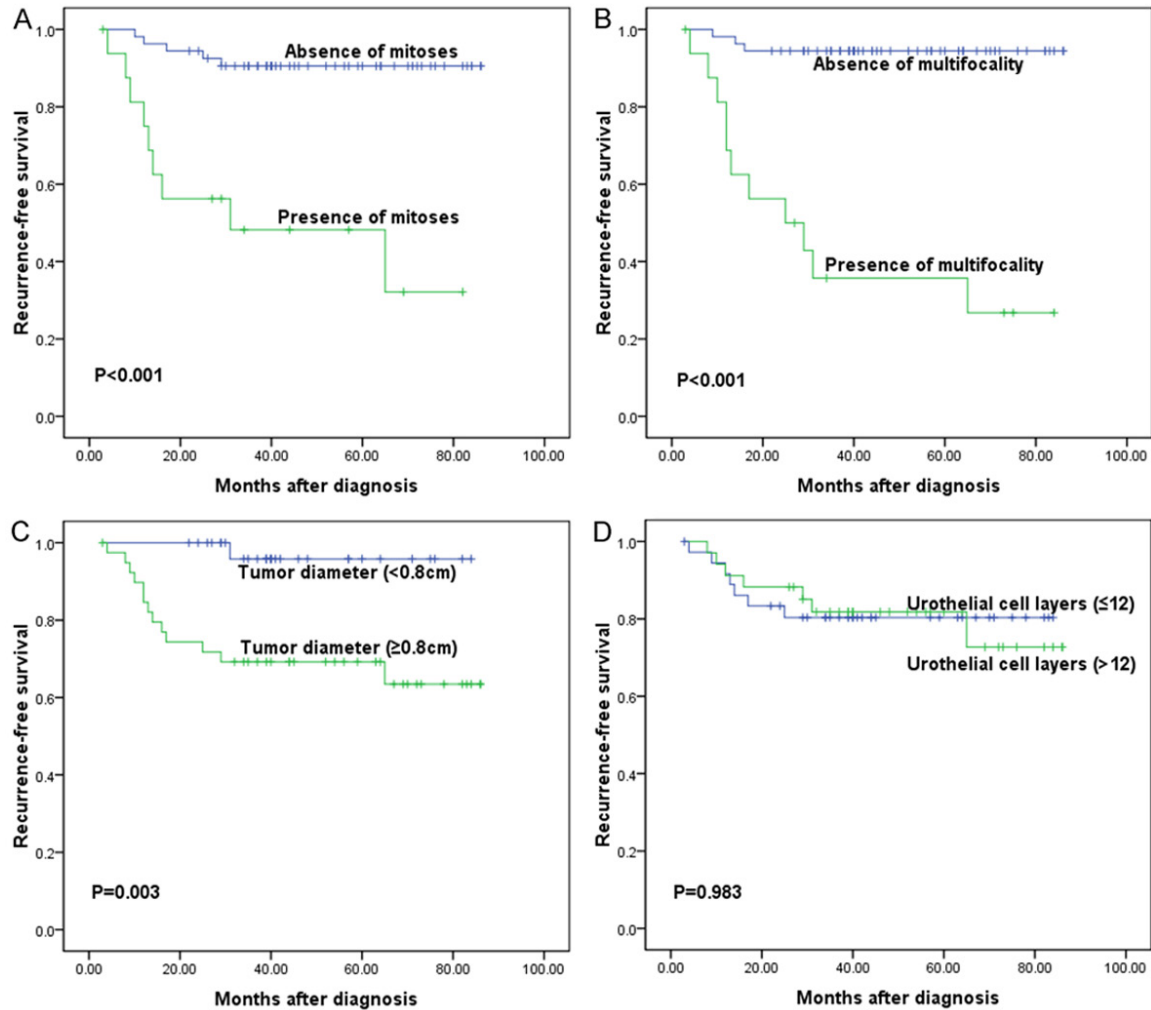
Figure 1. Survival curves of recurrence-free survival and clinicopathologcial factors including mitoses, multifocality, tumor diameter and urothelial cell layers.

gional recurrence during the follow up of average 50 months, 16.9% of patients progressed to the higher grade non-invasive papillary urothelial neoplasms and only 2.8% of patients recurred yet as PUNLMP at the same observed period. No patients with PUNLMP occurred stage progression (> pTa) and none died in the follow-up intervals. Which was consistent with prior studies [5, 8, 11]. However, one research of 116 patients with non-invasive papillary urothelial tumors [12] revealed only 1 patient died of progression to invasive bladder carcinoma. According to our results, although the incidence of PUNLMP recurrence was low, we found that once the recurrence was present for PUNLMP, the possibility of progression to higher grade remained to be quite large (12/14 = 85.7%). A literature reported that the recurrence rate of

low grade papillary urothelial carcinoma was significantly higher than that in PUNLMP (71% vs. 35%) and 2.4% of stage progression (> pTa) was taken up in low-grade carcinomas [5] and Harry W et al. demonstrated that 1 patient with low grade papillary urothelial carcinomas has died of bladder cancer [11]. For high grade papillary urothelial carcinoma, 73% of recurrence rate and 15% of incidence of death from bladder cancer were shown [13, 14]. Therefore, the evidence confirmed that low and high grade papillary urothelial carcinoma more easily recur and died compared with PUNLMP, the prognosis of low and high grade papillary urothelial carcinoma is worse than that of PUNLMP, although rarely progressed in stage and grade for PUNLMP, they still became life threatening when the progression occurred, indicating that
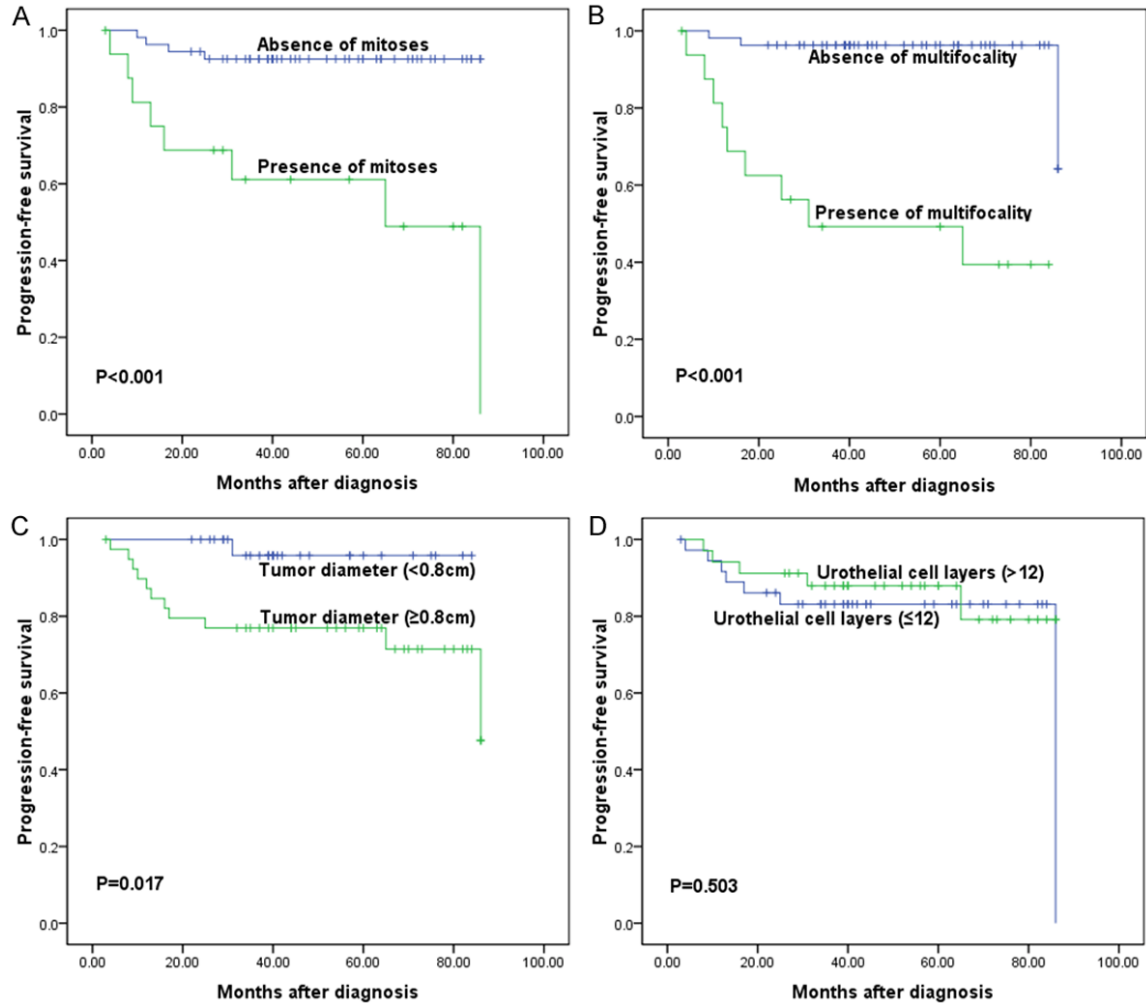
Figure 2. Survival curves of progression-free survival and clinicopathologcial factors including mitoses, multifocality, tumor diameter and urothelial cell layers.

the suitable means for the control of recurrence in patients with PUNLMP should be provided by the urologists.

To the best of our knowledge, the presence of mitoses meant rapidity of cell proliferative activity. Although the rare and infrequent mitoses were found for PUNLMP by microscopy, the presence of mitoses remained to predict the RFS and PFS of patients with PUNLMP by univariate and multivariate analyses. We have shown that the RFS and PFS of PUNLMP with mitoses were significantly shorter than those of PUNLMP without mitoses. This result was in agreement with studies showing a correlation of mitotic frequency with RFS in patients with superficial bladder carcinoma [15, 16], but their studies included the patients of bladder tumors with stage Ta and T1, and our study

firstly reported that the presence of mitoses was associated with prognosis of patients with PUNLMP. In addition, several studies have shown that P53 and MIB-1 index had the prognostic significance for the patients with PUNLMP and low grade [16], and patients with PUNLMP revealed a Ki-67 index less than 10% [17], but these staining did not provide more significant advantages than the mitoses defined by microscopy. Therefore, the status of the mitoses could be considered as more beneficial marker for the prediction of prognosis for PUNLMP due to the method was the economic and easily observed.

Univariate and multivariate analysis revealed that PUNLMP patients with tumor diameter greater than or equal to 0.8 cm or multiple lesions had a worse RFS and PFS, suggesting

Table 3. Univariate and multivariate analyses of progression-free survival

Variable	Univariate analysis			Multivariate analysis	
	All cases	HR (95% CI)	P value	HR (95% CI)	P value
Gender			0.198		
Female	19	Reference			
Male	52	33.792 (0.159-7.163E3)			
Age (years)			0.082		
≤ 52	36	Reference			
> 52	35	3.208 (0.864-11.911)			
Tumor multifocality			< 0.001	13.163 (2.760-62.770)	0.001
No	54	Reference			
Yes	17	18.778 (4.040-87.271)			
Tumor diameter (cm)			0.045	6.487 (0.822-51.209)	0.076
≤ 0.8	31	Reference			
> 0.8	40	8.251 (1.053-64.675)			
Mitoses			0.001	3.644 (1.067-12.443)	0.039
Absent	54	Reference			
Present	17	7.610 (2.276-25.445)			
Urothelial cell layers			0.506		
≤ 12	37	Reference			
> 12	34	0.676 (0.213-2.142)			

that tumor diameter (≥ 0.8 cm) and multifocality at initial diagnosis were inversely associated with tumor recurrence and progression, this similar conclusion was confirmed by a study for 34 cases with PUNLMP [8]. Therefore, long-term follow-up was also necessary to the PUNLMP patients with microscopic mitoses, multiple lesions and larger tumors, and strict clinical surveillance should be performed to identify early recurrent tumors. Recently, a study of patients with PUNLMP in ureter found that organ-sparing endoscopic treatments should be the choice of preference [18]. Thus, whether semirigid and flexible cystoscopy could be selected to the treatment of PUNLMP in bladder according to the different site of bladder lesion, this speculation needed to be supported in the further study.

In summary, PUNLMP was a rare urothelial neoplasm with somewhat recurrence and progression. PUNLMP with mitoses by microscopy revealed a more aggressive behavior. Age, tumor multifocality and tumor diameter were also critical prognostic factors. A larger or multicentric cohort of prospective study was needed.

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Disclosure of conflict of interest

None.

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