CME/SAM

Prognostic Significance of the 2004 WHO/ISUP Classification for Prediction of Recurrence, Progression, and Cancer-Specific Mortality of Non–Muscle-Invasive Urothelial Tumors of the Urinary Bladder

A Clinicopathologic Study of 1,515 Cases

Chin-Chen Pan, MD,[1,3] Yen-Hwa Chang, MD, PhD,[2] Kuang-Kuo Chen, MD, PhD,[2] Hui-Jung Yu, MD,[1,3] Chih-Hao Sun, MD,[1,3] and Donald M. T. Ho, MD[1,3]

Key Words: Non–muscle-invasive urothelial carcinoma; 2004 World Health Organization/International Society of Urological Pathology classification; Recurrence; Progression

DOI: 10.1309/AJCP12MRVVHTCKEJ

Upon completion of this activity you will be able to:
- define the significance of 2004 World Health Organization (WHO)/International Society of Urological Pathology (ISUP) classification of papillary urothelial tumors.
- correlate the 2004 WHO/ISUP grade with recurrence, progression, and cancer-specific mortality of urinary bladder non–muscle-invasive urothelial tumors.
- analyze the significant prognostic factors of urinary bladder non–muscle-invasive urothelial tumors.

The ASCP is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The ASCP designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*™ per article. This activity qualifies as an American Board of Pathology Maintenance of Certification Part II Self-Assessment Module.

The authors of this article and the planning committee members and staff have no relevant financial relationships with commercial interests to disclose.

Questions appear on p 817. Exam is located at www.ascp.org/ajcpcme.

Abstract

To verify prognostic significance of the 2004 World Health Organization (WHO)/International Society of Urological Pathology (ISUP) grading systems, we retrospectively studied the tumors of 1,515 patients who underwent transurethral resection of primary non–muscle-invasive urothelial tumors (pTa, 1,006 patients; pT1, 509 patients) confined to the bladder. Cases were classified according to the 2004 WHO/ISUP systems as 212 cases of papillary urothelial neoplasm of low malignant potential (PUNLMP), 706 low-grade papillary urothelial carcinomas (LPUCs), and 597 high-grade papillary urothelial carcinomas (HPUCs). PUNLMP showed the statistically significantly lowest recurrence cumulative incidence compared with the other tumor types. There were significant differences and trends for higher progression and cancer-specific mortality cumulative incidence in the following order: PUNLMP, LPUC, pTa HPUC, and pT1 HPUC. No differences of progression and cancer-specific mortality cumulative incidence were found between pTa and pT1 LPUC. Our study validates the usefulness of the 2004 WHO/ISUP system to classify urothelial tumors into prognostically distinct categories that would contribute to the design of therapeutic and monitoring strategies for patients with non–muscle-invasive bladder urothelial tumors.

The grading of papillary urothelial neoplasms has been a long-standing issue of debate. Among numerous grading systems, the 1973 World Health Organization (WHO) system is the most commonly used.[1] However, a major limitation is its arbitrary definitions. In 1998, the International Society of Urological Pathology (ISUP) proposed a new grading system,[2] which was adopted in large measure by the WHO in 2004.[3] The new 2004 WHO/ISUP scheme, with the strength of clear-cut criteria for each entity and the aim of eliminating subjective and arbitrary interpretation, greatly improves the ambiguous language that marked the 1973 WHO system.

In this study, we evaluated the efficiency of the 2004 WHO/ISUP classification for prediction of recurrence, progression, and cancer-specific mortality. The usefulness of the 2004 WHO/ISUP system has been described in a few reports, with sample size varying from 49 to 504 cases.[4-12] We collected a large cohort of patients with primary bladder non–muscle-invasive (pTa and pT1) urothelial tumors treated by transurethral resection (TUR). The large sample permitted us to stratify cases to procure detailed information from different strata.

Materials and Methods

Study Subjects

This study was approved by the institutional review board of Taipei Veterans General Hospital, Taipei, Taiwan

(No. 96-06-10A). During the 15-year period from 1991 to 2005, a total of 2,191 patients at Taipei Veterans General Hospital received a pathology diagnosis of bladder urothelial tumor. Of these, a total of 1,515 patients (1,307 men and 208 women) had non–muscle-invasive tumors confined to the bladder, without primary urothelial neoplasms elsewhere. They were treated by TUR with or without intravesical instillation (IVI). Patients who underwent partial or radical cystectomy were not included in this study. To minimize interobserver variability, all pathology material was reviewed by 1 investigator (C.-C.P). Tumors were reviewed and graded according to the 2004 WHO/ISUP classification as papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade papillary urothelial carcinoma (LPUC), or high-grade papillary urothelial carcinoma (HPUC) **Image 1**. Information regarding multiplicity was obtained from surgery notes and pathology reports.

Complete management records of adjuvant therapy were available for 874 patients. A total of 592 patients received IVI. IVI included thiotepa for 4 patients, mitomycin-C for 300, epirubicin for 61, doxorubicin for 29, and bacillus Calmette-Guérin for 97. The remaining patients received a combination of the aforementioned regimens.

Patient Follow-up

The follow-up protocol was composed chiefly of periodic cystoscopy every 3 months for 3 years, followed by every 6 months for 2 years and then yearly for 5 years. Follow-up records were obtained by reviewing the medical records, the pathology archive, and the cancer registry file of the cancer registry center of our institute. Recurrence was defined as the reappearance of histopathologically confirmed urothelial neoplasm in the bladder. Cases with recurrence within 3 months of primary diagnosis were excluded, owing to the possibility of residual

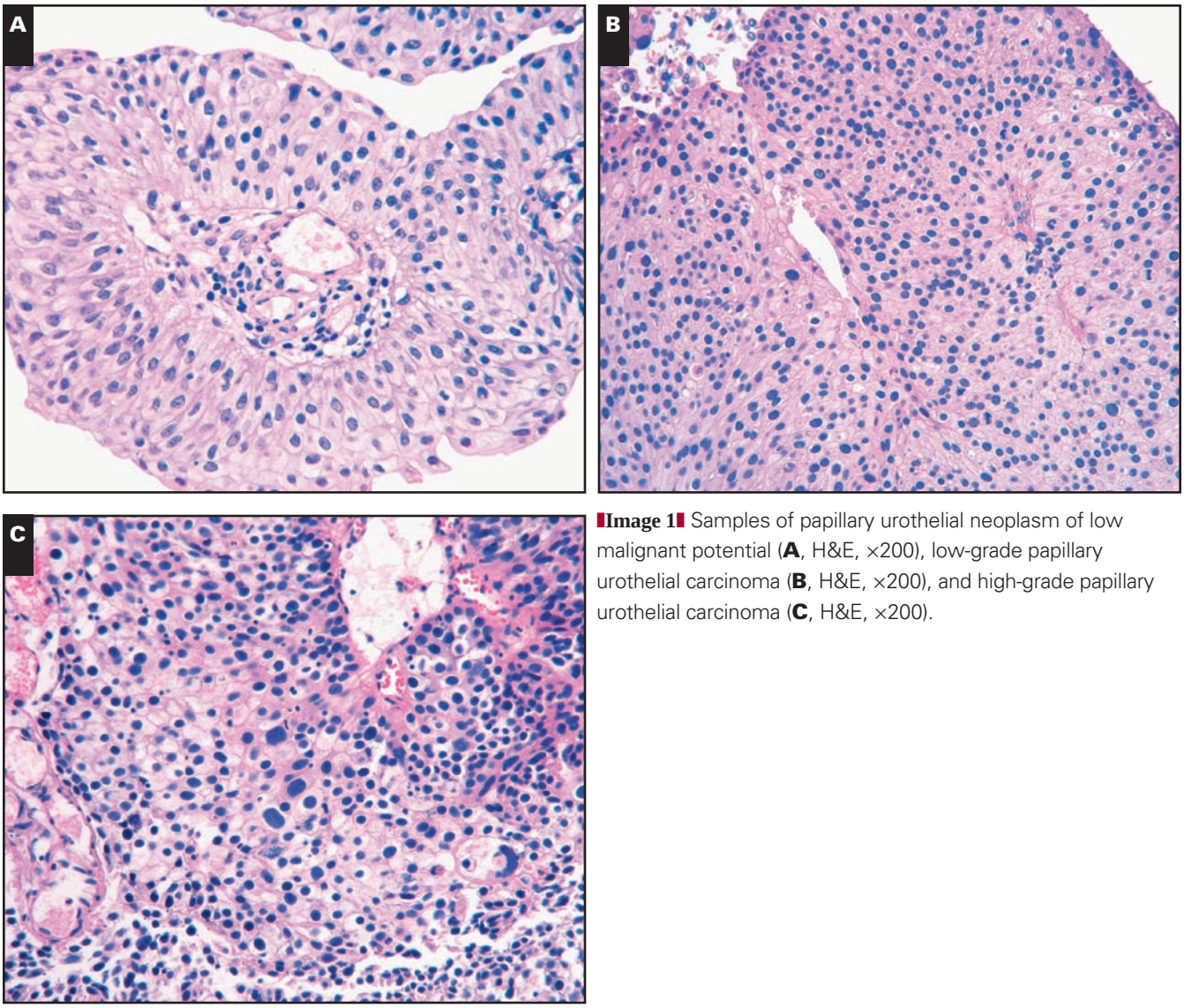

Image 1 Samples of papillary urothelial neoplasm of low malignant potential (**A**, H&E, ×200), low-grade papillary urothelial carcinoma (**B**, H&E, ×200), and high-grade papillary urothelial carcinoma (**C**, H&E, ×200).

DOI: 10.1309/AJCP12MRVVHTCKEJ

tumor rather than true recurrence. Progression was defined as an advance in stage, diagnosis of metastasis, or death caused by tumor. Prior recurrence rate (primary; recurrent ≤1 recurrence per year; recurrent >1 recurrence per year) was defined as previously.[13] Patients who were alive and without the event of interest (recurrence, progression, and cancer-specific mortality) were censored at the last date of follow-up. Deaths before the event of interest were analyzed as a competing risk.

Statistical Analysis

Relations between parameters were examined by using the Fisher exact test or χ^2 test. The distribution of age among grades was assessed by 1-way analysis of variance and Scheffe comparison. Time to event distributions were estimated by means of cumulative incidence functions to properly take into account the patients who died (competing risk) before the end point of interest. Given the presence of competing risk, it is more appropriate to report cumulative incidence curves rather than disease-free Kaplan-Meier curves.[14] Considering sample size and effect of IVI, we performed survival analysis first on the entire data set (1,515 patients) and then focused on cases with available management records (874 patients). Statistical analyses were computed with the Stata software program (Stata, College Station, TX) or R Project for Statistical Computing supplemented with Cmprsk library (http://www.r-project.org).

Results

The case numbers of PUNLMP, pTa LPUC, pT1 LPUC, pTa HPUC, and pT1 HPUC were 212 (14.0%), 603 (39.8%), 103 (6.8%), 191 (12.6%), and 406 (26.8%), respectively. Patient age ranged from 23 to 92 years, with a mean of 71 years. The mean ± SD age of patients with PUNLMP was 65.4 ± 14.6 years, for patients with LPUC was 71.0 ± 9.8 years, and for patients with HPUC was 72.6 ± 9.6 years. Differences in age between these subtypes were statistically significant ($P < .0001$ for PUNLMP vs the other 2 groups; $P = .022$ for LPUC vs HPUC). There was a statistically significant positive correlation between grade and pT stage ($P < .0001$). The mean follow-up times were 81 months (range, 1-215 months; median, 74 months) for patients who were alive and 43 months (range, 1-182 months; median, 33 months) for patients who died.

A total of 425 patients (28.1%) had multiple tumors, and 52 (3.4%) had simultaneous carcinoma in situ. The latter may be an underestimate because not all patients underwent biopsy of the bladder mucosa at the time of tumor resection to find flat lesions.

Incidence of Recurrence, Progression, and Cancer-Specific Mortality

A total of 484 patients (31.9%) experienced recurrence. The incidence rates of recurrence for PUNLMP, LPUC, and HPUC were 17.9%, 35.0%, and 34.0%, respectively. The incidence of recurrence for PUNLMP was significantly lower ($P < .0001$) than that for the other types. When all grades were considered, there was no significant difference in recurrence between pTa and pT1 tumors (31.0% vs 33.0%). Patients with multiple tumors showed significantly higher recurrence (47.1%) than those with single tumors (26.0%) ($P < .0001$). IVI in patients with LPUC reduced the incidence of recurrence from 41.0% to 31.8% ($P = .031$). However, IVI did not modify the risk of recurrence for PUNLMP or HPUC.

A total of 222 patients (14.7%) experienced tumor progression. Tumors progressed in 1.9%, 6.5%, and 28.8% of patients with PUNLMP, LPUC, and HPUC, respectively, and in 8.0% and 26.9% of pTa and pT1 tumors, respectively. Differences in progression incidence between paired grades and pT stage were all statistically significant ($P < .0001$). IVI reduced the overall progression rate from 17.4% to 10.0% ($P = .001$).

None of the patients with PUNLMP died of the disease. Of patients with initial diagnoses of LPUC and HPUC, 2.0% and 21.9%, respectively, eventually died of these cancers. The incidences of cancer-specific mortality were 3.0% and 22.0% for pTa and pT1 tumors, respectively. Differences in cancer-specific mortality rates were significant between paired grades and pT stage ($P < .0001$). IVI reduced the incidence of cancer-specific mortality from 11.8% to 5.1% of all cases ($P = .0002$).

Univariate and Multivariate Analyses

The recurrence cumulative incidence plot stratified by tumor grade and pT stage **Figure 1A** revealed that PUNLMP showed the lowest cumulative incidence, whereas the cumulative incidence curves for LPUC and HPUC overlapped with each other. The cumulative incidence plots for progression **Figure 1B** and cancer-specific mortality **Figure 1C** showed that patients with PUNLMP had the lowest cumulative incidence, followed by patients with LPUC, in which pTa and pT1 did not differ significantly, and then pTa HPUC and pT1 HPUC, in order.

If only pTa tumors were considered, PUNLMP showed significant lower recurrence cumulative incidence than LPUC and HPUC **Figure 2A**. There were significant differences in the cumulative incidence of progression **Figure 2B** and cancer-specific mortality **Figure 2C** between PUNLMP and LPUC, and between LPUC and HPUC.

Table 1 summarizes the results of univariate and multivariate statistical analyses based on the 1,515 patients. Univariate analysis showed that tumor grade, pT stage, patient age, multiplicity, and prior recurrence rate were significant risk factors for recurrence. pT and patient age were removed from the multivariate model, owing to lack of independent significance. Tumor grade, pT, and patient age were significant prognostic factors for progression by univariate analysis and

DOI: 10.1309/AJCP12MRVVHTCKEJ

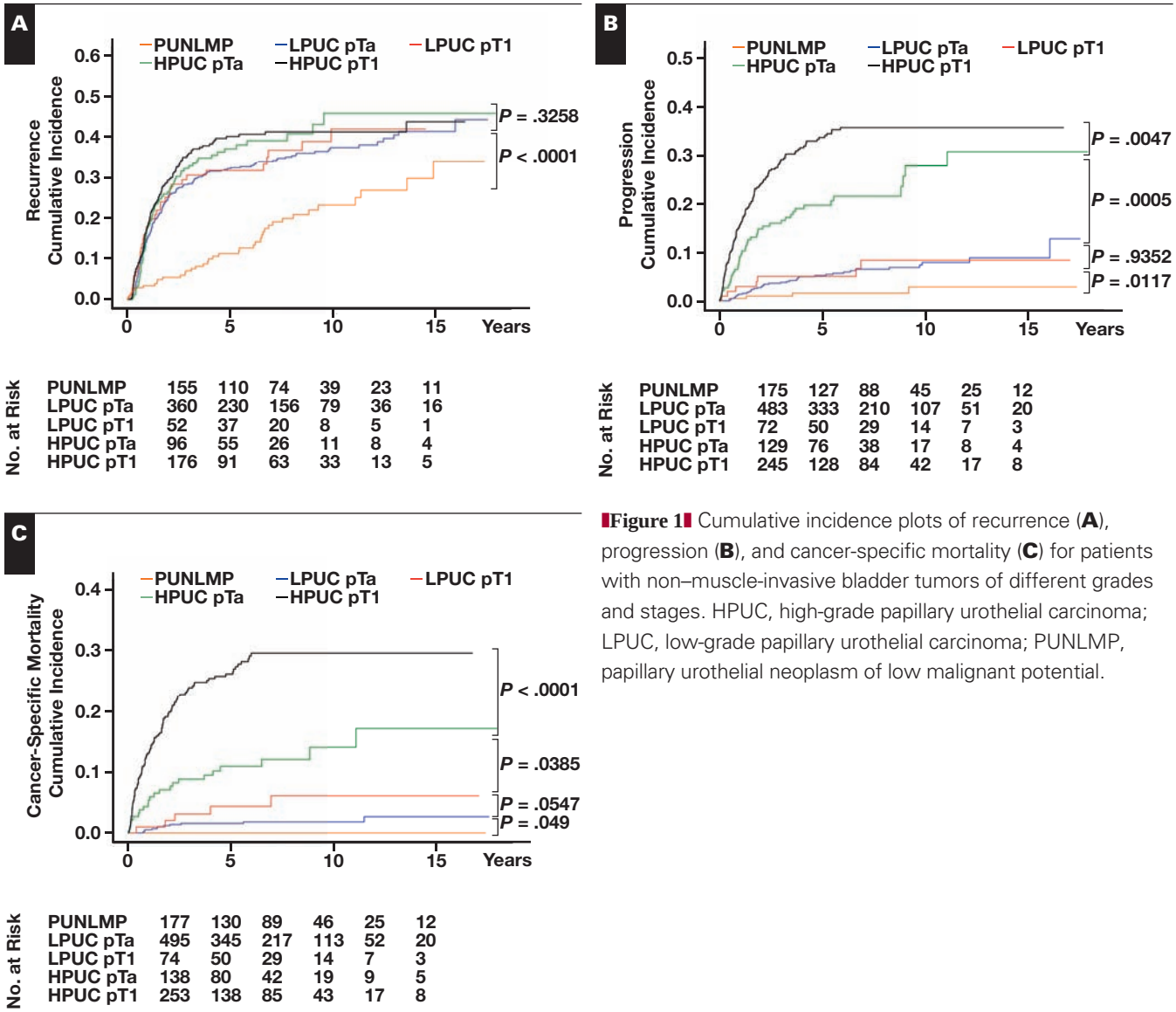

Figure 1 Cumulative incidence plots of recurrence (**A**), progression (**B**), and cancer-specific mortality (**C**) for patients with non–muscle-invasive bladder tumors of different grades and stages. HPUC, high-grade papillary urothelial carcinoma; LPUC, low-grade papillary urothelial carcinoma; PUNLMP, papillary urothelial neoplasm of low malignant potential.

by stepwise multivariate regression analysis. Both univariate and multivariate analyses demonstrated that high-grade tumor and pT were associated with cancer-specific mortality.

Table 2 lists the results of univariate and multivariate statistical analyses limited to the 874 patients with available record of IVIs. Probably due to shrinkage of sample size, there was variation about the significance of certain variables, yet most factors retained significance. Multivariate analysis demonstrated a statistically significant protective effect of IVI on recurrence (relative risk, 0.74; $P = .015$), progression (relative risk, 0.43; $P < .0001$), and cancer-specific mortality (relative risk, 0.28; $P < .0001$).

Discussion

Recurrence rates for non–muscle-invasive urothelial carcinoma reportedly vary between 15% and 70%.[15] The probability of progression ranges from 7% to 40%.[13] The recurrence rate and progression rate of this series fell within the ranges. It is noted that we adopted a more conservative approach to interpreting recurrence. While some authors defined fulgurated lesions without pathologic material and resected lesions with pathologic diagnosis as recurrence,[16-19] we only considered histopathologically proven cases. The recurrence rate of our series (32.0%) is similar to that reported in the series by Oosterhuis et al,[8] who also considered only histopathologically confirmed recurrences (34%). Without pathologic confirmation, it cannot be definitely ascertained whether the cystoscopically "suspicious" lesions represent a true neoplasm or an inflammatory process such as papillary hyperplasia or cystitis. Although the recurrence rate in the series was lower than in some prior studies, we believe that it reflected definitive recurrences with the neoplastic nature verified histopathologically.

DOI: 10.1309/AJCP12MRVVHTCKEJ

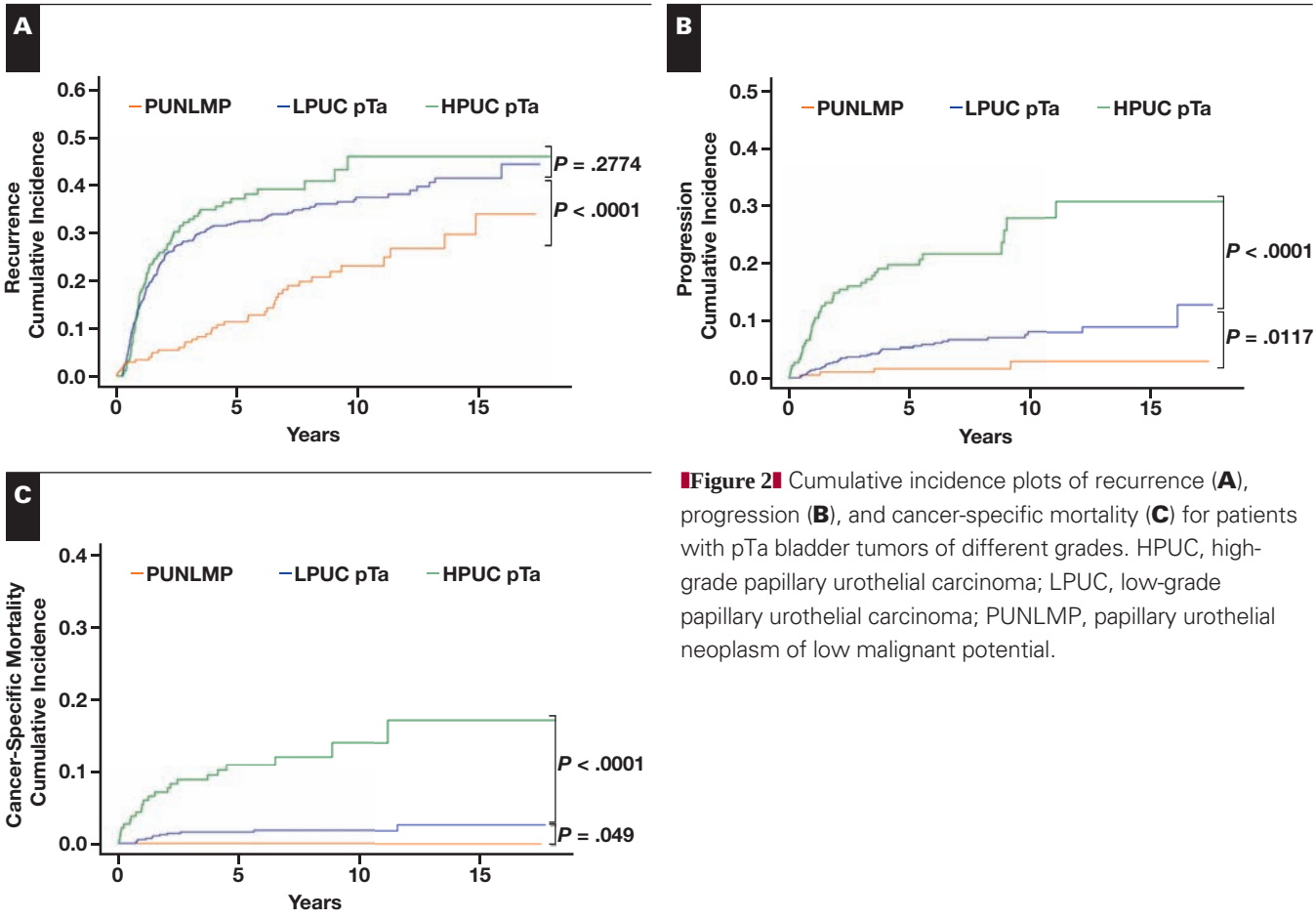

Figure 2 Cumulative incidence plots of recurrence (**A**), progression (**B**), and cancer-specific mortality (**C**) for patients with pTa bladder tumors of different grades. HPUC, high-grade papillary urothelial carcinoma; LPUC, low-grade papillary urothelial carcinoma; PUNLMP, papillary urothelial neoplasm of low malignant potential.

Although the 2004 WHO/ISUP classification adopts a unified definition for each urothelial tumor entity, it is still under discussion whether this advantage can be translated to clinical relevance. Cheng et al[5] studied 105 patients who underwent cystectomy and found that WHO/ISUP grade at TUR was associated with pT stage at cystectomy. Desai and coworkers[6] analyzed 120 non–muscle-invasive bladder urothelial tumors and reported that WHO/ISUP grade correlated with tumor stage, recurrence, and progression when analyzed as papilloma and PUNLMP vs LPUC vs HPUC. Pich and coworkers[9] studied 19 cases of PUNLMP and 43 cases of pTa LPUC. Similarly, Alsheikh et al[4] studied 20 cases of PUNLMP and 29 of LPUC. The series by Pich et al[9] and Alsheikh et al[4] revealed a higher rate for recurrence, progression, and cancer-specific mortality for LPUC compared with PUNLMP. Samaratunga et al[10] studied 124 pTa bladder tumors but did not identify the significance of differences in recurrence among the WHO/ISUP grades. Oosterhuis et al[8] studied 322 patients with primary pTa bladder tumors and found a small yet significant difference in 5-year progression-free survival between PUNLMP and HPUC; however, 5-year progression-free survival was not significantly different between grades. Yin and Leong[12] studied 84 cases of pTa bladder urothelial tumors and found that recurrence rates at 36 months significantly differed between PUNLMP and LPUC and between LPUC and HPUC. Holmäng and Johansson[7] reviewed 555 surgically treated patients with renal pelvis or ureteral urothelial tumors. They noted a significant difference in survival between LPUC and HPUC, but not between PUNLMP and LPUC. However, when stage was taken into consideration, the prognostic value of histologic grade was limited to high-grade, stage T3 cancers. Schned et al[11] analyzed 504 patients with pTa bladder urothelial tumors. The authors found that survival times decreased progressively from PUNLMP to HPUC and concluded that the WHO/ISUP system has several advantages: more detailed diagnostic criteria, the ability to define a lesion with minimal malignant potential, and the ability to discern a larger group of patients needing closer surveillance.

One of the shortcomings of prior studies, which precluded arriving at convincing evidence for the grading system's clinical relevance, was limited sample size and case composition. Many series only included pTa tumors, and tumor grade was not always considered together with stage. In the present

DOI: 10.1309/AJCP12MRVVHTCKEJ

Table 1
Univariate and Stepwise Multivariate Regression Analyses for Recurrence, Progression, and Cancer-Specific Mortality in 1,515 Non–Muscle-Invasive Bladder Tumors Without Considering Intravesical Instillation

	Univariate		Multivariate	
Variable	***P***	**RR (95% CI)**	***P***	**RR (95% CI)**
Recurrence				
Grade				
PUNLMP	(Reference)		(Reference)	
LPUC	<.0001	2.21 (1.58-3.11)	<.0003	1.83 (1.39-2.42)
HPUC	<.0001	2.63 (1.87-3.72)	<.0001	2.04 (1.53-2.72)
pTa vs pT1	.0063	1.31 (1.11-1.52)	Removed	
Patient age	.0027	1.02 (1.01-1.03)	Removed	
Multiplicity	<.0001	2.24 (1.92-2.61)	<.0001	1.98 (1.69-2.32)
Prior recurrence rate	<.0001	3.14 (2.70-3.66)	<.0001	2.92 (2.44-3.49)
Progression				
Grade				
PUNLMP	(Reference)		(Reference)	
LPUC	.014	3.58 (1.29-9.96)	.038	2.95 (1.25-6.96)
HPUC	<.0001	19.5 (7.24-52.63)	<.0001	12.4 (5.29-29.08)
pTa vs pT1	<.0001	3.80 (3.03-4.76)	.0044	1.56 (1.21-2.01)
Patient age	.0005	1.03 (1.01-1.04)	.039	1.02 (1.00-1.03)
Multiplicity	.083	1.28 (1.01-1.62)	Removed	
Prior recurrence rate	.061	1.12 (0.18-1.18)	Removed	
Cancer-specific mortality				
Grade				
PUNLMP	(Reference)		(Reference)	
LPUC	.174	3.13 (0.60-16.25)	Removed	
HPUC	<.0001	35.31 (7.27-171.57)	<.0001	8.20 (5.00-13.43)
pTa vs pT1	<.0001	7.67 (5.54-10.6)	<.0001	2.67 (1.84-3.87)
Patient age	.024	1.02 (1.01-1.04)	Removed	
Multiplicity	.75	1.06 (0.78-1.43)	Removed	
Prior recurrence rate	.1191	3.05 (0.46-3.78)	Removed	

CI, confidence interval; HPUC, high-grade papillary urothelial carcinoma; LPUC, low-grade papillary urothelial carcinoma; PUNLMP, papillary urothelial neoplasm of low malignant potential; RR, relative risk.

study, we recruited a statistically sufficient number of cases that had long-term follow-up. We stratified cases into every grade and stage. Each subgroup contained more than 100 cases. Thus, we were able to compare all important end points of observation pertinent to non–muscle-invasive bladder cancer among different subsets.

The results of the present study establish the efficacy of the 2004 WHO/ISUP classification of urothelial carcinoma. Tumor grade was the single salient factor that remained in all 3 multivariate regression models for recurrence, progression, and cancer-specific mortality. In terms of recurrence, PUNLMP showed the significantly lowest recurrence rate and excelled against all other groups. After segregating PUNLMP, the other subgroups did not show significant differences in recurrence. Regarding progression and cancer-specific mortality, cumulative incidence curves showed an apparent trend of worsening prognosis with higher grade and advancing stage. Compared with stage, tumor grade was more predictive of progression and cancer-specific mortality. The biologic behavior of urothelial tumors is first determined by grade, then by stage within the same grade. Tumors of higher grade generally behave more aggressively than those of lower grade, regardless of stage. It is exemplified by the small group of pT1 LPUCs that accounted for 7.0% of all cases and 15.1% of LPUCs in our series. These LPUCs, even with lamina propria invasion, did not significantly differ from noninvasive LPUCs and still had a better prognosis than noninvasive pTa HPUCs in terms of progression and cancer-specific mortality. Although we did not substage the lamina propria invasion, it is plausible that the unusual lamina propria invasion in LPUC is focal and does not affect the prognosis greatly. On the contrary, HPUC generally portends a higher risk, even before acquiring the ability of invasion. When only pTa tumors were considered, there were also significant differences between PUNLMP, LPUC, and HPUC, suggesting that before invasion, histologic grade still had a major role in determining the biologic behavior of the tumor.

Our study addressed the legitimacy of PUNLMP as a separate entity. PUNLMPs, when diagnosed strictly by the new criteria, showed a low propensity to recur and a negligible risk of progression and never resulted in tumor-related death. The indolent character of PUNLMP justifies removal of the label of carcinoma, instead designating it as a neoplasm.

A limitation of the present study was its retrospective nature. Some potentially deleterious conditions and factors that can influence outcome, such as tumor size and concomitant

DOI: 10.1309/AJCP12MRVVHTCKEJ

Table 2
Univariate and Stepwise Multivariate Regression Analyses for Recurrence, Progression, and Cancer-Specific Mortality in 874 Non–Muscle-Invasive Bladder Tumors, Including the Status of Intravesical Instillation

	Univariate		Multivariate	
Variable	***P***	**RR (95% CI)**	***P***	**RR (95% CI)**
Recurrence				
Grade				
PUNLMP	(Reference)		(Reference)	
LPUC	.0059	1.76 (1.17-2.65)	.049	1.48 (1.07-2.06)
HPUC	.0001	2.28 (1.51-3.45)	.0048	1.79 (1.28-2.52)
pTa vs pT1	.0023	1.45 (1.19-1.78)	Removed	
Patient age	.24	1.01 (0.99-1.02)	Removed	
Multiplicity	<.0001	2.26 (1.86-2.74)	<.0001	2.10 (1.71-2.58)
Prior recurrence rate	<.0001	2.96 (2.44-3.58)	<.0001	2.76 (2.18-3.50)
Intravesical instillation*	.1384	0.84 (0.66-1.06)	.015	0.74 (0.60-0.91)
Progression				
Grade				
PUNLMP	(Reference)		(Reference)	
LPUC	.148	2.44 (0.73-8.23)	Removed	
HPUC	<.0001	12.77 (4.03-40.42)	<.0001	6.76 (4.57-10.01)
pTa vs pT1	<.0001	3.01 (2.20-4.13)	Removed	
Patient age	.0015	1.03 (1.02-1.05)	Removed	
Multiplicity	.0016	1.84 (1.34-2.53)	Removed	
Prior recurrence rate	.220	1.55 (0.22-2.45)	Removed	
Intravesical instillation	.0019	0.55 (0.40-0.77)	<.0001	0.43 (0.32-0.61)
Cancer-specific mortality				
Grade				
PUNLMP	(Reference)		(Reference)	
LPUC	.2241	11.84 (0.04-3,610.5)	Removed	
HPUC	<.0001	12.79 (3.12-52.36)	<.0001	20.11 (7.76-52.13)
pTa vs pT1	<.0001	6.50 (4.10-10.30)	.017	2.14 (1.27-3.61)
Patient age	.017	1.04 (1.01-1.06)	Removed	
Multiplicity	.044	1.65 (1.01-2.49)	Removed	
Prior recurrence rate	.349	4.55 (0.01-5.17)	Removed	
Intravesical instillation	.0005	0.41 (0.27-0.63)	<.0001	0.28 (0.19-0.44)

CI, confidence interval; HPUC, high-grade papillary urothelial carcinoma; LPUC, low-grade papillary urothelial carcinoma; PUNLMP, papillary urothelial neoplasm of low malignant potential; RR, relative risk.
* For LPUC, RR = 0.75; CI = 0.57-0.99; *P* = .03.

carcinoma in situ, could not be reliably assessed. Furthermore, we did not address the issue of interobserver discrepancy. In this study, all cases were reviewed by 1 pathologist for the purpose of interpretative consistency. In real practice, a certain level of diagnostic variation undoubtedly exists.[20] Further consensus meetings and educational conferences and programs should improve the situation. We anticipate wider acceptance and proper use of the classification system among pathologists and urologists so that histologic grading can be a truly valuable indicator that contributes to the design of therapeutic and monitoring strategies for patients with non–muscle-invasive bladder urothelial tumors.

From the [1]Department of Pathology and [2]Division of Urology, Department of Surgery, Taipei Veterans General Hospital; and [3]National Yang-Ming University, Taipei, Taiwan.

Supported by grant NSC-96-2320-B-010-034 from the Taiwan National Science Council, Taipei.

Address reprint requests to Dr Pan: Dept of Pathology, Taipei Veterans General Hospital, No. 201, Shi-Pai Rd, Sec 2, Taipei, 11217 Taiwan.

Acknowledgments: We thank biostatistician Pui-Ching Lee for assistance in biostatistical tasks and the staff of the Cancer Registry Center for kind provision of patients' follow-up data.

References

1. Mostofi FK. *Histological Typing of Urinary Bladder Tumours*. Geneva, Switzerland: World Health Organization; 1973.
2. Epstein JI, Amin MB, Reuter VR, et al. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. *Am J Surg Pathol*. 1998;22:1435-1448.
3. Eble JN, Sauter G, Epstein JI, et al. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs*. Lyon, France: IARC Press; 2004.
4. Alsheikh A, Mohamedali Z, Jones E, et al. Comparison of the WHO/ISUP classification and cytokeratin 20 expression in predicting the behavior of low-grade papillary urothelial tumors. *Mod Pathol*. 2001;14:267-272.
5. Cheng L, Neumann RM, Weaver AL, et al. Grading and staging of bladder carcinoma in transurethral resection specimens: correlation with 105 matched cystectomy specimens. *Am J Clin Pathol*. 2000;113:275-279.

DOI: 10.1309/AJCP12MRVVHTCKEJ

6. Desai S, Lim SD, Jimenez RE, et al. Relationship of cytokeratin 20 and CD44 protein expression with WHO/ISUP grade in pTa and pT1 papillary urothelial neoplasia. *Mod Pathol.* 2000;13:1315-1323.
7. Holmäng S, Johansson SL. Urothelial carcinoma of the upper urinary tract: comparison between the WHO/ISUP 1998 consensus classification and WHO 1999 classification system. *Urology.* 2005;66:274-278.
8. Oosterhuis JW, Schapers RF, Janssen-Heijnen ML, et al. Histological grading of papillary urothelial carcinoma of the bladder: prognostic value of the 1998 WHO/ISUP classification system and comparison with conventional grading systems. *J Clin Pathol.* 2002;55:900-905.
9. Pich A, Chiusa L, Formiconi A, et al. Biologic differences between noninvasive papillary urothelial neoplasms of low malignant potential and low-grade (grade 1) papillary carcinomas of the bladder. *Am J Surg Pathol.* 2001;25:1528-1533.
10. Samaratunga H, Makarov DV, Epstein JI. Comparison of WHO/ISUP and WHO classification of noninvasive papillary urothelial neoplasms for risk of progression. *Urology.* 2002;60:315-319.
11. Schned AR, Andrew AS, Marsit CJ, et al. Survival following the diagnosis of noninvasive bladder cancer: WHO/International Society of Urological Pathology versus WHO classification systems. *J Urol.* 2007;178:1196-1200.
12. Yin H, Leong AS. Histologic grading of noninvasive papillary urothelial tumors: validation of the 1998 WHO/ISUP system by immunophenotyping and follow-up. *Am J Clin Pathol.* 2004;121:679-687.
13. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol.* 2006;49:466-477.
14. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res.* 2007;13:559-565.
15. Allard P, Bernard P, Fradet Y, et al. The early clinical course of primary Ta and T1 bladder cancer: a proposed prognostic index. *Br J Urol.* 1998;81:692-698.
16. Guney S, Guney N, Canogullari Z, et al. Ta T1 low and intermediate transitional cell carcinoma of the bladder: recurrence rates and the timing of check cystoscopies within the first year. *Urol Int.* 2008;80:124-128.
17. Holmang S, Hedelin H, Anderstrom C, et al. Recurrence and progression in low grade papillary urothelial tumors. *J Urol.* 1999;162:702-707.
18. Holmang S, Johansson SL. Stage Ta-T1 bladder cancer: the relationship between findings at first followup cystoscopy and subsequent recurrence and progression. *J Urol.* 2002;167:1634-1637.
19. Leblanc B, Duclos AJ, Benard F, et al. Long-term followup of initial Ta grade 1 transitional cell carcinoma of the bladder. *J Urol.* 1999;162:1946-1950.
20. Murphy WM, Takezawa K, Maruniak NA. Interobserver discrepancy using the 1998 World Health Organization/International Society of Urologic Pathology classification of urothelial neoplasms: practical choices for patient care. *J Urol.* 2002;168:968-972.

DOI: 10.1309/AJCP12MRVVHTCKEJ

HOLOGIC®

First and Only FDA Cleared
Digital Cytology System

Genius™ Cervical AI

Genius™ Review Station

Genius™ Digital Imager

Empower Your Genius With Ours

Make a Greater Impact on Cervical Cancer
with the Advanced Technology of the
Genius™ Digital Diagnostics System

Click or Scan
to discover more

genius™
DIGITAL DIAGNOSTICS