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Practical uropathology

The 2004 World Health Organization/International Society of Urological Pathology classification system for non-muscle-invasive bladder cancer☆

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1. Introduction

Urothelial carcinoma is the most common neoplasm of the bladder. More than half of all bladder urothelial carcinomas present as papillary, non-muscle-invasive bladder cancers (NMIBCs), being either noninvasive (Ta) or lamina propria invasive (T1). The rest are high-grade and muscularis propria invasive. Because these two tumor groups behave differently in recurrence, progression, and cancer-related mortality, different treatment strategies are applied. NMIBCs are usually treated by transurethral resection (TUR) followed by intravesical instillation, whereas high-grade, muscle-invasive tumors are eligible for cystectomy. Due to the unfavorable prognosis of muscle-invasive tumors, prognostic indicators that are able to predict a subset of NMIBC likely to progress are needed to tailor more aggressive surveillance and management.

2. 1973 World Health Organization classification

Among various clinicopathologic parameters, grade and stage are two most powerful prognosticators. Although TUR specimens allow for determination of pathologic stage (pT) up to pT2 provided muscularis propria is adequately sampled,[1] tumor grade is an indispensible element in the pathologic evaluation on all instances. However, 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.[2] A major limitation is its arbitrary definitions. The following statement is the sole description of the difference among WHO Grades 1, 2, and 3 as written in the original WHO 1973 blue book: "Grade 1 tumors have the least degree of anaplasia compatible with the diagnosis of malignancy, Grade 3 applies to tumors with the most severe degrees of cellular anaplasia, and Grade 2 lies in between". Although "anaplasia" is further defined as "increased cellularity, nuclear crowding, disturbances of cellular polarity, failure of differentiation from the base to the surface, polymorphism, irregularity in the size of cells, variations of shape and chromatin pattern of the nuclei, displaced or abnormal mitotic figures, and giant cells", there is no detailed description regarding how those features are applied to grade the tumor. The vagueness of the definition results in most cases falling into the intermediate category (Grade 2) by default. Also, many pathologists are reluctant to call a tumor Grade 3 unless the tumor manifests marked ominous features. For example, our data collected from the surgical pathologic archive of Taipei Veterans General Hospital from 1991 to 1998 showed that Grade 3 tumors only accounted for around 11% of all NMIBCs (unpublished data).

3. 2004 WHO/ISUP classification

In 1998, the International Society of Urological Pathology (ISUP) proposed a new grading system,[3] which was adopted in a large measure by WHO in 2004.[1] The 2004 WHO/ISUP system is a modified version of the scheme proposed by Malmström et al.[4] Papillary lesions/tumors are classified as papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade papillary urothelial carcinoma or high-grade papillary urothelial carcinoma. 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. Fig. 1 shows the algorithm of diagnosing papillary NMIBC. On the basis of the 2004 WHO/ISUP

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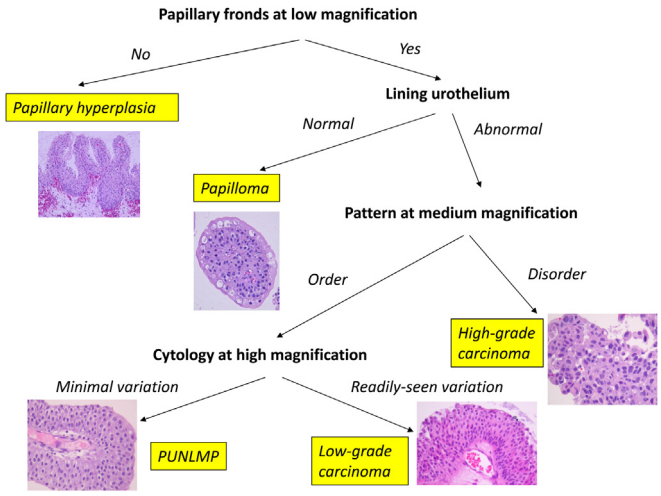

Fig. 1. Flow chart of the differential diagnosis of papillary urothelial lesions/tumors.

classification, the PUNLMP, low-grade papillary urothelial carcinoma, and high-grade papillary urothelial carcinoma accounted for 14%, 47%, and 39%, respectively, in our series of 1515 NIMBCs.[5]

Following are brief descriptions regarding the entities defined in the 2004 WHO/ISUP system.

3.1. Papillary urothelial hyperplasia

Papillary urothelial hyperplasia lacks true branching papillary fronds, but consists of undulating urothelium arranged into mucosal narrow papillary folds of varying heights. The cytologic findings in papillary hyperplasia are similar to those in normal urothelium. Papillary hyperplasia is a likely precursor lesion to low-grade papillary urothelial neoplasms. It is reasonable to suggest that patients should be followed-up, even though *de novo* papillary hyperplasia will not progress to urothelial neoplasia in most instances. If papillary hyperplasia is found in an individual with a prior history of urothelial neoplasm, it indicates early recurrence that warrants continued close follow-up.

3.2. Urothelial papilloma

Urothelial papillomas consists of papillary fronds lined by normal appearing urothelium. Although the criteria for diagnosis do not include the absolute number of cell layers, the urothelium should not be obviously thicker than normal urothelium, otherwise the lesion had better be classified as PUNLMP. Papillomas are rare and typically, but not exclusively, occur in younger patients.

3.3. PUNLMP

PUNLMP is characterized by papillae with predominantly orderly architecture and minimal cytologic atypia. PUNLMPs at low magnification differ from papillomas by having thicker urothelium. A properly diagnosed PUNLMP never invades and metastasizes (see discussion below).

3.4. Low-grade papillary urothelial carcinoma

Low-grade papillary urothelial carcinoma shows an orderly appearance but easily recognizable variations in architecture and cytologic features (polarity, nuclear size, shape, and chromatin texture). The majority of low-grade carcinoma are noninvasive (Ta). In the uncommon cases that invade the lamina propria (T1), the invasion is mostly focal.[6] A diagnosis such as low-grade urothelial carcinoma with a stage higher than T1 should be met with criticism.

3.5. High-grade papillary urothelial carcinoma

High-grade papillary urothelial carcinoma shows a predominant pattern of disorder and/or marked cytologic atypia. High-grade carcinomas frequently invade and metastasize. Carcinomas with extensive lamina propria invasion or stage higher than T1 are virtually all high-grade. High-grade carcinomas have a higher association with larger tumor size, multiplicity, and carcinoma *in situ*.[7]

4. Translation of 1973 WHO to 2004 WHO/ISUP system

A potential confusion about the two grading systems concerns the relationship between the old and new classification. There is no one-to-one translation between the two systems. The definition of papilloma in the 1973 WHO system is the same as that in the 2004 WHO/ISUP system. At the other end of the grading extreme, all 1973 WHO Grade 3 tumors are assigned to the high-grade carcinoma category in the 2004 WHO/ISUP system. By contrast, there is no direct translation to the 2004 WHO/ISUP classification for 1973 WHO Grades 1 and 2 carcinomas.[8] This change of definition may entail some difficulties in applying a nomogram or prognostic table that employ the 1973 WHO system.[9] Also, previous articles where the 1973 WHO terminologies were directly translated into the 2004 WHO/ISUP ones should be interpreted with caution.

5. Prognostic significance

There are marked trends of higher risks for recurrence, progression, and cancer-specific mortality with higher grades.[5,10–22] Table 1 lists the ranges of risks reported in previous studies. The considerable variability in the reported recurrence and progression rates may be related to the duration of follow-up, different inclusion criteria for diagnosing recurrence (histologically proven cases vs. cases diagnosed solely based on cystoscopic/cytologic findings), and progression (any advance of stage, advance to muscle-invasive disease, progression to higher grade/carcinoma *in situ*). Our series showed that PUNLMP had a recurrence rate of 17.9%, a progression rate of 1.9%, and a 0% cancer mortality rate, where recurrence was defined as the reappearance of histopathologically confirmed urothelial neoplasm in the bladder and progression was defined as any advance in stage (from pTa to pT1–4, from pT1 to pT2–4), diagnosis of metastasis, or death caused by tumor. The recurrence rate, progression rate, and cancer mortality rate of low-grade carcinomas were 35.0%, 6.5%, and 2.0%, respectively. By contrast, 34.0% of high-

Table 1
Reported risk of recurrence, progression, and cancer-specific mortality by papillary urothelial neoplasm.

	Papilloma	PUNLMP	Low-grade carcinoma	High-grade carcinoma
Recurrence	0–31	17–52	34–77	34–73
Progression	0	0–7	4–18	8–35
Cancer-specific mortality	0	0–1[a]	0–5	4–22

Data are presented as %.
PUNLMP = papillary urothelial neoplasm of low malignant potential.
[a] Only one patient with PUNLMP who died of progressive bladder cancer was reported.

Table 2
Bootstrapped (200×) Kaplan-Meier survival estimate for recurrence-free survival, progression-free survival, and cancer-specific survival for patients receiving intravesical instillation (1,102 cases).

	Recurrence-free survival 95% CI				Progression-free survival 95% CI				cancer-specific survival 95% CI			
	1 yr	3 yr	5 yr	8 yr	1 yr	3 yr	5 yr	8 yr	1 yr	3 yr	5 yr	8 yr
PUNLMP	93.2	80.2	83.6	78.9	99.0	98.0	96.9	96.9	100	100	100	100
	92.8–93.5	79.7–80.7	83.2–84.0	78.5–79.4	98.9–99.2	97.8–98.2	96.6–97.2	96.7–97.2	—	—	—	—
LPUC Ta	85.9	70.1	66.3	61.8	98.6	95.7	93.6	91.1	99.5	98.4	98.4	97.6
	85.7–86.1	69.9–70.4	66.0–66.6	61.5–62.1	98.5–98.6	95.6–95.8	93.5–93.8	90.9–91.3	99.5–99.6	98.4–98.5	98.4–98.6	97.5–97.7
LPUC T1	83.3	67.3	65.4	59.1	96.9	93.7	92.1	87.9	99.0	96.5	93.6	91.4
	82.7–83.8	66.5–68.0	64.6–66.1	58.3–59.8	96.6–97.1	93.3–94.0	91.7–92.5	87.4–88.5	98.7–99.0	96.2–96.8	93.2–94.0	90.9–91.8
HPUC Ta	85.4	65.2	57.7	54.4	91.0	82.6	78.8	73.7	94.4	90.9	88.2	86.8
	85.0–85.7	64.7–65.8	57.2–58.3	53.9–55.0	90.8–91.3	82.2–83.0	78.3–79.1	73.2–74.2	94.1–94.6	90.5–91.2	87.9–88.6	86.4–87.1
HPUC T1	85.1	63.9	55.1	49.8	85.6	70.8	64.4	61.3	87.1	74.3	70.4	65.7
	84.8–85.4	63.5–64.3	54.8–55.5	49.3–50.2	85.3–85.8	70.5–71.2	64.0–64.7	60.9–61.7	86.9–87.3	74.0–74.6	70.1–70.7	65.4–66.1

Data are presented as %.
CI = confidence interval; HPUC = high-grade papillary urothelial carcinoma; LPUC = low-grade papillary urothelial carcinoma; PUNLMP = papillary urothelial neoplasm of low malignant potential.

grade carcinomas recurred, 28.8% progressed, and 21.9% resulted in cancer death.

Taking both grade and stage into consideration, we are able to identify significant differences and trends for higher progression and cancer-specific mortality cumulative incidence in the following order: PUNLMP, low-grade carcinoma; Ta, high-grade carcinoma; and T1, high-grade carcinoma (Fig. 2).[5,7] Tables 2 and 3 show our updated 1-year, 3-year, 5-year, and 8-year bootstrapped recurrence-free, progression-free, and cancer-specific survivals for patients with NMIBC treated by TUR with or without adjuvant intravesical instillation.

Compared with stage, tumor grade was more predictive of progression and cancer-specific mortality for patients with NMIBC. The biologic behavior of urothelial tumors is first determined by grade, then by stage within the same grade. It should be noted that a T1 low-grade papillary urothelial carcinoma has better prognosis than a Ta high-grade papillary urothelial carcinoma. This seemingly paradoxical finding is related to the nature of urothelial tumors and also to the surgical modality. The TUR procedure removes visible tumor and a part of the bladder tissue rather than the entire bladder; therefore, whether residual or multifocal tumors remain largely determines the subsequent course of the disease. It is plausible that T1 low-grade papillary urothelial carcinomas are mostly eradicable by TUR, and even if some recur their indolent nature and limited ability to invade ensure that the stage remains unchanged. Contrary to low-grade papillary urothelial carcinomas, high-grade papillary urothelial carcinomas, although noninvasive at initial presentation sometimes, have a remarkable association with multifocality and carcinoma *in situ*; thus, they possess a propensity for progression that leads to cancer-specific mortality.[6]

6. PUNLMP controversies

The most controversial aspect of the WHO/ISUP grading system is the category of PUNLMP. Accumulated data have shown a definite, yet lower, incidence of recurrence in PUNLMP in comparison with low-grade papillary urothelial carcinoma. The progression rate is negligible, with most series reporting a null figure. All previous studies also noted a 0% mortality rate with the exception of Oosterhuis et al[18] who reported the death of one patient (out of 116) as a consequence of progression and dissemination of an invasive bladder carcinoma. Given the indolent nature of PUNLMP, it is reasonable to discourage the use of the term “carcinoma” in patients with PUNLMP because the expected clinical behavior is better reflected by the terminology “low malignant potential”.[15]

Urologists often express their concerns about PUNLMP as to whether the patients are justified to be exempt from follow-up cystoscopic examination. Because even a benign papilloma still bears a low likelihood to recur, it is judicious to follow-up all patients with every sort of papillary neoplasm. Some investigators have proposed that patients with PUNLMP may be submitted to fewer cystoscopies if the number of lesions is few and no recurrences are seen during initial surveillance period. The benefit of

Table 3
Bootstrapped (200×) Kaplan-Meier survival estimate for recurrence-free survival, progression-free survival, and cancer-specific survival for patients who did not receive intravesical instillation (661 cases).

	Recurrence-free survival 95% CI				Progression-free survival 95% CI				Cancer-specific survival 95% CI			
	1 yr	3 yr	5 yr	8 yr	1 yr	3 yr	5 yr	8 yr	1 yr	3 yr	5 yr	8 yr
PUNLMP	96.2	94.1	91.8	88.2	100	100	100	100	100	100	100	100
	95.9–96.5	93.8–94.4	91.3–92.2	87.6–88.7	—	—	—	—	—	—	—	—
LPUC Ta	87.1	74.9	71.4	67.0	97.3	93.5	92.0	88.1	98.9	97.2	97.1	96.0
	86.8–87.5	74.4–75.4	71.0–71.9	66.5–67.6	97.1–97.5	93.2–93.8	91.7–92.3	87.7–88.5	98.8–99.0	97.1–97.4	96.9–97.3	95.6–96.1
LPUC T1	83.1	75.4	69.3	69.2	93.1	88.8	88.3	87.9	96.6	92.7	92.4	92.4
	82.1–84.1	74.2–76.6	68.0–70.6	67.8–70.5	92.5–93.8	88.2–89.4	87.7–88.9	87.2–88.6	96.1–97.0	92.0–93.4	91.7–93.1	91.7–93.1
HPUC Ta	90.9	77.3	65.8	65.4	89.1	73.5	67.5	64.4	89.5	78.0	71.8	68.0
	90.4–91.6	76.3–78.2	64.7–66.8	64.3–66.7	88.5–89.6	72.6–74.4	66.5–68.6	63.3–65.4	88.9–90.1	77.2–78.7	70.7–72.8	66.9–69.1
HPUC T1	84.2	71.3	69.1	69.1	71.6	50.8	46.2	41.2	73.2	53.0	48.6	43.7
	83.7–84.7	70.7–72.0	68.6–69.6	68.6–69.6	71.1–72.2	50.1–51.4	45.5–46.8	40.6–41.8	72.7–73.8	52.4–53.6	48.0–49.3	43.0–44.4

Data are presented as %.
CI = confidence interval; HPUC = high-grade papillary urothelial carcinoma; LPUC = low-grade papillary urothelial carcinoma; PUNLMP = papillary urothelial neoplasm of low malignant potential.

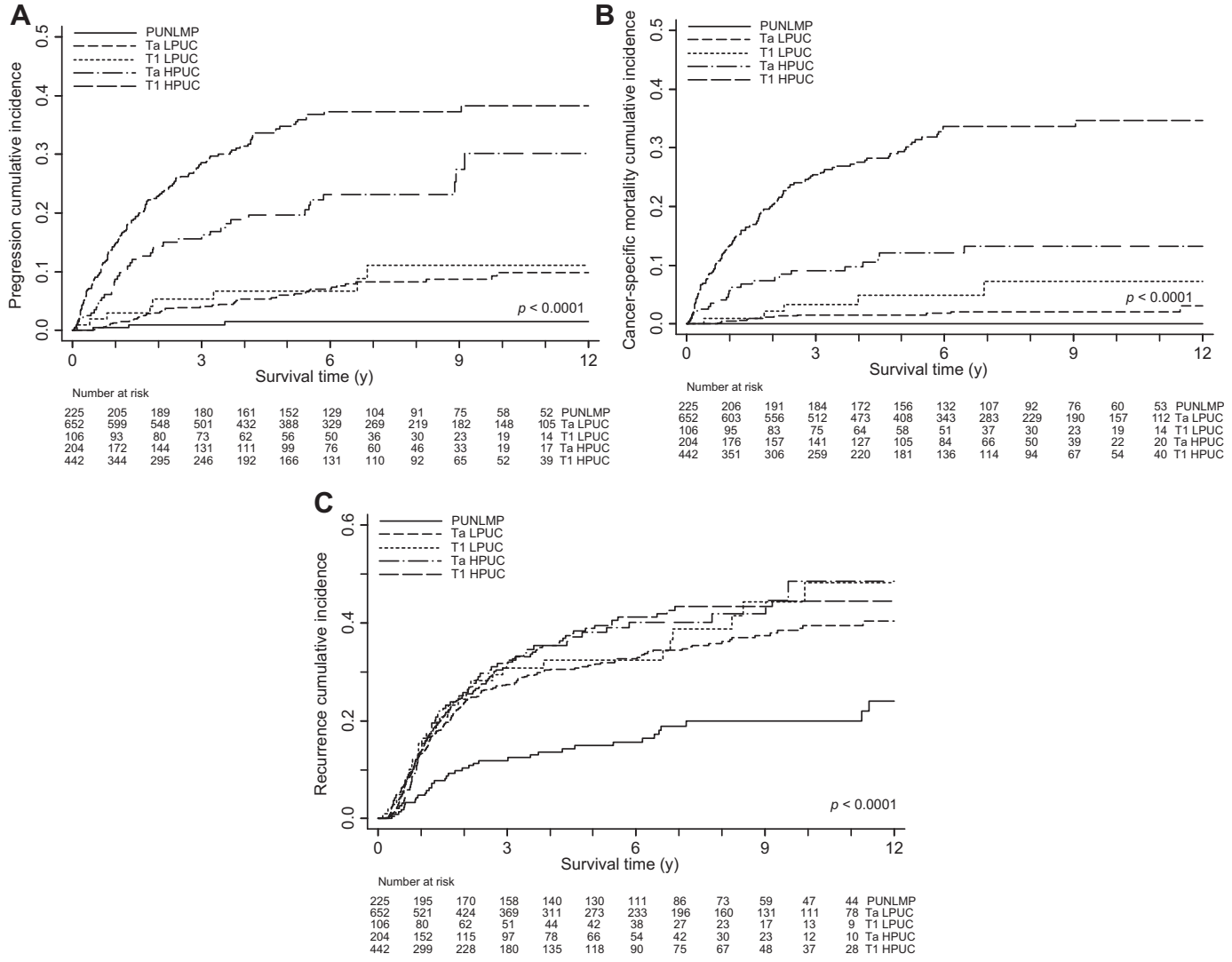

Fig. 2. Cumulative incidence plots of (A) progression, (B) cancer-specific mortality, and (C) recurrence for patients with non-muscle-invasive bladder tumors of different grades and stages. HPUC = high-grade papillary urothelial carcinoma; LPUC = low-grade papillary urothelial carcinoma; PUNLMP = papillary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

intravesical instillation to treat PUNLMP awaits further investigations to assess.

7. Conclusion

The 2004 WHO/ISUP system has advantages, but also limitations. Even with a clearer definition than the 1973 WHO system, interobserver reproducibility still leaves something to be desired.[23] In real practice, a certain level of diagnostic variation undoubtedly exists. Further consensus meetings and educational conferences and programs should improve the situation. The grading system requires refinement in terms of tumor heterogeneity. Utility of biological and molecular markers may enhance the efficacy of the grading, yet so far there have not been markers sufficient to replace the histological grading.

Currently, the 2004 WHO/ISUP scheme has been adopted in the National Comprehensive Cancer Network guidelines for treating bladder cancers (http://www.nccn.org). We anticipate wider acceptance and proper use of the classification system among pathologists and urologists so that histological grading can be a truly valuable indicator that contributes to the design of therapeutic and monitoring strategies for patients with urothelial cancer.

Conflicts of interest statement

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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