ELSEVIER

Urologic Oncology: Seminars and Original Investigations 38 (2020) 440–448

UROLOGIC ONCOLOGY

Clinical-Bladder cancer

Papillary urothelial neoplasm of low malignant potential (PUN-LMP): Still a meaningful histo-pathological grade category for Ta, noninvasive bladder tumors in 2019?

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Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.1016/j.urolonc.2019.10.002

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Received 1 August 2019; received in revised form 23 September 2019; accepted 2 October 2019

Abstract

Background: Papillary urothelial neoplasm of low malignant potential (PUN-LMP) was introduced as a noninvasive, noncancerous lesion and a separate grade category in 1998. Subsequently, PUN-LMP was reconfirmed by World Health Organization (WHO) 2004 and WHO 2016 classifications for urothelial bladder tumors.

Objectives: To analyze the proportion of PUN-LMP diagnosis over time and to determine its prognostic value compared to Ta-LG (low-grade) and Ta-HG (high-grade) carcinomas. To assess the intraobserver variability of an experienced uropathologist assigning (WHO) 2004/2016 grades at 2 time points.

Materials and methods: Individual patient data of 3,311 primary Ta bladder tumors from 17 hospitals in Europe and Canada were available. Transurethral resection of the tumor was performed between 1990 and 2018. Time to recurrence and progression were analyzed with cumulative incidence functions, log-rank tests and multivariable Cox-regression stratified by institution. Intraobserver variability was assessed by examining the same 314 transurethral resection of the tumorslides twice, in 2004 and again in 2018.

Results: PUN-LMP represented 3.8% (127/3,311) of Ta tumors. The same pathologist found 71/314 (22.6%) PUN-LMPs in 2004 and only 20/314 (6.4%) in 2018. Overall, the proportion of PUN-LMP diagnosis substantially decreased over time from 31.3% (1990−2000) to 3.2% (2000−2010) and to 1.1% (2010−2018). We found no difference in time to recurrence between the three WHO 2004/2016 Ta-grade categories (log-rank, $P = 0.381$), nor for LG vs. PUN-LMP (log-rank, $P = 0.238$). Time to progression was different for all grade categories (log-rank, $P < 0.001$), but not between LG and PUN-LMP (log-rank, $P = 0.096$). Multivariable analyses on recurrence and progression showed similar results for all 3 grade categories and for LG vs. PUN-LMP.

Conclusions: The proportion of PUN-LMP has decreased to very low levels in the last decade. Contrary to its reconfirmation in the WHO 2016 classification, our results do not support the continued use of PUN-LMP as a separate grade category in Ta tumors because of the similar prognosis for PUN-LMP and Ta-LG carcinomas.

Keywords: Bladder; Cancer; Carcinomas; Grade; WHO; Nonmuscle-invasive; Urothelial

1. Introduction

Non−muscle-invasive bladder cancer (NMIBC) is a heterogeneous disease, as is illustrated by the variability in recurrence and progression rates among NMIBC patients [1]. Histological grade is an important prognostic factor, especially for progression [1−3]. The classical 3-tier system for grade is the WHO1973 system [4] assigning urothelial carcinomas to histomorphological grades (G1−3) based on the degree of cellular anaplasia. The main reasons to propose a new classification system in 1998 by the World Health Organization (WHO) / International Society of Urological Pathology (ISUP) were the lack of clear definitions for the 3 WHO 1973 grades and the high percentage of NMIBC classified as G2. In 2004 and subsequently in 2016, the WHO reconfirmed this classification system as proposed in 1998: papillary urothelial neoplasm of low malignant potential (PUN-LMP), low-grade (LG) and high-grade (HG) papillary urothelial carcinoma [5−7]. MacLennan et al. [8] reported in 2007 that the proportion of PUN-LMP varied from 12% to 39% in five NMIBC studies, indicating that shortly after its introduction, PUN-LMP was not a rare lesion like urothelial papilloma, which is a very rare and benign lesion in the spectrum of papillary bladder tumors [9−11].

With the adoption of WHO 2004/2016, the new category of PUN-LMP, which is not associated with a "cancer" label,

was confirmed [5–7]. PUN-LMP was by its definition a noninvasive, Ta neoplasm with minimal cytonuclear atypia. The introduction of the WHO/ISUP classification system in 1998 was meant to reduce observer variability among pathologists by formulating clear histological criteria for papillary lesions [5]. In PUN-LMP, papillae are delicate and polarity is preserved. Proliferation of cells is increased, but there is minimal variation in cytological and histological features among cells [5–7]. However, subsequent studies on reproducibility of WHO 2004/2016 showed that observer variability did not really improve by defining these detailed histological criteria [3,12–14].

From a clinical point of view, the 1998 WHO/ISUP classification suggested that patients with PUN-LMP would have lower recurrence rates compared to patients with LG/HG carcinomas and that patients with PUN-LMP/LG carcinoma would have close to no progressions compared to HG cases [5]. However, several review articles which appeared in the time period 2006–2010 reported that recurrence and progression rates of PUN-LMP patients were close to those in LG carcinomas [1,8–10,15,16]. For example, Hofmann et al. [9] reported that recurrence varied between 25% and 60% in 11 studies, indicating that PUN-LMP still required surveillance as low-risk NMIBC [15,16].

In the present multicenter study, we analyzed the proportion of PUN-LMP over the last 3 decades across a range of institutions. We also evaluated the prognostic value of PUN-LMP compared to primary, noninvasive (Ta) LG and HG carcinomas.

2. Materials and methods

2.1. Patients, treatment, and follow-up

For this multicenter study, we retrospectively collected individual patient data (IPD) on 5,295 primary NMIBC patients from 17 hospitals in Europe and Canada. Each center provided both WHO 1973 and WHO 2004/2016 grades. First transurethral resection of the tumor (TUR) was performed between 1990 and 2018. We excluded 125 cases for the following reasons: duplicate entries; missing grade or stage information; carcinoma in situ-only; muscle-invasive tumor at re-TUR; less than 3 months of follow-up and death, progression or radical cystectomy within 3 months. For the remaining 5,170 patients, the highest number of cases per center was 738 patients (Barcelona-Puigvert) and the lowest 100 patients (Paris-Tenon). For the prognostic part of this study, the 1,859 T1 NMIBCs were excluded leaving IPD on 3,311 primary, Ta, noninvasive bladder tumors for these analyses. Decisions on (adjuvant) treatment and follow-up were made at the physician's discretion [3]. Patients were followed for time to first recurrence and time to progression. Recurrence was defined as histological confirmation of a bladder tumor. Progression was defined as development of muscle-invasive and/or metastatic disease.

2.2. Pathology review

At the only Canadian study site ($n = 314$), the same tissue slides were reviewed twice by an experienced uropathologist (TvdK), first in 2004 and again in 2018. For this analysis on intraobserver variability of WHO 2004/2016, 163 Ta and 151 T1 NMIBC from Toronto-University Health Network (UHN) were included. The pathologist was blinded for grade and clinical outcome. At the other participating centers, a pathology review was deemed necessary if information on WHO1973 or WHO 2004/2016 was not provided in the pathology report or patient file, or if the primary TUR date was before 1998.

2.3. Statistical analyses

We used medians, first, and third quartiles to summarize continuous data. Frequencies and percentages were calculated for categorical data. Intraobserver variability between the first and second round of review (Toronto-UHN) was presented with agreement percentages and Cohen's kappa statistic. Agreement percentages were calculated based on the number of patients for whom the pathologist assigned the same grade for each WHO 2004/2016 grade category. Taking the date of the primary TUR as the starting point, time to recurrence and time to progression per WHO 2004/2016 grade category were estimated using cumulative incidence functions with death prior to the event considered to be a competing risk. They were compared with log-rank tests stratified by institution. When 3 groups were compared, an overall log-rank test stratified by institution was used. The curves were curtailed at 15-years follow-up. Patients with no event were censored at the last date of follow-up. Multivariable Cox-proportional hazard models stratified by institution were used to compare the prognostic values for recurrence and progression between WHO 2004/2016 Ta-grade categories taking into account gender (female/male), age (≤70/>70 years), multiplicity (solitary/multiple), size (<3 cm/≥3 cm), presence of carcinoma in situ (no/yes), single instillation of intravesical chemotherapy (no/yes), intravesical chemotherapy induction (no/yes), Bacillus Calmette-Guérin induction (no/yes), and primary TUR date (before 2000/after 2000). The prognostic factor analyses were done with both the original data from Toronto and the data after the pathology review in 2018. In this report, the calculations with the original data from the Toronto cohort are shown in the figures and multivariable analyses. SPSS software (SPSS 22.0; IBM, Armonk, NY, USA) and Stata Statistical Software (StataCorp. 2011; Release 12.1; College Station, TX: StataCorp LP) were used to perform the statistical analyses. Tests were 2-sided and statistical significance was assumed if $P < 0.05$.

3. Results

In total, IPD for 3,311 patients with primary (first diagnosis), Ta tumors from 17 hospitals were included. Baseline

Table 1
Baseline patient and tumor characteristics of the 3,311 primary (first diagnosis) Ta Bladder Tumor Patients included in the study. Tumors from Toronto-UHN were reviewed in 2004 and in 2018; WHO 2004/2016 grades of the 1st round (2004) are included in this table

Characteristic	No. of patients (%)
Gender, *n (%)*	
Male	2,617 (79.0)
Female	694 (21.0)
Age in years, median (IQR)	68.0 (59.0–75.0)
WHO2004/2016, *n (%)*	
PUN-LMP	127 (3.8)
LG	2,204 (66.6)
HG	980 (29.6)
Number of tumors, *n (%)*	
Solitary	2,258 (68.2)
Multiple	1,031 (31.1)
Missing	22 (0.7)
Tumor size, *n (%)*	
<3 cm	2,341 (70.7)
≥3 cm	770 (23.3)
Missing	200 (6.0)
Presence of CIS, *n (%)*	
No	3,159 (95.4)
Yes	152 (4.6)
Single instillation, *n (%)*	
No	1,628 (49.2)
Yes	1,371 (41.4)
Missing	312 (9.4)
Chemo induction, *n (%)*	
No	2,783 (84.1)
Yes	508 (15.3)
Missing	20 (0.6)
BCG induction, *n (%)*	
No	2,796 (84.4)
Yes	484 (14.6)
Missing	31 (0.9)

BCG = Bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high-grade carcinoma; IQR = interquartile range; LG = low-grade carcinoma; PUN-LMP = papillary urothelial neoplasm of low malignant potential; WHO2004/2016 = World Health Organization 2004/2016 grading system.

patient and tumor characteristics of these 3,311 patients are presented in Table 1. For patients without recurrence, median follow-up was 38.4 months (Interquartile Range: 18.3–71.5 months). Recurrence(s) were reported in 42.4% (1405/3311) and progression in 4.1% (135/3311) of patients. Of all included tumors, only 3.8% (127/3311) were initially diagnosed as PUN-LMP (Table 1).

3.1. PUN-LMP diagnosis over time

Only 10/17 hospitals diagnosed 1 or more PUN-LMP(s). Looking at the primary TUR dates, Table 2a shows that PUN-LMP diagnosis substantially decreased over time from 31.3% (1990–2000) to 1.1% (2010–2018). Table 2b shows the same trend for the 10 sites that diagnosed PUN-LMP, i.e. from 32.7% (1990–2000) to 2.5% (2010–2018). If we condensed the time periods to 1990–2005 and 2005–2018, the proportions of PUN-LMP were 15.6% and 1.4%, respectively. In Suppl. Fig. 1, the incidence of PUN-LMP by year is plotted in a line graph.

Table 2a
Proportion of WHO2004/2016 Ta-grade categories for all 17 included sites over 3 different time periods. Please note that time was the date of the primary, first resection of the bladder tumor

	WHO2004/2016 Ta-grade categories			
Time period	PUN-LMP (%)	LG (%)	HG (%)	Total (%)
1990–2000	67 (31.3)	101 (47.2)	46 (21.5)	214 (100.0)
2000–2010	40 (3.2)	804 (63.9)	414 (32.9)	1,258 (100.0)
2010–2018	20 (1.1)	1,299 (70.6)	520 (28.3)	1,839 (100.0)
Total (%)	127 (3.8)	2,204 (66.6)	980 (29.6)	3,311 (100.0)

HG = high-grade carcinoma; LG = low-grade carcinoma; PUN-LMP = papillary urothelial neoplasm of low malignant potential; WHO2004/2016 = World Health Organization 2004/2016 grading system.

Table 2b
Proportion of WHO2004/2016 Ta-grade categories for the 10 sites that diagnosed PUN-LMP (10/17 sites) over 3 different time periods. Please note that time was the date of the primary, first resection of the bladder tumor

	WHO2004/2016 Ta-grade categories			
Time period	PUN-LMP (%)	LG (%)	HG (%)	Total (%)
1990–2000	67 (32.7)	94 (45.9)	44 (21.5)	205 (100.0)
2000–2010	40 (3.9)	632 (61.5)	356 (34.6)	1,028 (100.0)
2010–2018	20 (2.5)	551 (70.2)	214 (27.3)	785 (100.0)
Total (%)	127 (6.3)	1,277 (63.3)	614 (30.4)	2,018 (100.0)

HG = high-grade carcinoma; LG = low-grade carcinoma; PUN-LMP = papillary urothelial neoplasm of low malignant potential; WHO2004/2016 = World Health Organization 2004/2016 grading system.

3.2. Intraobserver variability

To assess the intraobserver variability of the WHO 2004/2016 system at different points in time, 2 review sessions

Table 3
Results of the 2 review sessions (in 2004 and in 2018) by the same pathologist (TvdK) assigning WHO2004/2016 grades using the same slides of 314 Ta and T1 Bladder Tumors from Toronto-UHN

	1st review WHO2004/2016 *(performed in 2004)*			
2nd review WHO2004/2016 *(performed in 2018)*	PUN-LMP	LG	HG	Total
PUN-LMP	**18**	2	0	20
LG	53	**84**	4	141
HG	0	14	**139**	153
Total	71	100	143	314

HG = high-grade carcinoma; LG = low-grade carcinoma; PUN-LMP = papillary urothelial neoplasm of low malignant potential; WHO2004/2016 = World Health Organization 2004/2016 grading system.
*Both Ta and T1 tumors from Toronto-UHN were included. Agreement percentages between the 1st and 2nd review round were comparable if only Ta tumors were included (data not shown).

were done by the same pathologist (TvdK); the first in 2004 and the second in 2018. The results for Ta and T1 tumors are shown in Table 3. In the 2004 review, the pathologist examining the same slides found 71/314 (22.6%) PUN-LMPs as opposed to only 20/314 (6.4%) in the 2018 review. The agreement percentage for PUN-LMP was only 24.7% while, for LG and HG carcinomas, agreement percentages were 53.5% and 88.5%, respectively ($\kappa = 0.63$; 95% Confidence Interval [CI], 0.56–0.69). If we only included Ta lesions, similar percentages were observed (data not shown).

3.3. Prognostic value of Ta WHO 2004/2016 grade categories

3.3.1. Recurrence

Recurrence at 1 year follow-up was 19.2% (95% CI, 12.3–26.1), 18.4% (95% CI, 16.6–20.2) and 20.7% (95% CI, 18.2–23.2) for PUN-LMP, LG and HG carcinomas, respectively. At 5 years follow-up, recurrence was 51.2% (95% CI, 41.8–60.6), 48.3% (95% CI, 45.8–50.8), and 45.4% (95% CI, 41.9–48.9) for PUN-LMP, LG and HG carcinomas, respectively. Figure 1a displays the cumulative risk of recurrence per WHO 2004/2016 Ta-grade category. No significant difference in time to recurrence could be detected between the three WHO 2004/2016 Ta-grade categories (log-rank, $P = 0.381$).

For the 10 sites that diagnosed PUN-LMP, the cumulative risk of recurrence per WHO 2004/2016 Ta-grade category is visualized in Figure 1b. Time to recurrence did not differ between the three WHO 2004/2016 Ta-grade categories (log-rank, $P = 0.318$), nor did it differ between LG and PUN-LMP (log-rank, $P = 0.238$). Moreover, in multivariable analysis, recurrence did not significantly differ between all grade categories ($P = 0.697$), nor did it differ between HG carcinomas and PUN-LMP (Hazard Ratio [HR] 1.15, 95% CI, 0.83–1.60, $P = 0.402$) or LG carcinomas and PUN-LMP (HR 1.10, 95% CI, 0.82–1.47, $P = 0.539$) (Table 4a).

3.3.2. Progression

In total, 3.9% (5/127) of PUN-LMP patients progressed compared to 2.6% (57/2204) LG and 7.4% (73/980) HG carcinoma patients. At 3 years follow-up, progression was 0.8% (95% CI, 0.0–2.6) for PUN-LMP, 1.2% (95% CI, 0.6–1.8) for LG and 4.9% (95% CI, 3.3–6.5) for HG NMIBC. Progression at 5 years follow-up was 2.6% (95% CI, 0.0–5.7), 2.1% (95% CI, 1.3–2.9) and 7.5% (95% CI, 5.5–9.5) for PUN-LMP, LG and HG carcinomas, respectively. The overall P value for time to progression was statistically significant (log-rank, $P < 0.001$). Fig. 2 displays the cumulative risk of progression per WHO 2004/2016 Ta-grade category during 15 years follow-up.

For the 10 sites that diagnosed PUN-LMP, time to progression was different for the 3 grade categories (log-rank, $P < 0.001$), but not between LG carcinomas and PUN-LMP (log-rank, $P = 0.096$). In multivariable analysis, progression was different for HG carcinomas and PUN-LMP (HR 4.00,

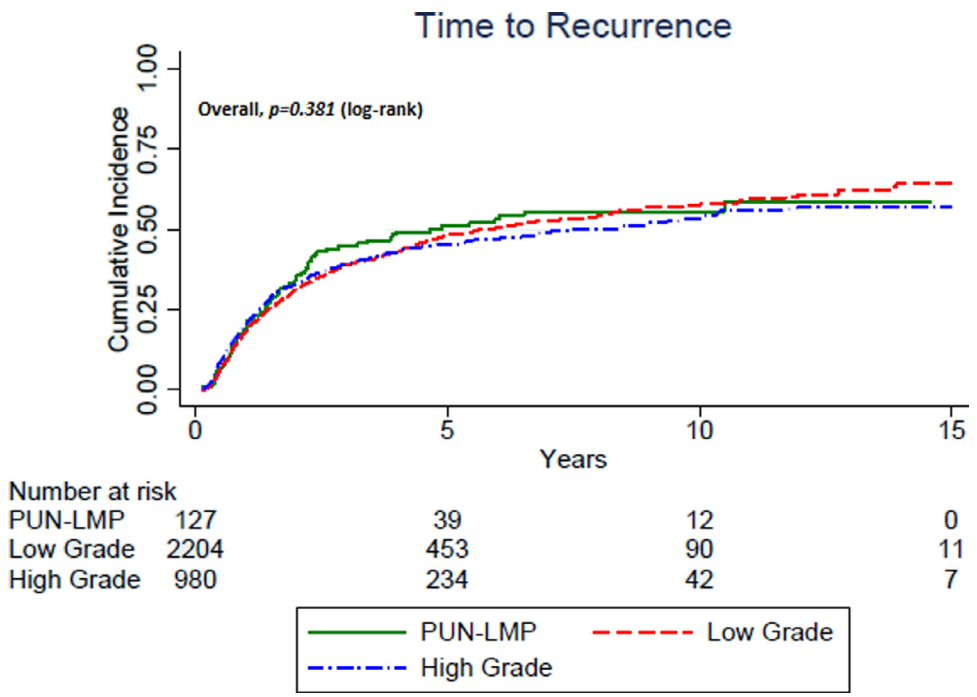

Fig. 1a. Cumulative incidence curves displaying the risk of recurrence for all 3311 primary, Ta tumors per WHO2004/2016 grade category.* WHO2004/2016 = World Health Organization 2004/2016 grading system. *Tumors from Toronto-UHN were reviewed twice, once in 2004 and once in 2018. WHO2004/2016 grades of the 1st round (2004) are included in this figure. Please note that recurrence per WHO2004/2016 grade category was comparable for both rounds (data not shown).

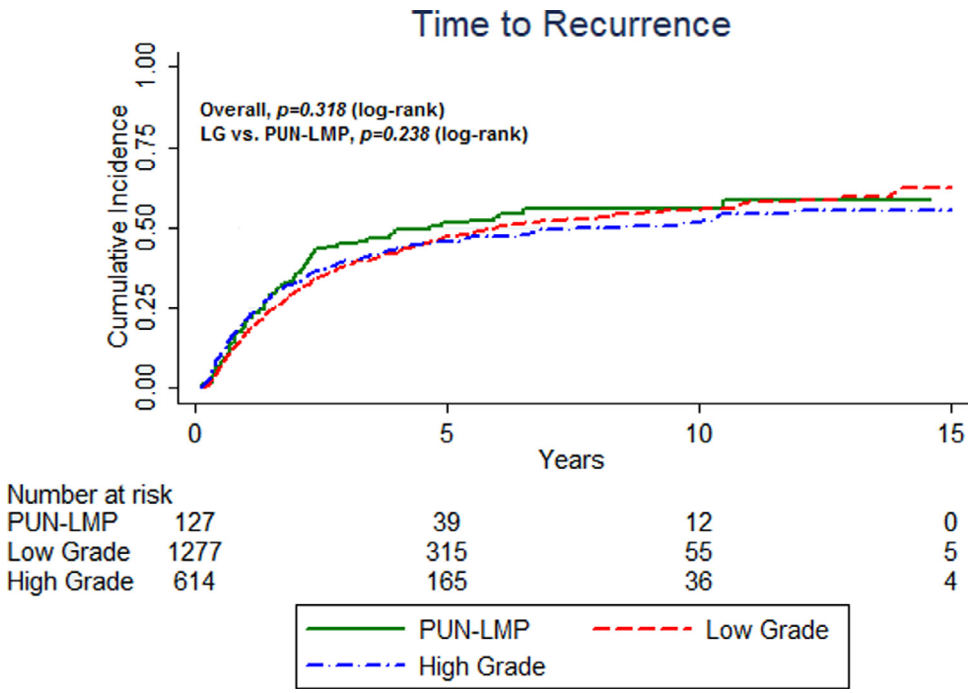

Fig. 1b. Cumulative incidence curves displaying the risk of recurrence for 2,018 primary, Ta tumors per WHO2004/2016 grade category. Only sites that have diagnosed PUN-LMP (10/17 sites) were included here.* ; PUN-LMP = papillary urothelial neoplasms of low malignant potential; WHO2004/2016 = World Health Organization 2004/2016 grading system.*Tumors from Toronto-UHN were reviewed twice, once in 2004 and once in 2018. WHO2004/2016 grades of the 1st round (2004) are included in this figure. Please note that recurrence per WHO2004/2016 grade category was comparable for both rounds (data not shown).

Table 4a
Multivariable analysis of recurrence for the 10 sites that diagnosed PUN-LMP ($n = 2,018$) if Ta tumors were graded according to the original WHO2004/2016 grade categories: PUN-LMP, LG and HG. If PUN-LMP and LG are combined within 1 grade category, recurrence did not differ from HG: HR 0.98 (95% CI, 0.85−1.13, $P = 0.760$) (all 17 sites; $n = 3,311$)*

	Recurrence		
Multivariable analysis*	HR	95% CI	*P* value
Tumor grade (WHO2004/2016)	-	-	0.697
LG vs. PUN-LMP	1.10	0.82−1.47	0.539
HG vs. PUN-LMP	1.15	0.83−1.60	0.402
Gender	1.08	0.90−1.29	0.426
Age	**1.18**	**1.01−1.37**	**0.035**
Multiplicity	**1.65**	**1.41−1.94**	**<0.001**
Tumor size	**1.45**	**1.22−1.72**	**<0.001**
Presence of CIS	**1.76**	**1.26−2.47**	**0.001**
Single instillation	0.86	0.68−1.09	0.212
Chemo induction	0.84	0.66−1.06	0.146
BCG induction	**0.66**	**0.51−0.85**	**0.001**
Primary TUR date	0.83	0.55−1.24	0.360

BCG = Bacillus Calmette-Guérin; CI= confidence interval; CIS = carcinoma in situ; HG = high-grade carcinoma; HR= Hazard Ratio; LG = low-grade carcinoma; PUN-LMP = papillary urothelial neoplasms of low malignant potential; TUR = transurethral resection; WHO2004/2016= World Health Organization 2004/2016 grading system.

* Analyses were stratified by institution. Tumors from Toronto-UHN were reviewed twice, once in 2004 and once in 2018. WHO2004/2016 grades of the 1st round (2004) were included in these analyses.
The bold values are the statistical significant predictors; *P* value <0.05.

Table 4b
Multivariable analysis of progression for the 10 sites that diagnosed PUN-LMP ($n = 2,018$) if Ta tumors were graded as PUN-LMP, LG and HG (WHO2004/2016). If PUN-LMP and LG carcinomas were combined into 1 grade category, progression differed from HG carcinomas in multivariable analysis: HR 2.46 (95% CI, 1.58−3.83, $P < 0.001$) (all 17 sites; $n = 3,311$)*

	Progression		
Multivariable analysis*	HR	95% CI	*P* value
Tumor grade (WHO2004/2016)	**-**	**-**	**<0.001**
LG vs. PUN-LMP	1.56	0.57−4.26	0.384
HG vs. PUN-LMP	**4.00**	**1.43−11.20**	**0.008**
Gender	1.58	0.83−3.02	0.167
Age	1.16	0.74−1.82	0.527
Multiplicity	**1.76**	**1.10−2.81**	**0.018**
Tumor size	**2.54**	**1.58−4.08**	**<0.001**
Presence of CIS	**2.72**	**1.36−5.44**	**0.005**
Single instillation	0.58	0.30−1.11	0.102
Chemo induction	0.57	0.28−1.19	0.136
BCG induction	0.94	0.52−1.68	0.826
Primary TUR date	0.77	0.21−2.81	0.693

BCG = Bacillus Calmette-Guérin; CI= confidence interval; CIS = carcinoma in situ; HG = high-grade carcinoma; HR= Hazard Ratio; LG = low-grade carcinoma; PUN-LMP = papillary urothelial neoplasms of low malignant potential; TUR = transurethral resection; WHO2004/2016= World Health Organization 2004/2016 grading system.

* Analyses were stratified by institution. Tumors from Toronto-UHN were reviewed twice, once in 2004 and once in 2018. WHO2004/2016 grades of the 1st round (2004) are included in these analyses.
The bold values are the statistical significant predictors; *P* value <0.05.

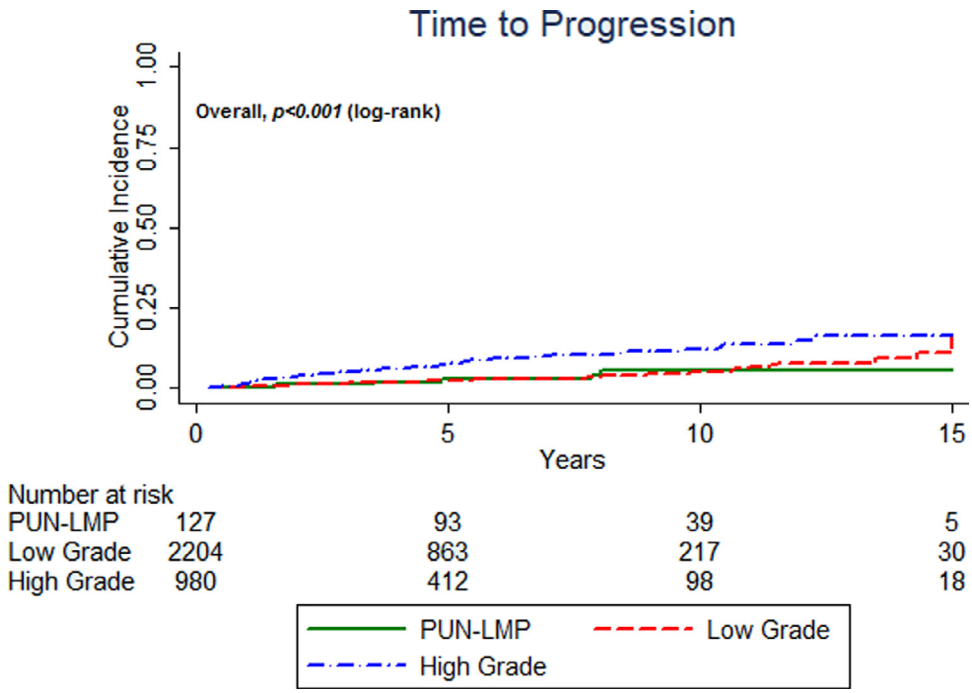

Fig. 2. Cumulative incidence curves displaying the risk of progression for all 3,311 primary, Ta tumors per WHO2004/2016 grade category.* WHO2004/2016= World Health Organization 2004/2016 grading system. *Tumors from Toronto-UHN were reviewed twice, once in 2004 and once in 2018. WHO 2004/2016 grades of the 1st round (2004) are included in this figure. Please note that progression per WHO2004/2016 grade category was comparable for both rounds (data not shown).

95% CI, 1.43−11.20, $P = 0.008$), but not between LG carcinomas and PUN-LMP (HR 1.56, 95% CI, 0.57−4.26, $P = 0.384$) (Table 4b).

The cohort from Toronto comprised 163/3,311 (4.9%) cases. The same analyses on recurrence and progression outlined above were also done using the data from the review in 2018. The results were almost identical (data not shown).

3.4. Correlation between WHO 1973 and WHO 2004/2016

Of the included Ta tumors, 33.9% (1,121/3,311) were graded G1, 54.4% (1,803/3,311)

G2 and 11.7% (387/3,311) G3. In total, 78.7% (100/127) of PUN-LMP tumors were graded G1, while 45.9% (1,012/2,204) of LG carcinomas were graded G1 by WHO1973. The remaining 21.3% (27/127) of PUN-LMPs were graded G2, whereas 53.6% (1182/2,204) of LG carcinomas were graded G2 and 0.5% (10/2,204) G3.

4. Discussion

In 2016, the WHO reconfirmed PUN-LMP as a separate category for Ta, noninvasive bladder tumors after its first introduction nearly 20 years earlier (WHO/ISUP 1998) [5,7]. In the present study, the overall proportion of PUN-LMP was only 3.8% (127/3,311) in a large cohort of primary Ta urothelial bladder tumors. A strong decline in PUN-LMP diagnosis was evident with a decrease from 31.3% before 2000 to only 1.1% after 2010. The same trend was observed if the same pathologist graded the same slides twice, first in 2004 (23% PUN-LMP) and again in 2018 (6% PUN-LMP). Moreover, we found no difference in recurrence and progression for PUN-LMP compared to Ta-LG carcinomas.

Observer variability is a recognized problem in the determination of bladder tumor grade [3,13,14]. A recent systematic review comprised 3 studies that reported on observer variability. Interobserver agreement of WHO 2004/2016 ranged from 43%−82% (κ:0.17−0.52) and intraobserver agreement from 71%−93% (κ:0.56−0.83) [13]. In an earlier study with 173 patients, the same pathologist (TvdK) graded a set of 173 slides with an interval of 6 months between the 2 rounds of grading [14]. The percentage agreement then for PUN-LMP and LG were 62% and 71%, respectively. In the current study with an assessment of intraobserver agreement after a longer (14 years) time period, the agreement percentage for PUN-LMP (24.7%) was much lower than expected from the literature, while agreement percentages for LG and HG carcinomas (53.5% and 88.5%, respectively) remained rather high [13,14]. Please note that the shift from PUN-LMP to LG carcinomas caused a somewhat lower than expected agreement percentage for LG as well. At least for the uropathologist (TvdK) who twice graded the same series of primary bladder lesions in 2004 and 2018, this analysis showed that many "original" PUN-LMPs are currently classified as LG disease. By looking at the TUR-dates, our study also showed

that the proportion of PUN-LMP of all Ta tumors declined over time from 31% (before 2000) to 1% (2010−2018) while the proportion of LG NMIBC increased over time from 47% (before 2000) to 71% (2010−2018) and the proportion of HG NMIBC remained stable around 22% (before 2000) to 28% (2010−2018). MacLennan et al. [8], analyzing studies published shortly after the introduction of PUN-LMP in 1998, also reported that PUN-LMP was quite frequently (12%−39%) diagnosed in noninvasive bladder tumors. This is in accordance with the "early" PUN-LMP proportion (31.3%) in the present study in Ta tumors only. In line with our results, Mangrud et al. [17] found that only 1% (2/193) of noninvasive tumors were classified as PUN-LMP. The tumors were diagnosed between 2002 and 2007 and reviewed by several pathologists after 2009. Again in line with our results, May et al. [18] reported a proportion of PUN-LMP between 0% and 4% for 4 observers grading 200 Ta tumors. After a consensus meeting, only 1/200 cases (0.5%) remained PUN-LMP. The TURs were done between 1997 and 2004 and pathology review was done between 2004 and 2010. In conclusion, our and other more recent results confirm the trend of vanishing PUN-LMP diagnosis [17,18] and it seems that pathologists have more or less stopped calling a papillary lesion PUN-LMP after 2010. We suggest 2 reasons for this phenomenon. With advancing insight, pathologists may have started to apply the criteria for PUN-LMP more stringently or because the first studies did not show an improvement in observer variability and/or clinical relevance compared to LG disease [8−18]. By now, the incidence of PUN-LMP has made it a rare lesion, getting close to the incidence of urothelial papilloma [6,7,11,17]. Moreover, we have shown that the vast majority of former PUNLMPs are currently classified as LG carcinomas.

Tumor grade is an important prognostic factor in NMIBC, especially for prediction of progression [1−3]. With regards to PUN-LMP, the original aim was to identify papillary lesions with such a low rate of recurrence and (almost) no progression that PUN-LMP could be seen as a noncancerous category in the bladder tumor spectrum [5−7]. However, recurrence and progression rates were more or less comparable to LG NMIBC and G1 NMIBC (WHO 1973) in the first reviews that appeared on PUN-LMP, which evaluated studies from before 2005 [1,8−10,15,16]. Although May et al. [18] and Mangrud et al. [17] intended to provide data on PUN-LMP prognosis, their number of PUN-LMP cases (3/393 cases in both studies combined) was too low for this objective. In the present large study with IPD on 3,311 primary Ta patients, we were able to do prognostic factor analyses for recurrence and progression with 127 and 76 (after review in 2018 of the Toronto-UHN cases) PUN-LMPs. We found that PUN-LMP and LG carcinomas did not differ in prognosis for either recurrence or progression, even in the later time period (s) of low PUN-LMP incidence. Our IPD results are also in accordance with the recent systematic review by Soukup et al. [13], which concluded that recurrence and progression were comparable for 624 PUN-LMP and 1303 G1 noninvasive bladder tumors. In the EAU guidelines, PUN-LMP cases are classified as low-risk tumors and the recommendations for follow-up are similar to small, primary, and solitary TaG1/LG tumors [3]. Our findings and the ones by Soukup et al. confirm that PUN-LMP surveillance should be the same as for low-risk (Ta) G1/LG carcinoma [13]. From a molecular point of view, PUN-LMP was also found to have similar frequencies of *FGFR3* mutations and p53, Ki-67, and p27 alterations as LG/G1 NMIBC [11,19]. If we compare PUN-LMP to the WHO 1973 classification system, we found that, as expected, G1 (WHO 1973) is more strongly correlated to PUN-LMP than to LG carcinomas, which is illustrated by the fact that 78.7% of PUN-LMP patients were graded as G1, while 45.9% of LG patients were graded as G1 in the current study.

Limitations of this study were the retrospective setting, differences in adjuvant treatment, and the absence of central pathology review. Hence, pathologists did not receive any additional training on the WHO 2004/2016 grading criteria for Ta bladder tumors, especially not for PUN-LMP. Also, this resulted in a small number of grading inconsistencies: 9 HG/G1 and 10 LG/G3. We decided not to exclude these 19 cases, as this paper primarily focuses on the WHO 2004/2016 system and because it comprises only a very small proportion (0.6%) of the cases. The strengths of the current study include the IPD of a large series of primary, previously untreated, Ta bladder tumors with "real-world" data from 17 well known hospitals in Europe and Canada.

5. Conclusions

The incidence of the PUN-LMP diagnosis has strongly declined over the past 2 decades. It seems that, after 2010, pathologists have almost stopped calling a noninvasive papillary lesion PUN-LMP. The vast majority of the "vanishing" PUN-LMP diagnosis are currently classified as LG carcinomas. Recurrence and progression rates proved comparable for PUN-LMP and Ta-LG carcinomas, indicating that their surveillance should be identical as already outlined in the EAU-NMIBC guidelines. Consequently, our results do not support the continued use of PUN-LMP as a separate grade category in noninvasive papillary bladder tumors because, even if the incidence of PUN-LMP is low, the prognosis of PUN-LMP and Ta-LG carcinomas was similar.

Acknowledgments

The present study was conducted under the auspices of the EAU-NMIBC guidelines panel. The EAU central guidelines office approved the protocol and appropriate ethical approval was obtained at each site.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.10.002.

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