The Importance of Being Grade 3

A Plea for a Three-tier Hybrid Classification System for Grade in Primary Non-muscle-invasive Bladder Cancer

European Association of Urology

Brief Report

The Importance of Being Grade 3: A Plea for a Three-tier Hybrid Classification System for Grade in Primary Non–muscle-invasive Bladder Cancer

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Article info

Abstract

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Grade is an important determinant of progression in non–muscle-invasive bladder cancer. Although the World Health Organization (WHO) 2004/2016 grading system is recommended, other systems such as WHO1973 and WHO1999 are still widely used. Recently, a hybrid (three-tier) system was proposed, separating WHO2004/2016 high grade (HG) into HG/grade 2 (G2) and HG/G3 while maintaining low grade. We assessed the prognostic performance of HG/G3 and HG/G2. Three independent cohorts with 9712 primary (first diagnosis) Ta-T1 bladder tumors were analyzed. Time to progression was analyzed with cumulative incidence functions and Cox regression models. Harrell's C-index was used to assess discrimination. Time to progression was significantly shorter for HG/G3 than for HG/G2 in multivariable analyses (cohort 1: hazard ratio [HR] = 1.92; cohort 2: HR = 2.51, and cohort 3: HR = 1.69). Corresponding progression risks at 5 yr were 18%, 20%, and 18% for HG/G3 versus 7.3%, 7.5%, and 9.3% for HG/G2, respectively. Cox models using hybrid grade performed better than models with WHO2004/2016 (all cohorts; *p* < 0.001). For the three cohorts, C-indices for WHO2004/2016 were 0.69, 0.62, and 0.75, while, for hybrid grade, C-indices were 0.74, 0.68, and 0.78, respectively. Subdividing the HG category into HG/G2 and HG/G3 stratifies time to progression and supports the recommendation to adopt the hybrid grading system for Ta/T1 bladder cancers.

ADVANCING PRACTICE

What does this study add?
Our study of 9712 primary Ta-T1 bladder tumors from three independent cohorts shows that high grade (HG)/grade 3 (G3) tumors have a significantly shorter time to progression and higher progression risks than HG/G2 tumors. Therefore, separating the heterogeneous HG category into HG/G2 and HG/G3 is advised for both clinical decision-making (mitomycin vs Bacillus Calmette-Guérin vs radical cystectomy) and as a stratification factor in randomized clinical trials investigating novel therapeutic intravesical agents in HG non–muscle-invasive bladder cancer, to ensure balanced representation of HG/G2 and HG/G3 in trial arms.

Clinical Relevance
This study highlights the importance of categorizing high-grade non–muscle-invasive bladder cancer (NMIBC) into two distinct groups: HG/G2 and HG/G3. The authors' research shows that patients with HG/G3 tumors have a significantly worse prognosis than those with HG/G2 tumors. By using a three-tier hybrid grading system, clinicians can more accurately predict disease progression and tailor treatment strategies accordingly. This approach can lead to improved risk stratification, optimizing therapy escalation or de-escalation, and enabling more precise monitoring based on individual risk profiles. (Laura Bukavina, MD, MPH).

Patient Summary
To determine the optimal treatment and surveillance strategy for patients with non–muscle-invasive bladder cancer, it is crucial to understand its position within the spectrum of disease progression. Pathological information, including tumor grade, can help in predicting the risks of progression. Our findings indicate that differentiating high-grade cancer into grades 2 and 3 is important and recommended, as patients with grade 3 tumors have a worse prognosis than those with grade 2 tumors.

Histological grade is an important predictor of progression in non–muscle-invasive bladder cancer (NMIBC) [1]. Although the World Health Organization (WHO) 2004/2016 classification (categories: papillary urothelial neoplasm of low malignant potential [PUN-LMP], low grade [LG], and high grade [HG]) grading system is recommended, WHO1973 (categories: grade [G] 1, G2, and G3) and WHO1999 grading (categories: PUN-LMP, LG, HG/G2, and

HG/G3) are still used. Recently, a hybrid three-tier grading system was proposed, separating the clinically heterogeneous WHO2004/2016 HG category into HG/G2 and HG/G3 while maintaining LG (Fig. 1A) [2–6]. The current study assesses the prognostic significance of being G3 compared with G2 in patients diagnosed with HG NMIBC.

We utilized three different cohorts with primary Ta-T1 NMIBC, excluding patients with <3 mo of follow-up, pro-

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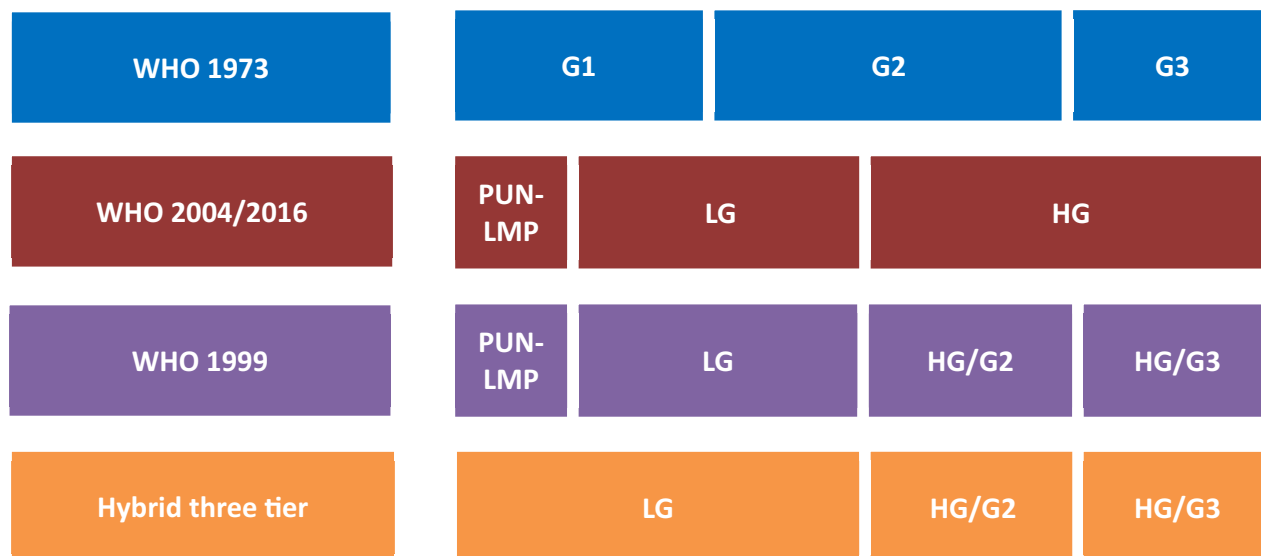
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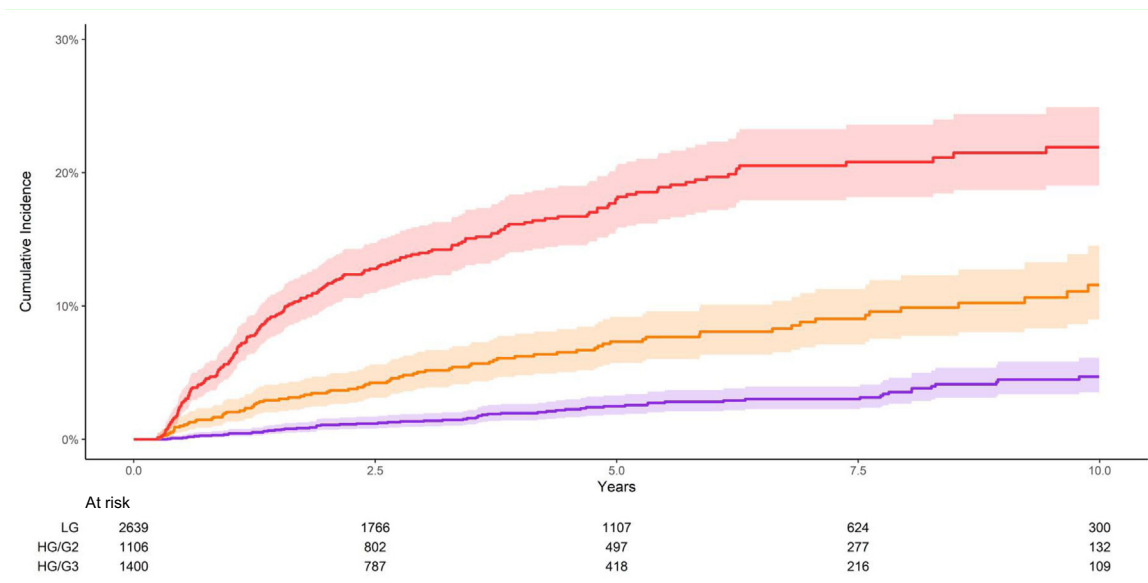
Fig. 1 – (A) Diagram with four (WHO1973, WHO 2004/2016, WHO1999, and hybrid (three-tier)) systems for grade in NMIBC. A graphical comparison of different categories per grading system and the cutoffs between grades are shown. (B) Cumulative incidence curves displaying the risk of progression for LG, HG/G2, and HG/G3 carcinomas (hybrid grade) for cohort 1 (ie, the EAU-NMIBC cohort) in 5145 primary Ta/T1 bladder cancer patients. Time to progression was statistically signi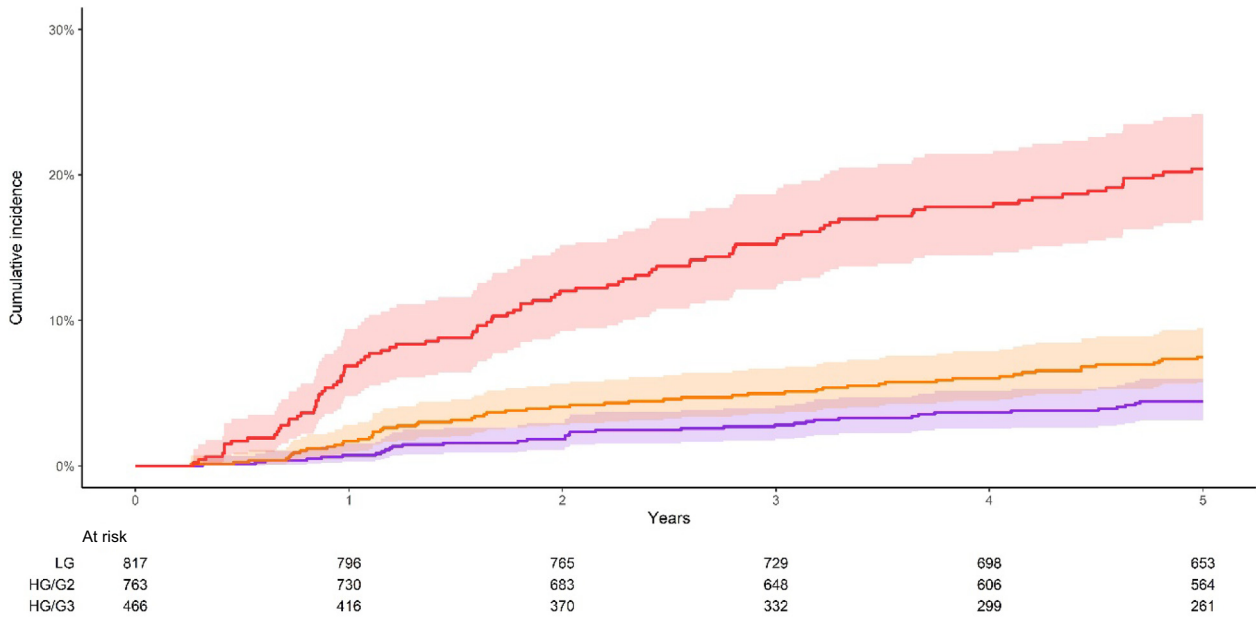ficantly shorter for HG/G3 versus HG/G2 (logrank, $p < 0.001$) and for HG/G2 versus LG (logrank, $p < 0.001$). Purple line = LG; orange line = HG/G2; and red line = HG/G3. (C) Cumulative incidence curves displaying the risk of progression for LG, HG/G2, and HG/G3 carcinomas (hybrid grade) for cohort 2 (ie, the Swedish cohort) in 2046 primary Ta/T1 bladder cancer patients. Time to progression was statistically significantly shorter for HG/G3 versus HG/G2 (logrank, $p < 0.001$) and for HG/G2 versus LG (logrank, $p = 0.008$). Purple line = LG; orange line = HG/G2; and red line = HG/G3. (D) Cumulative incidence curves displaying the risk of progression for LG, HG/G2, and HG/G3 carcinomas (hybrid grade) for cohort 3 (ie, the Scottish cohort) in 2521 primary Ta/T1 bladder cancer patients. Time to progression was statistically significantly shorter for HG/G3 versus HG/G2 (logrank, $p < 0.001$) and for HG/G2 versus LG (logrank, $p < 0.001$). Purple line = LG; orange line = HG/G2; and red line = HG/G3. G = grade; HG = high grade; LG = low grade; NMIBC = non–muscle-invasive bladder cancer; PUN-LMP = papillary urothelial neoplasm of low malignant potential; WHO = World Health Organization; WHO1973 = World Health Organization 1973 grading system; WHO 2004/2016 = World Health Organization 2004/2016 grading system.

gression, or cystectomy within 3 mo (cohort 1, n = 86; cohort 2, n = 173; cohort 3, n = 106). After these exclusions, the first (retrospective) cohort contained 5145 patients diagnosed between 1990 and 2018 (17 hospitals in Europe and Canada). The second (population-based) cohort consisted of 2046 patients diagnosed between 2013 and 2014 in Sweden. The third (prospective) cohort comprised 2521 patients diagnosed between 2014 and 2017 in Scotland

C

At risk						
LG	817	796	765	729	698	653
HG/G2	763	730	683	648	606	564
HG/G3	466	416	370	332	299	261

D

At risk						
LG	1419	1310	1174	1023	799	423
HG/G2	391	351	301	260	212	93
HG/G3	709	588	495	410	304	158
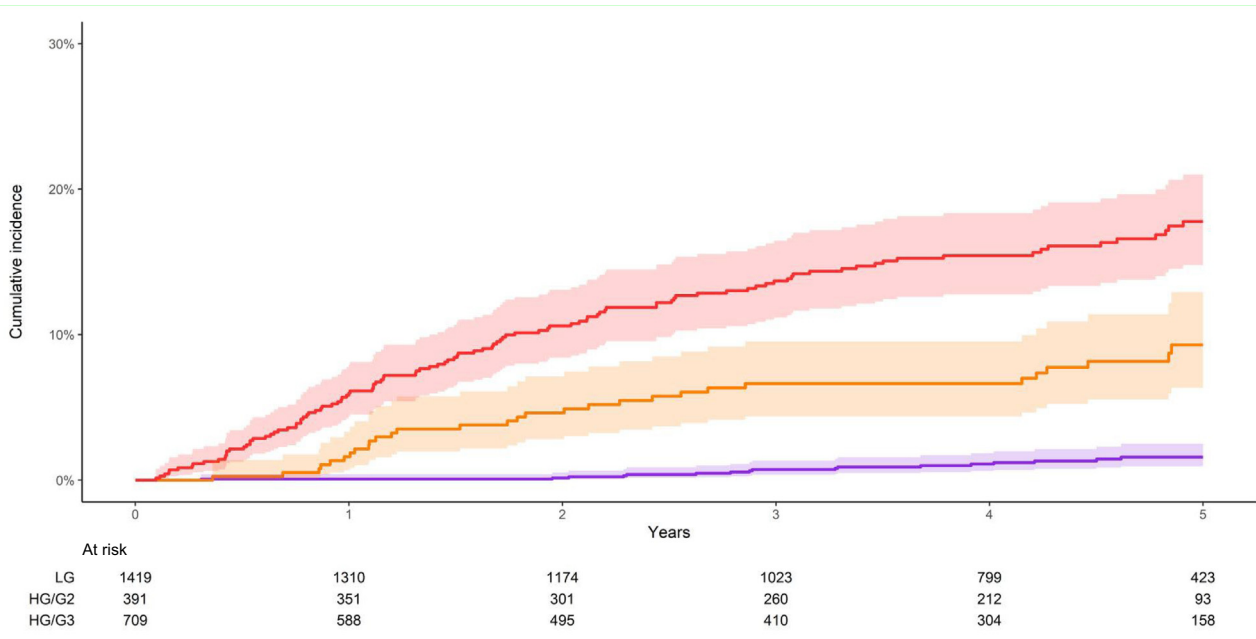
Fig. 1 (*continued*)

[7]. A three-tier hybrid grading system consisting of LG (including PUN-LMP), HG/G2, and HG/G3 was applied in retrospect (without a pathology review) to the three cohorts, constructed by using both WHO1973 and WHO2004/2016 (similar to WHO2022; cohorts 1 and 3) and WHO1999 (cohort 2), with PUN-LMP included in the LG category.

Cumulative incidence curves, with death as a competing event and the date of primary diagnosis as a starting point, were used to estimate the time to recurrence, progression (muscle-invasive and/or metastatic disease) [1], and bladder cancer (BC)-related death. Overall survival (OS) was estimated using all-cause death in Kaplan-Meier functions. Patients without events were censored at their date of last

follow-up. Curves were compared with the log-rank test. Cox proportional hazard models (complete case analysis) were used to compare the prognostic value of HG/G3 versus HG/G2, adjusting for stage (Ta/T1), gender (female/male), age (≤70/>70 yr), multiplicity (solitary/multiple), size (<3/$\geq$3 cm), concomitant carcinoma in situ (no/yes), and induction instillation therapies with chemotherapy (no/yes) or Bacillus Calmette-Guérin (BCG; no/yes). Prognostic performances of the Cox models (WHO2004/2016 vs hybrid grade) were compared with log-likelihood ratio tests. Harrell's concordance (C) index was used to estimate the prognostic accuracy of the models with bootstrap methods (1000×) to estimate 95% confidence intervals (CIs). A comparison between LG and HG/G2 and a subgroup analysis for Ta and T1 were conducted similarly to the methods outlined above. Patient characteristics are presented in Table 1.

In the first (EAU-NMIBC) cohort, the median follow-up time was 47.3 mo (interquartile range [IQR]: 23.6–85.1) for patients without progression. In total, 383 patients progressed. Time to progression was shorter for patients with HG/G3 than for those with HG/G2 ($p < 0.001$). Progression risks at 5 yr were 2.5% (95% CI: 1.8–3.3%) for LG, 7.3% (95% CI: 5.7–9.2%) for HG/G2, and 18% (95%CI: 16–20%) for HG/G3 (Fig. 1B). In a multivariable analysis, time to progression was shorter for HG/G3 than for HG/G2 (hazard ratio [HR] 1.92; 95% CI: 1.43–2.59). The Cox model with hybrid grading performed better than WHO2004/2016 (log-likelihood $p < 0.001$). Harrell's C-indices were 0.69 (95% CI: 0.67–0.71) for WHO2004/2016 and 0.74 (95% CI: 0.71–0.76) for hybrid grading (Supplementary Table 1).

In the second (Swedish BladderBaSe) cohort, the median follow-up time was 60 mo (IQR: 60.0–60.0) for patients without progression. In total, 188 patients progressed. Time to progression was shorter for patients with HG/G3 than for those with HG/G2 ($p < 0.001$). Progression risk at 5 yr was 4.4% (95% CI: 3.2–6.0%) for LG, 7.5% (95% CI: 5.8–9.5%) for HG/G2, and 20% (95% CI: 17–24%) for HG/G3 (Fig. 1C). In a multivariable analysis, time to progression was shorter for HG/G3 than for HG/G2 (HR 2.51; 95% CI: 1.71–3.67). The Cox model including hybrid grading performed better than WHO2004/2016 (log-likelihood $p < 0.001$). Harrell's C-indices were 0.63 (95% CI: 0.59–0.64) for WHO2004/2016 and 0.68 (95% CI: 0.64–0.72) for hybrid grading (Supplementary Table 1).

In the third (Scottish) cohort, the median follow-up time was 50.4 mo (IQR: 30.2–61.5) for patients without progression. In total, 165 patients progressed. Time to progression was shorter for patients with HG/G3 than for those with HG/G2 ($p < 0.001$). Progression risks at 5 yr were 1.6% (0.95–2.5%) for LG, 9.3% (95% CI: 6.3–13%) for HG/G2, and 18% (95% CI: 15–21%) for HG/G3 (Fig. 1D). In a multivariable analysis, time to progression was shorter for HG/G3 than for HG/G2 (HR 1.69; 95% CI: 1.07–2.66). The Cox model including hybrid grading performed better than WHO2004/2016 (log-likelihood $p = 0.019$). Harrell's C-indices were 0.75 (95% CI: 0.73–0.77) for WHO2004/2016 and 0.78 (95% CI: 0.75–0.80) for hybrid grading (Supplementary Table 1).

Similar results to those described for progression were also found for time to BC-related death and OS, whereas no statistically significant differences were found in time to recurrence (Supplementary material, Supplementary Tables 1–3, and Supplementary Fig. 1–3). Within the Ta and T1 subgroups, the prognostic values of the grading systems were comparable with those of the whole cohorts, and the LG category had a longer time to progression than the HG/G2 category (Supplementary material and Supplementary Tables 4–6).

Our study using three large cohorts (9712 patients) supports a grading system that considers increased progression risks associated with being HG/G3 (according to WHO1973 or WHO1999) versus HG/G2, that is, 18–20% for HG/G3 versus 7–9% for HG/G2 at 5 yr. Treating all HG patients the same may lead to both under- or overtreatment, whereas separating HG into HG/G2 and HG/G3 could further individualize treatment by considering adjuvant chemotherapy instillations instead of BCG for HG/G2 and early radical cystectomy for HG/G3.

In a systematic review, only seven studies (in total, 1263 patients) allowed a direct comparison of progression to muscle-invasive disease between WHO1973 and WHO2004/2016 [8]. Although both grading-systems were prognostic for progression, WHO1973 identified more aggressive tumors within the relatively large subset of HG tumors. Subsequently, van Rhijn et al [2] and Jahnson et al [9] showed that a four-tier combination of WHO1973 and WHO2004/2016 (LG-G1, LG-G2, HG/G2, and HG/G3) was a better predictor of progression than either (WHO1973 or WHO2004/2016) system alone. In addition, the study from Jahnson et al [9] comprised 71% HG tumors at a central pathology review, emphasizing the clinical heterogeneity within the HG group. However, as the difference in progression between LG/G1 and LG/G2 proved less relevant from a clinical perspective and molecular-genetic data pointed at HG/G3 as a separate entity [4], the International Society of Urological Pathology (ISUP) proposed a three-tier hybrid grading system [5]. Subsequently, Downes et al [3] showed (in 609 patients) that this system was superior to WHO2004/2016. Additionally, an international survey revealed that a four-tier system was not favored by pathologists (ISUP) and urologists (European Association of Urology), while a hybrid grading system was considered a promising alternative for the future as a majority believed that separate reporting of HG/G3 would have a significant clinical impact [10].

Limitations of this study are the variation in treatment protocols and different grading descriptions of G3 for WHO1973 and WHO1999 (making meta-analytic methods less appropriate), mostly European populations, and a lack of a central pathology review (see the Supplementary material for a more detailed discussion on this topic). A notable strength lies in the plethora of individual patient data from diverse, independent cohorts, including retrospective, population-based, and prospectively collected data. Thus, the consistency of findings across these cohorts strengthens the validity and reliability of our findings.

To conclude, prognostic accuracy of the (three-tier) hybrid grading system was better than that of the

Table 1 – Distribution of patient, tumor, and adjuvant treatment characteristics

		Cohort 1	Cohort 2	Cohort 3
Total number of patients		5145	2046	2521
Age, median (IQR)		68 (60–76)	72 (66–80)	73 (65–80)
Sex, n (%)	Male	4125 (80)	1541 (75)	1787 (71)
Stage, n (%)	Ta	3292 (64)	1524 (74)	1851 (73)
	T1	1853 (36)	522 (26)	670 (27)
WHO1973 grade, n (%)	G1	1208 (24)	–	382 (15)
	G2	2537 (49)	–	1429 (57)
	G3	1400 (27)	–	710 (28)
WHO2004/2016 grade, n (%)	LG	2639 (51)	817 (40)	1420 (56)
	HG	2506 (49)	1229 (60)	1101 (44)
Hybrid grade, n (%)	LG	2639 (51)	817 (40)	1420 (56)
	HG/G2	1106 (22)	763 (37)	391 (16)
	HG/G3	1400 (27)	466 (23)	710 (28)
Concomitant CIS, n (%)	Yes	474 (9.2)	103 (5.0)	252 (10)
Size, n (%)	≥3 cm	1578 (31)	484 (24)	714 (28)
	Missing	298	–	76
Multiplicity, n (%)	Multiple	1762 (34)	555 (27)	783 (31)
	Missing	33	–	18
Induction chemotherapy instillations, n (%)	Yes	716 (14)	147 (7.2)	234 (9.3)
	Missing	30	–	420
Induction BCG instillations, n (%)	Yes	1528 (30)	405 (19)	509 (20)
	Missing	39	–	420

BCG = Bacillus Calmette-Guérin; CIS = carcinoma in situ; EAU = European Association of Urology; G = tumor grade; IQR = interquartile range; HG = high grade; LG = low grade; NMIBC = non–muscle-invasive bladder cancer; PUN-LMP = papillary urothelial neoplasm of low malignant potential; T = tumor stage; WHO = World Health Organization.

Details for the three participating cohorts comprising in total 9712 patients with primary Ta/T1 non–muscle-invasive bladder cancer are shown. Hybrid grade in cohort 1 (EAU-NMIBC) and cohort 3 (Scottish collaborative) consisted of WHO1973 and WHO2004/2016. Hybrid grade in cohort 2 (Swedish BladderBaSe) was derived from WHO1999 (see also Fig. 1A). Of note, PUN-LMP (cohort 1, 76 cases; cohort 2, 52 cases) and LG tumors were combined in the LG category because their prognosis was similar [1,2,5,10].

WHO2004/2016 system, and a subgroup of HG patients with worse prognosis can be identified by including G3. Based on the present study, subdividing the large HG category into HG/G2 and HG/G3 conveys clinically meaningful information and is strongly recommended.

Appendix A. Contributors and their affiliation(s)

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Supplementary material

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References

[1] Sylvester RJ, Rodríguez O, Hernández V, et al. European Association of Urology (EAU) prognostic factor risk groups for non-muscle-invasive bladder cancer (NMIBC) incorporating the WHO 2004/2016 and WHO 1973 classification systems for grade: an update from the EAU NMIBC Guidelines Panel. Eur Urol 2021;79:480–8.

[2] van Rhijn BWG, Hentschel AE, Bründl J, et al. Prognostic value of the WHO1973 and WHO2004/2016 classification systems for grade in primary Ta/T1 non-muscle-invasive bladder cancer: a multicenter European Association of Urology Non-muscle-invasive Bladder Cancer Guidelines Panel study. Eur Urol Oncol 2021;4:182–91.

[3] Downes MR, Lajkosz K, Kuk C, Gao B, Kulkarni GS, van der Kwast TH. The impact of grading scheme on non-muscle invasive bladder cancer progression: potential utility of hybrid grading schemes. Pathology 2022;54:425–33.

[4] Liedberg F, Lauss M, Patschan O, et al. The importance of being grade 3: WHO 1999 versus WHO 2004 pathologic grading. Eur Urol 2012;62:620–3.

[5] van der Kwast T, Liedberg F, Black PC, et al. International Society of Urological Pathology expert opinion on grading of urothelial carcinoma. Eur Urol Focus 2022;8:438–46.

[6] Reis LO, Dal Col LSB, Capibaribe DM, de Mendonça GB, Denardi F, Billis A. Presence and predominance of histological grade 3 define cT1HG bladder cancer prognostic groups. Investig Clin Urol 2022;63:21–6.

[7] Mariappan P. The scottish bladder cancer quality performance indicators influencing outcomes, prognosis, and surveillance (Scot BC Quality OPS) clinical project. Eur Urol Focus 2021;7:905–8.

[8] Soukup V, Čapoun O, Cohen D, et al. Prognostic performance and reproducibility of the 1973 and 2004/2016 World Health Organization grading classification systems in non-muscle-invasive bladder cancer: a European Association of Urology Non-muscle Invasive Bladder Cancer Guidelines Panel systematic review. Eur Urol 2017;72:801–13.

[9] Jahnson S, Jancke G, Olsson H, Aljabery F. Bladder cancer grading using the four-tier combination of the World Health Organization (WHO) 1973 and WHO 2004 classifications. BJU Int 2023;132:656–63.

[10] Beijert IJ, Cheng L, Liedberg F, et al. International opinions on grading of urothelial carcinoma: a survey among European Association of Urology and International Society of Urological Pathology members. Eur Urol 2023;83:S1445–6.