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Platinum Priority – Bladder Cancer

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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

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Abstract

Background: The European Association of Urology (EAU) prognostic factor risk groups for non–muscle-invasive bladder cancer (NMIBC) are used to provide recommendations for patient treatment after transurethral resection of bladder tumor (TURBT). They do not, however, take into account the widely used World Health Organization (WHO) 2004/2016 grading classification and are based on patients treated in the 1980s.
Objective: To update EAU prognostic factor risk groups using the WHO 1973 and 2004/2016 grading classifications and identify patients with the lowest and highest probabilities of progression.
Design, setting, and participants: Individual patient data for primary NMIBC patients were collected from the institutions of the members of the EAU NMIBC guidelines panel.
Intervention: Patients underwent TURBT followed by intravesical instillations at the physician's discretion.
Outcome measurements and statistical analysis: Multivariable Cox proportional-hazards regression models were fitted to the primary endpoint, the time to progression to muscle-invasive disease or distant metastases. Patients were divided into four risk groups: low-, intermediate-, high-, and a new, very high-risk group. The probabilities of progression were estimated using Kaplan-Meier curves.
Results and limitations: A total of 3401 patients treated with TURBT ± intravesical chemotherapy were included. From the multivariable analyses, tumor stage, WHO 1973/2004–2016 grade, concomitant carcinoma in situ, number of tumors, tumor size, and age were used to form four risk groups for which the probability of progression at 5 yr varied from <1% to >40%. Limitations include the retrospective collection of data and the lack of central pathology review.
Conclusions: This study provides updated EAU prognostic factor risk groups that can be used to inform patient treatment and follow-up. Incorporating the WHO 2004/2016 and 1973 grading classifications, a new, very high-risk group has been identified for which urologists should be prompt to assess and adapt their therapeutic strategy when necessary.
Patient summary: The newly updated European Association of Urology prognostic factor risk groups for non–muscle-invasive bladder cancer provide an improved basis for recommending a patient's treatment and follow-up schedule.

1. Introduction

To facilitate adjuvant treatment recommendations and adapt surveillance schedules, it is important to be able to accurately predict the short-term and long-term probabilities of disease recurrence and progression for a patient with non–muscle-invasive bladder cancer (NMIBC) after transurethral resection of bladder tumor (TURBT).

The European Association of Urology (EAU), the American Urological Association (AUA)/Society of Urologic Oncology (SUO), and the National Institute for Health and Care Excellence (NICE) have all proposed stratification of patients into prognostic factor risk groups, while the National Comprehensive Cancer Network (NCCN) uses the pathological stage and grade [1]. The EAU, whose guidelines have been endorsed by more than 50 urological societies and associations, recommends stratification of patients into three prognostic factor risk groups: low, intermediate, and high risk, which includes a subgroup of the highest-risk tumors [2]. These risk groups were inspired by the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Tract Cancer Group risk tables for the probability of progression to muscle-invasive disease [3]. Since then, additional publications, including those from CUETO [4,5], the EORTC [6], and other groups [7–9],

have further refined our understanding of the importance of prognostic factors in NMIBC.

The EORTC risk tables [3] include the following six factors: prior recurrence rate, number of tumors, maximum tumor diameter, tumor stage, 1973 WHO grade [10], and the presence of concomitant carcinoma in situ (CIS).

The current EAU risk groups were developed based on the EORTC risk tables, which used the 1973 WHO grading classification, and included patients diagnosed and treated in the 1980s. These have not been updated with more recently treated patients or with the more recent and widely used WHO 2004/2016 grading classification system [11].

Since the current EAU guidelines recommend the use of both the WHO 1973 and 2004/2016 grading classifications [2,12], the prognostic factor risk groups need to be updated to remain applicable in current daily clinical practice.

The objectives of this study were to:

1 Update the current prognostic factor risk groups based on the WHO 1973 grading classification;
2 Update the EAU NMIBC Guidelines Panel prognostic factor risk groups with the WHO 2004/2016 grading classification; and
3 Identify patients with the lowest and highest probabilities of progression for each of these grading systems.

2. Patients and methods

2.1. Patients

In 2016 and 2017, the EAU NMIBC Guidelines Panel developed and launched a "Protocol for an individual patient data (IPD) prognostic factor study of the WHO 1973 and 2004/2016 classification systems for grade and the 2006 EORTC risk score in patients with primary Ta T1 urothelial carcinoma of the bladder". One of the aims was to update the prognostic factor risk groups using the WHO 2004/2016 and 1973 grading classification systems, the subject of this paper. Other aims included an assessment of papillary urothelial neoplasm of low malignant potential (PUN-LMP) tumors [13] and a comparison of the prognostic value of the WHO 1973 and 2004/2016 grading classifications [14].

Patient eligibility criteria included: primary, TaT1 urothelial carcinoma of the urinary bladder, with or without concomitant CIS; diagnosis after 1 January 1990, minimum follow-up of 3 mo; and no cystectomy within 3 mo from primary TURBT. Treatment and follow-up were at the physician's discretion. Exclusion criteria included: CIS without concomitant papillary tumor; previous history of muscle-invasive disease; concomitant upper tract urothelial carcinoma; variant pathologies; and immediate cystectomy for NMIBC.

The primary outcome was time to progression, calculated from the date of the initial diagnostic TURBT to the date of the first development of muscle-invasive disease, either at follow-up TURBT or at the time of cystectomy, N+, or M + disease. Deaths due to unrelated causes before progression were censored at the date of death. Patients without an event were censored at the date of their last follow-up visit for recurrence.

Participating institutions were those of the members of the EAU NMIBC Guidelines Panel, representing mostly expert, university hospitals from eight European countries and Canada. The goal was to include at least 2000 cases. Data were collected using a predefined standardized form that underwent several rounds of quality control together with the institutions.

2.2. Statistical methods

As the goal was to update the current risk groups based on grade, the number of tumors (single vs multiple) and tumor size (<3 cm vs ≥3 cm) were analyzed in accordance with current EAU guidelines, as the prognostic importance of these cut-points has been consistently shown [3–7,9]. WHO 2004/2016 PUN-LMP and low grade (LG) tumors were combined into a single group because the proportion of PUN-LMP tumors has decreased to very low levels and the prognosis of PUN-LMP and Ta-LG carcinomas is similar [13]. Age was also analyzed, with a recoding for ease of use into two groups (≤70 yr vs >70 yr) on the basis of the prognostic importance of this cut-point in previous publications [4,5,7,15]. Gender was not analyzed as it has not been found to be of either clinical or prognostic importance for progression in previous publications.

Multivariable Cox proportional-hazards regression models stratified by institution were fitted to the primary endpoint, time to progression. Internal validation was performed by generating 1000 bootstrap random

Table 1 – Patient and tumor characteristics

Parameter	Result
Age (yr)	
First quartile	60
Median	68
Third quartile	76
Gender, *n* (%)	
Female	729 (21)
Male	2672 (79)
Number of tumors, *n* (%)	
Single	2379 (70)
Multiple	1022 (30)
Maximum diameter, *n* (%)	
<3 cm	2432 (72)
≥3 cm	969 (28)
Tumor stage, *n* (%)	
Ta	2644 (78)
T1	757 (22%)
Concomitant CIS, *n* (%)	
No	3310 (97)
Yes	91 (2.7)
WHO grade 1973, *n* (%)	
G1	1130 (33)
G2	1874 (55)
G3	397 (12)
WHO grade 2004/2016, *n* (%)	
Low grade	2349 (69)
High grade	1052 (31)
EAU risk group 1973, *n* (%)	
Low	633 (19)
Intermediate	1853 (54)
High	915 (27)
Repeat TURBT, *n* (%)	
No	2696 (79)
Yes	556 (16)
Unknown	149 (4.4)
Initial treatment, *n* (%)	
TURBT alone	1572 (46)
TURBT + chemotherapy	1829 (54)

CIS = carcinoma in situ; EAU = European Association of Urology; TURBT = transurethral resection of bladder tumor; WHO = World Health Organization.

samples with replacement. Model discrimination at 5 yr and 10 yr was assessed with Harrell's bias-corrected *c* index ($0 \leq c \leq 1$), which is the probability that for two patients chosen at random, the patient who experiences progression first has a higher probability of progression according to the model. A *c* value of 0.50 represents agreement by chance, while *c* = 1.0 represents perfect discrimination. Model calibration, which was assessed at 5 and 10 yr, compared bias-corrected estimates of Cox predicted progression probabilities and observed Kaplan-Meier estimates.

On the basis of their coefficients in the multivariable Cox models, a weight for each level of each variable was obtained. The weights that corresponded to a given patient's characteristics were summed. Patients were then divided into four groups according to their total score: low, intermediate, high, and very high risk. The choice of cut-points was based on the probabilities of progression using the current WHO 1973 EAU risk groups: no more than approximately 1% in the low-risk group at 5 yr and approximately 10% in the high-risk group at 5 yr, but with the goal of identifying a very high-risk subgroup with a progression probability of at least 20% at 5 yr.

For each risk group, Kaplan-Meier time to progression failure curves and observed probabilities of progression at 1, 5, and 10 yr were obtained, along with their 95% confidence intervals.

All statistical analyses were carried out using Stata v16.1, except for the *c* index and the model calibration, which were calculated using the *RMS* package in R v4.0.3.

3. Results

3.1. Patients

Individual patient data were received for 5295 patients from 17 institutions. After a quality control review of the patient eligibility criteria, data completeness, and inconsistencies, 150 patients were excluded, leaving 5145 patients [14].

In addition, 1528 patients who started induction bacillus Calmette-Guérin (BCG) after TURBT, 960 of whom received maintenance BCG, were also excluded since multivariable analyses of the current data showed that BCG after TURBT reduced the risk of progression compared to TURBT ± chemotherapy. Furthermore, 17 patients for whom treatment information was unavailable and 199 patients with missing data for the number of tumors or tumor size were excluded. The 556 patients who had a repeat TURBT were not excluded. Consistent with another publication [16], repeat TURBT did not reduce the risk of progression, with detrusor muscle being present in 78% of primary TURBT specimens. Thus, data for 3401 primary patients were used to estimate the probability of progression after TURBT and to construct progression risk groups (Supplementary Table 1).

Patients were diagnosed from 1990 to 2018, half of them after 2010. The initial treatment was TURBT alone in 1572 patients (46%), and TURBT plus a single instillation or induction chemotherapy in 1829 patients (54%).

Patient and tumor characteristics are provided in Table 1. The median age was 68 yr and 79% were males. Tumor characteristics were primary (100%), single tumor (70%), tumor <3 cm in diameter (72%), Ta tumor (78%), concomitant CIS (3%), G3 tumor (12%), and HG tumor (31%). Using the current EAU risk stratification with WHO 1973, 27% were high-risk tumors.

Table 2 – Multivariable analyses of time to progression: WHO Grade 2004/2016 and 1973

Variable	Multivariable WHO 2004/2016		Multivariable WHO 1973	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age				
≤70 yr	1		1	
>70 yr	1.72 (1.24–2.40)	0.001	1.62 (1.14–2.31)	0.007
Number of tumors				
Single	1		1	
Multiple	1.64 (1.17–2.29)	0.004	1.63 (1.15–2.29)	0.006
Maximum diameter				
<3 cm	1		1	
≥3 cm	1.97 (1.41–2.77)	<0.001	1.90 (1.35–2.67)	<0.001
Stage				
Ta	1		1	
T1	2.20 (1.53–3.16)	<0.001	2.18 (1.50–3.17)	<0.001
Concomitant CIS				
No	1		1	
Yes	2.76 (1.62–4.70)	<0.001	2.41 (1.33–4.36)	0.004
WHO 2004/2016 grade				
Low grade	1			
High grade	2.33 (1.58–3.42)	<0.001		
WHO 1973 grade				
G1			1	
G2			2.36 (1.41–3.94)	<0.001 (2 df)
G3			4.52 (2.44–8.37)	
Harrell's bias-corrected *c*	5 yr: 0.80		5 yr: 0.80	
	10 yr: 0.79		10 yr: 0.79	

CI = confidence interval; CIS = carcinoma in situ; df = degrees of freedom; HR = hazard ratio.

3.2. Prognostic factors for progression

The 25th percentile, median, and 75th percentile of the follow-up duration for patients not progressing was 1.9, 3.9, and 7.2 yr, respectively. A total of 168 patients progressed, while 471 patients died of an unrelated cause before progression. Progression numbers are given in Supplementary Table 2 according to patient and tumor characteristics.

Multivariable analyses of time to progression are presented in Table 2. In both models, Harrell's bias-corrected *c* index was 0.80 at 5 yr and 0.79 at 10 yr. Supplementary Figure 1A–D provides model calibration plots at 5 and 10 yr. In both models, the predicted and observed probabilities of progression at 5 yr were close; the 90th percentile of the error was 0.004. At 10 yr, when there were fewer patients in follow-up, the 90th percentile of the error increased to 0.010 (WHO 2004) and 0.018 (WHO 1973), with the difference appearing for progression-free rates of 80% or less.

3.3. Prognostic factor risk groups

From the multivariable analyses in Table 2, the weights used to calculate the progression scores are provided in Table 3. Summing these weights, Table 3 also presents the total progression scores by risk group for both the WHO 2004/2016 and 1973 classifications.

Table 3 – Weights used to calculate the total progression scores and the progression risk group scores

Variable	WHO 2004/2016	WHO 1973
Age		
≤70 yr	0	0
>70 yr	55	32
Number of tumors		
Single	0	0
Multiple	50	32
Maximum diameter		
<3 cm	0	0
≥3 cm	65	43
Stage		
Ta	0	0
T1	80	52
Concomitant CIS		
No	0	0
Yes	100	58
WHO 1973 grade		
G1		0
G2		58
G3		100
WHO 2004/2016 grade		
LMP-low grade	0	
High grade	85	
Maximum total score	435	317

Risk group	Total progression score[a]	
	WHO 2004/2016	WHO 1973
Low risk	0–80	0–52
Intermediate risk[b]	85–150	58–133
High risk	165–305	142–233
Very high risk	315–435	242–317

CIS = carcinoma in situ; LMP = low malignant potential; WHO = World Health Organization.
[a] Sum of the weights.
[b] Patients with concomitant CIS were reclassified into the high-risk group.

The clinical compositions of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 and WHO 1973 grading classifications are provided in Table 4. An online app and apps for iOS and Android are being developed to facilitate determination of a patient's risk group.

Table 5 presents the probabilities of progression and 95% confidence intervals for the current EAU risk groups and for the new WHO 2004/2016 and 1973 risk groups at 1, 5, and 10 yr.

Kaplan-Meier time-to-progression curves are provided in Figure 1A–C. Through choice of the cut-points, probabilities of progression in the low-, intermediate-, and high-risk groups for the current EAU risk groups and for the corresponding new WHO 2004/2016 and 1973 risk groups are similar, and at 5 yr range from <1% in the low-risk groups to approximately 10% in the high-risk groups. In the new WHO 2004/2016 and 1973 very high-risk groups, the probability of progression at 5 yr is approximately 40%.

4. Discussion

Current EAU guidelines recommend the use of both the WHO 1973 and WHO 2004/2016 grading classifications [2,12], both of which have been shown to be of prognostic importance [14,17]. An important limitation of the current EAU prognostic factor risk groups is that they only take into account the WHO 1973 grade, and not the now widely used WHO 2004/2016 grade.

Despite the fact that both the EORTC and the CUETO scoring systems on which the current WHO 1973 EAU risk groups are based could accurately predict which patients would not progress to muscle-invasive disease, neither scoring system could accurately identify which patients would progress [18].

In an external validation, Vetter et al [19] concluded that the EORTC and CUETO risk scores could reasonably predict progression, with *c* indices ranging from 0.72 to 0.82; however, treatment with BCG and progression rates varied across the three cohorts included and no information was provided about how accurately they could identify which patients would progress in the high-risk groups.

Compared to the EORTC risk groups for progression, Rieken et al [20] found that the EAU risk groups reclassified 11.8% of patients into a higher risk group. The accuracy in predicting progression in the high-risk groups remained low and patients received various adjuvant instillations after TURBT, including BCG.

The current paper has addressed these limitations and concerns by developing new, separate, prognostic factor risk groups that include the WHO 2004/2016 and 1973 grading classifications for which the probability of progression of primary Ta/T1 NMIBC after TURBT is not confounded by treatment with BCG.

The progression-free probabilities at 5 yr in the low-risk groups are similar, approximately 99%. There are, however, more patients in the WHO 2004/2016 low-risk group

Table 4 – Clinical composition of the new European Association of Urology non–muscle-invasive bladder cancer prognostic factor risk groups based on WHO 2004/2016 or WHO 1973 grading classification systems

Risk group	
Low risk	• A primary, single, Ta LG/G1 tumor ≤3 cm in diameter without CIS in a patient ≤70 yr
	• A primary LG/G1 tumor with at most ONE of the following additional clinical risk factors:
	◦ Age >70 yr
	◦ Multiple tumors
	◦ Tumor diameter ≥3 cm
	◦ Stage T1
Intermediate risk	• Patients without CIS who are not included in either the low-, high-, or very high-risk groups
High risk	• All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group
	• All CIS patients, EXCEPT those included in the very high-risk group.
	Stage, grade with additional clinical risk factors:[a]
	• Ta LG/G2 or T1 G1, no CIS with all 3 risk factors
	• Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors
	• T1 G2 no CIS with at least 1 risk factor
Very high risk	Stage, grade with additional clinical risk factors:[a]
	• Ta HG/G3 and CIS with all 3 risk factors
	• T1 G2 and CIS with at least 2 risk factors
	• T1 HG/G3 and CIS with at least 1 risk factor
	• T1 HG/G3 no CIS with all 3 risk factors

[a]The additional clinical risk factors are age > 70 yr, multiple tumors, and tumor diameter ≥ 3 cm.

CIS = carcinoma in situ; HG = high grade; LG = low grade; TURBT = transurethral resection of bladder tumor.
Note that papillary urothelial neoplasia of low malignant potential and LG carcinoma were combined into one LG category because we have previously shown in the same data set that the prognosis of these two categories is similar [13]. Only one of the two grading systems is required to use this table:
- LG/G1 is LG in WHO 2004/2016 and G1 in WHO 1973.
- LG/G2 is LG in WHO 2004/2016 and G2 in WHO 1973.
- HG/G3 is HG in WHO 2004/2016 and G3 in WHO 1973.
Patients with recurrent disease should be included in the intermediate-, high-, or very high-risk group according to their other prognostic factors. On the basis of the published literature, patients with CIS in the prostatic urethra, lymphovascular invasion, and micropapillary, plasmacytoid, sarcomatoid, or neuroendocrine variant histology should all be included in the very high-risk group. More data are required to accurately classify other variant histologies as being high risk or very high risk.

Table 5 – Probability of progression by risk group

Risk group	Probability of progression, % (95% CI)		
	1 yr	5 yr	10 yr
Current EAU risk groups			
Low (*n* = 633)	0	0.20 (0.03–1.4)	1.9 (0.54–6.6)
Intermediate (*n* = 1853)	0.46 (0.23–0.91)	2.8 (2.0–3.9)	8.1 (6.0–11)
High (*n* = 915)	4.7 (3.5–6.4)	12 (10–15)	14 (11–17)
New risk groups with WHO 2004/2016			
Low (*n* = 1705)	0.06 (0.01–0.43)	0.93 (0.49–1.7)	3.7 (2.3–5.9)
Intermediate (*n* = 845)	1.0 (0.50–2.0)	4.9 (3.4–7.0)	8.5 (5.6–13)
High (*n* = 752)	3.5 (2.4–5.2)	9.6 (7.4–12)	14 (11–18)
Very high (*n* = 99)	16 (10–26)	40 (29–54)	53 (36–73)
New risk groups with WHO 1973			
Low (*n* = 876)	0.12 (0.02–0.82)	0.57 (0.21–1.5)	3.0 (1.5–6.3)
Intermediate (*n* = 1793)	0.65 (0.36–1.2)	3.6 (2.7–4.9)	7.4 (5.5–10)
High (*n* = 662)	3.8 (2.6–5.7)	11 (8.1–14)	14 (10–19)
Very high (*n* = 70)	20 (12–32)	44 (30–61)	59 (39–79)

CI = confidence interval; EAU = European Association of Urology; WHO = World Health Organization.

because WHO 2004/2016 LG includes both WHO 1973 G1 tumors and some G2 tumors, with a corresponding decrease in the number of patients in the WHO 2004/2016 intermediate-risk group.

There are fewer patients in the new combined WHO 1973 high- and very high-risk groups than in the current EAU high-risk group (22% vs 27%). In the new WHO 2004/2016 and 1973 very high-risk groups, which comprise between 2% and 3% of the patients included, the probabilities of progression at 5 years have increased from 12% in the current EAU high-risk group to 40% and 44% in the new WHO 2004/2016 and 1973 very high-risk groups, respectively.

Although the very high-risk groups represent only a small subgroup of patients included in this analysis, they make up 15% (WHO 1973) and 18% (WHO 2004/2016) of the 1528 BCG patients who were excluded. It is thus essential to be able to accurately identify this small subgroup of very-high risk patients to seriously consider immediate cystectomy.

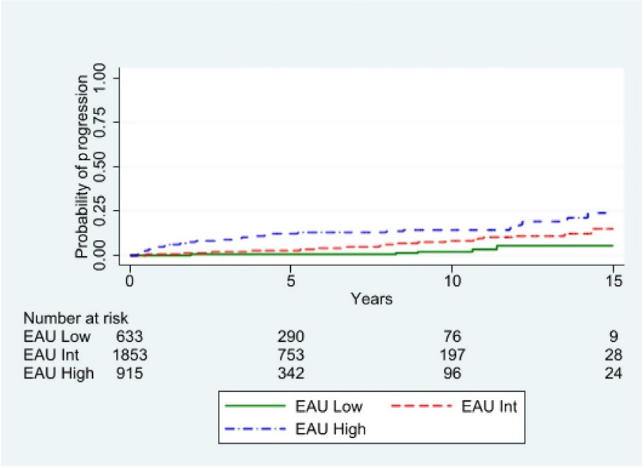
The new WHO 2004/2016 and 1973 very high-risk groups thus identify patients with a higher probability of progression compared to the current EAU high risk group, while maintaining the same low probability of progression in the low risk patients.

The differences between the new EAU risk groups and the AUA risk groups, which explicitly take recurrent patients into account, are minimal, except in the AUA high risk group which includes BCG failure in HG patients and patients with a potentially heterogeneous prognosis, which the EAU has split into two groups of high and very high risk.

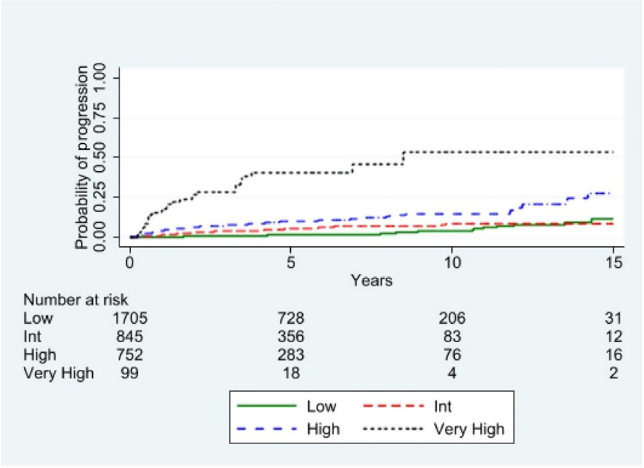
There are several limitations to be noted in this study. A retrospective study, which involved 17 institutions, was the only way get long term follow up data, however there may have been errors in coding and data extraction from hospital records. A stringent data quality control was applied to reduce the risk of bias. Half of the patients were diagnosed before 2010. Since then, there have been improvements in diagnosis and TURBT, possibly leading to lower progression rates in current day patients.

The initial treatment was not given in accordance with current guidelines in many cases, especially in the high-risk patients for whom BCG is the recommended treatment. This could be seen as a limitation, although guideline adherence is low, even in patients who should receive BCG [21,22]. This has, however, allowed us to study the probability of progression after TURBT, unaffected by adjuvant BCG, in these high- and very high-risk patients. Although the number of patients in the very high-risk groups is small and the confidence intervals for the probability of progression are wide, the probability of progression in the very high-risk group is very high, thus providing vital information when choosing between organ preservation and radical cystectomy for these patients. Reasons for nonadherence within

(A)



(B)



(C)

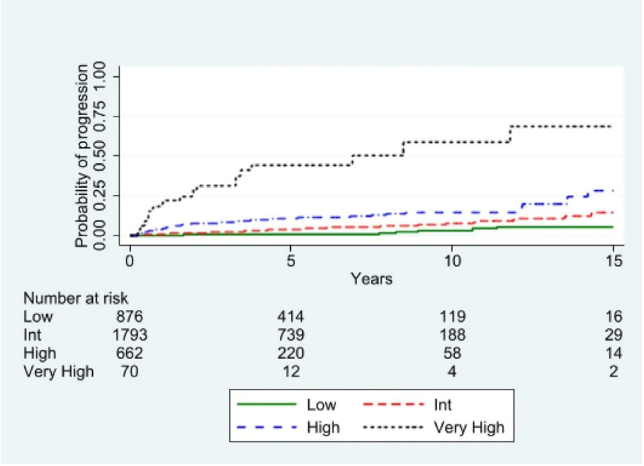


Fig. 1 – Time to progression for (A) current EAU risk groups with the WHO 1973 classification; (B) new EAU risk groups with the WHO 2004/2016 classification; and (C) new EAU risk groups with the WHO 1973 classification. EAU = European Association of Urology; WHO = World Health Organization; Int = intermediate.

institutions were compiled and do not suggest a patient selection bias.

Although there was a local pathology review in some institutions, cases were not re-evaluated in a central pathology review. This reflects daily practice, in which a central review is generally not feasible before starting intravesical treatment after TURBT. In addition, all institutions were part of tertiary referral centers.

The main limitation concerns the fact that data were not collected on certain clinical and pathological factors thought to be associated with a poor prognosis, such as the depth of lamina propria invasion in patients with stage T1 disease [23].

The protocol excluded the following patients:

(1) Patients with recurrent disease: the prior recurrence rate was the least important variable in the EORTC progression risk score [3]. Patients with recurrent disease should be included in the intermediate-, high-, or very high-risk groups according to their other prognostic factors.
(2) Patients with primary CIS without a papillary tumor: these patients were not included because the objective was to assess the WHO 2004/2016 and WHO 1973 grading classification systems. This is a heterogeneous group owing to the use of different technologies for their detection. Data on the prognosis for these patients are limited. Prognosis depends on various factors, including whether the patient has (1) asymptomatic focal primary CIS, which is the earliest and least aggressive form of the disease or (2) symptomatic diffuse primary CIS [24,25]. As the prognosis for primary CIS can be highly variable, with a non-negligible risk of extravesical extension and progression, this should be included in the high-risk group.

Patients with the following characteristics were likewise not studied and should be included in the very high-risk group:

- The presence of CIS in the prostatic urethra is associated with a higher risk of progression [8].
- Lymphovascular invasion in TURBT specimens is associated with a higher risk of pathological upstaging to muscle-invasive disease [26–29].
- Some forms of variant histology of urothelial carcinoma (especially micropapillary, plasmacytoid, sarcomatoid, and neuroendocrine types) also have very poor prognosis [2,29–33].

Finally, stratification of patients based on addition of molecular markers to the current prognostic factors is promising but is not yet suitable for routine clinical practice [2].

5. Conclusions

This study provides updated prognostic factor risk groups that incorporate the WHO 2004/2016 and WHO 1973 grading systems and estimate a patient's probability of progression of NMIBC. For patients falling into the new very high-risk group, urologists should be very prompt to assess and adapt their therapeutic strategy when necessary.

Author contributions: Richard J. Sylvester had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Drafting of the manuscript: Sylvester.
Critical revision of the manuscript for important intellectual content: Rodríguez, Hernández, Turturica, Bauerová, Bruins, Bründl, van der Kwast, Plass, Brisuda, Rubio-Briones, Seles, Hentschel, Kusuma, Huebner, Cotte, Mertens, Volanis, Cussenot, Subiela Henríquez, de la Peña, Pisano, Pešl, van der Heijden, Herdegen, Zlotta, Hacek, Calatrava, Mannweiler, Bosschieter, Ashabere, Haitel, Côté, El Sheikh, Lunelli, Algaba, Alemany, Soria, Runneboom, Breyer, Nieuwenhuijzen, Llorente, Molinaro, Hulsbergen-van de Kaa, Evert, Kiemeney, N'Dow, Čapoun, Soukup, Dominguez-Escrig, Cohen, Palou, Gontero, Burger, Zigeuner, Mostafid, Shariat, Rouprêt, Compérat, Babjuk, van Rhijn.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.12.033.

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