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Accuracy of the European Association of Urology (EAU) NMIBC 2021 scoring model in predicting progression in a large cohort of HG T1 NMIBC patients treated with BCG.

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BACKGROUND: Recently, the European Association of Urology Guidelines Panel updated the prognostic factor risk groups model for non–muscle-invasive bladder cancer (NMIBC) with the introduction of a new group of patients at Very high risk (VHR). Furthermore, three additional clinical risk factors (i.e., age > 70 years, multiple papillary tumors; tumor diameter > 3 cm) were proposed. However, the new scoring model was created by analyzing data from patients who did not receive BCG intravesical therapy.

METHODS: This is a retrospective multicenter study analyzing data of 920 patients with HGT1 NMIBC that underwent ReTUR e following BCG intravesical therapy. Patients were stratified into risk groups according to the 2021 new EAU NMIBC prognostic factor risk groups model. This study aimed to identify variables related to disease progression in a large cohort of HGT1 NMIBC patients who underwent both Re-TURB and BCG intravesical immunotherapy.

RESULTS: Median follow-up was 51 months (IQR 41-75), according to EAU NMIBC 2021 scoring model 179 (19.5%) patients were at VHR. Progression-free survival at 5 years was 68.2% and 59.9% for the whole sample and the VHR group, respectively. At multivariable regression model size >3 cm, multifocal tumor, concomitant CIS and LVI were identified as independently associated with disease progression.

CONCLUSIONS: Although patients at VHR are more likely to experience disease progression during follow-up, the European Association of Urology (EAU) NMIBC 2021 scoring model appears to be suboptimal in patients who underwent ReTUR and intravesical BCG therapy.

Keywords: Non-muscle invasive bladder cancer, Progression, Bacillus Calmette-Guerin (BCG), EAU

Introduction

Bladder cancer (BC) is the ninth most common cancer worldwide [1] and occurs in 75% of the cases as non-muscle invasive BC (NMIBC) [2,3]. Although it is possible to achieve complete eradication of the tumor with transurethral resection of the bladder (TURB), NMIBC patients have a significant risk of recurrence and progression to muscle-invasive bladder cancer (MIBC). Therefore, in case of invasion of the lamina propria (T1), a second resection (repeated TURB [Re-TURB]) followed by intravesical instillations with bacillus Calmette Guerin (BCG) is indicated, as this management pathway has demonstrated to reduce the risk of progression[4,5]. However, given the heterogeneity of NMIBC patients, their risk stratification is fundamental to choose the best therapeutic strategy for each patient. The EAU guidelines suggest stratifying the patients into risk groups based on the probability of progression to MIBC. Recently, the European Association of Urology Guidelines Panel updated the risk group definitions, identifying four risk groups (i.e., low, intermediate, high, and very high) based on the probability of progression to MIBC [2]. One of the new features is the introduction of the "very high risk" (VHR) group. Furthermore, in addition to pathological features, such as the presence of associated carcinoma in situ (CIS) or lymphovascular invasion (LVI), three additional clinical risk factors (i.e., age > 70 years, multiple papillary tumors; tumor diameter > 3 cm) are used to discriminate high-risk and VHR patients.

However, the new scoring model was created by analyzing data only from patients who did not receive BCG intravesical therapy. Very few data are currently available to inform clinicians about the risk and predictors of progression of patients who underwent TURBT plus Re-TURB and BCG intravesical therapy.

Therefore, this study aimed to identify variables related to disease progression in a large cohort of HGT1 NMIBC patients who underwent both Re-TURB and BCG intravesical immunotherapy and to test the accuracy of the new EAU scoring system in identifying those at the highest risk of progression specifically in this setting of patients.

Materials and methods

Study design and population

This is a retrospective multicentric cohort study analyzing data of 920 patients with HGT1 urothelial BC treated from January 2002 to December 2012 at 13 Italian high-volume centers. Institutional review board approval at each institution was obtained, with all participating sites providing institutional data sharing agreements before the initiation of the study. Written informed consent was obtained for all patients.

Patients with HGT1 urothelial BC who underwent a second endoscopic resection within 4-6 weeks followed by BCG intravesical therapy were included in the study [2]. The second resection included the resection of any residual disease and the resample of the initial resection area. BCG intravesical therapy included an induction course with a 6-weekly schedule and a maintenance course consisting of 3 weekly instillations at 3, 6, 12, 18, 24, 30, and 36 months.

Exclusion criteria were: adjuvant intravesical chemotherapy, concomitant upper tract urothelial cancer (UTUC) and lack of data on tumor characteristics or follow-up. Patients presenting HGT1 tumor at Re-TURB were excluded because the presence of HGT1 BC at second resection has shown to be strongly associated with progression and an independent adverse prognostic factor of progression [6].

The follow-up schedule included cystoscopy and urine cytology every 3 months for the first two years, every 6 months thereafter until 5 years, and then yearly, while upper tract imaging scans were performed yearly.

Variable of interest and other variables

Patients were stratified into risk groups according to the 2021 new EAU NMIBC prognostic factor risk groups model using the EAU risk group calculator (available at www.nmibc.net). The primary outcome was the accuracy of the EAU updated prognostic factor risk group model in predicting the disease progression in HGT1 patients treated with intravesical BCG immunotherapy. The secondary outcome was the evaluation of predictors of progression in this setting of patients.

Included variables in the analysis were age, gender, smoking status, multifocality and size of the tumor, presence of CIS, and LVI at final histology. Progression was defined as the diagnosis of muscle-invasive disease, either at TURBT or at the time of cystectomy, N+, or M + disease during the follow-up.

Statistical analysis

Categorical variables were reported as frequencies and proportions; continuous variables were reported as median and interquartile ranges (IQR). Patient groups were compared with chi-squared tests for categorical variables, while the Mann-Whitney test was used for the continuously coded variables. Kaplan-Meier (KM) method was used to estimate progression-free survival (PFS). Log-rank tests were applied for pair-wise comparison of survival estimates. Univariable and multivariable Cox regression models were fitted to evaluate the correlation between independent variables and the risk of progression. The accuracy of the prognostic factor risk groups model in predicting progression was assessed using Harrell's concordance index (c-index).

All statistical analyses were performed using Stata/SE, version 17 (Stata Corp. LP, College Station, TX, USA). All tests were two-sided, and statistical significance was set at <0.05.

Results

Patient characteristics are summarized in Table 1. The median age was 71 years (IQR 65-78), and most patients (N=737, 80.1%) were male.

According to the 2021 new EAU NMIBC prognostic factor risk groups, 179 (19.5%) patients were classified as VHR, while 741 (80.5%) as HR.

With a median follow-up of 51 months (IQR 41-75), 239 (25.6%) patients progressed, median time to progression was 46 months (IQR 37-58); PFS was 97.7% (95% confidential interval [CI] 96.5-98.5), 79.0% (95% CI 75.6-81.9) and 68.2% (95% CI 63.9-72.1) at 1, 4 and 5 years, respectively.

Considering only patients at VHR, PFS at 1, 4 an 5 years were 97.1% (95% CI 93.2-98.8); 69.6% (95% CI 60.7-76.9.6) and 59.9% (95% CI 49.8-68.6), respectively.

Furthermore, on KM analysis patients at VHR had significantly worse PFS rates compared to those at HR (p<0.001) (Figure 1). The c-index of EAU NMIBC prognostic factor risk groups for progression was 0.55.

Table 2 reports the results of the univariable and multivariable analyses of prognostic factors for progression.

Tumor >3cm (hazard ratio (HR) 2.14, 95% CI 1.58−2.91, P<0.001), multifocality (HR 1.40, 95% CI 1.08−1.80, P=0.009), presence of CIS (HR 1.80, 95% CI 1.31−2.48, P<0.001) and LVI (HR 1.41, 95% CI 1.02−2.96, P=0.034) were predictors of progression on univariable regression analysis, as well as belonging to the VHR group (HR 1.70, 95% CI 1.27−2.26, P<0.001). On the contrary, age > 70 years was not a predictor of progression (HR 1.01, 95% CI 0.78−1.30, P=0.938).

Furthermore, on multivariable regression model size >3 cm (HR 2.07, 95% CI 1.52−2.81, P<0.001), multifocality (HR 1.34, 95% CI 1.04−1.74, P=0.023), presence of CIS (HR 1.75, 95% CI 1.27−2.40, P=0.001) and LVI (HR 1.50, 95% CI 1.08−2.08, P=0.015) remained independent predictors of progression.

According to the results of the Cox regression model, we tested the accuracy of a new prognostic factor risk groups model excluding the variable “age >70 years” from the additional clinical risk factors and adding the variable LVI (Figure 2). The c-index for progression of this new scoring model was 0.56 (HR 1.61 95% CI 1.25−2.08, P<0.001).

Discussion

In this multicentric retrospective study, we investigated the accuracy of the recently introduced EAU Prognostic Factor Risk Group (i.e., 2021 EAU NMIBC scoring model) in predicting progression in a highly selected large cohort of HGT1 patients who underwent Re-TURB and BCG intravesical therapy. Furthermore, we identified clinical factors that were independently associated with progression.

First, we found that patients classified as VHR are more likely to progress to MIBC than HR patients, with a c-index of 0.55.

Until recently, the EAU stratification into risk groups was based on 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 [7]. However, these tables were based on a series of patients diagnosed and treated more than 40 years ago. Indeed, several scoring systems were subsequently proposed for selected patients [8,9]. A model designed to predict recurrence and progression in a BCG-treated population was presented by the Club Urologico Español de Tratamiento Oncologico

(CUETO); however, the scheme of BCG instillations was different from that suggested by the current guidelines [10].

An update of the EAU Prognostic Factor Risk Group was based on an IPD meta-analysis in primary patients and provided the calculation of their progression scores. Sylvester et al. reported a risk of progression at 5 years for patients at VHR of 40%, which is in line with our findings' estimates [11]. Of note, Lobo et al. reported a significantly lower risk of progression in VHR patients with BC treated with BCG, suggesting that treatment with BCG reduced the discriminative ability of the 2021 EAU prognostic factor risk groups for predicting progression, which appears to be overestimated in these patients [12]. The relatively high risk of progression in our population, despite BCG therapy, could be explained by the exclusive presence in the cohort of patients with HGT1 BC.

An accurate prediction of the risk of progression is the basis for optimal clinical decision-making in high-risk patients. Indeed, patients who might benefit from an immediate RC should be identified and counselled accordingly, since such an invasive approach has shown to improve oncological outcomes in this selected cohort [13]. Indeed, some authors suggested that RC after progression to muscle-invasive disease has an unfavorable prognosis and worse outcomes than immediate RC[14]. On the other hand, RC has relevant morbidity and mortality rates [15], as well as a significant impact on patients' quality of life. Consequently, a proper selection of a candidate for immediate RC is mandatory to avoid the overtreatment of NMIBC patients [16].

Many clinical and pathological factors have been studied as predictors of progression in patients with NMIBC.

Gontero et al. identified the dimension of the tumor > 3cm, presence of CIS, and age >70 years as independent predictors of progression in a large cohort of HGT1 BC patients; however, only 38.2% of the patients received maintenance course with BCG and the 54.6% did not undergo second resection [17].

Similarly, Hurle et al. reported that patients aged >70, with the presence of a multifocal tumor or who developed an early recurrence were more likely to progress to MIBC disease [18].

The main strength of our study is the exclusion from the analysis of those patients who did not receive BCG, did not undergo a second resection and those presenting with an HGT1 disease at Re-TURB, leading to a highly selected population of HGT1 BC patients.

Nevertheless, the results reported in our study are comparable with those reported by Gontero.

The impact of age on BC oncological outcomes is widely debated [19]. Some authors suggested that BCG may be less effective in elderly patients [20]. However, in our population, age over 70 years has not been shown to be a predictor of progression.

Of note, BCG has also been shown to be effective in the case of CIS, although its efficacy may vary depending on the CIS subtype[21].

Accordingly, we developed a new prognostic risk groups model that follows the approach of the guidelines but excludes age as an additional risk factor and includes in the VHR group all the patients with LVI, leading to similar discriminatory capacity yet simplifying the classification process.

The pretreatment neutrophil-to-lymphocyte ratio was recently related to recurrence and progression risk in NMIBC patients [22].

In an analysis of outcomes and prognostic factors in 15,215 HGT1 BC patients, deep lamina propria invasion had the most significant negative impact on oncological outcomes [23]. Indeed, T1 substaging has been demonstrated to be of prognostic value in several retrospective cohort studies [24]; however, although guidelines recommend its use, the optimal substaging system has not yet been identified [25].

Unfortunately, these data are unavailable for our population; new studies integrating these findings with clinical risk factors are needed since they could lead to ~~even~~ better patient selection.

To the best of our knowledge, this is the largest study evaluating the 'new' risk group definitions in a selected population of VHR NMIBC patients undergoing TURB plus BCG intravesical therapy. Our study shows that more than 70% of patients did not progress to muscle-invasive disease, thus confirming the benefit of BCG therapy for these patients.

Our study is not devoid of limitations. Firstly, given its retrospective nature, it is impossible to entirely exclude the impact of unmeasured confounding factors.

Secondly, some prognostic factors potentially correlated with worse outcomes were not analyzed, such as Type 2 diabetes mellitus, preoperative inflammatory markers and body mass index [26-28].

Considering the median follow-up of 51 months, in interpreting the data it should be regarded that survival analysis at five years could be underpowered and prone to biases.

Furthermore, due to the multicenter design of the study, there could have been surgical and pathological heterogeneity related to a large number of involved surgeons and uropathologists; however, in all centers, slides were reviewed by dedicated uro-pathologists, and surgical procedures were performed with the same approach.

Lastly, we could not assess the impact of possible therapeutic strategies alternatives or in addition to BCG [29].

Our intention was to evaluate the accuracy of the updated EAU risk groups in a real-life population treated according to the EAU guidelines. Future perspectives might encompass the use of artificial intelligence to refine current predicting models [30].

Conclusions

According to our results, patients classified at VHR according to the 2021 EAU NMIBC scoring model are more likely to develop a disease progression than those at HR. However, the accuracy of this model appears to be suboptimal in patients that underwent Re-TURB and intravesical BCG therapy. New prospective randomized trials are needed to identify those patients who might benefit from a more radical approach.

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All authors contributed to the manuscript and read and approved the final version of the manuscript.

TABLES

Table 1: Characteristics of patients for the overall cohort		
		Overall population (n= 920)
Follow-up, median (IQR)		51 (41-75)
Age, median (IQR)		71 (65-78)
Age stratification , n (%)	<70	447 (48.6)
	>70	472 (51.4)
Gender, n (%)	Male	737 (80.1)
	Female	183 (19.9)
Smoking status, n (%)	Never smoke	270 (29.4)
	Active smokers or former	650 (70.6)
Multiple papillary tumours, n (%)	No	564 (61.3)
	Yes	356 (38.7)
Tumor size, n (%)	≤3 cm	348 (37.9)
	>3 cm	571 (62.1)
Concomitant CIS, n (%)	No	809 (87.9)
	Yes	111 (12.1)
LVI	No	781 (84.9)
	Yes	139 (15.1)
2021 EAU prognostic factor risk groups	High risk	741 (80.5)
	Very high risk	179 (19.5)

IQR: interquartile range; CIS: Carcinoma in situ; LVI: Limphovascular invasion; EAU: European Association of Urology;

Table 2: Univariable and multivariable Cox regression of time to progression

	Univariable			Multivariable		
	HR	CI 95%	p-value	HR	CI 95%	p-value
Age <70, >70	1.01	0.78 - 1.30	0.938	1.04	0.80 - 1.34	0.755
Gender Male, Female	0.97	0.70 – 1.33	0.857	0.90	0.65 – 1.25	0.539
Smoking status Never, former or smoker	1.03	0.78 - 1.36	0.817	0.88	0.66 – 1.17	0.407
No. Of tumors Single, multiple	1.40	1.08 - 1.80	**0.009**	1.34	1.04 – 1.74	**0.024**
Tumor dimension <3cm, >3cm	2.14	1.58 - 2.91	**>0.001**	2.09	1.53 – 2.84	**>0.001**
Concomitant CIS No, Yes	1.80	1.31 - 2.48	**>0.001**	1.80	1.29– 2.49	**>0.001**
LVI No, Yes	1.41	1.02 - 1.96	**0.034**	1.49	1.07 – 2.07	**0.017**
2021 EAU prognostic factor risk groups HR, VHR	1.64	1.26 - 2.12	**>0.001**			

HR: Hazard ratio; CIS: Carcinoma in situ; LVI: Limphovascular invasion; EAU: European Association of Urology; HR: high risk; VHR: Very high risk

TITLES OF FIGURES

Figure 1.— Kaplan-Meier analysis for progression-free survival stratified according to the 2021 new EAU NMIBC prognostic factor risk groups model.

Figure 2.— Kaplan-Meier analysis for progression-free survival stratified according to a new prognostic risk groups model that follows the approach of the guidelines based on the results of the Cox regression model. Age>70 years was excluded as an additional risk factor while all patients with LVI were included in the VHR group.