

# Risk factor assessment in high-risk, bacillus Calmette–Guérin-treated, non-muscle-invasive bladder cancer

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**Objective:** To assess the risk factors associated with recurrence, progression and survival in high-risk non-muscle-invasive bladder cancer (NMIBC) patients treated with bacillus Calmette–Guérin (BCG) and validate the European Organization for Research and Treatment of Cancer (EORTC) and Spanish Urological Club for Oncological Treatment (CUETO) scores.

**Patients and methods:** We retrospectively analyzed all BCG-treated NMIBC patients from 1998 to 2012. Multiple variables were tested as risk factors for recurrence-free survival and progression-free survival (PFS). Variables included age, sex, grade, stage, tumor size, number of tumors, carcinoma in situ (CIS), recurrence status, BCG strain used, smoking status, use of re-staging transurethral resection and use of single immediate postoperative instillation. We also tested the accuracy of EORTC and CUETO scores in predicting recurrence and progression.

**Results:** Overall, 123 patients were analyzed. Median (interquartile range) follow-up was 49 months. The 5-year overall survival, cancer-specific survival, recurrence-free survival and PFS were 75.0%, 89.3%, 59.4% and 79.2%, respectively. On univariate analysis, multiple tumors ( $\geq 3$ ), concomitant CIS and smoking influenced recurrence. Regarding progression, multiple tumors, concomitant CIS and Connaught strain (vs Tice) negatively influenced PFS on univariate and multivariate analyses were independent prognostic factors. CUETO scores were accurate, with a slight overestimation, while EORTC score was not predictive of recurrence or progression.

**Conclusion:** In this study, CIS and tumor multiplicity were unfavorable predictors of recurrence and progression in patients with NMIBC receiving BCG. CUETO model was superior to EORTC risk tables in predicting recurrence and progression in our BCG-treated patient population. Nonetheless, both scores overestimated recurrence and progression rates. Prospective trials are needed to validate our findings.

**Keywords:** BCG, bladder cancer, progression, recurrence

## Introduction

Bladder cancer is by far the most common malignancy of the urinary tract. In Europe, it represents the 4th most common neoplasia in men and the 14th in women. In the European Union, its incidence is estimated at 123,000 cases per year, with a yearly mortality rate of over 40,000 people.<sup>1</sup> Beyond the medical burden, bladder cancer also represents an important economic issue, being the most expensive cancer per case from diagnosis to death.<sup>2</sup> Two-thirds of new bladder cancers are non-muscle-invasive bladder carcinomas (NMIBCs).<sup>3</sup>

High-risk NMIBC, such as pT1G3 and carcinoma in situ (CIS), with unfavorable long-term outcome, represents a therapeutic dilemma with two main treatment options available: intravesical bacillus Calmette–Guérin (BCG) instillations for a conservative approach and radical cystectomy.<sup>4</sup> The first option exhibits tolerability issues<sup>5,6</sup> and

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might decrease the chances of healing if treatment fails.<sup>7,8</sup> Furthermore, BCG production has recently shown its limits, with worldwide BCG shortage. Radical cystectomy, on the other hand, is a major surgery associated with high complication rates and could represent overtreatment for many NMIBC patients. Various prognostic factors have been described, and scoring models have been developed to predict the risk of recurrence and progression, in order to offer the best possible treatment to NMIBC patients.<sup>9,10</sup>

The aim of this study was to explore risk factors for NMIBC recurrence and progression and validate the European Organization for Research and Treatment of Cancer (EORTC)<sup>9</sup> and Spanish Urological Club for Oncological Treatment (CUETO)<sup>10</sup> scoring systems on an external cohort of high-risk patients who received BCG as the initial treatment and discern potential new risk factors of poor outcome.

## Patients and methods

After obtaining approval from the local ethics committee, we retrospectively reviewed the clinical and pathologic features of 200 successive patients treated with BCG instillations in the Department of Urology, Cliniques Universitaires de Bruxelles, Hôpital Erasme-ULB, from January 1998 to December 2012. Patients gave informed consent to use their data for this study. The following data were included: age, sex, pathologic grade and stage, tumor size, number of tumors, presence of CIS, recurrence status, BCG instillations scheme used, BCG strain used, smoking status, use of restaging transurethral resection (re-TUR), use of single immediate postoperative instillation of chemotherapy (SIPIC), and EORTC<sup>9</sup> and CUETO<sup>10</sup> scores. Adverse events and exact cycle duration were recorded, but will be described in detail separately. The evaluated end-points were overall survival, cancer-specific survival (CSS), recurrence-free survival, progression-free survival and muscle-invasive free survival (MIFS).

Recurrence was defined as follows: reappearance of tumor (any grade and any stage) during follow-up. Progression was defined as progression to muscle-invasive disease, development of lymph node (N+) disease or distant metastasis (M1).<sup>11</sup> Exclusion criteria were the following: history of muscle-invasive urothelial cancer, of pelvic irradiation and previous BCG instillations. re-TUR was proposed to patients in whom the primary resection was macroscopically incomplete or no muscle tissue was found on pathologic examination of the transurethral resection (TUR) specimen.

## Instillation scheme

Induction scheme of six-weekly instillations started 2–6 weeks after the initial TUR or re-TUR. Full dose of BCG

was instilled with a Connaught strain (Immucyst-Sanofi-Pasteur® 81 mg) from 1998 to 2006, followed by Tice strain (Oncotice-MSD® 60 mg) from 2006 to 2012. Cystoscopy and cytology, eventually associated with bladder biopsies, were performed after the induction cycle. If no residual tumor was found, maintenance instillations could be offered in a scheme of three-weekly instillations every 3 months for a maximum duration of 3 years. NMIBC found after induction instillations was not considered as recurrence, but as persistence, and six new BCG induction instillations were generally offered. Time zero was then reset at the day of the second TUR, and the first induction instillations were not counted in the instillation scheme.

## Follow-up

During the first 2 years, patients were offered cystoscopy and cytology every 3 months and during the following 3 years, cystoscopy and cytology were offered every 6 months and yearly thereafter.

## Statistical analysis

Kaplan–Meier survival method and a stepwise forward Cox logistic regression model were used to compare risk factors for overall survival, CSS, recurrence-free survival, progression-free survival and MIFS on univariate analysis (log-rank test). Variables analyzed included age (<60, 60–70, >70), sex, pathologic grade (G1, G2, G3) and stage (pTa vs pT1), tumor size (<3 vs >3 cm), number of tumors (<3 vs ≥3), presence of CIS, recurrence status (primary vs recurrent <1/year vs recurrent ≥1/year), BCG strain used (Tice vs Connaught), smoking status (never, stopped vs active), use of re-TUR and use of SIPIC. The actual recurrence and progression rates across EORTC and CUETO categories were compared to the expected rates based on such nomograms. We considered *p* values <0.05 as statistically significant, and statistically significant risk factors of interest were evaluated in multivariate analysis. All statistical analyses were carried out with Medcalc® version 13.2.2 for Windows® (Medcalc Software, Oostende, Belgium).

## Ethics

This study was approved by the Local Ethics Review Board at the Cliniques Universitaires de Bruxelles, Hôpital Erasme-ULB under approval number 021/406.

## Results

Overall, we identified 200 patients treated with BCG. Seventy-seven were excluded from the analysis, as 35 had history of former BCG instillations, 11 of muscle-invasive

urothelial neoplasia, 5 of pelvic irradiation, 1 had BCG instillations on the upper urinary tract and 2 due to missing oncologic data. Twenty-three patients had CIS only and were excluded as many evaluated factors did not apply (number, size, stage, EORTC and CUETO scores). One hundred and twenty-three patients were finally retained for the analysis. Characteristics of the population are shown in Table 1. Mean (interquartile range) follow-up was 49 (28–81) months and the median was 56 months (range 2–181). Survival statistics of the global cohort are shown in Table 2. In this study, 42/123 (32%) had a recurrence, 19/123 (17%) had a progression and 9/123 (7%) died during the follow-up available. Globally, 95.9% of patients were treated with at least a six-weekly induction course; 69.9% had some sort of maintenance therapy and 28.9% had a maintenance therapy of over 1 year.

Results from univariate and multivariate analyses are shown in Tables 3 and 4, respectively. Concerning recurrence, univariate analysis showed significant correlation

with the number ( $\geq 3$ ), CIS and smoking (even stopped). In multivariate analyses, concomitant CIS and tumor multiplicity showed significant correlation (Table 4). When exploring progression to muscle-invasive disease, a significant correlation with number of tumors ( $\geq 3$ ), concomitant CIS and type of strain (Connaught) was found on univariate analysis (all  $p < 0.05$ ). In multivariate analyses, concomitant CIS and tumor multiplicity showed significant correlation to the risk of progression (Table 5).

EORTC risk tables did not distinctly separate patients for recurrence (Figure 1) and progression (Figure 2), but only for MIFS ( $p < 0.05$ ). Recurrence rates for all categories, as well as progression rates for the highest risk category (EORTC progression score  $\geq 14$ ) were significantly lower than those described by EORTC.<sup>9</sup>

CUETO scoring model significantly separated patients into distinctive groups for recurrence ( $p < 0.01$ ; Figure 3), progression ( $p < 0.05$ ) and MIFS ( $p < 0.05$ ; Figure 4). Recur-

**Table 1** Population characteristics (N=123)

Age (years)		Tumor size, mm	
Mean–median (extremes)	68–69 (37–97)	>30	37 (30%)
<b>Sex</b>		≤30	86 (70%)
Men	109 (89%)	<b>Recurrence</b>	
Women	14 (11%)	Primary	78 (63%)
<b>Histologic stage</b>		>1 recurrence/year	29 (24%)
Ta	14 (11%)	≤1 recurrence/year	16 (13%)
Ta+CIS	7 (6%)	<b>Smoking status</b>	
T1	61 (50%)	Active	61 (49%)
T1+CIS	41 (33%)	Stopped	32 (26%)
		Never smoked	29 (24%)
<b>Histologic grade (WHO 1973)<sup>24</sup></b>		Unknown	1 (1%)
G1	8 (7%)	<b>SIPIC</b>	24 (19%)
G2	19 (15%)	<b>re-TUR</b>	27 (22%)
G3	96 (78%)	<b>BCG strain, mg</b>	
<b>Histologic grade (WHO 2004)<sup>25</sup></b>		Tice 60	102 (83%)
Low	15 (12%)	Connaught 81	21 (17%)
High	108 (88%)		
<b>Number of tumors</b>			
Single	70 (57%)		
Multiple	53 (43%)		

**Abbreviations:** BCG, bacillus Calmette–Guérin; CIS, carcinoma in situ; re-TUR, restaging transurethral resection; SIPIC, single immediate postoperative instillation of chemotherapy; WHO, World Health Organization.

**Table 2** Overall survival statistics

	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years
OS	95.7%	91.9%	87.4%	80.0%	74.9%	70.0%	68.0%	62.4%
CSS	99.3%	97.6%	95.7%	92.3%	89.2%	87.3%	84.8%	84.8%
RFS	82.7%	73.9%	65.7%	60.0%	58.6%	56.9%	54.7%	54.7%
PFS	92.1%	89.0%	85.4%	83.3%	83.3%	81.6%	81.6%	81.6%
BIS	92.8%	90.4%	86.6%	84.4%	81.5%	79.9%	79.9%	79.9%
Nb at risk	130	118	92	72	54	40	31	21

**Abbreviations:** BIS, bladder in situ; CSS, cancer-specific survival; Nb, number; OS, overall survival; PFS, progression-free survival; re-TUR, restaging transurethral resection; RFS, recurrence-free survival.

**Table 3** Univariate analysis of risk factors

Factor		Recurrence				Progression		
		Nb (%)	OR	95% CI	p	OR	95% CI	p
Sex	Male	109 (89)	1.33	0.53–3.35	NS	1.15	0.29–4.60	NS
	Female	14 (11)	0.75	0.30–1.90		0.87	0.22–3.49	
Age (years)	<60	26 (21.1)	Ref	Ref	Ref	Ref	Ref	Ref
	60–70	37 (30.1)	1.77	0.77–4.07		1.87	0.55–6.39	
	>70	60 (48.8)	1.59	0.75–3.39		NS	3.08	
Grade	1	10 (8.1)	Ref	Ref	Ref	Ref	Ref	Ref
	2	27 (22.0)	0.44	0.14–1.37		0.57	0.19–1.72	
	3	86 (69.9)	0.98	0.35–2.73		NS	1.75	
Number	<3	97 (78.9)	0.37	0.17–0.81	<0.01	0.38	0.13–1.14	<0.05
	≥3	26 (21.1)	2.70	1.24–5.86		2.61	0.88–7.75	
Size (mm)	<30	86 (69.9)	0.98	0.49–1.95	NS	1.12	0.41–3.02	NS
	>30	37 (30.1)	1.02	0.51–2.03		0.90	0.33–2.42	
CIS	No	75 (61.0)	0.48	0.26–0.91	<0.05	0.33	0.13–0.84	<0.05
	Yes	48 (39.0)	2.07	1.09–3.92		3.02	1.18–7.69	
Stage	Ta	22 (18)	0.57	0.28–1.19	NS	–	–	<0.05
	T1	101 (82)	1.74	0.84–3.61		–	–	
Recurrence	Primary	78 (63.4)	0.76	0.40–1.43	NS	0.83	0.33–2.09	NS
	Recurrent	45 (36.6)	1.31	0.70–2.47		1.21	0.48–3.06	
	<1/year	29 (23.6)	0.95	0.46–1.94		0.91	0.31–2.65	
	>1/year	16 (13.0)	2.10	0.79–5.59		NS	1.77	
Strain	Tice	87 (70.7)	1.18	0.61–2.30	NS	0.41	0.15–1.14	<0.05
	Connaught	36 (29.3)	0.85	0.44–1.65		2.43	0.88–6.68	
SIPIC	No	100 (81.3)	1.21	0.54–2.72	NS	1.87	0.58–6.02	NS
	Yes	23 (18.7)	0.83	0.37–1.86		0.53	0.17–1.72	
Smoking	Never	30 (24.4)	Ref	Ref	<0.01	Ref	Ref	NS
	Stopped	32 (26.0)	2.88	1.18–7.03		2.09	0.59–7.35	
	Active	61 (49.6)	1.07	0.52–2.20		0.93	0.31–2.77	
re-TUR	No	96 (78.0)	0.73	0.34–1.54	NS	0.36	0.12–1.10	<0.05
	Yes	27 (22.0)	1.38	0.65–2.92		2.74	0.91–8.29	
	0–4	24 (19.5)	Ref	Ref		Ref	Ref	
CUETO score	5–6	40 (32.5)	4.21	1.84–9.64	<0.01	–	–	<0.05
	7–9	40 (32.5)	6.22	2.67–14.52		0.44	0.16–1.23	
	≥10	19 (15.5)	9.24	3.27–26.14		2.27	0.81–6.34	
EORTC score	0–4	26 (21.1)	Ref	Ref	Ref	Ref	Ref	Ref
	5–9	85 (69.1)	1.57	0.76–3.24		0.37	0.14–0.97	
	≥10	12 (9.8)	1.78	0.57–5.63		NS	2.73	

**Abbreviations:** CIS, carcinoma in situ; CUETO, Spanish Urological Club for Oncological Treatment; EORTC, European Organization for Research and Treatment of Cancer; Nb, number; NS, not significant; OR, odds ratio; Ref, reference; re-TUR, restaging transurethral resection; SIPIC, single immediate postoperative instillation of chemotherapy.

**Table 4** Multivariate analysis of risk factors for NMIBC recurrence

Factor	HR	95% CI	p-value
Number of tumors ≥3	2.46	1.31–4.65	<0.01
CIS	1.85	1.00–3.44	0.05

**Abbreviations:** CIS, carcinoma in situ; HR, hazard ratio; NMIBC, non-muscle-invasive bladder cancer.

**Table 5** Multivariate analysis of risk factors for NMIBC progression

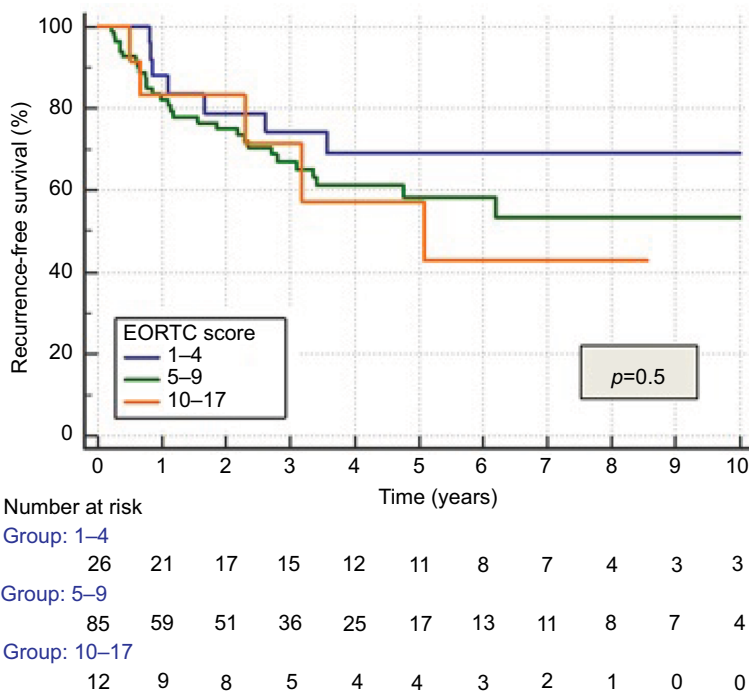
Factor	HR	95% CI	p-value
Number of tumors ≥3	2.49	1.00–6.17	0.05
CIS	2.9	1.15–7.38	<0.05

**Abbreviations:** CIS, carcinoma in situ; HR hazard ratio; NMIBC, non-muscle-invasive bladder cancer.

rence rates matched the lower limits described by CUETO, except for the lowest risk group (CUETO recurrence score <5), where we found even lower rates. MIFS was 100% for patients at the lowest risk of progression. Progression rates for patients at higher risk corresponded to the lower limit described by CUETO.<sup>10</sup>

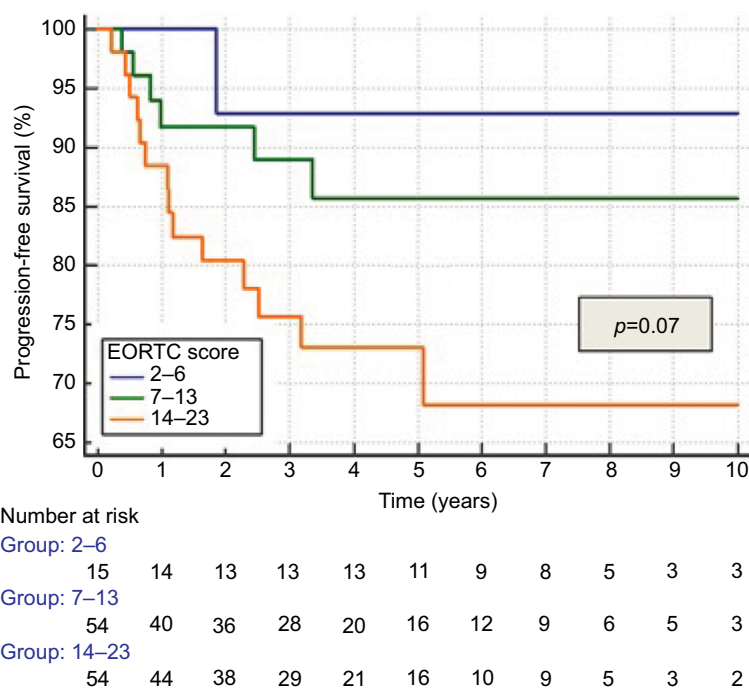
## Discussion

The two most widely used NMIBC scoring systems, EORTC and CUETO, were applied to this retrospective, BCG-treated cohort to determine which model could be preferred as a prognostic model in patients with NMIBC.



Recurrence rates (%)			
EORTC score	1 year	2 years	3 years
1-4	12.0	21.0	31.0
5-9	17.9	24.9	41.7
≥10	16.7	16.7	42.9
Total	16.5	23.3	39.1

**Figure 1** Recurrence according to EORTC score.  
**Abbreviation:** EORTC, European Organization for Research and Treatment of Cancer.

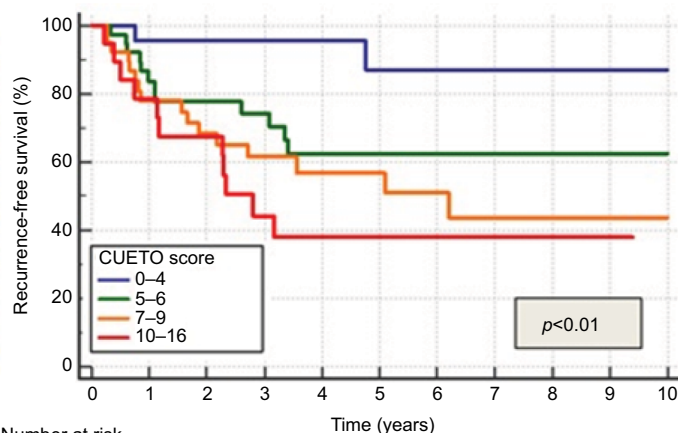


Progression rate (%)			
EORTC score	1 year	2 years	5 years
2-6	0.0	7.1	7.1
7-13	8.3	8.3	14.3
≥14	11.5	19.6	26.9
Total	8.7	13.4	19.0

**Figure 2** Progression according to EORTC score.  
**Abbreviation:** EORTC, European Organization for Research and Treatment of Cancer.

EORTC risk tables are mainly based on non-BCG-treated patients (<200 patients were treated by BCG and no maintenance regimen was administered).<sup>9</sup> They were not adequate in our population due to overestimation and poor discrimination of recurrence and progression rates. This overestimation is consistent with the conclusions reported by large multi-institutional studies.<sup>12-14</sup>

CUETO scoring model, especially designed for BCG-treated patients, was more accurate than EORTC model in our BCG-treated cohort to discriminate patients at risk of recurrence and progression. CUETO score still overestimated recurrence and progression rates, but to a lesser extent than EORTC score. Our recurrence and progression rates are comparable to the lower limits described by the

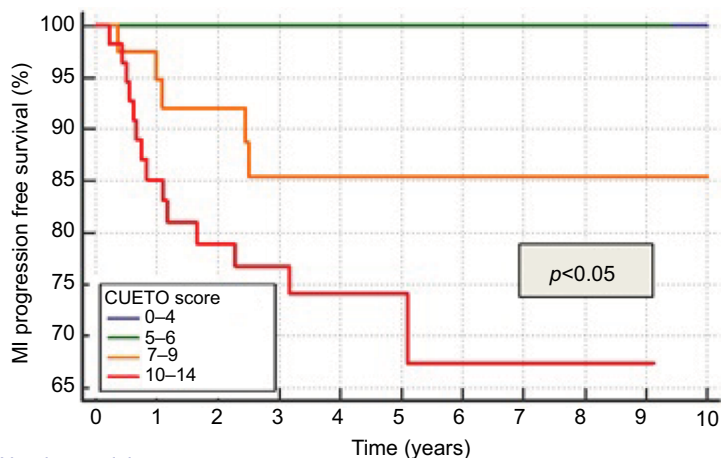


Recurrence rate (%)			
CUETO score	1 year	2 years	5 years
0-4	4.3	4.3	13.0
5-6	16.2	22.2	37.5
7-9	22.2	31.6	43.2
≥10	21.4	32.6	62.1
Total	16.5	23.3	39.1

Number at risk

Group	0	1	2	3	4	5	6	7	8	9	10
Group: 0-4	24	21	18	13	13	9	8	7	4	3	2
Group: 5-6	40	28	25	19	14	11	7	6	4	3	3
Group: 7-9	40	26	21	17	12	10	7	5	4	3	2
Group: 10-16	19	14	12	7	2	2	2	2	1	1	0

**Figure 3** Recurrence according to CUETO score.  
**Abbreviation:** CUETO, Spanish Urological Club for Oncological Treatment.



MI progression rate (%)			
CUETO score	1 year	2 years	3 years
0-4	0.0	0.0	0.0
5-6	0.0	0.0	0.0
7-9	5.2	8.0	14.6
≥10	14.9	21.1	25.9
Total	8.7	12.5	16.8

Number at risk

Group	0	1	2	3	4	5	6	7	8	9	10
Group: 0-4	16	14	14	14	11	9	8	5	3	3	
Group: 5-6	9	7	6	5	5	4	3	2	2	2	0
Group: 7-9	40	35	31	23	19	17	14	11	5	5	5
Group: 10-14	58	42	37	29	18	12	6	5	4	1	0

**Figure 4** Progression according to CUETO score.  
**Abbreviations:** MI, muscle invasive; CUETO, Spanish Urological Club for Oncological Treatment..

CUETO group, which is consistent with the results reported by Xylinas et al.<sup>13</sup> CUETO score was able to discriminate our BCG-treated patients in distinct risk groups. It could be particularly helpful for patients at very low risk of recurrence and progression in individualizing patient treatment and follow-up. Not a single CUETO low-risk patient progressed to muscle-invasive disease. In this study, patients at highest

risk of progression had a 5-year progression rate of around 25% to muscle-invasive disease. This value cannot justify aggressive (radical cystectomy) primary treatment in all highest risk patients and most of them can safely be treated with intravesical BCG instillations.

Although CUETO scoring model has been found to be superior to EORTC in defining the risk of recurrence and

progression in this study, there are several publications comparing both scores and reflecting not only some identical interpretations, but also different results with controversial discussions in predicting recurrence or progression in NMIBC patients.<sup>13–16</sup> The discriminative power of both scoring models, in terms of recurrence and progression, is quite poor when applied to external cohorts.<sup>13–16</sup> The question is challenging due to the basic heterogeneous characteristics of patients in such studies. Cambier et al confirmed heterogeneous prognosis in NMIBC high-risk patients treated with 1–3 years of maintenance BCG.<sup>17</sup> Unfortunately, as CIS patients were excluded from that study, we could not apply their nomogram to our patient population. There is, therefore, an urgent need to find more accurate ways to define very high-risk patients who might be candidates for alternative treatment or early cystectomy.

Recently, Gontero et al, in a large retrospective multicenter study, reported that a subgroup of pT1G3 patients with age >70 years, tumor size >3 cm and concomitant CIS had a higher risk of progression.<sup>18</sup> In our retrospective population, age (>70 years), concomitant CIS and number of tumors ( $\geq 3$ ) were the risk factors associated with progression in multivariate analysis (tumor size had no significant impact on outcome). If all three risk factors are present, more aggressive treatment options should be considered.

Trying to improve outcome prediction, we further analyzed other variables not included in the scoring systems. For example, smoking status was significantly associated with recurrence on univariate analysis. Patients who had stopped smoking had surprisingly higher recurrence rates than active and never smokers. As a well-known risk factor for developing bladder cancer,<sup>4</sup> smoking status should, whenever possible, be reported in NMIBC patients. In univariate analysis, Connaught strain was adversely associated with MIFS and CSS. In multivariate analysis, Connaught strain stayed the only factor significantly associated with worse CSS. These results could, at least partially, be explained by the fact that Connaught-treated patients represent an older cohort (1998–2006) than Tice-treated patients (2006–2012). Indeed, Connaught-treated patients received significantly less SIPIC, although SIPIC did not significantly influence patient outcome in our population. Nonetheless, we must be cautious with any misinterpretation of this result, as contrasting results were recently reported in a prospective randomized trial where Connaught strain was superior to Tice.<sup>19</sup> The effect of the BCG strain used needs to be further evaluated and should be explicitly specified in BCG-related studies.

In the future, especially in times of BCG shortage, further risk factors that were not evaluated in this study should be studied to help stratifying NMIBC patients and guide clinical decision making more accurately. Potential candidates are more precise details in pathologic diagnosis, such as lymphovascular involvement<sup>20</sup> and extent of lamina propria invasion,<sup>21</sup> evaluation of circulating tumor cells<sup>22</sup> and next-generation sequencing with determination of genetic markers such as FGFR-3 (favorable) and Tp53 (unfavorable).<sup>23</sup>

The limits of this study are notably its retrospective design and the small sample size. All patients were not managed with a standardized treatment regimen following current standards, as in a real-life setting. It should be noted that the EORTC tables were designed for all stages of NMIBC, and not only for those receiving BCG, making the comparison of our results to those of the EORTC highly biased. Pathologic slides, although initially examined by a senior pathologist, were not reviewed for the purpose of this study. All patients, however, received BCG instillations after initial TUR. Also, 95.9% of patients received at least a six-weekly induction course and 69.9% received some sort of maintenance therapy. Nonetheless, only 28.9% received instillations for an optimal duration over 1 year. Nevertheless, our recurrence and progression rates correspond to the lower limits described by the CUETO scoring model. The actual recurrence and progression rates of patients treated with current standards of care are likely to be even lower, making the overestimation<sup>13–18</sup> of EORTC and CUETO scores even more important.

## Conclusion

High-risk NMIBC patients remain a urologic challenge. Current scoring systems, CUETO and EORTC, show low discrimination ability for very high-risk patient selection. CUETO scoring system overestimates rates of recurrence and progression in adequately treated high-risk NMIBC patients, but to a lesser extent than the EORTC scoring system. In this study, the patients at highest risk of progression were older (>70 years), had multiple tumors ( $\geq 3$ ) and concomitant CIS, and might be candidates for early cystectomy. New accurate prognostic markers to define very high-risk NMIBC patients and prospective trials are mandatory and should contribute to optimize existing predictive models.

## Disclosure

The authors report no conflicts of interest in this work.

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