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Research Article

Utility of EORTC and CUETO Scoring Models in the Estimation of Recurrence and Progression of Non-Muscle-Invasive Bladder Cancer

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Abstract

Objectives: Worldwide, Non-Muscle-Invasive Bladder Cancer (NMIBC) patients are characterized by a high rate of recurrence and progression highlighting the need for a valuable prognostic estimation for better management of this disease. Thus, the present preliminary study was planned to evaluate the validation of the European Organization for Research and Treatment of Cancer (EORTC) and the Spanish Urological Club for Oncological Treatment (CUETO) risk tables to predict recurrence and progression in Moroccan patients with NMIBC.

Methods: A total of 56 NMIBC patients that have undergone transurethral resection of bladder tumor (TURBT), between January 2017 and May 2021, were recruited. The recurrence and progression rates at 1 and 5 years were calculated for each patient using EORTC and CUETO scoring models and compared to EORTC and CUETO risk tables. Kaplan-Meier was performed to validate stratification and difference between the four groups obtained. A univariate analysis using the Cox regression test was realized to evaluate the association between prognostic factors with recurrence and progression of the disease.

Results: For the 56 NMIBC patients, the median follow-up duration was 49.68 months. In this cohort, 43 patients had recurrent tumors, and 27 showed progression to an advanced stage and/or grade. At 1-year progression and recurrence rates were higher than the values predicted by the EORTC and CUETO risk tables, while both tables overestimate the long-term risk probabilities of recurrence and progression. Only the CUETO model successfully stratified our patients with statistically significant differences between the four groups of recurrence (p=0.005). Of particular interest, univariate Cox analysis indicated that only prior recurrence rate had a significant effect on both recurrence-free survival (p=0.04) and progression-free survival (p=0.037).

Conclusion: CUETO scoring model is better than EORTC for recurrence stratification in Moroccan patients with NMIBC. Both models overestimate risk in 1-year and underestimate risk in 5-years. A prospective study should be realized in large cohorts to establish an ideal prognosis model for Moroccan NMIBC patients.

Keywords: EORTC, CUETO, recurrence, progression, NMIBC, Morocco

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Bladder cancer (BC) is the eleventh most common cancer worldwide, with more than 573 278 new cases diagnosed in 2020.[1] Approximately 75 % of bladder cancer cases are non-muscle-invasive cancers (NMIBC), and 20% of them progress to muscle-invasive types during patients' lifetimes.[2]

Superficial bladder tumors are a group of tumors characterized by histological and prognostic heterogeneity, including papillary tumors that respect the basement membrane (pTa), Lamina propria (pT1) containing connective tissues between urothelium and detrusor muscle, and carcinoma in situ (CIS), characterized by low coherence and adherence of epithelial cells.[3,4] In this field, the main problems faced by clinicians are the difficulty to compare the efficacy of treatment modalities and proposing unified treatment recommendations.

An updated version of the non-invasive muscle bladder cancer (NIMBC) guidelines was released in 2021 by The European Association of Urology (EAU) to provide practical recommendations on clinical management and to harmonize treatment approaches. Accordingly, patients are stratified into four groups: low-, intermediate-, high- and very high-risk groups, and patients' risk groups can be determined using the European Organization for Research and Treatment of Cancer (EORTC) risk tables and EAU risk group calculator to predict the risk of tumor recurrence and progression after Transurethral resection of Bladder Tumor (TURBT).[5]

In 2006, the EORTC organization proposed a table model to assess the score for Ta-T1 BC and to predict the risk of recurrence and progression in each patient in both the short and long terms. This approach is the most frequently applied and validated model and is based on 6 clinical and pathologic factors: stage, grade, tumor size, number of tumors, previous disease recurrence, and concomitant in situ carcinoma (CIS).[6] The main limitation of the EORTC approach is still the difficulty of predicting the small number of patients treated with BCG.[7,8] Moreover, it was reported that EORTC taboverestimatemate both the recurrence and the progression of BCG-treated patients.[9]

To overcome this limitation, the Spanish Urological Club for Oncological Treatment (CUETO) group has created and validated a scoring model focusing on BCG-treated patients.[10] This approach was developed and validated to predict the short- and long-term risks of recurrence and progression in patients treated with BCG. The CUETO scoring system is based on the evaluation of seven prognostic factors: Age, gender, prior recurrence, number of tumors, tumor stage and grade, and presence of concomitant CIS.[11]

The aim of the present study was to externally validate the risk stratification schemes of EORTC and CUETO scoring models on a cohort of Moroccan patients with NMIBC. The two models were applied to calculate each patient their estimated recurrence and progression rates compared to the real risk of patients to highlight the opportunity to introduce these risks' assessment in the global management of bladder cancer in Morocco.

Methods

Patients

A retrospective study, based on a prospective cohort, was designed to analyze data of 73 patients treated with transurethral resection of a bladder tumor (TUR-BT) at the Urology Department of the Military Hospital of Instruction Mohamed V (MHIMV) in Rabat - Morocco, between the January 2017 and May 2021, with up to 19 years follow-up. The following inclusion criteria were taken into account during the revision process: (a) Patients had to be diagnosed, for the first time, with primary Ta/T1 urothelial bladder tumor or in situ carcinoma, and (b) the grades and stages of tumors were determined and confirmed by histo-pathological reports, (c) follow-up duration of recruited patients was more than 12 months. Patients diagnosed with a muscle-invasive type of bladder cancer (MIBC) were excluded from this study.

The study protocol was approved by the Ethics Committee for Biomedical Research, Faculty of Medicine and Pharmacy of Rabat – Morocco (Ref 82/19), and written informed consents were obtained from all recruited patients.

Follow-up

In this retrospective study, information collected was used to generate a subsequent database that included the clinico-pathological factors used in the elaboration of the EORTC and CUETO models, including sex, age, tumor size (<3 cm or ≥3 cm), number of tumors (single or multiple), the prior recurrence rate, T category, presence of concomitant in situ carcinoma, grade, and intravesical therapy. Cases with pathologically confirmed recurrence were noted in the follow-up database at the time of the first recurrence. Tumors were defined as progressive profiless if they progress into muscle-invasive tumors, metastatic diseases, or from low to high grade.

Recurrence-free survival (RFS) was calculated from the first treatment assignment to the date of the first recurrence or the last follow-up visit. Progression-free survival (PFS) was calculated from the first treatment assignment to the date of the first progression detected, the date of death, or the last follow-up visit.

A recurrence event was defined as the time between the first TURBT treatment and the occurrence of the recurrence or progression. Progression event was accepted athe s initiation of progresion, or death of the patient due to disease progression. Patients, noted without recurrence or progression were confirmed at the time of the last cystoscopy and urinary cytology for recurrence and progression analysis. The time of recurrence and progression disease was performed by two urologists and confirmed by another urologist.

Statistical Analysis

The scores of progression and recurrence risks at 1 and 5 years were estimated for all 56 patients using the EORTC (https://www.eortc.be/tools/bladdercalculator) and CUETO (https://www.aeu.es/Cueto.html) models.[6,7] Accordingly, all patients were classified into the four risk groups: low-risk, Intermediate-risk, high-risk and very high-risk. Progression and recurrence risks were evaluated for all patients and the subgroup of BCG-treated patients after TURBT.

The EORTC scoring model was performed with respect to the following criteria: the number of tumors (single, 2–7 or ≥8), tumor size (<3 cm or ≥3 cm), prior recurrence rate (primary, ≤1 recurrence/year, >1 recurrence/year), T stage (Ta or T1), concomitant CIS (yes/no), and grade (1, 2 or 3).[6] The CUETO scoring model incorporated gender, age (<60, 60–70, >70 years), recurrent tumor (yes/no), number of tumors (≤3 or >3), T stage (Ta or T1), concomitant CIS (yes/no), and grade (1, 2, or 3).[7]

Patient scores were then stratified into 4 risk groups, and a probability of recurrence and progression risk in 1 and 5 years were estimated in order to compare them with the real rates.

Survival analysis was conducted using Kaplan-Meier methods to evaluate progression and recurrence curves obtained with EORTC and CUETO risk groups; the log-rank test was used to compare the difference between groups. A univariate analysis using the cox-regression model was performed to evaluate the association between prognostic factors with recurrence and progression of disease.

For statistical validation, IBM SPSS version 23 was used to calculate the p values, and $p<0.05$ was interpreted as statistically significant.

Results

Pathological analysis of the 73 recruited bladder cancer patients showed that 17 patients had muscle-invasive bladder cancer (MIBC) and were consequently excluded from the study. The retained 56 non-muscle-invasive bladder cancer (NMIBC) cases were mostly men (54/56) with a median age of 65.96 years.

Clinico-pathological characteristics of tumors are summarized in Table 1 and show that most patients had more than

Table 1. The clinic-pathological characteristics of tumor's patients

Socio-clinical information		Anatomo-pathological characterization	
Characteristic	**N (%)**	**Characteristic**	**N (%)**
Age		Concomitant CIS	
< 70 years	37 (66.07%)	Yes	4 (07.15%)
> 70 years	19 (33.93%)	No	52 (92.85%)
Gender		Tumor Grade	
Male	54 (96.42%)	Low (G1/G2)	27 (48.22%)
Female	2 (3.58%)	High (G3)	29 (51.78%)
T Stage		Recurrence	
pTa	20 (35.71%)	No	13 (23.22%)
pT1	36 (64.29%)	yes	43 (76.78%)
No. of Tumors		prior recurrence rate	
1	17 (30.35%)	Recurrent < = 1 per year	27 (48.22%)
2-5	16 (28.57%)	Recurrent > 1 per year	12 (21.42%)
≥ 5	23 (41.08%)	primary	17 (30.36%)
Tumor Size		Progression	
< 3 cm	25 (44.65%)	No	29 (51.78%)
≥ 3 cm	31 (55.35%)	yes	27 (48.22%)
Intravesical Therapy		Survival	
No	33 (58.92%)	Alive	48 (85.71%)
BCG	23 (41.08%)	Death	8 (14.29%)

5 multifocal tumors (41.08%), 55.35% of patients had tumor size ≥ 3 cm, and most cases were diagnosed with pT1 stage (64.29%). Anatomo-pathological analysis showed that there are as many high-grade cases (51.75%) as there are low-grade cases (48.22%,) and only 7.14% of cases exhibited concomitant CIS (4/56).

In this study, the average duration of follow-up was 49.68 months, and all recruited patients had complete data with a minimum 1-year follow-up. After an initial TUR-BT, recurrence was observed in 43 patients (73.21%), while progression was observed in 27 patients (48.21%).

Using the EORTC recurrence score of each patient, 1 (1.78%), 8 (14.28%), 23 (41.08%) and 24 (42.86%) patients were classified into the low-, intermediate, high- and very high-risk groups, respectively. Using the progression score, corresponding values were 1 (1.8%), 12 (21.4%), 25 (44.7%) and 18 (32.1%) patients using the progression score. Comparison of probabilities of progression and recurrence rates by risk group at 1 year and 5 years are reported in Tables 2 and 3, respectively, and compared to reference probabilities reported by Sylvester et al.[6] Overall, the probabilities of recurrence and progression at 1 year ranged from 0 % to 79.2% and from 0% to 41.7%, respectively. Exception was made for the low-risk group; all scores were overestimated compared to scores reported in the EORTC risk tables.

At 5 years, the probability of recurrence ranged from 0%

Table 2. Prediction of disease recurrence and progression in patients with non-muscle invasive bladder cancer using EORTC risk table at 1 year

Group of patients according to the risk score	Recurrence status		
	No. of Patients	N° of patients and rate of recurrence	Predicted recurrence rates according to EORTC risk tables % (95% CI)
Low risk	1	0 (0%)	15% (10-19%)
Intermediate risk	8	3 (37.5%)	24% (21-26%)
High risk	23	17 (73.9%)	38% (35-41%)
Very high risk	24	19 (79.2%)	61% (55-67%)
	Progression status		
	No. of patients	N° of patients and rate of progression	Predicted progression rates according to EORTC risk tables % (95% CI)
Low risk	1	0 (0%)	0.2% (0-0.7%)
Intermediate risk	12	5 (41.7%)	1% (0.4-1.6%)
High risk	25	10 (40%)	5 % (4-7%)
Very high risk	18	3 (16.7%)	17% (10-24%)

Table 3. Prediction of disease recurrence and progression in patients with non-muscle invasive bladder cancer using EORTC risk table at 5 years

Group of patients according to the risk score	Recurrence status		
	No. of Patients	N° of patients and rate of recurrence	Predicted recurrence rates according to EORTC risk tables % (95% CI)
Low risk	1	0 (0%)	31% (24-37%)
Intermediate risk	8	1 (12.5%)	46% (42-49%)
High risk	23	4 (17.4%)	62% (58-65%)
Very high risk	24	6 (25%)	78% (73-84%)
	Progression status		
	No. of patients	N° of patients and rate of progression	Predicted progression rates according to EORTC risk tables % (95% CI)
Low risk	1	0 (0%)	0.8% (0-1.7%)
Intermediate risk	12	2 (16.7%)	6% (5-8%)
High risk	25	3 (12.0%)	17% (14-20%)
Very high risk	18	3 (16.7%)	45% (35-55%)

to 25% and all obtained scores were underestimated to that reported by the EORTC table. Regarding the progression rate, the probability of progression ranged from 0 to 16.7%. This probability was underestimated for low- high- and very high-risk groups and overestimated for intermediate-risk groups.

Using the CUETO recurrence score of each patient, 10 (17.85%), 11 (19.64%), 26 (46.43%) and 9 (16.08%) patients were classified into the low-, intermediate-, high-, very high-risk groups, respectively. Using the progression score, corresponding values were 13 (23.21%), 8 (14.29%), 14 (25.00%) and 21 (37.5%) patients. Comparison of probabilities of progression and recurrence rates by risk groups at 1 year and 5 years are reported in Tables 4 and 5, respectively, and compared to reference probabilities reported by Fernandez-Gomez et al.[7] Overall, the probabilities of recurrence and progression at 1 year ranged from 10% to 88.9% and from 23.1% to 50%, respectively. The CUETO risk tables underestimated the risk of recurrence and progression in 1 year. After 5 years of the initial TRU-BT, the probability of recurrence and progression ranged from 0% to 26.9% and from 7.1% to 25%, respectively. The risk scoring of predicting recurrence in 5 years was lower in all risk groups than those described by Fernandez-Gomez et al.[7] The probabilities of progression for low- and intermediate-risk groups were higher than the reference values reported in the CUETO risk tables, and conversely, they were for high- and very high-risk groups.

Table 4. Prediction of recurrence and progression rates in patients with non-muscle invasive bladder cancer using CUETO scoring model at 1 year

Group of patients according to the risk score	Recurrence status		
	No. of patients	N° of patients and rate of recurrence	Predicted recurrence rates according to CUETO risk tables % (95% CI)
Low risk	10	1 (10%)	8.2% (5.9-10.5%)
Intermediate risk	11	9 (81.8%)	12% (8-16%)
High risk	26	21 (80.8%)	25% (20-31%)
Very high risk	9	8 (88.9%)	42% (28-56%)
	Progression status		
	No. of patients	N° of patients and rate of progression	Predicted progression rates according to CUETO risk tables % (95% CI)
Low risk	13	3 (23.1%)	1.17% (0.15-2.19%)
Intermediate risk	8	4 (50%)	3.00% (0.82- 5.18%)
High risk	14	7 (50%)	5.55% (2.73-8.37%)
Very high risk	21	7 (33.3%)	13.97 (6.64-21.30%)

Table 5. Prediction of recurrence and progression rates in patients with non-muscle invasive bladder cancer using CUETO scoring model at 5 year

Group of patients according to the risk score	Recurrence status		
	No. of expected patients	N° of patients and rate of recurrence	Predicted recurrence rates according to CUETO risk tables % (95% CI)
Low risk	10	0 (0%)	21.0 % (17.33-24.63%)
Intermediate risk	11	2 (18.2%)	35.6% (29.18-41.96%)
High risk	26	7 (26.9%)	47.6% (40.55-54.75%)
Very high risk	9	2 (22.22%)	67.61% (53.67-81.55%)
	Progression status		
	No. of expected patients	N° of patients and rate of progression	Predicted progression rates according to CUETO risk tables % (95% CI)
Low risk	13	3 (23.1%)	3.76% (1.90-5.62%)
Intermediate risk	8	2 (25%)	11.69% (7.57-15.81%)
High risk	14	1 (7.1%)	21.26% (15.85-26.67%)
Very high risk	21	2 (9.52%)	33.57% (23.06-44.08%)

Univariate Cox analysis indicated that only Prior recurrence rate had a significant effect on both recurrence-free survival (p=0.04) and progression-free survival (p=0.037); the other parameters, including gender, age, BCG treatment, grade, stage, tumor size, number of tumors and the presence of concomitant CIS, had no significant effect in this cohort (p>0.05) (Table 6).

In this study, the difference between risk groups of recurrence and progression according to EORTC and CUETO models was calculated using the Kaplan-Meier method and was evaluated by the log-rank test (Fig. 1). EORTC scoring model showed no significant difference between the recurrence (p=0.40) and progression (p=0.64) scores, respectively. Of particular interest, the CUETO risk stratification showed a worse discriminating ability for recurrence scores between risk groups (p=0.005). However, for the progression analysis, there was no significant difference between groups (p=0.43).

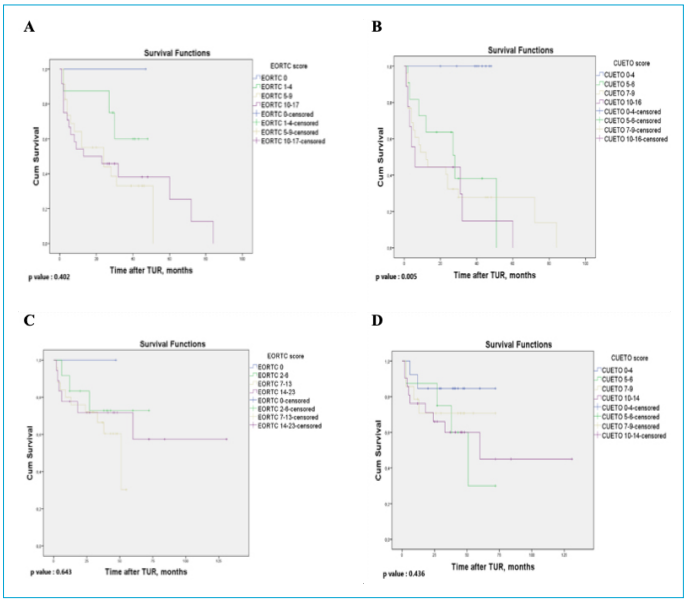

Figure 1. Kaplan-Meier survival curves of risk of recurrence, using EORTC recurrence score **(a)** and CUETO recurrence score **(b)**, and of progression using EORTC progression score **(c)** and CUETO progression score **(d)**.

Table 6. Univariate cox regression analysis for predicting recurrence and progression

	Recurrence-free survival		Progression-free survival	
	HR (95% CI)	p	HR (95% CI)	p
Gender				
Female	1.00	0.712	1.00	0.624
Male	1.457 (0.197 - 10.762)		21.247 (0.000 – 4307808.777)	
Age				
≥70	1.00	0.724	1.00	0.087
<70	1.006 (0.975-1.037)		1.042 (0.994 – 1.092)	
BCG				
Not treated	1.00	0.244	1.00	0.860
Treated	1.535 (0.746 – 3.160)		0.921 (0.367 – 2.308)	
Stages				
pTa	1.00	0.763	1.00	0.587
pT1	1.113 (0.555 - 2.231)		1.309 (0.496 – 3.457)	
Grades				
LG	1.00	0.542	1.00	0.231
HG	0.809 (0.409 - 1.599)		1.770 (0.695 – 4.503)	
Tumor size				
< 3 cm	1.00	0.093	1.00	0.572
≥ 3 cm	1.835 (0.903 – 3.731)		0.771 (0.313 – 1.900)	
N° of tumors				
1	1.00		1.00	0.618
2-5	0.631 (0.276 – 1.446)	0.521	1.148 (0.668 – 1.973)	
≥ 5	0.743 (0.327 – 1.684)		-	
Concomitant CIS				
No	1.00	0.934	1.00	0.623
Yes	0.948 (0.270 – 3.333)		0.600 (0.078 – 4.602)	
Prior recurrence rate				
Primary	1.00		1.00	0.037
Recurrent < 1 per year	0.035 (0.004 – 0.269)	0.004	2.034 (1.044 – 3.964)	
Recurrent > 1 per year	0.578 (0.282 – 1.183)		-	

Discussion

In Morocco, growing interest is given to bladder cancer as there's an increasing number of diagnosed cases and related deaths. In 2020, there were 2268 new cases diagnosed with bladder cancer, with 1268 deaths.[1] Most new cases are diagnosed as NMIBC, being a group with a high risk of recurrence and progressive rates.[12] Thus, predicting recurrence and progression risks is of great interest in the context of target therapy for better management of bladder cancer disease.

Currently, EORTC and CUETO models are widely used for risk stratification of patients with NMIBC providing specific quantitative estimates of the short- and long-term risks of recurrence and progression, making them highly promising tools for a personalized therapeutic approach.[6,7]

The main advantages of these risk stratification models are that they use socio-clinical variables that are available in patients' records, and the estimation of recurrence and progression rates is very easy and practical for clinical purposes.

To the best of our knowledge, this is the first external validation in Morocco and was conducted on a cohort of 56 patients with NMIBC with up to 19 years of follow-up.

In this study, progression and recurrence risk at one year were higher than risks probabilities presented in the EORTC and CUETO risk rates, except for progression/recurrence rates of the low-risk group.

Our results clearly showed that the EORTC risk table overestimated the risk of recurrence and progression for only the low-risk group, and the CUETO risk table underestimated the risk for recurrence and progression. This funding is in disagreement with results reported by Dovey et al. showing that both risk tables tended to overestimate both recurrence and progression rates at 1 year.[13]

For both models, our long-term finding, at 5 years, was underestimated as compared to the predicted values in the EORTC and CUETO risk tables, except in the intermediate-risk group of patients. Similar results were obtained on 123 Belgian patients[14] and 205 Brazilian patients,[15] highlighting that EORTC and CUETO tables overestimated the recurrence and progression risks at 5 years. Conversely, the study conducted by Almeida et al. on 205 Brazilian patients with bladder cancer showed that using the EORTC scoring model, they had an overestimation of the risk of recurrence in 1 year and an underestimation in 5 years.[16]

The Kaplan-Meier method was used to assess the probabilities of recurrence and progression based on both models, and the difference between the risk groups was compared with the log-rank test. Accordingly, using the EORTC risk table, no significant difference was reported in recurrence-free survival and progression-free survival rates between the risk groups. Nevertheless, previous studies have reported that the EORTC tool has high discrimination for predicting recurrence and progression.[17–19] This difference could be mainly due to the low number of cases in our study that would be considered as a sampling bias.

Of particular interest, the CUETO model showed a significant difference between groups for RFS rate ($p=0.005$), unlike PFS ($p=0.436$). These findings are in accordance with the results of Chung and Coll. Showing a great association with recurrence ($p<0.001$) but not with progression ($p=0.423$).[20] Our results are in contrast with a previous study showing that CUETO estimates progression better than recurrence.[21]

Our results have indicated that the EORTC risk scores did not enable stratification, neither the risk of recurrence nor the risk of progression. In contrast, the CUETO model successfully stratified our patients into 4 groups for recurrence, unlike for the progression risks in our Moroccan population. The ability of EORTC and CUETO to stratify risk groups is controversial, depending on the studied populations. Dalkilic and Coll.[19] have reported that the EORTC and CUETO models successfully stratified the recurrence and progression into 4 risk groups in their cohorts, whereas Xu and Coll.[9] showed that only the EORTC model was able to stratify patients with statistically different probability for recurrence and progression.

The univariate Cox regression analysis showed that most studied prognostic factors, including age, gender, BCG immunotherapy, tumor size, number of tumors, stage, and grade, are not related to recurrence and progression. Interestingly, the prior recurrence rate showed a significant association with both recurrence and progression and could be a promising predictor factor for bladder cancer follow-up.

In this study, BCG treatment was not applied to some patients who were at high risk due to adverse effects or had contraindications to BCG medication. Among the 56 recruited NMIBC cases, 23 have received BCG treatment during the study period (41.1%). This sample is too low to assess the recurrence and progression rates of BCG-treated patients according to EORTC and CUETO scoring systems.

This preliminary study is very informative and clearly showed the feasibility, usefulness and ease of use of both EORTC and CUETO scoring models for progression and recurrence prediction in Morocco. However, the study pres-

ents some limitations, mainly due to the low number of recruited patients, that has largely affected the power of the study. A large study with a consistent and multicenter cohort with a long-term follow-up is needed to really appreciate the high value of these scoring tables and to construct a valid prognostic model for Moroccan patients with NMIBC. Additionally, to better predict the cancer progression, it will be interesting to consider the cis type in future explorations.

Disclosures

Ethics Committee Approval: Hospital name: Mohammed V Military Hospital in Rabat-Morocco, Date: December 2017, number of patients: 56 (Ref 82/19).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.A., A.A.B.; Design – M.E.M., A.A.; Supervision – M.E.M., M.A.; Materials – C.H.A., M.E.A., H.E.A.; Data collection and/or processing – C.H.A., M.T., I.H., M.B., M.O.; Analysis and/or interpretation – C.H.A., L.B., A.F.M., M.A.; Literature search – C.H.A., C.I.; Writing – C.H.A., M.A., M.O.; Critical review – M.E.M., A.A.

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