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CASE REPORT

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Analysis of external validation for recurrence and progression of EORTC and CUETO risk scores for non-muscle invasive bladder cancer

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Abstract

Bladder cancer (BCa) is the seventh most common tumor diagnosed in the male population and the eleventh when considered both genres. Of urologic tumors, the BCa is the second most incident. For a better follow-up of BCa, the prognostic factors were reason of several studies in the last few years. The risk factors stratification is important to classify and assists the treatment, based on the risk of recurrence and progression. There are two scores widely used in daily practice to stratify the risk of recurrence and progression, the European Organization for Research and Treatment Cancer (EORTC) and Club Urológico Español de Tratamento Oncológico (CUETO). The EORTC score for BCa has its limitations, it was based on studies previous to use of Bacille Calmette-Guerin (BCG), to overcome this limitation it was developed the CUETO score, which predicts recurrence and progression of BCa in patients who underwent BCG. We review the most recent studies about the use of risk scores for BCa, although they are widely used, there are still a lack of validation works and information about their safety and effectiveness. We compiled the data of this paper to analysis the external validation for recurrence and progression of EORTC and CUETO scores for non-muscle invasive bladder cancer and concluded that risk scores successfully stratified recurrence and progression, despite having a tendency to overestimate the rates.

Keywords: *risk score, external validation, EORTC, CUETO, bladder cancer, progression, recurrence*

Introduction

Bladder cancer (BC) is the seventh most common tumor diagnosed in the male population and the eleventh when considered both genres [1]. Of urologic tumors, the BC is the second most incident [2]. It's incidence increases with age and reaches the peak between 50 and 70 years, is three times more common in men than in women [2,3]. More than 60% of all BC and half of 165.000 BC worldwide deaths per year occur in developing countries [3]. Among the risks factors for BC, the most important is tobacco smoking, related in 50% of the cases. Occupational exposure, use of analgesic based on phenacetin and chronic infections or inflammation of bladder are other factors described [1-3]. Of all new BC cases, about 70% are non-muscle invasive (NMIBC) [2,3]. By definition, these tumors are restricted to mucosa and lamina propria and includes the tumors with pathological stage Ta, T1 e CIS [1,2]. For a better follow-up of BC, the prognostic factors were reason of several studies in the last few years [4,5]. The various factors and the heterogeneity of the tumors make the rate of progression and recurrence very variable with recurrence rates of 15-70% in the first year and progression rates between 7-40% in five years [5,6]. The risk factors stratification is important to classify and assists the treatment, based on the risk of recurrence and progression [7].

There are two scores widely used in daily practice to stratify the risk of recurrence and progression, the European Organization for Research and Treatment Cancer (EORTC) and Club Urológico Español de Tratamento Oncológico (CUETO). The aim of this manuscript is to review the most recent studies about the use of risk scores for BC, although they are widely used, there are still a lack of validation works and information about their safety and effectiveness.

EORTC risk Score

The EORTC risk score was developed by Sylvester et al, which published a study evaluating 2596 patients randomized in seven trials, with the objective of elaborating a score that evaluates the probability of recurrence and progression in 1 and 5 years after transurethral resection of bladder (TURB) [5]. It has analyzed several variables and established the use of 6 clinical and pathological parameters (tumor stage, tumor grade, number of tumors, size, presence of Carcinoma in Situ (CIS) and prior recurrence rate) for analysis of recurrence and progression. The score is calculated for each patient depending on its characteristics and ranges from 0-17 for recurrence and 0-23 for progression, 0 being good prognosis and 17 or 23 for poor prognosis (Table 1) [5,8].

According to the score calculated by the risk factors, it was established a probability of recurrence and progression, which can be analyzed in the Table 2 [5]. When evaluating each risk factor, the most important prognostic factor for recurrence is the number of tumors and for progression is the presence of CIS, factors that represent the biological aggressiveness of the disease.

The EORTC score for BC has its limitations, it was based on studies previous to use of BacilleCalmette-Guerin (BCG) and almost 20% of patients did not use any kind of intra vesical therapy [5,9]. In addition, the formulation of the scores did not take into account the adjuvant treatment with single immediate chemotherapy, use of BCG and second TURB [10].

To overcome this limitation it was developed a new score, the CUETO, which predicts recurrence and progression of BC in patients who underwent BCG [9].

Risk Factors of Recurrence and Progression		
Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2 to 7	3	3
≥ 8	6	3
Tumor size		
<3 cm	0	0
≥ 3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 rec/yr	2	2
> 1 rec/yr	4	2
T Category		
Ta	0	4
T1	1	0
CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

CUETO risk score

BCG immunotherapy reduces the risk of progression and must be the agent of choice in intermediary and high-grade bladder tumors. Despite the benefit, a part of the patients presents a treatment failure [11]. To better evaluate this subgroup, it was necessary to elaborate a risk score to evaluate recurrence and progression after the use of BCG.To elaborate the CUETO risk score, it was evaluate recurrence and progression factors after use of intra vesical BCG on 1062 patients with NMIBC in 4 CUETO trials [9].

The score is calculated from 0 (good prognosis) to 14 for progression and 16 for recurrence (poor prognosis). The patients were categorized into 4 groups and the probabilities of recurrence and progression were calculated at 1, 2 and 5 years. The gender factor was not used for progression, just as the Tumor (T) classification was not used for recurrence [9,12] (Table 2).

External validation of EORTC risk score

After the publication of Sylvester et al. [12] several studies were carried out evaluating if the EORTC risk score and if it could be used as a predictive tool for progression and recurrence in urological practice.

Almeida et al. [13] and Busato et al. [14] evaluated prospectively 205 patients in Brazil, with recurrence rates of 28% in 1 year and 57.1% in 5 years and compared the results with Sylvester et al. [5]. The probability of recurrence at 1 year was lower in all groups in relation to Sylvester et al. and in 5 years the risk was higher, except in the group with score 0. Despite the EORTC score overestimate the recurrence, presents statistical validation, and can be used by urologists as a tool and risk stratification [13]. The progression is less common than recurrence, however presents worse outcome [14]. The progression rate at 1 year was 3.4% and 19.1% at 5 years, rates lower than EORTC, except in the intermediate risk

Probability of recurrence and progression according to EORTC score						
% 1 yr (95% CI)			% 2 yr (95% CI)		% 5 yr (95% CI)	
Score	Recurrence	Progression	Recurrence	Progression	Recurrence	Progression
0-4	8.24 (5.91-10.57)	1.17 (0.15-2.19)	12.6 (9.76-15.44)	2.16 (0.77-3.55)	20.98 (17.33-24.63)	3.76 (1.9-5.62)
05-Jun	12.07 (7.95-16.19)	3 (0.82-5.18)	22.28 (16.93-27.63)	4.97 (2.34-7.6)	35.57 (29.18-41.96)	11.69 (7.57-15.81)
07-Sep	25.36 (19.56-31.16)	5.55 (2.73-8.37)	39.61 (32.93-46.29)	11.95 (7.93-15.97)	47.65 (40.55-54.75)	21.26 (15.85-26.67)
10 or greater	41.79 (28.06-55.53)	13.97 (5.54-21.3)	52.55 (38.48-66.62)	24.81 (15.6-34.02)	67.61 (53.67-81.55)	33.57 (23.06-44.08)

Table 1. EORTC risk score.

Score risk factors for recurrence and progression calculation		
Factor	Recurrence score	Progression score
Gender		
M	0	0
F	3	0
Age		
<60	0	0
60-70	1	0
>70	2	2
Recurrent tumor		
No	0	0
Yes	4	2
No. tumors		
>3	0	0
<3	2	1
T category		
Ta	0	0
T1	0	2
Associated Tis		
No	0	0
Yes	2	1
Grade		
G1	0	0
G2	1	2
G3	3	6
Total scores	0-16	0-14

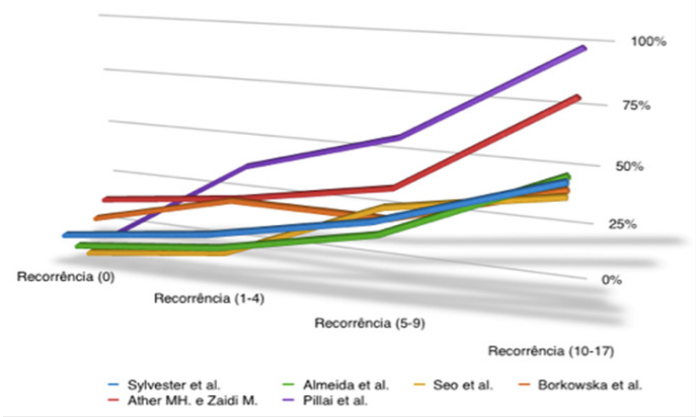

Figure 1. Comparison of recurrence rates according to risk score in 1 year.

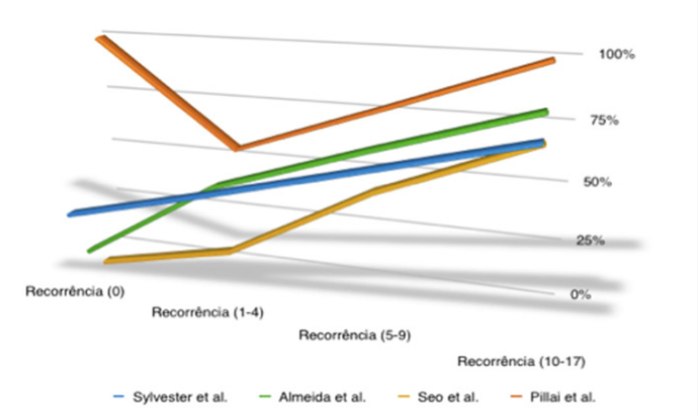

Figure 2. Comparison of recurrence rates according to risk score in 5 years.

Probability of recurrence and progression at 1,2 and 5 years						
	% 1 yr (95% CI)		% 2 yr (95% CI)		% 5 yr (95% CI)	
Score	Recurrence	Progression	Recurrence	Progression	Recurrence	Progression
0-4	8.24 (5.91-10.57)	1.17 (0.15-2.19)	12.6 (9.76-15.44)	2.16 (0.77-3.55)	20.98 (17.33-24.63)	3.76 (1.9-5.62)
05-Jun	12.07 (7.95-16.19)	3 (0.82-5.18)	22.28 (16.93-27.63)	4.97 (2.34-7.6)	35.57 (29.18-41.96)	11.69 (7.57-15.81)
07-Sep	25.36 (19.56-31.16)	5.55 (2.73-8.37)	39.61 (32.93-46.29)	11.95 (7.93-15.97)	47.65 (40.55-54.75)	21.26 (15.85-26.67)
10 or greater	41.79 (28.06-55.53)	13.97 (5.54-21.3)	52.55 (38.48-66.62)	24.81 (15.6-34.02)	67.61 (53.67-81.55)	33.57 (23.06-44.08)

Table 2. CUETO risk score.

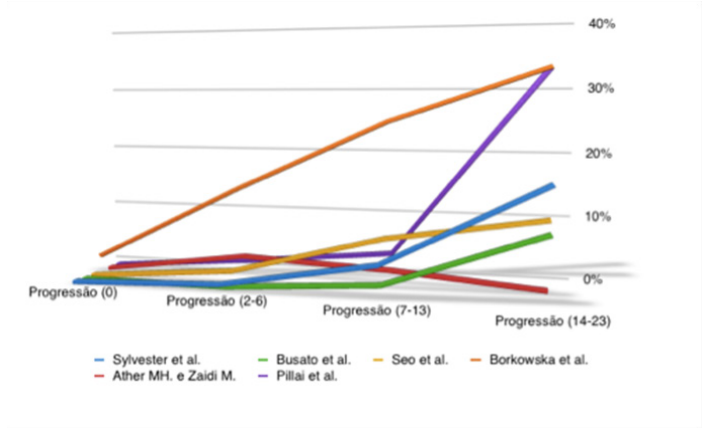

Figure 3. Comparison of progression rates according to risk score in 1 year.

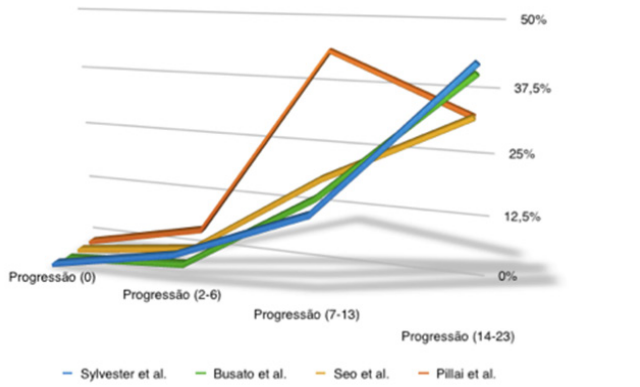

Figure 4. Comparison of progression rates according to risk score in 5 years.

group. Despite the EORTC score overestimate rates, especially in high-risk groups, the score successfully stratified the progression of Brazilian patients in this study [14].

Seo KW et al. [15] also evaluated recurrence and progression in 251 patients after BCG adjuvant therapy. All the rates of recurrence and progression of this study are lower than Sylvester et al. [5]. In relation to progression, there is no significant difference in rates. This study validates the use of EORTC score to clinical use [15].

Fernandez-Gomez et al. [10] of the CUETO group analyzed 1062 patients treated with BCG. After stratified evaluation of recurrence and progression at 1 and 5 years, recurrence rates were lower in all groups. As to progression, lower rates were found in patients at high risk. Despite the correct stratification (c-index similar to Sylvester et al. [12]) of the population sample of this author, the EORTC score overestimate recurrence and progression rates [10]).

In another study, Borkowska et al. [8], analyzed recurrence and progression rates of 91 polish patients and compared the results with Sylvester et al. [8]. After 1 year of treatment, recurrence was observed in 25% of patients and progression in 12.1%. Recurrence rates of this study were lower in all groups, except in risk subgroup 1-4, in relation to progression, rates were higher in all groups when compared to EORTC. Concluding that recurrence rates were overestimated and progression underestimated [8].

Atheretal. [16] compared recurrence and progression rates of 92 patients submitted to TURB and mitomycin C. Patients at intermediate and high risks received BCG adjuvant. All had 1 year follow up and their data compared to EORTC. Recurrence rate in 1 year was 37% and progression rate 2.2%. The rates, by subgroup, of recurrence were similar and progression rates were lower, when compared to EORTC rates [16].

Pillai et al. [17] published a study with the objective of validating the EORTC risk score for BC. In a population of 109 patients, rates of recurrence and progression at 1 and 5 years were compared with EORTC rates. The recurrence and progression rates were 63.3% and 12.8% respectively. The recurrence rates in all groups of this study were higher than the EORTC rates. Concerning progression, subgroup 4 presented higher rates, while subgroup 1 and 2 had similar rates. Subgroup 3 presented similar rates at 1 year, but higher at 5 years. The concordance rates of the present study with EORTC were 62% and 63% for recurrence at 1 and 5 years respectively and for progression, the concordance were 65 and 67% respectively. The author considers that it was not possible to validate the EORTC risk score in this evaluated population [17].

The EORTC risk score has a limited accuracy in predicting recurrence and progression of CB [9]. Analyzing the studies of Almeida et al. [13], Busato et al. [14], Seo et al. [15], Fernandez-Gomez J et al. [10], and Borkowska et al. [8], on external validation, the score tends to overestimate the risks of recurrence and progression of the patients [9,16]. Several factors may justified these overestimated rates, but perhaps the main factor and bias of the Sylvester et al. study is the inclusion of few patients submitted to adjuvant therapy with BCG [9,10]. The EORTC risk score is structured in six trials that used intra vesical chemotherapy regimens after TURB. Nowadays, this treatment is considered inferior when compared to BCG in patients with intermediate or high risk [9]. According to the EAU guidelines, the indication of adjuvant treatment should be preferentially performed with BCG, which has been proven by several studies that show a superiority of BCG in relation chemotherapy for recurrence and progression (Figures 1-4) [3].

External validation of CUETO risk score

Bacillus Calmette-Guerin is the most effective therapy for NMIBC. In EORTC series only 171 patients were treated with bacillus Calmette-Guerin. For that reason, Fernandez-Gomez, et al. [12] developed a risk stratification model to provide accurate estimates of recurrence and progression probability after BCG.

CUETO score was not designed for patients without BCG, when Xylinas et al. [9] evaluated its performance in predicting disease recurrence and progression in all cohort of patients, the discriminative ability of this model was significantly lower than EORTC. In this way, the analyses restricted to patients treated with BCG improved discrimination (C-index=0.597 and 0.645 for recurrence and progression respectively), but still overestimated recurrence and exhibited a poor calibration to progression [9].

Kohjimotoet al. [18], retrospectively reviewed data on 366 patients with NMIBC treated with BCG and assigned points for recurrence and progression based on EORTC and CUETO scores. The CUETO model successfully stratified recurrence and progression, however EORTC did not stratified. The C-index for recurrence were 0.514 and 0.576 respectively for EORTC and CUETO, for progression were 0.693 and 0.764 respectively [18].

Rosevear et al. [19], analyses a total of 1,106 patients with NMIBC in a multicenter phase II study of combination BCG plus Interferon alfa. The aim of this study was to investigated the ability of CUETO model to stratify the recurrence risk. The overall recurrence rate in this population was 48.9% at 2 years followup, higher than the 32.6% of recurrence described by Fernandez-Gomez et al. [19]. The recurrence rates between this population were (42%, 48%, 58% and 74%) and that in the CUETO (21%, 36%, 47% and 67%) in the four subgroups respectively. There were some factors could explain that difference in rates. All the patients of this study received combination BCG plus Interferon alfa and the cycles of BCG induction and maintenance were different. However, CUETO score successfully stratified the patient risk for recurrence [19].

Vedder et al. [20] included 1892 patients, in a multicenter study from three countries, with NMIBC who underwent TURB and evaluated progression and recurrence according to EORTC and CUETO risk scores. During the follow up, 44% patients had a recurrence and 14% a progression. The EORTC and CUETO scores could not predict recurrence properly (C-index between 0.55 to 0.61 for EORTC and 0.56 to 0.59 for CUETO). The risk prediction was better for progression (C-index between 0.72 and 0.81 for EORTC and 0.74 and 0.2). The authors conclude that the discriminatory ability to available risk scores is poor for recurrence and moderate for progression in primary NMIBC [20].

Conclusion

The EORTC and CUETO risk scores successfully stratified recurrence and progression risks of NMIBC in several studies, despite having a tendency to overestimate the rates. Risk models are useful to predict recurrence and progression and are a valuable tool in daily practice.Nevertheless, the EORTC and CUETO scores need improvement. It is essential to add new risks markers such as FGFR3 and Ki67 [20] or additional factors like lymphovascular invasion [9], which improved prediction of recurrence and progression [9,13,14,20].

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