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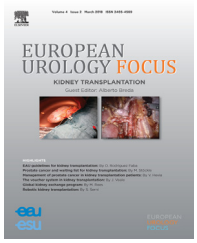

Review – Urothelial Cancer

Risk Stratification Tools and Prognostic Models in Non–muscle-invasive Bladder Cancer: A Critical Assessment from the European Association of Urology Non-muscle-invasive Bladder Cancer Guidelines Panel

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Abstract

Context: This review focuses on the most widely used risk stratification and prediction tools for non–muscle-invasive bladder cancer (NMIBC).
Objective: To assess the clinical use and relevance of risk stratification and prediction tools to enhance clinical decision making and counselling of patients with NMIBC.
Evidence acquisition: The most frequent, currently used risk stratification tools and prognostic models for NMIBC patients were identified by the members of the European Association of Urology (EAU) Guidelines Panel on NMIBC.
Evidence synthesis: The 2006 European Organization for Research and Treatment of Cancer (EORTC) risk tables are the most widely used and validated tools for risk stratification and prognosis prediction in NMIBC patients. The EAU risk categories constitute a simple alternative to the EORTC risk tables and can be used for comparable risk stratification. In the subgroup of NMIBC patients treated with a short maintenance schedule of bacillus Calmette-Guerin (BCG), the Club Urológico Español de Tratamiento Oncológico (CUETO) scoring model is more accurate than the EORTC risk tables. Both the EORTC risk tables and the CUETO scoring model overestimate the recurrence and progression risks in patients treated according to current guidelines. The new concept of conditional recurrence and progression estimates is very promising during follow-up but should be validated.

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Conclusions: Risk stratification and prognostic models enable outcome comparisons and standardisation of treatment and follow-up. At present, none of the available risk stratification and prognostic models reflects current standards of treatment. The EORTC risk tables and CUETO scoring model should be updated with previously unavailable data and recalculated.
Patient summary: Non-muscle-invasive bladder cancer is a heterogeneous disease. A risk-based therapeutic approach is recommended. We present available risk stratification and prediction tools and the degree of their validation with the aim to increase their use in everyday clinical practice.

1. Introduction

Approximately 75% of bladder cancer patients present with non-muscle-invasive tumour. Non-muscle-invasive bladder cancer (NMIBC) is a heterogeneous disease with high prevalence and recurrence rates [1]. Even though exophytic NMIBC can completely be eradicated by transurethral resection (TUR), the recurrence rate can be as high as 80% during long-term follow-up [2]. The aim of adjuvant treatment is to prevent tumour recurrence and decrease the risk of tumour progression including the development of muscle-invasive disease, which is less frequent but potentially life threatening. A risk-based therapeutic approach is recommended to determine the most efficient treatment and frequency of follow-up while maintaining the maximum possible quality of life in all patients [3]. Prognostication and risk assessment are also essential for patient counselling and inclusion in clinical trials.

We expect the following from a valid prognostic model:

1. Discrimination: To stratify patients in groups with different prognoses (ie, recurrence and progression rates are significantly different between patients in the low-, intermediate-, and high-risk groups). Patients within the same risk group should have a similar risk of an event.
2. Calibration: To accurately predict the course of disease (to accurately estimate the short- and long-term rates of disease recurrence and progression over time) in individual patients.

The validity of a prognostic model is thus based both on the correlation between observed and predicted probabilities of the event (calibration) and on its ability to distinguish subjects with different prognoses (discrimination). Discrimination of the prognostic model is usually assessed by Harrell's bias-corrected concordance index C, which represents the percentage of patient pairs in which the predicted and observed outcomes are in agreement, that is, the probability that, among two patients chosen at random, the patient who had the event first had a higher probability of having the event according to the model. When the C-index is equal to 0.5, there is no discrimination (agreement by chance), and when it is 1, there is discrimination with perfect concordance [4–6].

When determining prognostic tools, we look for parameters available at the time of diagnosis that are related to the event that we are trying to predict. Most prognostic models are based on clinical and pathological tumour characteristics that are associated with an aggressive course and a poor prognosis [7,8]. However, the treatment received can also influence the course of the disease; therefore, selection of the source population is of great importance. Ideally, all patients should be treated according to current guidelines to make conclusions relevant.

The aim of this paper is to review the most frequent, currently used risk stratification tools and prognostic models in NMIBC patients, present their advantages and shortcomings, and determine the population of patients for which each tool is most appropriate.

2. Evidence acquisition

This narrative review is based on a search of the English literature performed in March 2018 using MEDLINE (via PubMed). The following keywords were used: bladder cancer; risk stratification; scoring system; scoring model; risk tables; and risk calculator. The only criterion for study relevance was its relation to the topic. All selected publications were reviewed and analysed. A narrative synthesis was used for a qualitative data synthesis.

3. Evidence synthesis

3.1. Models used for risk stratification and prognosis prediction

3.1.1. European Organization for Research and Treatment of Cancer risk tables

The European Organization for Research and Treatment of Cancer (EORTC) scoring system and risk tables were published in 2006, and are currently the most widely used and validated prediction model in NMIBC [4]. The prognostic value of clinical and pathological factors was analysed in a group of patients randomised in seven studies between January 1979 and September 1989. A total of 2596 eligible patients were included in the analysis, most of them with favourable characteristics: 54% had primary tumours, 56%

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Ta, 10% grade 3, and 4% concomitant carcinoma in situ (CIS). Seventy-eight percent of the patients received intravesical treatment, <10% received an immediate instillation of chemotherapy after TUR, only 7% were treated with bacillus Calmette-Guerin (BCG) but without maintenance, and 21% of the patients did not receive intravesical treatment. A second-look TUR was not practiced. Median follow-up was 3.9 yr.

The scoring system is based on clinical and pathological factors that are commonly assessed and have been found to be of prognostic importance in previous publications. The most important prognostic factors for recurrence were the number of tumours and their size, and the prior recurrence rate. The most important prognostic factors for progression were the T category, grade (G1–3, World Health Organization [WHO] 1973), and the presence of concomitant CIS (factors that represent the biological aggressiveness of the disease). A weight (score) for each variable was obtained based on the coefficients of variables in the multivariate model (Table 1). The EORTC risk tables also provide specific quantitative estimates of the risk of recurrence and progression in individual patients at 1 and 5 yr. The probabilities of recurrence and progression at 1 yr are presented in Table 2. Concordance index C for tumour recurrence at both 1 and 5 yr was 0.66, and for tumour progression it was 0.74 at 1 yr and 0.75 at 5 yr.

Sylvester et al [7] emphasised the fact that most of the patients included in the analysis were treated with chemotherapy and only 171 patients were treated with BCG but without maintenance, which is recommended for high-risk patients today. The consequence of this is that the recurrence and progression rates that are reported may be higher than those found in current clinical practice (ie, overestimation), especially in patients with high-risk NMIBC [4].

Table 1 – Weights used to calculate the disease recurrence and progression EORTC scores.

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2–7	3	3
≥8	6	3
Tumour diameter (cm)		
<3	0	0
≥3	3	3
Prior recurrence rate		
Primary	0	0
≤1 recurrence/yr	2	2
>1 recurrence/yr	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

CIS = carcinoma in situ; EORTC = European Organization for Research and Treatment of Cancer.

Table 2 – Probability of recurrence and progression according to total EORTC score.

Recurrence score	Probability of recurrence at 1 yr		Probability of recurrence at 5 yr		Recurrence risk group
	%	95% CI	%	95% CI	
0	15	10–19	31	24–37	Low risk
1–4	24	21–26	46	42–49	Intermediate risk
5–9	38	35–41	62	58–65	Intermediate risk
10–17	61	55–67	78	73–84	High risk
Progression score	**Probability of progression at 1 yr**		**Probability of progression at 5 yr**		**Progression risk group**
	%	95% CI	%	95% CI	
0	0.2	0–0.7	0.8	0–1.7	Low risk
2–6	1	0.4–1.6	6	5–8	Intermediate risk
7–13	5	4–7	17	14–20	High risk
14–23	17	10–24	45	35–55	High risk

CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer.

3.1.2. *Club Urológico Español de Tratamiento Oncológico scoring model*

This model provides risk stratification and estimates of recurrence and progression probabilities in patients treated with a short maintenance schedule of adjuvant intravesical BCG. The scoring model is based on the data obtained from 1062 patients with intermediate- and high-risk NMIBC included in four Club Urológico Español de Tratamiento Oncológico (CUETO) trials comparing different intravesical BCG treatments. Instillations were administered once a week for 6 consecutive weeks, and thereafter six additional instillations were repeated at 2-wk intervals. It means that each patient received a total of 12 instillations in 5–6 mo. Median follow-up was 69 mo, and the methodology was similar to that used in the EORTC study. The model focuses on clinical and pathological factors that were commonly assessed and found to be of prognostic importance [5]. Statistically significant prognostic factors for recurrence were gender, age, grade, tumour status (recurrent and primary), and multiplicity. Statistically significant prognostic factors for progression were age, grade, tumour status, and T category (Table 3). For recurrence, the calculated risks using the CUETO scoring model were lower than those obtained with the EORTC risk tables. For progression, probabilities were lower only in patients with high-risk tumours. However, both scoring systems yielded a similar probability of progression in most patients with T1G1–2 tumours and in a limited number of patients with T1G3 tumours (primary, single, <3 cm, and without associated CIS). In the CUETO model, gender was considered for recurrence and age was considered for both recurrence and progression. Both gender and age can probably influence response to intravesical immunotherapy. Tumour size was not included as a prognostic factor for recurrence or progression. The probabilities

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Table 3 – Weights used to calculate disease recurrence and progression in the CUETO scoring model.

Factor	Recurrence	Progression
Gender		
Male	0	0
Female	3	0
Age (yr)		
< 60	0	0
60–70	1	0
> 70	2	2
Number of tumours		
≤ 3	0	0
> 3	2	1
Recurrent tumour		
No	0	0
Yes	4	2
Category		
Ta	0	0
T1	0	2
Concurrent CIS		
No	0	0
Yes	2	1
Grade		
G1	0	0
G2	1	2
G3	3	6
Total score	0–16	0–14

CIS = carcinoma in situ; CUETO = Club Urológico Español de Tratamiento Oncológico.

of recurrence and progression at 1 and 5 yr are presented in Table 4. Concordance index C for tumour recurrence was 0.636 and 0.644, and for tumour progression it was 0.687 and 0.7 at 1 and 5 yr, respectively [5].

A limitation of the CUETO model is that repeat TUR and immediate instillation were not performed. The CUETO maintenance schedule was considerably shorter than the 1–3 yr of maintenance currently recommended by the EAU for BCG, and the unconventional schedule raises the question of whether this model is applicable to patients treated according to current guidelines.

Table 4 – Probability of recurrence and progression according to total CUETO score.

Recurrence score	Probability of recurrence at 1 yr		Probability of recurrence at 5 yr	
	%	95% CI	%	95% CI
0–4	8	6–11)	21	17–25)
5–6	12	8–16	36	29–42
7–9	25	20–31	48	41–55
≥10	42	28–56	68	54–82
Progression score	**Probability of progression at 1 yr**		**Probability of progression at 5 yr**	
	%	95% CI	%	95% CI
0–4	1	0.2–2	4	2–6
5–6	3	1–5	12	8–16
7–9	6	3–8	21	16–27
≥10	14	7–21	34	23–44

CI = confidence interval; CUETO = Club Urológico Español de Tratamiento Oncológico.

3.1.3. *EORTC nomograms and risk groups in patients treated with 1–3 yr of maintenance BCG (2016 EORTC scoring model)*

The CUETO scoring model is based on patients treated with a maintenance schedule that is shorter than the current recommendation [3]. Therefore, Cambier et al [9] analysed 1812 patients from two EORTC randomised trials with intermediate- and high-risk NMIBC without CIS who received induction BCG and 1–3 yr of maintenance BCG. Routine repeat TUR was not performed in high-risk patients and median follow-up was 7.4 yr. Statistically significant prognostic factors for recurrence were the prior recurrence rate (≤1/yr vs >1/yr) and number of tumours (less than four tumours vs four or more tumours), and for progression these were tumour grade and stage.

The authors distinguished between early and late recurrence, where late recurrence was after the first follow-up cystoscopy (>4.5 mo after randomisation). The recurrence rates after 1 and 5 yr were 14.0% and 28.3% in the best prognostic group of patients with a prior recurrence rate of ≤1/yr and less than four tumours compared with 33.0% and 51.7% in the worst prognostic group of patients with a prior recurrence rate of >1/yr and four or more tumours, respectively. The best prognostic group of TaG1 tumours had progression probabilities of 1.9% at 1 yr and 7.1% at 5 yr. The worst prognostic group of T1G3 patients had progression probabilities of 11.4% at 1 yr and 19.8% at 5 yr. The C-index for late tumour recurrence was 0.56, and for tumour progression it was 0.64. As part of the study, a nomogram was constructed to predict 1- and 5-yr survival. The most important factors for disease-specific survival were the same as for progression, that is, stage and grade. T1G3 patients had the worst prognosis, with 1- and 5-yr disease-specific death rates of 4.8% and 11.3%, respectively [9]. Limitations of the study are that patients did not undergo repeat TUR, some patients were treated with one-third dose of BCG, and patients with CIS were not included.

3.1.4. *Dynamic prognostication using conditional recurrence and progression estimates*

Cancer prognosis is typically assessed at diagnosis and estimated over a certain interval of time (eg, 5-yr survival). These estimates become less relevant when the length of follow-up increases, and the impact of prognostic factors assessed at diagnosis decreases. In contrast to the classical concept, conditional estimates measure the probability that a patient will survive some additional number of years without an event if they have not already experienced an event at a given point in time. Conditional recurrence and progression estimates may provide better and more dynamic estimates of outcome probabilities at each follow-up point, and may thereby help individualise prediction of prognosis, patient counselling, and surveillance scheduling.

In a single-centre cohort of 1292 consecutive patients with newly diagnosed Ta/T1 bladder cancer, conditional recurrence and progression were evaluated. The recurrence and progression rates decreased with time. The impact of all prognostic factors progressively decreased with time, and

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no variable was associated with recurrence after 24 recurrence-free months. Tables with dynamic prognostic information at all time points can be used during regular follow-up visits for patient counselling and surveillance planning, as well as for clinical trial design (ie, biomarker for avoidance, delay of surveillance cystoscopy) [10] (Table 5).

3.1.5. *Risk stratification by the European Association of Urology categories*

The European Association of Urology (EAU) NMIBC guidelines originally used EORTC risk score for recurrence and progression risk stratification, as shown in Table 2 [11]. To facilitate risk group assignment, treatment, and follow-up recommendations, simplified risk group stratification based on the EORTC risk score for progression was introduced in 2013 [12]. The EAU risk categories are presented in Table 6.

The effect of risk group stratification by the EORTC risk tables and the simplified EAU risk categories was compared on disease-specific outcomes in a large multi-institutional database of 5122 patients with NMIBC. Compared with EORTC risk stratification, EAU categories reclassified 37.9% of patients into a higher-risk group of recurrence and 11.8% into a higher-risk group of progression. Despite the reclassification, disease-specific outcomes of patients stratified by the EAU risk groups were comparable with the ones provided by the EORTC risk tables. The reason was that the EORTC score was calculated separately for recurrence and progression, whereas EAU classification assigned the patients to one general risk group, and in all cases, the increase in recurrence or progression risk by the application of the EAU categories eventually did not lead to any change in treatment recommendations. The EAU categories could be regarded as an alternative tool for treatment decision making [13].

Table 5 – Conditional recurrence and progression rates in patients with NMIBC who reached certain time after TURB without recurrence or progression, respectively.

Post-TURB time (mo)/risk	Conditional recurrence rate, %[a]						Conditional progression rate, %					
	6	12	24	36	48	60	6	12	24	36	48	60
Baseline	13	26	36	41	45	47	1	2	4	6	7	7
Low	6	11	19	26	30	31	0	1	2	2	2	2
Intermediate	13	27	39	44	49	51	1	1	2	2	3	4
High	16	29	38	42	45	47	3	4	9	11	12	13
6 mo		16	28	33	38	41		1	3	5	6	6
Low	–	6	14	20	25	28	–	1	2	2	2	2
Intermediate	–	17	31	37	43	45	–	0.4	1	1	3	4
High	–	18	29	33	38	40	–	2	6	10	11	11
12 mo			15	22	28	31			2	4	5	5
Low	–	–	9	15	21	25	–	–	1	1	1	1
Intermediate	–	–	18	26	33	35	–	–	1	1	2	3
High	–	–	14	20	25	29	–	–	5	8	9	10
24 mo				9	16	20				2	3	3
Low	–	–	–	8	14	18	–	–	–	0	0	0
Intermediate	–	–	–	10	19	22	–	–	–	0.3	2	3
High	–	–	–	7	14	18	–	–	–	4	5	6
36 mo					9	13					1	2
Low	–	–	–	–	8	12	–	–	–	–	0	0
Intermediate	–	–	–	–	10	15	–	–	–	–	1	3
High	–	–	–	–	8	13	–	–	–	–	1	2
48 mo						5						1
Low	–	–	–	–	–	5	–	–	–	–	–	0
Intermediate	–	–	–	–	–	5	–	–	–	–	–	1
High	–	–	–	–	–	6	–	–	–	–	–	1

NMIBC = non–muscle-invasive bladder cancer; TURB = transurethral resection of the bladder.

[a] For example: if there is no recurrence for 48 mo after TURB, overall risk of recurrent disease at 60 mo is 5%.

3.1.6. *Risk stratification in clinical practice guidelines*

Clinical practice guidelines on NMIBC stratify patients into risk groups based on combined pathological and clinical features reflecting the likelihood of recurrence and progression. A comparison of the risk stratification model used in the EAU guidelines with models used in the American Urological Association (AUA) and National Institute for Health and Care Excellence guidelines is presented in Table 6 [3,14,15]. The National Comprehensive Cancer Network guidelines use only pathological stage and grade for their risk-adapted treatment algorithm and flow charts instead of a more comprehensive risk stratification model [16].

3.1.7. *Categorisation of patients with intermediate-risk NMIBC*

Intermediate-risk disease is a heterogeneous category that has traditionally comprised all patients excluded from the low- or high-risk categories. The simple and practical definition from the International Bladder Cancer Group (IBCG) and AUA is that it includes multiple and/or recurrent low-grade Ta tumours [14,17]. The IBCG has also proposed a risk stratification model for intermediate-risk NMIBC patients and a management algorithm that considers number (>1) and size (>3 cm) of tumours, timing (recurrence within 1 yr) and frequency (more than one per year) of recurrence, and previous treatment. In patients without these risk factors, a single immediate instillation of chemotherapy is advised. In those with one to two risk factors, adjuvant intravesical therapy (intravesical chemotherapy or maintenance BCG) is recommended, and previous intravesical therapy should be considered when choosing between these adjuvant therapies. For those patients with three to four risk factors, maintenance BCG is recommended. The IBCG risk stratification model is based on expert opinion, as evidence-based recommendations for subgroups of intermediate-risk patients are unavailable.

Lammers et al [18] created a prediction model for recurrence probabilities in intermediate-risk patients treated with intravesical chemotherapy. Five relevant predictors for recurrence-free survival (RFS) were identified: history of recurrences, history of intravesical treatment, grade 2, multiple tumours, and adjuvant treatment with epirubicin. The C-indices for this RFS model were 0.60, 0.62, and 0.63 at years 1, 2, and 5, respectively. Based on their analysis, intermediate-risk patients were stratified into three subgroups (minor, moderate, and major risk of recurrence), which could be treated differently. Limitations of the study are that it is focused only on patients treated with intravesical chemotherapy, it does not give any information related to the risk of tumour progression, and one of the relevant predictors (adjuvant treatment with epirubicin) is not known at the time of diagnosis. In addition, the study does

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Table 6 – Risk stratification of NMIBC in clinical practice guidelines.

Low risk	Intermediate risk	High risk
EAU		
Primary, solitary, LG/G1 <3 cm, no CIS	All tumours not defined in the two adjacent categories	T1 tumour
		HG/G3 tumour
		CIS
		Multiple, recurrent, and large (>3 cm) Ta G1G2 tumours (all conditions must be present)
		Subgroup of highest-risk tumours: T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, lymphovascular invasion
AUA		
Low-grade solitary Ta ≤3 cm	Recurrence within 1 yr of low-grade Ta	High-grade T1
PUNLMP	Solitary, low grade, Ta, >3 cm	Recurrent, high grade, Ta
	Multifocal, low grade, Ta	High grade, Ta, >3 cm
	High grade, Ta, ≤3 cm	Multifocal, high grade, Ta
	Low grade, T1	Any CIS
		Any BCG failure in high-grade cases
		Any variant histology
		Any LVI
		Any high-grade prostatic urethral involvement
NICE		
Solitary, pTaG1, <3 cm	Solitary, pTaG1, >3 cm	pTaG3
Solitary, pTaG2 (low grade), <3 cm	Multifocal, pTaG1	pT1G2
PUNLMP	Solitary, pTaG2 (low grade), >3 cm	pT1G3
	Multifocal, pTaG2 (low grade)	pTis (CIS)
	pTaG2 (high grade)	Aggressive variant histology of urothelial carcinoma
	Any pTaG2 (grade no further specified)	
	Any low-risk NMIBC recurring within 12 mo	

AUA = American Urological Association; BCG = bacillus Calmette-Guerin; CIS = carcinoma in situ; EAU = European Association of Urology; HG = high grade; LG = low grade; LVI = lymphovascular invasion; NICE = National Institute for Health and Care Excellence; NMIBC = non–muscle-invasive bladder cancer; PUNLMP = papillary neoplasm of low malignant potential.

not provide any information on how to stratify patients with intermediate-risk NMIBC into subgroups with a different risk of recurrence, thereby limiting their use in clinical practice.

3.1.8. *Categorisation of patients with high-risk NMIBC*

Intravesical BCG instillation therapy is a standard of treatment for high-risk NMIBC. Despite BCG maintenance, T1G3 patients had poor prognosis in Cambier et al's [9] study with a 5-yr progression rate of 19.8% and a 5-yr disease-specific death rate of 11.3%. The most important clinical issue is to identify which T1G3/HG patients will progress despite "optimal" diagnosis, treatment, and follow-up. The EAU guidelines have therefore defined a group of NMIBC patients with the highest risk of tumour progression, and recommend an early or immediate radical cystectomy instead of conservative treatment with BCG (Table 6). The following adverse prognostic factors may offer additional information in the decision-making process: female sex, CIS in the prostatic urethra in men, T1G3 tumours in bladder (pseudo) diverticulum, tumour stage at the time of second TUR of the bladder (TURB), lymphovascular invasion, and an unusual variant histology of urothelial carcinoma. Nevertheless, data supporting the categorisation of high-risk NMIBC patients with these prognostic factors are still limited [19–23].

In a large retrospective multicentre study of 2451 T1G3/HG patients who received BCG as their initial treatment (38% of whom received maintenance BCG), Gontero et al [24] divided patients into four risk groups for progression according to the number of adverse prognostic factors among age ≥70 yr, tumour size ≥3 cm, and presence of concomitant CIS. Progression rates at 10 yr were 17.3%, 25.3%, 32.2%, and 52.0% for patients with zero, one, two, and three adverse factors, respectively. Two risk groups were proposed for cancer-specific survival according to the presence of both age ≥70 yr and tumour ≥3 cm; the cancer-specific death rates at 10 yr were 31.7% for patients with both factors present, as opposed to 12.9% for patients without either factor. Patients with none of these factors and those with one factor had similar CIS. Patients with the highest risk of tumour progression, that is, the simultaneous presence of all three of these adverse prognostic factors, should be considered for more aggressive treatment.

3.2. *The 2006 EORTC scoring model in combination with biomarkers*

Molecular grade based on *fibroblast growth factor receptor 3 (FGFR3)* gene mutation status and MIB-1 expression increased the discrimination of the EORTC risk score for progression from 0.749 to 0.817 in a multi-institutional study based on the data from 230 patients with primary NMIBC [25]. In contrast, only marginal improvement in the discrimination of the EORTC risk tables and the CUETO scoring model by adding five immunohistochemically detected prognostic biomarkers (p21, p27, p53, Ki-67, and

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cyclinE1) was described in a prospective study observing 131 patients with high-grade NMIBC [26]. Another set of molecular markers (p53, p21 waf1/cip, Bcl-2, CyclinD1, and metallothionein 9) was tested in combination with the EORTC risk tables. Information about possible improvement of the discrimination was limited because only 42 patients were included in the study [27]. Clearly, more studies are needed in the area of biomarkers to help improve risk stratification and treatment selection of NMIBC.

3.3. Validation of risk stratification tools and prognostic models

Validation of a prognostic model is the process showing that a model works satisfactorily for patients other than those in the original dataset used to develop the model.

3.3.1. External validation on data from randomised controlled trials

3.3.1.1. Evaluation of models commonly used for outcome prediction in a Dutch cohort treated with intravesical chemotherapy. The study compared the observed recurrence and progression with expected outcomes according to the EORTC risk tables and the CUETO scoring model outcomes in the Dutch cohort collected from three randomised controlled trials (1045 patients). As all the patients were treated with intravesical chemotherapy, it was possible to compare the outcomes of undertreated patients (patients who should have received more aggressive treatments according to the guidelines, eg, BCG, radical cystectomy) with adequately treated patients (patients who received intravesical chemotherapy according to the guidelines). Observed recurrence probabilities in the Dutch cohort were lower than the expected recurrence probabilities calculated by the EORTC tables and higher than the expected probabilities calculated by the CUETO scoring model. Expected and actual progression rates were similar in both models. Patients who did not receive adequate treatment according to the EAU guidelines had significantly worse outcomes for both recurrence and progression [28].

3.3.1.2. Validation of the EORTC risk tables on the CUETO cohort of patients. The CUETO cohort was described in chapter 3.1.2. The variable prior recurrence rate was not available in the CUETO dataset, and two separate analyses were performed. At first, all patients with recurrent tumours were considered to have no more than one recurrence per year, and consequently, they were assumed to have more than one recurrence per year. The 2006 EORTC model was able to successfully stratify recurrence and progression risks in the CUETO cohort. However, the discriminative ability for progression was decreased. The EORTC risk tables overestimated the risks of recurrence in all risk groups of the CUETO series and the probabilities of progression in higher-risk patients, especially at 5 yr [29].

3.3.1.3. Validation of the CUETO model using the 2016 EORTC maintenance BCG data set. In the study of Cambier et al [9], the CUETO model did not perform as well when applied to 2016 EORTC data. The C-indices for recurrence and progression decreased from 0.64 to 0.48 and from 0.69 to 0.53, respectively. Applied to 2016 EORTC data, the CUETO model underestimated the risk of recurrence in good-risk patients and overestimated the risk of progression at 5 yr in poor-risk patients.

3.3.2. External validation of the EORTC risk tables and the CUETO scoring model on data from multi-institutional cohorts

EORTC risk group stratification has been evaluated in two multi-institutional Japanese studies. In the study by Ieda et al [30], >87% of the 856 patients were classified in the intermediate-risk group. There were no significant differences in recurrence rates between the groups according to the EORTC recurrence risk classification (low vs intermediate-low, $p = 0.11$; intermediate-low vs intermediate-high, $p = 0.51$; intermediate-high vs high, $p = 0.71$). Differences in progression rates were not statistically significant, except between patients in the intermediate- and high-low–risk groups ($p < 0.001$). Comparable results were reported by Sakano et al [31] in a cohort of 372 patients with complete data; 12 (3.2%), 344 (92.5%), and 16 (4.3%) patients were classified into low-, intermediate-, and high-risk group, respectively. The risk group stratification of the EORTC risk tables could be less applicable in Japanese patients due to the reported high proportion of patients in the intermediate-risk group.

Validity of the EORTC and CUETO risk scores in patients with primary NMIBC was evaluated on a cohort of 1892 European patients from three countries (Spain, Denmark, and The Netherlands). Multiple imputation was used to handle missing data for concomitant CIS (52% missing) and the number of tumours (18% missing). Detailed information on adjuvant treatment was not known. Neither the EORTC tables nor the CUETO score could precisely separate low- from high-risk patients with respect to disease recurrence. The EORTC and CUETO risk scores could reasonably predict progression, while prediction of recurrence was inaccurate (Table 7). C-indices were not significantly different between the EORTC and CUETO risk scores in all three populations. In this study, the CUETO score discriminated better in the overall population than in the subgroup analysis of patients receiving BCG treatment. The authors concluded that the discriminative ability of currently available risk scores is poor for recurrence and moderate for progression in primary NMIBC [32].

Xylinas et al [33] assessed the predictive performance of the EORTC risk tables and the CUETO scoring model in a large multicentre cohort of 4689 NMIBC patients. The EORTC tables overestimated the risk of disease recurrence in high-risk patients. The CUETO model underestimated the risk of recurrence in low-risk patients and overestimated it in high-risk patients. However, both models overestimated the risk of disease progression in high-risk patients. Regarding the prediction of disease progression, there was no definite difference between the values presented by the EORTC risk tables and the CUETO scoring model. Discrimination of the EORTC tables was even lower in the subgroup of patients treated with BCG (0.554 and 0.576 for disease

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Table 7 – External validation of the EORTC risk tables and the CUETO scoring model.

Study (1 st author, year, Ref)	Number of patients	Ethnicity	Follow-up (mo)	Model evaluated	Immediate single post-operative chemotherapy (%)	Course of intravesical chemotherapy (%)	BCG (%)	Maintenance of BCG (%)	reTUR (%)	EORTC, recurrence, C-index	EORTC, progression, C-index	CUETO, recurrence, C-index	CUETO, progression, C-index	Recurrence at 1 yr (%)	Recurrence at 5 yr (%)	Progression at 1 yr (%)	Progression at 5 yr (%)	Risk stratification	Authors' conclusion
Ieda (2016) [30]	856	Japanese	31	EORTC	6.9	6.5	25.7	2.5	16									Insignificant differences	
Sakano (2011) [31]	592	Japanese	37	EORTC		31.9	15.5	0										92.5% intermediate risk	EORTC tables are not applicable
Vedder (2014) [32]	1892	Europeans	120	EORTC, CUETO		13–22	17–30		0.55–0.61	0.56–0.59	0.72–0.81	0.74–0.82							Discriminatory ability poor for recurrence and moderate for progression
Xylinas (2013) [33]	4689	Europe, USA	57	EORTC, CUETO	51		11	All BCG treated		0.60	0.66	0.52	0.62						Both models exhibit poor discrimination
Almeida (2016) [34]	205	Brazilian	64	EORTC		11.7	22.4			0.72 at 1 yr and 0.7 at 5 yr									Adequate
Busato Júnior (2016) [35]	205	Brazilian	64	EORTC		11.7	22.4				0.86 at 1 yr and 0.78 at 5 yr					3.4	19.1		Useful
Ding (2014) [36]	301	Chinese	46	EORTC	61.1	61.1	0	0						2–58	12–85	1.2– 30	2.9–50	significant difference	Applicable
Hernández (2011) [37]	417	Spanish	59	EORTC	70.3	3.3	8.2							26	53.5	4.9	8.4		Accurate
Kğlğnç (2017) [38]	348	Turkish	55	EORTC	89.7	31.9	45.1	0		0.82	0.94			37.4	74.1	10.1	28.4		Accurate
Altieri (2012) [39]	259	Italian	72	EORTC	73.0	57.0	23.0	87.5	22.0					21.6	35.9	3.9	9.6		Recommended
Kohjimoto (2014) [40]	366 BCG treated	Japanese	60	EORTC, CUETO	0	0	100	0		0.51	0.69	0.58	0.76					Better of CUETO	Good CUETO
Miyake (2015) [41]	106 primary T1HG	Japanese	54	CUETO		13	54	0	12			0.56	0.64	20.0	55.0	4.1	17.3	Successful	Applicable
Pillai (2011) [42]	109	English	60	EORTC		19.3				0.62 at 1 yr and 0.63 at 5 yr	0.65 at 1 yr and 0.67 at 5 yr				63.3		12.8		Unable to validate
Seo (2010) [43]	251	Korean	69	EORTC	0	0	100	100						0, 9.2, 37.9, 50.0	0, 13.2, 46.8, 72.0	0, 1.8, 7.8, 11.4	0, 3.5, 20.8, 34.3		Useful
Xu (2013) [44]	363	Chinese	36	EORTC, CUETO	79	100	0	0		0.71	0.77	0.66	0.74					Successfully by EORTC, not by CUETO	EORTC valid, CUETO less applicable
Choi (2014) [45]	531	Korean	58	EORTC, CUETO			53			0.76	0.70	0.84	0.75					EORTC better for progression, CUETO for recurrence	Both systems showed value
Ajili (2013) [46]	112	Tunisian	30	EORTC	0	0	100	0						0, 14.2, 31.3, 85.7					Significant concordance
Ather (2009) [47]	92	Pakistani	38	EORTC										20.0, 28.2, 40.5, 83.3					Significant concordance
Borkowska (2013) [48]	91	Polish	12	EORTC										13.7, 30, 30, 50		2.7, 14.3, 25.0, 33.3			Limited usefulness

BCG = bacillus Calmette-Guerin; CUETO = Club Urológico Español de Tratamiento Oncológico; EORTC = European Organization for Research and Treatment of Cancer; reTUR = repeat transurethral resection.

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recurrence and progression, respectively). Conversely, discrimination of the CUETO model increased in BCG-treated patients (0.597 and 0.645 for disease recurrence and progression, respectively). Differences are provided in Table 7. Including only patients who were not treated with BCG, discrimination of the EORTC tables improved and that of the CUETO model decreased.

3.3.3. *External validation of the EORTC risk tables and the CUETO scoring model on data from local cohorts*

In total, 15 other studies validated the EORTC risk tables and the CUETO scoring model in different local cohorts [34–48]. Results are presented in Table 7. Most of the studies have shown the value of both tools. Significant differences in the interpretation of the results have to be considered; therefore, the authors' conclusions have been included in the table.

3.4. *Discussion*

The EORTC risk tables are the most used and best validated tool for risk stratification and prognosis prediction in NMIBC patients. The EAU risk categories are a simple alternative to the EORTC risk tables and can be used for comparable risk stratification. In a subgroup of NMIBC patients treated with BCG, the CUETO scoring model is more accurate than the EORTC risk tables. New concepts of conditional recurrence and progression estimates seem to be promising and useful especially during follow-up of patients, but needs to be validated.

One of the most important drawbacks of all available scoring models is that they are based on populations that were treated differently from the current standard. Changes in disease management such as a second TURB; a single, immediate, postoperative intravesical instillation of chemotherapy; and BCG treatment including maintenance may improve the prognosis and cause the scoring models to overestimate the risk of recurrence and progression in patients treated according to current guidelines [3]. Risk stratification tools and prognostic models should be based on a population with optimal therapy. Unfortunately, no such tools are currently available. For this reason, the EORTC risk tables and the CUETO scoring model should be updated with previously unavailable data and recalculated. If we had such a new scoring model available, it would be possible to state that this scoring model gives an accurate estimate of the prognosis when a patient is treated according to the current standard. This might increase the generally known low compliance with guidelines [49]. An update would also allow the replacement of 1973 WHO G_{1-3} classification with the 2004 WHO low/high grade, which is the current standard grading system. In addition, novel risk factors such as lymphovascular invasion and variant histology could be included [50].

Risk stratification and prognosis estimation should be performed when NMIBC is diagnosed. At present, scoring models use clinical and pathological variables that are known at the time of diagnosis, are commonly assessed, and have been found to be of prognostic importance. Evaluation of some variables is subjective. Estimation of tumour size during TURB is inaccurate, as well as determining the number of tumours in patients with diffuse lesions. Tumour stage and histological grade are associated with high observer variability [51,52]. All these inaccuracies may lead to an incorrect tumour classification, which makes the process of validation complicated. Replacement of clinical prognostic factors by molecular ones would potentially be beneficial; however, no molecular markers have currently been recommended for widespread use in routine clinical practice. Molecular grade (*FGFR3*/MIB-1) increased the accuracy for progression in the multivariate model, but it is still waiting for its validation [25]. The use of genomics in risk stratification of bladder cancer patients is one of the promising future perspectives. Information from the Cancer Genome Atlas–MIBC project, which produced a comprehensive, open-access catalogue of DNA alterations, enables grouping of tumours into distinct molecular subtypes with different prognoses. However, most sequencing efforts have focused on MIBC and a significant unmet need is to translate this knowledge to NMIBC [53,54].

Racial differences in tumour characteristics were found during the process of scoring system validation. In several studies validating the EORTC risk tables in Asian populations, the majority of patients were classified in the intermediate-risk group with 92.5%, 87.8%, and 78.0% in the studies by Sakano et al [31], Ieda et al [30] and Xu et al [44], respectively. Scoring systems might not have general applicability, and those that work well in Caucasian populations might be less suitable in Asian populations. Therefore, external validation of any new scoring system in local contemporaneous cohorts remains important.

In addition, it is important to mention that for a risk model to have clinical significance, assessing the C-index and calibration is not sufficient. Clinical decision analysis using variable approaches such as the clinical decision curve analysis are necessary to assess the differential net benefits and the misclassification risks of the assessed model compared with current standards of care [55].

The previously presented information may be summarised in the following recommendations for the use of risk stratification tools and prognostic models in clinical practice:

1. Use the EAU risk categories for a risk-adapted approach to treating NMIBC patients.
2. Use the EORTC risk tables for individual prognosis estimation in NMIBC patients treated with adjuvant intravesical chemotherapy.
3. Use the IBCG risk stratification model for further risk subclassification of intermediate-risk NMIBC patients.
4. Use the CUETO model for prognosis estimation in NMIBC patients treated with a short schedule of adjuvant intravesical BCG.
5. Use the EORTC nomograms and risk groups for prognosis estimation in NMIBC patients treated with 1–3 yr of adjuvant intravesical BCG.
6. Use the concept of conditional recurrence and progression estimates during follow-up, and modify the follow-up strategy according to the ongoing risk of recurrence/progression.

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4. Conclusions

Risk stratification and prognostic models are of great importance because they enable standardisation of the treatment and follow-up, and data comparison. Available scoring systems should be updated to match current standards of treatment. The low overall performance of the models reflects the unmet need for accurate biomarkers that measure the inherent biological potential of the tumours in the context of the microenvironment and host factors in general.

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Study concept and design: Soukup, Čapoun, Cohen, Hernández, Burger, Compérat, Gontero, Lam, Mostafid, Palou, van Rhijn, Rouprêt, Shariat, Sylvester, Yuan, Zigeuner, Babjuk.
Acquisition of data: Soukup, Čapoun.
Analysis and interpretation of data: Soukup, Čapoun.
Drafting of the manuscript: Soukup, Čapoun.
Critical revision of the manuscript for important intellectual content: Cohen, Hernández, Burger, Compérat, Gontero, Lam, Mostafid, Palou, van Rhijn, Rouprêt, Shariat, Sylvester, Yuan, Zigeuner, Babjuk.
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