

Validation of EORTC, CUETO and EAU risk stratification in prediction of recurrence, progression and death of patients with initially non-muscle invasive bladder cancer (NMIBC): a cohort analysis with systematic review.

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Abstract

Purpose: To validate and summarize current evidence about the reliability of EORTC, CUETO and EAU risk stratification in prediction of recurrence, progression and death of patients with initially non-muscle-invasive bladder cancer (NMIBC). **Methods:** Retrospective cohort analysis of 322 patients with newly diagnosed NMIBC. We assessed the concordance (Harrell's c-index) of our results with calculated risk scores in Cox proportional hazard regression models and utilized receiver operating characteristic curve analysis (area under curve; AUCROC). Lastly, to further confirm our observations we conducted a systematic review. **Results:** 1-year and 5-year c-indices ranged from 0.55 to 0.66 for recurrence and from 0.72 to 0.82 for progression. AUCROC of predictions ranged from 0.46 for 1-year recurrence risk based on CUETO groups to 0.82 for 1-year progression risk based on EAU risk groups. The accuracy of prediction was lower for patients treated with BCG maintenance immunotherapy. EORTC model (overall c-index $c=0.64$; 95%CI:0.61-0.68) was superior to EAU ($p=0.035$; $c=0.62$; 95%CI: 0.59-0.66) and CUETO ($p<0.001$; $c=0.53$; 95%CI:0.50-0.56) model in recurrence prediction. EORTC model ($c=0.82$; 95%CI:0.77-0.86) also performed better than CUETO ($p=0.008$; $c=0.73$; 95%CI:0.66-0.81) but there was no sufficient evidence that it performed better than EAU ($p=0.572$; $c=0.81$; 95%CI:0.77-0.84) for predicting progression. EORTC and CUETO comparably predicted progression in BCG-treated EAU high-risk patients ($p=0.48$). **Conclusions:** The division into risk groups by EORTC, CUETO and EAU offered moderately accurate predictions about recurrence and progression of NMIBC, which emphasizes the urgent need for the development of more personalized and accurate predictive tool. EORTC provided the best recurrence and progression prediction.

Introduction

According to GLOBOCAN, bladder cancer (BC) is the most common malignancy of the urinary tract. It is the 7th most common cancer in men and the 17th in women. In the European Union, the age-standardized incidence rate is 27 per 100 000 in men and 6 per 100 000 in women.

In general, 75% of newly diagnosed bladder cancer are non-muscle-invasive (NMIBC) which is characterized by the high rate of recurrence and progression, despite local treatment.[1] This requires patients to follow a regular schedule of visits and conduction of many potentially superfluous procedures (as cystoscopy). Remaining 25% of newly diagnosed bladder cancers are of the muscle-invasive type (MIBC). As MIBC needs a radical treatment (cystectomy, radiotherapy, chemotherapy), prediction of recurrence and progression from NMIBC to MIBC remains a perennial topic of research.[2]

NMIBC is generally associated with 5-year survival higher than 88%,[3] however, up to 70% of NMIBC tumors recur after initial treatment, and are associated with 10–20% lifetime risk of progression to MIBC. [4] In case of MIBC, the prognosis is much more unfavorable, as 5-years survival rate ranges from 63% to even 15%.[3] Thus, in 2006 EORTC (European Organisation for Research and Treatment of Cancer) developed a risk stratification tool to predict 1- and 5-year probability of recurrence and progression after transurethral resection of bladder tumor (TURBT).[5] The topic was followed in 2009 by CUETO (Club Urológico Español de Tratamiento Oncológico), which published a comparable risk model adapted for

patients receiving BCG (Bacillus Calmette-Guerin) maintenance immunotherapy.[6] Both the EORTC and CUETO model stratify patients into 4-risk groups based on a retrospective analysis of clinical trial data and are based mainly on gender, age, tumor size and extent (defined as T in TNM staging), concomitant Tis (carcinoma in situ), grade, number of tumors and recurrence status. Additionally, the most recent guidelines of European Association of Urology (EAU) also define a 3-group risk stratification algorithm utilizing the same features.[2] EAU categories reclassified about 38% patients into a higher risk group of recurrence and 12% into a higher risk of progression.[7]

The study providing EORTC classification did not include patients treated with BCG, the CUETO only included patients with a short maintenance schedule of BCG therapy and the EAU risk stratification is based mainly on the risk of progression, not recurrence. The universal assessment of the risk of recurrence and progression in NMIBC is, therefore, still an unsolved issue and the performance of those systems for real-life mixed and heterogeneous cohorts remains uncertain.

Despite extensive research, those scales remain the golden standard of NMIBC risk stratification and none of them were proved superior to each other. The aim of this work was to validate and summarize current evidence about the reliability of EORTC, CUETO and EAU risk stratification in the prediction of recurrence, progression and death of patients with initially non-muscle invasive bladder cancer.

Methods

This retrospective cohort analysis included patients with newly diagnosed NMIBC who were treated with transurethral resection of the bladder tumor (TURBT) in the Department of Urology of The Hospital Ministry of the Interior and Administration in Łódź during a 10-year period (since January 2005 to December 2015) and who were later followed until August 2017 in terms of the disease recurrence, progression or death.

Following inclusion criteria were applied during the revision process: (1) patients had to be primarily diagnosed with urothelial bladder tumor, (2) ECOG Scale of Performance Status (PS) equals 0 or 1 at the time of first resection (control for comorbidities), (3) first resection was performed during the accrual period from 2005 to 2015, (4) NMIBC (Ta, Tis or T1 stage of tumor extent) was confirmed by histopathological report following the first procedure. If the first resection was not complete, the second procedure was conducted as described below. If the muscle-invasive type of bladder cancer (MIBC) was diagnosed (during first or second TURBT procedure) the patient was not included in further analysis. If initial performance status initial imaging studies showed advanced or disseminated disease (invasion of the perivesical or adjacent tissue, locally or distant metastases) those patients were not qualified for the analysis. Exclusion criteria were met by the patients with insufficient follow-up (who didn't show up on the first follow-up visit after 3 months from TURBT procedure). Acquired initial clinical (age at diagnosis, sex, smoking status, hematuria at diagnosis, number of tumors, a diameter of tumor) and pathological factors (T stage according to current TNM classification, grading) were later used for risk estimation using EORTC[8], CUETO[9], and EAU risk stratification[2] algorithms. Definitions for disease recurrence and

progression followed those defined in original articles[6, 8] and were also consistent with recent recommendations [10] but the progression was defined as the presence muscle-invasive disease ($\geq T2$; to ascertain the consistency with previous publications).

TURBT procedures and follow-up

All TURBT procedures were performed by the same team of 5 urologists according to standard procedure protocol and current EAU guidelines. Each procedure was supervised by the specialist with at least 5-year experience. Whole visible tumors were resected with a best possible proper margin of normal tissue was maintained. After the surgery, patients were not subjected to any immediate post-operative chemotherapy. All collected specimens were examined by a pathologist (specialist) according to the 1973 World Health Organization (WHO) classification system and staged using TNM system. The second TURBT was performed if the first resection was not complete, if T1 stage was reported or if the presence of muscle fibers was not confirmed by a pathologist in the specimen from the high-risk patient. Delay associated with the second resection after the TURBT had to be no longer than 6 weeks. Additional treatment with BCG maintenance could be ordered as a result of the doctors' case conference.

In follow-up, patients underwent cystoscopy every 3 months for 2 years and every 6 months in the following years. The procedures were performed by the same team of urologists. Next TURBT procedure was performed in case of suspected recurrence or progression. All endpoints had to be confirmed by pathologists' reports. Overall survival data of the selected cohort were acquired upon the author's request to the Polish Ministry of Digital Affairs.

Statistical analysis

Intragroup associations were assessed using Pearson's Chi-squared test (with Yates' continuity correction if appropriate), Spearman's rank correlation rho, one-tailed 1-sample proportions test, unpaired and paired t-test and Wilcoxon rank sum test with continuity correction. Survival analysis was conducted using Kaplan-Meier estimate with analysis using univariate Cox's proportional hazards model as well as log-rank test. In the modeling, as part of assumptions testing the correlation between Schoenfeld residuals and (transformed) time using a Chi-square test was assessed. The concordance with EORTC, CUETO and EAU risk stratification groups was estimated using Harrell's c-index for right-censored event times, with a value of 1.0 indicating the perfect concordance. As concordance (c-index) is understood as a weighted (by time weight) mean of Somers' d rank at each event time, weighted one-sample t-test has been used to compare the differences in means of Sommer's d—comparing the concordance of Cox's proportional hazards models utilizing different risk stratification models. Mean Sommer's d value and its confidence interval was converted to Harrell's c-index (c) using the formula: $c = (d+1)/2$. The predictive ability of those algorithms was additionally assessed using the area under receiver operating characteristic curve (AUC ROC) for prespecified periods of 1 and 5 years since first TURBT procedure. Estimated cumulative incidences were calculated for multistate outcomes, including death as a competing risk. As predefined features were crucial for treatment recommendations no missing data had to be imputed. All statistical

analyses were performed using STATISTICA 13 (TIBCO software, USA) and R statistical programming language.

Systematic review

Our results were finally presented in the context of previous research by conducting the systematic review based on Ovid MEDLINE database. The query search was constructed as follows: (“EORTC” OR “CUETO” OR “EAU”) AND non-muscle-invasive bladder cancer AND (“progression” or “recurrence” or “survival”). This part of the analysis followed PRISMA guidelines and included the screening and full-text analysis by 2 authors (MJ and KS). The reasons for exclusion during screening were another study question, another study group and a review. The date of last search was 2018–10–31. The studies were included in the analysis if it followed similar inclusion criteria as in our study. The extraction was also performed by 2 authors (MJ and KS) independently and cross-checked. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies was used to assure the quality of included papers. Threshold of less than 12 stars was applied.

The study was approved by the Bioethics Committee of the Medical University of Lodz.

Results

Inclusion criteria were met by 389 patients, however, 67 were excluded from further analysis due to early lost in follow-up. The final group of 322 patients was characterized in Table 1. In our study group, the sex was not associated with smoking status ($p = 0.92$). Patients were significantly more often diagnosed because of hematuria than because of incidental finding during ultrasound examination (69% vs. 31%; $p < 0.01$). Sex also wasn't associated with the size of the tumor (diameter of less or more than 3 cm; $p = 0.29$) or with the existence of multiple tumors ($p = 1.00$). Similarly, smoking status also wasn't associated with multiple tumors ($p = 0.70$) and size of the tumor ($p = 0.39$). Patients of different sex ($p = 0.29$) and of different smoking status ($p = 0.93$) presented at a similar stage T in TNM. Smokers and non-smokers presented with similar tumor grading ($p = 0.62$) and were classified to similar risk groups ($p = 0.86$).

Median follow-up time was 48 months, with a maximum of 137 months. During that time 201 patients (62%; 95CI: 57–68%) experienced at least one recurrence and 40 patients (12%; 95%CI: 9%–17%) progressed. Both of these results were not greater than the lifetime risk reported in EAU guidelines (recurrence: vs. $\geq 70\%$, $p = 0.99$; progression: vs. $\geq 15\%$, $p = 0.92$). Median overall survival (OS) since the first diagnosis of NMIBC was 8.78 years (95%CI: 7.52–10.31; Figure 1A) with the greater cumulative incidence of death after recurrence or progression. (Figure 1B) Median recurrence-free survival (RFS) was 2 years (95%CI: 1.25–2.00) and median progression-free survival (PFS) was not reached (due to competing risk of death from other cause).

As shown in Table 2, even though sex is being used in CUETO scoring system it did not show significant association with the survival in univariate analysis. Existence of carcinoma in situ was not associated with modified RFS, PFS or OS. Diameter of greater than 3 cm did shorten the RFS and PFS, but not OS. It

was also noticeable that hematuria was significantly associated with shorter PFS and OS, although it is not used in any of the studied systems.

Due to large timespan of accrual and follow-up, changes in guidelines and high rate of consent withdrawal (48%) the BCG therapy was administered mostly, but not only, to patients of modern EAU high risk group ($p < 0.01$; 58 patients, 48%). Exactly 16 patients (19%) of medium and 18 patients (15%) of low risk group were also treated with BCG.

In the subgroup of high risk patients ($N = 120$), the patients who didn't withdraw their consent and were finally treated with BCG were younger (mean 66.4 years vs. 73.3 years; $p < 0.01$) and were rather smokers (23/35 vs. 12/50; $p = 0.02$). In the whole group the application of BCG therapy didn't influence the RFS (HR 1.09; 95%CI: 0.81–1.46) nor PFS (HR 0.55; 95%CI: 0.25–1.21), but in high risk group this effect was noticeable (for RFS: HR 0.50; 95%CI: 0.33–0.76; for PFS: HR 0.16; 95%CI: 0.07–0.40). The same observation wasn't noted for the OS, where BCG therapy extended the life of high risk patients (HR 0.18; 95%CI: 0.09–0.37) and also from all risk groups (HR 0.47; 95%CI: 0.29–0.74).

EAU, EORTC and CUETO risk groups

As shown in Figure 1C, EORTC model was superior to EAU and CUETO model in recurrence prediction. For progression prediction, EORTC model performed better than CUETO but there was no sufficient evidence that it also performed better than EAU. Noteworthy, all c-indices for progression prediction were greater than for recurrence. The cumulative incidences in different risk groups have been shown in Figure 2.

Risk stratification of overall survival using EAU-based groups lead to overall concordance (c-index) of 0.64; with 0.82 for 1-year and 0.65 for 5-year prediction. A similar observation was made for RFS (1-year c-index: 0.64; 5-year: 0.62), where medium and high risk groups were also associated with shorter RFS in comparison with low risk group, as shown in Table 2. EAU risk groups used as predictors had high model concordance for progression and death (Table 3).

As expected, each additional EORTC scoring point (HR: 1.19; 95%CI: 1.14–1.26) and CUETO point (HR: 1.07; 95%CI: 1.01–1.14) was associated with shortened RFS. The same was observed for progression (PFS, EORTC HR: 1.234; 95%CI: 1.16–1.31; CUETO HR: 1.64; 95%CI: 1.41–1.91). After conversion to defined 4 risk groups, we have calculated the c-index values comparing the concordance of reference risk stratification to our group. Results of this have been presented in Table 3.

To assess further the predictive abilities of reference scores and risk groups, we performed receiver operating characteristic (ROC) curve analysis for recurrence and progression in 1-year and 5-year periods. (Suppl. Figure 1) Shown in Table 5 the areas under the ROC curve (AUC) for prediction or recurrence ranged from 0.46 to 0.69; while for progression ranged from 0.66 to 0.82.

Our group consisted of 58 EAU high risk patients that we treated with BCG. In this group EORTC system achieved the concordance of 0.56 (95%CI: 0.48–0.63) for recurrence prediction. The CUETO achieved the concordance of 0.57 (95%CI: 0.50–0.65) in this scenario and it's performance was not better than EORTC

($p = 0.69$). For progression, the EORTC system yielded the c-index of 0.66 (95%CI: 0.35–0.98) and CUETO showed 0.55 (95%CI: 0.23–0.86). The difference between those 2 models was not statistically significant ($p = 0.48$), meaning that both EORTC and CUETO showed low and surprisingly comparable performance in EAU high risk patients who were treated with BCG.

Systematic Review

To further confirm our observations we have conducted the systematic review. Designed search query allowed for screening of 176 publications. On this stage, 40 publications were discarded as reviews, 77 due to another study questions and 24 due to another study groups. This resulted in 35 papers included in full text analysis, during which another 17 were excluded because of lack of appropriate analysis (no analysis of concordance) and 2 due to another study questions. None of the studies dropped out in quality analysis. Detailed results of this process were included as Suppl. Table 1. C-indices extracted from final 16 publications were appended to Table 4 and AUC values to the Table 5.

Discussion

In this study, we performed the validation of EORTC, CUETO and EAU risk stratification algorithms in prediction of recurrence, progression and death of patients with newly diagnosed NMIBC. Our analysis included 322 patients and in terms of intragroup associations confirmed observations from previous studies[11, 12]; allowing us to consider our study group representative. In our study group EORTC model presented with superior performance, although this performance is generally moderate and the difference, despite its statistical significance, may not be of clinical significance. The conduction of systematic review allowed us to summarize and confirm that state-of-the-art tools for risk stratification validate insufficiently in real clinical scenario and that it emphasizes the need for development of new models. To assure the completeness of the paper, we have assessed comprehensively not only the simplified risk groups presented in EAU, EORTC and CUETO publications but also the score that is used for the development of these risk groups.

In the case of NMIBC, risk stratification algorithms are in great demand as the progression to MIBC is associated with poor prognosis, which was shown not only by our analysis but several others.[13] Despite known risk factors and continuous repetition of TURBT procedures, the accuracy of recurrence and progression to MIBC is still unsatisfactory. As shown by our results and systematic review, poor discriminative abilities of the state-of-the-art risk stratification tools are problematic in both recurrence and progression forecasting. The latter, however, seems to be more accurately predicted by those tools.

We are the first one to report the statistically significant advantage of EORTC over EAU and CUETO in recurrence prediction. No paper before compared the c-indices directly with their 95%CI. The superiority, however, may be not relevant from the clinical point of view, because the c-index values are generally low. It may be, however, relevant to the progression prediction. Although we didn't find the difference in EAU and EORTC for this problem, EORTC proved its superiority over CUETO. This should be, however, considered with the fact that CUETO was initially developed for BCG-treated patients.

Although we acknowledge that discussed systems could be used for recurrent cases to assess prognosis, importantly, our study did analyze one the survival to the first recurrence. The rationale for this was the significant impact of the individual surgeon on the risk of recurrence after curative treatment of patients with NMIBC, as described earlier by the others, [14] and could aggravate the lead-time bias. This approach was adopted in several similar studies, e.g. by Shen et al. [15]

Our systematic analysis has also shown the inconsistency in reporting the validity of utilized stratification approaches. For example, very recent analysis of 301 patients by Wang et al.[16] or the analysis of 1436 patients by Rieken et al.[17] (e.g. in the group without immediate postoperative instillation of chemotherapy) could not be included in the review due to lack of c-index or AUCROC analysis. Even if the c-index values are reported, they are usually provided without 95% confidence interval, hence are unfit for meta-analysis. Nevertheless, most of the authors of cited papers indirectly confirm our observations. The accuracy of predictions was consistently decreased in patients treated with BCG in all included publications.[18]

At the time our analysis was finished, by the end of 2018, a critical assessment from the European Association of Urology Non-muscle-invasive Bladder Cancer Guidelines Panel has been published.[19] In this paper, the experts concluded that none of the available risk stratification and prognostic models reflects current standards of treatment. In the presented opinion the EORTC risk tables and CUETO scoring model should be updated with previously unavailable data and recalculated. Our data support this conclusion.

Multiple discrepancies between original publications and validation studies are reported in the reviewed material. For example, patients requiring second TURBT were dropped from the analysis in original CUETO and EORTC publications, while multiple recent papers didn't secure this criteria.[20]

Despite numerous attempts of new models development, in recent publication by Kim et al.[21] the authors achieved the c-index for 5-year recurrence and progression of 0.65 and 0.70, respectively. Considering possible overfitting of the model (c-index provided without external validation) and the fact that our validation proved EORTC to provide similar c-indices, its utility requires further extensive validation. Similarly, in the paper by Hong et al.[22] the AUCROC of proposed nomogram was 0.604 for the 5-year prediction of recurrence. In our study, without utilization of proposed nomograms, better validation AUCROC metrics were achieved by EAU risk groups, EORTC score and risk groups. Moreover, the recently proposed model for patients treated with 1–3 years of maintenance BCG [23] based only on grading and age was described with c-index of 0.59 for training and 0.56 validation sets for recurrence. Those values were covered by 95% CI for c-indices we have provided in this study and those were given for mixed population of both patients treated with BCG and not. Similar situation was note for progression, where authors provided c-indices of 0.72 and 0.64 for training and validation sets, respectively.

Lastly, it is worth mentioning that current risk stratification tools are hard to apply in the field of personalized medicine. For example, applying the standard cutoff of 50% probability, one can conclude

that classification into EORTC group of 38% probability of 1-year recurrence probability and 62% of 5-year probability would, per assumption, yield in 38% incorrect predictions for both timeframes. Currently available nomograms do not predict expected time of recurrence or progression, hence cannot be treated as predictive tests for particular patients. This means that despite description of general predictive potential using AUCROC or c-index parameters, analysis of these tools as predictive models in terms of their accuracy, sensitivity or specificity is futile.

Our study is not devoid of limitations associated with study design. As a retrospective analysis, possible recall and selection bias should be considered. This was partially tackled by integration of the results with data received from central registry. Because of this integration, we were able to double check our records. However, only overall survival was analyzed using the information from the central governmental registry. The data about recurrence and progression were obtained only from one institution and the bias associated with this is further aggravated by the fact the data was collected only from one facility and this facility isn't the only one in the region performing TURBT procedures. Patients choosing different facilities for further treatment had to be lost in follow-up. Additionally, the procedures were performed by multiple surgeons and were assessed by multiple pathologists. Comorbidities might also have an uncontrolled influence on treatment and decision making, however, based on the finding presented above we consider our sample representative for the population. Additionally, none of the patients was treated with immediate single intravesical instillation of gemcitabine. However, the recent evidence suggest that this further decreases the predictive performance of studied systems. [24]

Notwithstanding this, our study provides additional evidence on the validity of state-of-the-art risk stratification method on a fairly large sample and is the very first one trying to summarize current research and compare all 3 currently recommended methods of risk assessment to each other.

Conclusions

We confirmed and summarized the moderate performance of EAU, EORTC and CUETO risk groups in the prediction of recurrence and progression worldwide and highlighted the urgent need for the development of more personalized and accurate risk stratification algorithms for NMIBC. EAU and EORTC were shown to have better properties in the prediction of recurrence than CUETO. However, all of those systems are better in progression prediction. None of the methods was superior in predicting NMIBC progression.

Declarations

Authors' Contribution: Jobczyk - protocol/project development, data collection or management; Stawiski - protocol/project development, data collection or management, data analysis, manuscript writing/editing; Fendler - protocol/project development, manuscript writing/editing; Róžański - protocol/project development.

Compliance with Ethical Standards: None of the authors have the conflict of interest to declare. Written informed consent was obtained from all patients before treatment, which allowed for anonymous

retrospective analysis of collected data in concordance with Polish law. The study was approved by the local ethical committee at the Medical University of Lodz.

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Tables

Table 1. Group description

Feature		Details			
Predictors	Sex	Males: 74% (N=237)		Females: 26% (N=85)	
	EAU risk group	Low: 37% (N=119)	Medium: 26% (N=83)	High: 37% (N=120)	
	Age	Mean: 67.27±11.14 years, Median: 68 years			
	Smoking	Non-smokers: 70% (N=224)		Smokers: 30% (N=98)	
	T stage:	Ta: 63% (N=203)	Tis: 3% (N=9)	T1: 34% (N=110)	
	Grading	G1: 54% (N=174)	G2: 35% (N=113)	G3: 11% (N=35)	
	Number of tumors	Multiple: 36% (N=115)		Single: 64% (N=207)	
	Diameter	Less than 3 cm: 70% (N=226)		3 or more cm: 30% (N=96)	
Outcomes	BCG treated	Yes: 29% (N=92)		No: 71% (N=230)	
	EORTC recurrence risk group	1-year 15% / 5-year 31% risk: 31% (N=100)	1-year 24% / 5-year 26% risk: 37% (N=119)	1-year 38% / 5-year 62% risk: 32% (N=102)	1-year 61% / 5-year 78% risk: ~0% (N=1)
	EORTC progression risk group	1-year 0.2% / 5-year 0.8% risk: 39% (N=125)	1-year 1% / 5-year 6% risk: 30% (N=95)	1-year 17% / 5-year 45% risk: 4% (N=14)	1-year 5% / 5-year 17% risk: 27% (N=88)
	CUETO recurrence risk group	1-year 8.2% / 5-year 21% risk: 76% (N=244)	1-year 12% / 5-year 36% risk: 20% (N=64)	1-year 25% / 5-year 48% risk: 4% (N=12)	1-year 42% / 5-year 68% risk: 1% (N=2)
	CUETO progression risk group	1-year 1.2% / 5-year 3.7% risk: 77% (N=247)	1-year 3% / 5-year 12% risk: 16% (N=50)	1-year 5.5% / 5-year 21% risk: 8% (N=25)	1-year 14% / 5-year 34% risk: 0% (N=0)

Table 2. Risk factors of NMIBC recurrence, progression and death in univariate Cox regression analysis.

Factors present at the time of first TURBT procedure:	Univariate analysis									Used by		
	RFS			PFS			OS			EORTC	CUETO	EAU
	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p			
Males vs. <u>females</u>	1.12	0.82-1.53	0.47	1.45	0.67-3.15	0.35	1.33	0.81-2.172	0.26	No	Yes	No
Age at diagnosis (increase by 1)	1.01	0.99-1.02	0.42	1.04	1.01-1.1	0.01	1.08	1.05-1.1	<0.01	No	Yes	No
Non-smokers vs. <u>tobacco smokers</u>	0.81	0.6-1.1	0.17	0.95	0.48-1.86	0.88	0.66	0.41-1.05	0.08	No	No	No
Tis vs <u>Ta</u>	1.38	0.61-3.13	0.45	8.76	0.91-84.35	0.06	2.63	0.63-10.92	0.18	Yes	Yes	Yes
T1 vs <u>Ta</u>	2.11	1.59-2.8	<0.01	26.92	8.29-87.48	<0.01	2.13	1.43-3.18	<0.01	Yes	Yes	Yes
G2 vs <u>G1</u>	1.47	1.09-1.99	<0.01	8.74	3.32-23.03	<0.01	2.34	1.52-3.6	<0.01	Yes	Yes	Yes
G3 vs <u>G1</u>	2.54	1.69-3.84	<0.01	15.45	5.3-45.03	<0.01	2.75	1.5-5.05	<0.01	Yes	Yes	Yes
Multiple vs. <u>single tumor</u>	1.7	1.28-2.24	<0.01	2.63	1.4-4.92	<0.01	1.69	1.13-2.52	0.01	Yes	Yes	Yes
Diameter >3cm vs. <u><3 cm</u>	2.15	1.61-2.85	<0.01	3.12	1.68-5.83	<0.01	1.25	0.82-1.92	0.3	Yes	No	Yes
Hematuria vs <u>no hematuria</u>	1.09	0.81-1.47	0.55	2.30	1.02-5.19	<0.05	1.96	1.22-3.14	<0.01	No	No	No
EAU medium	1.55	1.07-2.25	0.02	2.3	0.39-13.85	0.36	1.84	1.05-3.22	0.03			

risk vs <u>low</u> risk												
EAU high risk vs <u>low</u> risk	2.46	1.77- 3.43	<0.01	21.94	5.27- 91.4	<0.01	2.77	1.73- 4.44	<0.01			

HR - hazard ratio; 95%CI - 95% confidence interval; RFS - recurrence-free survival; PFS - progression-free survival; OS - overall survival; underlined feature is considered as a reference in HR computation.

Table 3. Concordance of EAU risk group stratification.

	Recurrence		Progression		Survival	
	Overall	With BCG	Overall	With BCG	Overall	With BCG
1-year c-index	0.639	0.560	0.811	0.696	0.815	-
5-year c-index	0.631	0.540	0.785	0.635	0.651	0.608

Table 4. Concordance indices (c-index) for application of EORTC and CUETO risk stratification models with results of systematic review. C-index is given as percentage with 100 as maximal concordance (equivalent to 1.0).

		EORTC				CUETO			
		Recurrence		Progression		Recurrence		Progression	
		Overall	With BCG						
This study	1-year c-index	0.657	0.589	0.820	0.718	0.557	0.580	0.760	0.738
	5-year c-index	0.649	0.570	0.809	0.681	0.547	0.559	0.715	0.574
Fernandez-Gomez J et al. (2011)[25]	Overall c-index	0.630	-	-	-	-	-	-	-
Sylvester et al. (2006)[5]	1-year c-index	0.660	-	0.740	-	-	-	-	-
	5-year c-index	0.660	-	0.750	-	-	-	-	-
Fernandez-Gomez J et al. (2009)[6]	1-year c-index	-	-	-	-	0.636	-	0.687	-
	5-year c-index	-	-	-	-	0.644	-	0.700	-
Xylinas E et al. (2013) [18]	Overall c-index	0.597	0.554	0.662	0.576	0.523	0.597	0.616	0.645
Ravvaz K et al. (2017) [26]	1-year c-index	0.630	0.570	0.790	0.710	0.590	0.560	0.790	0.640
	5-year c-index	0.590	0.530	0.740	0.690	0.560	0.570	0.720	0.610
Tianyuan X et al. (2013) [27]	Overall c-index	0.711	-	0.768	-	0.663	-	0.741	-
Dalkilic A et al. (2018) [28]	5-year c-index	0.777	0.823	0.801	0.832	0.705	0.758	0.881	0.806
Pillai R et al. (2011)[29]	1-year c-index	0.620	-	0.650	-	-	-	-	-
	5-year c-index	0.630	-	0.670	-	-	-	-	-
Almeida et al. (2015)[30]	1-year c-index	0.700	-	-	-	-	-	-	-

	5-year c-index	0.720	-	-	-	-	-	-	-
Busato Junior W et al. (2015)[31]	1-year c-index	-	-	0.860	-	-	-	-	-
	5-year c-index	-	-	0.780	-	-	-	-	-
Choi S et al. (2014)[32]	Overall c-index	0.759	-	0.704	-	0.836	-	0.745	-
Vedder M et al. (2014) [33] <i>Spain</i>	Overall c-index	0.590	-	-	-	0.590	-	-	-
Vedder M et al. (2014) <i>Denmark</i>	Overall c-index	0.610	-	-	-	0.560	-	-	-
Vedder M et al. (2014) <i>The Netherlands</i>	Overall c-index	0.550	-	-	-	0.580	-	-	-

Table 5. Area under the ROC curves

			EAU risk groups	CUETO score	CUETO risk groups	EORTC score	EORTC risk groups
Recurrence	This study	1-year RFS	0.633	0.566	0.461	0.670	0.646
		5-year RFS	0.652	0.539	0.484	0.693	0.678
	Kılınç et al. (2017)[34] - 5-year RFS			-	-	-	0.773
	Hernandez et al. (2011)[35] - 1-year RFS			-	-	-	0.61
	Hernandez et al. (2011) - 5-year RFS			-	-	-	0.70
	Choi et al. (2014)[32] - 5-year RFS			0.894	-	0.832	-
Progression	This study	1-year PFS	0.821	0.674	0.770	0.803	0.801
		5-year PFS	0.805	0.664	0.728	0.802	0.788
	Kılınç et al. (2017) - 5-year PFS			-	-	-	0.901
	Hernandez et al. (2011) - 1-year PFS			-	-	-	0.58
	Hernandez et al. (2011) - 5-year PFS			-	-	-	0.55
	Choi et al. (2014) - 5-year PFS			0.724	-	0.722	-

Figures

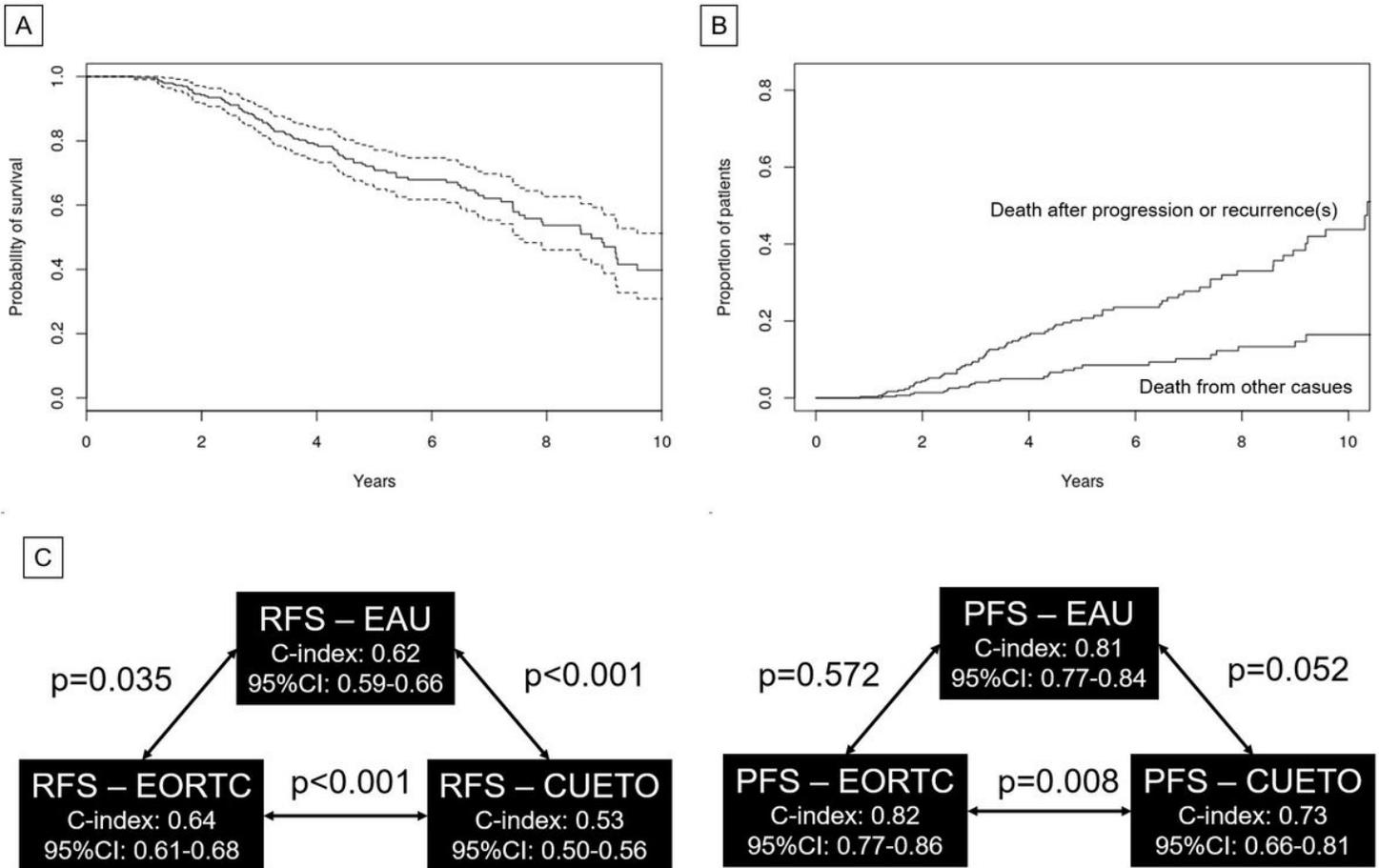


Figure 1

Figure 1. Overall survival of patients with diagnosed NMIBC. Panel A represents the Kaplan-Meier curve of overall survival in study group with its 95% confidence interval marked as dashed lines. Panel B presents the difference in proportion of patients dying after progression or recurrence and from other or uncertain causes in competing risk survival model. Panel C presents the overall c-index values for recurrence and progression prediction using selected scoring models with their 95% confidence interval (95%CI). Presented p-values represent the difference between in c-index calculated using one-sample weighted student's t-tests.

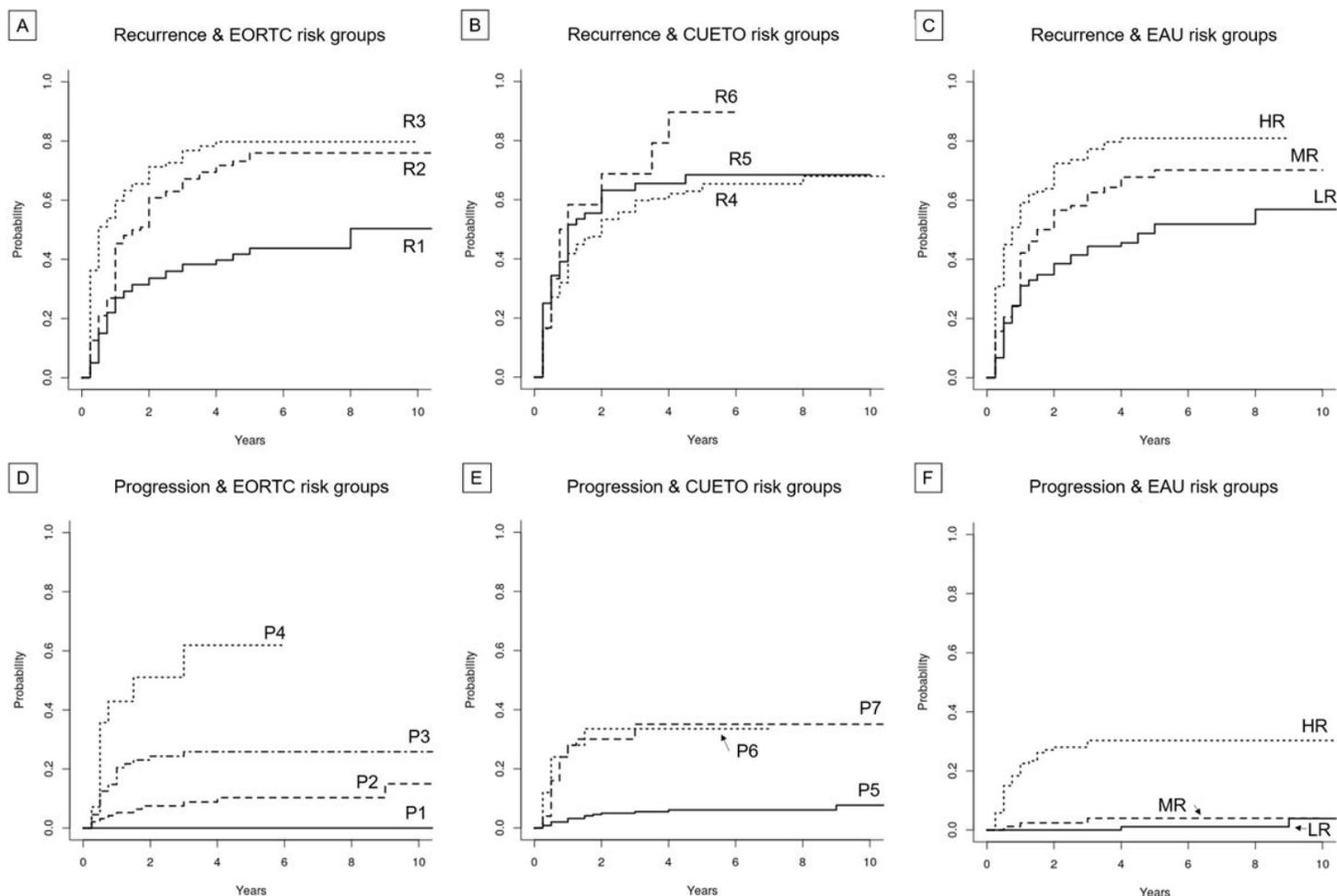


Figure 2

Figure 2. Cumulate incidence plots of recurrence and progression among patients in specific risk strata. Percent values are given to describe the plots in panels A, B, C and D are given for expected incidence of 1-year and 5-year recurrence or progression rates. Panel E and F represent the utility of EAU risk groups as described in guidelines. Cumulative incidence of death (competing risk) in subgroups as well as risk groups of 3 or fewer patients were discarded to enhance readability. Abbreviations: R1 – EORTC 1-year 15% and 5-year 31% risk of recurrence, R2 – EORTC 1-year 24% and 5-year 46% risk of recurrence, R3 – EORTC 1-year 38% and 5-year 62% risk of recurrence, R4 – CUETO 1-year 8.2% and 5-year 21% risk of recurrence, R5 – CUETO 1-year 12% and 5-year 36% risk of recurrence, R6 – CUETO 1-year 25% and 5-year 48% risk of recurrence, P1 – EORTC 1-year 0.2% and 5-year 0.8% risk of recurrence, P2 – EORTC 1-year 1% and 5-year 6% risk of recurrence, P3 – EORTC 1-year 5% and 5-year 17% risk of recurrence, P4 – EORTC 1-year 17% and 5-year 45% risk of recurrence, P5 – CUETO 1-year 1.2% and 5-year 3.7% risk of recurrence, P6 – CUETO 1-year 3% and 5-year 12% risk of recurrence, P7 – CUETO 1-year 5.5% and 5-year 21% risk of recurrence, LR – EAU Low Risk group, MR – EAU Medium Risk group, HR – EAU High Risk group.

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