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Research Report

Recurrence in Non-Muscle Invasive Bladder Cancer Patients: External Validation of the EORTC, CUETO and EAU Risk Tables and Towards a Non-Linear Survival Model

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Abstract.
BACKGROUND: EORTC, CUETO and EAU are the most commonly used risk stratification models for recurrence and progression in non-muscle invasive bladder cancer (NMIBC).
OBJECTIVE: We assessed the predictive value of the EORTC, CUETO and EAU risk group stratification methods for our population and explore options to improve the predictive value using Cox Proportional Hazards (CPH), Boosted Cox regression and a non-linear Random Survival Forest (RSF) model.
MATERIALS: Our retrospective database included of 452 NMIBC patients who underwent a transurethral resection of bladder tumor (TURBT) between 2000 and 2018 in our hospital. The cumulative incidence of recurrence was calculated at one- and five-years for all risk stratification methods. A customized CPH, Boosted Cox and RSF models were trained in order to predict recurrence, and the performances were compared.
RESULTS: Risk stratification using the EORTC, CUETO and EAU showed small differences in recurrence probabilities between the risk groups as determined by the risk stratification. The concordance indices (C-index) were low and ranged between 0.51 and 0.57. The predictive accuracies of CPH, Boosted Cox and RSF models were also moderate, with C-indices ranging from 0.61 to 0.64.
CONCLUSIONS: Prediction of recurrence in patients with NMIBC based on patient characteristics is difficult. Alternative (non-linear) approaches have the potential to improve the predictive value. Nonetheless, the currently used characteristics are unable to properly stratify between the recurrence risks of patients.

Keywords: Recurrence, risk stratification, non-muscle invasive bladder cancer, random survival forest, Cox Proportional Hazards

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INTRODUCTION

In urothelial bladder cancer, the differentiation between the non-muscle invasive bladder cancer (NMIBC) and the muscle invasive bladder cancer (MIBC) is important since prognosis and treatment options differ. The majority of patients (around 80%) is diagnosed with NMIBC [1, 2]. These patients have a good long-term survival prognosis [1]. None the less, recurrence rates as high as 78% have been reported [3]. Therefore, these patients are subjected to intensive follow-up as well as expensive additional treatment, leading to the highest life-long treatment costs of all cancers [4].

Transurethral resection of the bladder tumor(s) (TURBT) is the first step in the treatment of NMIBC. TURBT can be combined with immediate intravesical chemotherapy post-operatively, most often using mitomycin C (MMC), which has proven to reduce the risk of recurrence in low- and low to intermediate-risk patients [5–7] and probably in all risk groups [8]. Patients with an intermediate to high-risk bladder cancer can be treated using repetitive immunotherapy using the Bacillus Calmette-Guérin (BCG) vaccine or by a series of treatments using intravesical chemotherapy [5]. A way to assess the risk of a patient is to use one of the risk tables, designed to estimate the risk of recurrence and progression in NMIBC patients.

The European Organization for Research and Treatment of Cancer (EORTC) [3] and the Club Urológico Español de Tratamiento Oncológico (CUETO) [9] constructed risk tables to estimate the recurrence and progression probabilities. Within the European Association of Urology (EAU) Guidelines, the EAU risk categories are recommended to select the preferred treatment [5]. These EAU risk categories are based on the EORTC risk tables. The relation between recurrence and EAU risk categories has been less often studied than with the CUETO and EORTC risk tables [10].

The results of external validation studies of the EORTC and CUETO fluctuated between slightly better than 'tossing a coin' to highly predictive [11]. A possible explanation for the varying predictive performance is that the EORTC does not take into account the current standard treatments, as only less than 10% received an immediate instillation of chemotherapy, and BCG maintenance treatment was then not available. The CUETO was aimed specifically for BCG-treated patients, which is up to now the most effective therapy for NMIBC in reducing the recurrence and potentially the progression risk [6]. In general, both these risk stratification tools overestimate the recurrence risk with the current standard of treatment [11].

Accurate stratification of recurrence risks in NMIBC is shown to be difficult. In this study, we assess the predictive power of the EORTC, CUETO and EAU risk stratification for recurrence prediction. We aim to study potential improvement of the recurrence prediction by linear and non-linear survival modeling. These methodologies have the potential to improve the risk prediction. We compare the performance with the more common risk stratification methods. To this end, a Cox regression, boosted Cox regression and a non-linear modeling technique, Random Survival Forest, are evaluated for their added value in recurrence prediction.

MATERIALS AND METHODS

Patient selection

The Institutional Review Board of the Amsterdam UMC, location AMC, granted approval for this study (W17_327#17.380). A retrospective database was constructed using Data Management System (v.3.1.3, T & S Innovations, Utrecht, The Netherlands). A letter was sent to all patients who underwent a TURBT procedure between 2000 and 2018 at the Amsterdam UMC, location AMC. All patients got four weeks response time to opt out of the study. Out of 840 patients, 11 patients chose to opt out from the study.

Patients were included when a tumor was resected between 2000 and 2018 and if this tumor was staged as a Ta or T1 NMIBC, with or without concomitant CIS. Patients without a histopathological confirmed malignancy or patients with imaging confirmed nodal or distant metastasis were excluded from the study.

Data preparation

All data analysis was done in R Studio (version 1.2.1335, R Studio, Inc., Boston, MA). The dataset was randomly divided in two groups, 75% of the patients' data was used for training of the survival models (training-set), and the other 25% was used for assessment of the accuracy of the customized survival models (test-set). This random split was repeated ten times in order to assess the stability of the imputation and risk stratification methods. The median performance of those ten splits, as well as the 25% percentile (Q1) and 75% percentile (Q3) is reported.

Imputation

To account for missing data, random forest imputation was used (missForest_v1.4). Data regarding age at TURBT, gender, T-stage of the tumor, the time to recurrence or last follow up visit and the presence of previous malignancies in the patients were required to be complete in all cases. Of the incomplete variables, on average 9% of the data was missing. All variables included in this study had at least 75% of the data present, and in each included patient a minimum of 75% of the variables were known. Little's MCAR test (BaylorEdPsych_v0.5) showed that the missing data was at random. The missing values in the training-set were imputed using a random forest (maximum iterations was set 10, and the number of trees 100). The optimized random forest for the imputation of values was afterwards applied on both train- and test-set. This procedure was repeated 9 times, to impute the values for all ten random train- and test-sets.

Collinearity of variables

Collinearity of data was assessed using the overall and individual multi collinearity diagnostic measures (mctest_v1.2). In case of collinearity, the variable with the highest predictive power is selected for multivariable models.

Right censoring

In this study, the 'time to event' was defined as the time between first TURBT in the study period and a histopathological confirmed recurrence. Patients who did not develop a recurrence during the follow-up or passed away without developing a recurrence are censored at their last follow-up visit.

Assessment of existing risk-stratification methods

To assess the predictive power of the EORTC, CUETO and EAU risk stratification methods, a cumulative incidence plot was created. Subsequently, the probability of recurrence at one- and five-years was calculated for all risk-categories for all ten imputed datasets. In this analysis, the train- and test-set were combined to assess the predictive power.

Survival modeling

Cox regression

The Cox proportional hazards (CPH) regression is used to predict the recurrence-free survival time of patients. One important assumption when using CPH is that the hazard ratio is assumed to be constant over time. Covariates with a $p < 0.10$ in univariate CPH models are selected to be included in the multivariable CPH regression and the other multivariable survival models. Interaction terms were only considered when $p < 0.05$ in the majority of the data splits. Backward stepwise selection using the Akaike's Information Criterion (AIC) was used to optimize the trade-off of performance of the model and minimize the number of variables for the prediction.

Boosted cox regression. Boosting is an iterative technique used to increase the performance of machine learning techniques by combining many 'weak' learners into one strong learner. Component-wise likelihood-based boosting (CoxBoost_v.1.4) is performed with 100 steps to optimize the CPH model.

Random survival forests

Random survival forests (RSF) [12] are considered an extension to the random forest as proposed by Breiman in 2001 [13]. A RF is a collection of decision trees, which together come to a weighted answer. To build the decision trees and thereby random forests (randomForestSRC_v2.9.1), randomness is introduced in two stages. Firstly, a random selection of samples is taken to build the tree using bootstrapping. Secondly, each node of every tree is randomly assigned to (a subset of) variables. RFs are most commonly used for classification and regression problems. RFs have the advantage that the hazards can be non-linear, while the CPH models assume a constant (linear) hazard over time. This makes RSF usable for non-linear survival modeling.

Comparison between survival models

The performance of the survival models at one- and five-years is given as measures of diagnostic accuracy, e.g. sensitivity, negative predictive value (NPV) and accuracy. The concordance index (C-index) is also calculated for the survival models.

RESULTS

A total of 452 patients were included. The characteristics, including patient, tumor and treatment characteristics (of a single random split after imputation) are given in Table 1.

Table 1
Characteristics of the included patients (after one single imputation)

	Imputed survival set ($n=452$)	Non-imputed survival set ($n=452$)	
		Non-missing	Missing values
Male	339 (75%)	339 (75%)	–
Median age in years (Q1–Q3)	69 (61–77)	69 (61–77)	–
Age (<60Y, 60–70Y, >70Y)	108, 141, 203	108, 141, 203	–
CUETO	(24%, 31%, 45%)	(24%, 31%, 45%)	
History of smoking	362 (80%)	315 (70%)	65 (15%)
Currently smoking	145 (32%)	119 (26%)	68 (19%)
Previous malignancies	201 (44%)	201 (44%)	–
Histopathology of tumor			
T stage (Ta, T1)	358, 94	358, 94	–
	(79%, 21%)	(79%, 21%)	
Number of tumors (1, 2–7, ≥8)	247, 189, 16	234, 187, 16	15
EORTC	(55%, 42%, 4%)	(32%, 41%, 4%)	(3%)
Number of tumors (≤3, >3)	368, 84	348, 70	34
CUETO	(81%, 19%)	(77%, 15%)	(8%)
Tumor size (<3 cm, ≥3 cm)	342, 110	311, 94	47
	(76%, 24%)	(69%, 21%)	(10%)
Concomitant CIS	36 (8%)	32 (7%)	4 (1%)
Muscle present in TURBT specimen	323 (71%)	307 (68%)	28 (6%)
WHO'73 (Grade 1, 2, 3)	67, 238, 147	63, 234, 139	16
	(15%, 53%, 32%)	(14%, 52%, 31%)	(4%)
Recurrence rate	370, 59, 23	370, 57, 23	2
(Primary, ≤1rec/Y, >1rec/Y)	(82%, 13%, 5%)	(82%, 13%, 5%)	(0%)
Treatment after tumor resection			
Post-operative MMC	203 (45%)	198 (44%)	21 (5%)
Adjuvant BCG	98 (22%)	97 (21%)	7 (2%)
Recurrence	227 (50%)	227 (50%)	–
Median time to recurrence in years (Q1–Q3)	1.0 (0.5–2.5)	1.0 (0.5–2.5)	–
Median time to censoring in years (Q1–Q3)	4.2 (1.7–7.4)	4.2 (1.7–7.4)	–

Table 2
The median cumulative incidence (first quartile – third quartile) of recurrence at one- and five-years of the three most commonly used risk stratification tools. In the high-risk groups for the EORTC and CUETO the number of patients was low, and therefore no conclusions can be drawn from these groups

	Low risk	Low to intermediate risk	Intermediate to high risk	High risk	C-index
EORTC 1Y	0.11	0.31	0.34	0.13	0.56
	(0.11–0.11)	(0.30–0.31)	(0.34–0.35)	(0.00–0.25)	(0.55–0.57)±0.03
EORTC 5Y	0.41	0.59	0.55	0.56	
	(0.40–0.41)	(0.59–0.59)	(0.55–0.56)	(0.50–0.63)	
CUETO 1Y	0.24	0.33	0.30	0.17	0.52
	(0.24–0.24)	(0.32–0.34)	(0.29–0.32)	(0.17–0.28)	(0.52–0.52)±0.03
CUETO 5Y	0.52	0.54	0.59	0.63	
	(0.51–0.52)	(0.53–0.55)	(0.58–0.61)	(0.58–0.75)	
CUETO BCG-treated 1Y	0.34	0.33	0.48	–	0.51
	(0.33–0.34)	(0.33–0.36)	(0.41–0.53)		(0.48–0.52)±0.07
CUETO BCG-treated 5Y	0.56	0.43	0.56	–	
	(0.55–0.57)	(0.43–0.47)	(0.51–0.61)		
EAU 1Y	0.11	0.27		0.43	0.57
	(0.11–0.11)	(0.26–0.27)		(0.42–0.43)	(0.56–0.57)±0.03
EAU 5Y	0.41	0.54		0.64	
	(0.40–0.41)	(0.53–0.54)		(0.63–0.64)	

Accuracy of risk-stratification methods

The cumulative incidence of all three risk stratification models was calculated for each random split. The median cumulative incidences, with the first and third quartile are reported in Table 2. Note that the high-risk categories in the EORTC and CUETO contained few patients, i.e. five and ten patients at most, respectively

Table 3
The diagnostic accuracy of the three customized survival models at one- (1Y) and five-years (5Y)

	Cox proportional hazards		Boosted Cox model		Random survival forest	
	1Y $n=86.5$ Q1 : 86–Q3 : 90, 9 recurrences Q1 : 8–Q3 : 11	5Y $n=64$ Q1 : 63–Q3 : 64, 33 recurrences Q1 : 30–Q3 : 34	1Y $n=86.5$ Q1 : 86–Q3 : 90, 9 recurrences Q1 : 8–Q3 : 11	5Y $n=64$ Q1 : 63–Q3 : 64, 33 recurrences Q1 : 30–Q3 : 34	1Y $n=86.5$ Q1 : 86–Q3 : 90, 9 recurrences Q1 : 8–Q3 : 11	5Y $n=64$ Q1 : 63–Q3 : 64, 33 recurrences Q1 : 30–Q3 : 34
Sensitivity %	73	58	70	64	71	59
(Q1–Q3)	(54–85)	(52–74)	(53–75)	(48–85)	(61–84)	(51–72)
Specificity %	59	62	58	61	53	65
(Q1–Q3)	(55–62)	(60–65)	(54–63)	(51–65)	(41–56)	(59–69)
Accuracy %	60	60	59	60	55	61
(Q1–Q3)	(56–62)	(58–65)	(58–63)	(58–66)	(42–58)	(58–63)
PPV %	16	62	14	61	15	60
(Q1–Q3)	(14–18)	(56–65)	(12–19)	(57–66)	(13–18)	(56–68)
NPV %	96	63	94	63	94	63
(Q1–Q3)	(91–97)	(58–67)	(91–96)	(56–77)	(92–96)	(57–66)
AUC	0.66	0.69	0.70	0.72	0.62	0.69
(Q1–Q3)	(0.63–0.71)	(0.68–0.73)	(0.61–0.72)	(0.69–0.74)	(0.60–0.73)	(0.65–0.73)
C-index (Q1–Q3)	0.61 (0.60–0.64)		0.64 (0.61–0.65)		0.61 (0.59–0.62)	

The median value is reported with the first (Q1) and third quantile (Q3). PPV = positive predicted value, NPV = negative predictive value, C-index = concordance index.

and therefore no conclusions can be drawn from these groups.

Survival modeling

Four variables were included in the multi variable CPH model, the boosted CPH model and the RSF model. None of the interaction terms was significant, and therefore not included in the analysis. The four variables that were selected, with exclusion of variables with collinearity, were the WHO'73 grading, the number of tumors as defined by the CUETO (≤3, >3 tumors), the recurrence rate as defined by the EORTC (primary, ≤1rec/Y, >1rec/Y) and the age classification as defined by the CUETO (<60Y, 60–70Y, >70Y). The results of these customized survival models on the test-sets can be found in Table 3. This data shows C-indexes ranging from 0.61 to 0.64, showing enhanced performance compared with the EORTC, CUETO and EAU risk stratification methods. The median adjusted hazard ratios (HR) and median confidence intervals of the four selected variables of the multivariableCox regressions are given in Table 4. Although not all included variables were significant in all ten data splits, the AIC indicates that the trade-off of variables was most optimal when including all four variables in the CPH model.

Table 4
Adjusted hazard ratios (HR) from the multivariable Cox proportional hazards survival model

	HR (95% CI)
WHO'73 Grade	*
Grade 1	Reference
Grade 2	0.58 (0.38–0.89)
Grade 3	0.52 (0.33–0.82)
Age category CUETO	**
<60 Y	Reference
60–70 Y	1.81 (1.16–2.78)
>70 Y	2.70 (1.80–4.00)
Recurrence rate EORTC	
>1 rec/Y	Reference
≤1 rec/Y	0.48 (0.18–1.16)
Primary	1.86 (0.90–3.67)
Number of tumors CUETO	*
≤3 tumors	Reference
>3 tumors	1.85 (1.23–2.75)

The median HR is given with the median 95% confidence interval (CI). *indicates that the hazard ratio was significant in at least 7 out of 10 datasets, and **indicates significant findings in 10 out of 10 datasets.

DISCUSSION

The current risk stratification tools as provided by the EORTC, CUETO and EAU are unable to accurately stratify the risk of recurrence in NMIBC patients. Customized (non-linear) survival models have higher predictive power in our population; however, these differences are small. These results

suggest that prediction of recurrence in NMIBC is difficult in clinical practice.

The EORTC and EAU risk classification show slightly better predictive value than the CUETO risk stratification in our population. The concordance of the EORTC and CUETO risk groups with the risk of recurrence in our population are in line with previous reported concordances [11]. Kohjimoto et al. reported a lower C-index for the recurrence stratification using the EORTC score, however, in this Japanese population all patients were treated with BCG [14]. Vedder et al. reported similar agreement for the EORTC risk classification in diverse European populations [15]. The study of Kılınç et al. reported the best concordance with the EORTC. In their population, almost 90% of the patients received an immediate instillation of chemotherapy, and BCG was given in only 11% of the patients [16]. For the agreement with the CUETO, our findings are in the lower end of the spectrum, together with the study of Xylinas et al. [17]. In the study of Xylinas et al., similar percentage received an immediate instillation, and BCG was given in only 11% of the patients. Choi et al. reports the highest concordance with the CUETO risk stratification in a Korean population in which 53% was treated with BCG [18]. Little is published about the concordance of the EAU risk stratification for the prediction of recurrence. Jobcyzk et al. reported a concordance slightly higher than the concordance reported in this study [19]. Lammens et al. was able to make a subclassification in the EAU intermediate risk group, and reported C-indices varying between 0.60 and 0.63 [20].

Clearly, the reported concordance indices span a wide range. A possible explanation is the low-inter observer agreement in the assessment of the histopathological variables. Inter observer agreement of 38 to 89% has been reported for the grading of the tumor [11]. Consequently, grading seems to be highly subjective to the consulted pathologist. Next to grading of the tumor, also its staging introduces subjectivity. Assessment of the muscular is propria is found to be difficult, and thereby the pT1 tumors are frequently down-staged (up to 56%) or up-staged (up to 13%) in assessments made by other pathologists [21]. This variability is however most likely not only induced by pathologists, also urologists can introduce subjectivity by missing lesions, in particular CIS. The introduction of blue light cystoscopy using hexaminolevulinate increased the carcinoma-*in-situ* detection rate with 20%, and increased the detection of carcinoma-*in-situ* to 77% for a flexible scope and 88% for a rigid scope [22]. However, despite optimizing the diagnostic techniques with increasing costs, lesions can still be missed, thereby increasing the risk of recurrence.

The currently available risk stratification tools do not fully reflect the treatment-effects of the currently offered adjuvant therapies, as in the EORTC trial less than 10% received immediate instillation of chemotherapy [3]. The effect of BCG maintenance therapy was included in the CUETO risk tables. However, the maintenance window of 5 to 6 months is shorter than nowadays advised [9, 23]. These advents in therapy might explain the leveling of the recurrence-risk in the intermediate to high-risk groups. However, despite this potential treatment-effect, in our population the low-risk EORTC group has a higher recurrence rate than reported by Sylvester et al. [3].

This study included a relatively small number of patients, but is in line with the size of other comparative studies. The inclusion of more patients, preferable from other centers, could be used to increase the predictive power of for instance the RSF model. Possible variables that should be considered to include can be lympho vascular invasion, the T1 sub stage and the BCG treatment regimen. This might also open up the way for more elaborate survival modeling techniques, such as CPH inspired neural networks [24, 25], which are likely to perform better on large datasets. Those results might lead to new insights for treatment decision-making. When larger datasets become available, also the risk stratification for disease progression should be incorporated, as well as taking into account the effect of competing risks by loss of follow up and death of patients. Furthermore, possible prognostic markers could be extracted from histopathology images analyzed using image-based machine learning. Previous studies have proven that image-based machine learning can predict recurrence of prostate cancer [26]. Prediction of patient outcome has been performed in gliomas [27], pan-renal cell carcinoma [28] and colorectal cancer [29, 30] with the use of machine learning models based on histopathology images.

In this study, we focused on the prediction of recurrence, while accurate prediction of progression is of similar importance. However, in the gathered dataset, the numbers with progressive disease were too small for statistical assessment. The 39 patients with progression were located in all risk groups.

In conclusion, the currently available risk stratification models show low concordance rates in

the prediction of recurrence in our population. Our customized prediction models show slightly better performance, but accurate stratification between the risk groups remains difficult. New prognostic markers are needed to better predict the recurrence chances of patients with NMIBC. These better risk stratification could lead to better selection of adjuvant therapies, potentially reducing both patient burden and treatment costs.

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AUTHOR CONTRIBUTIONS

Project development: ML, IJ, HAM, DMB, TGL, JMO; Data collection: IJ; Data analysis: ML; Manuscript writing: ML, HAM; Manuscript editing: IJ, JMO, TGL, HAM, DMB.

CONFLICT OF INTEREST

HAM is co-founder and shareholder of Nico.lab.

DMB is founder and shareholder of Off road Medical.

The other authors declare that they have no conflict of interest.

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