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Clinical-Bladder cancer

Time to progression is the main predictor of survival in patients with high-risk nonmuscle invasive bladder cancer: Results from a machine learning-based analysis of a large multi-institutional database

Annamaria Porreca, Ph.D. [a,1], Marta Di Nicola, Ph.D. [a,1], Giuseppe Lucarelli, M.D. [b], Vartolomei Mihai Dorin, M.D. [c], Francesco Soria, M.D. [d], Daniela Terracciano, M.D. [e], Francesco Alessandro Mistretta, M.D. [f], Stefano Luzzago, M.D. [f], Carlo Buonerba, M.D. [g], Francesco Cantiello, M.D. [h], Andrea Mari, M.D. [i], Andrea Minervini, M.D. [i], Alessandro Veccia, M.D. [j], Alessandro Antonelli, M.D. [j], Gennaro Musi, M.D. [f], Rodolfo Hurle, M.D. [k], Gian Maria Busetto, M.D. [l], Francesco Del Giudice, M.D. [m], Simone Ferretti, M.D. [n], Sisto Perdonà, M.D. [o], Paola Del Prete, M.D. [p], Angelo Porreca, M.D. [q], Pierluigi Bove, M.D. [r], Nicolae Crisan, M.D. [s], Giorgio Ivan Russo, M.D. [t], Rocco Damiano, M.D. [h], Daniele Amparore, M.D. [u], Francesco Porpiglia, M.D. [u], Riccardo Autorino, M.D. [v], Mattia Piccinelli, M.D. [f], Antonio Brescia, M.D. [f], Sabin Octavian Tătaru, M.D. [w], Felice Crocetto, M.D. [x], Arturo Lo Giudice, M.D. [t], Ottavio de Cobelli, M.D. [f], Luigi Schips, M.D. [n,2], Matteo Ferro, M.D. [f,2], Michele Marchioni, M.D. [n,*]

[a] *Biostatistics Laboratory, Department of Medical, Oral and Biotechnological Sciences, "G. d'Annunzio" University of Chieti, Chieti, Italy*
[b] *Urology, Andrology and Kidney Transplantation Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy*
[c] *Department of Cell and Molecular Biology, George Emil Palade University of Medicine, Pharmacy, Sciences and Technology from Târgu Mureș, Târgu Mureș, Romania*
[d] *Division of Urology, Department of Surgical Sciences, Torino School of Medicine, Torino, Italy*
[e] *Department of Translational Medical Sciences, University Federico II, Napoli, Italy*
[f] *Department of Urology, IEO European Institute of Oncology, IRCCS, Milan, Italy*
[g] *CRTR Rare Tumors Reference Center, AOU Federico II, Napoli, Italy*
[h] *Department of Urology, Magna Graecia University of Catanzaro, Catanzaro, Italy*
[i] *Unit of Oncologic Minimally-Invasive Urology and Andrology, Department of Urology, Careggi Hospital, University of Florence, Florence, Italy*
[j] *Department of Urology, University of Verona, Verona, Italy*
[k] *Department of Urology, Humanitas Clinical and Research Hospital, Rozzano, Milan, Italy*
[l] *Department of Urology, University of Foggia, Foggia, Italy*
[m] *Department of Urology, La Sapienza University of Rome, Rome, Italy*
[n] *Urology Unit, Department of Medical, Oral and Biotechnological Sciences, "SS. Annunziata" Hospital, "G. d'Annunzio" University of Chieti, Chieti, Italy*
[o] *Uro-Gynecological Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, Fondazione "G. Pascale"-IRCCS, Naples, Italy*
[p] *Scientific Directorate, Istituto Nazionale per lo Studio e la Cura dei Tumori, Fondazione "G. Pascale"-IRCCS, Naples, Italy*
[q] *Department of Robotic Urologic Surgery, Abano Terme Hospital, Abano Terme, Italy*
[r] *Division of Urology, Department of Experimental Medicine and Surgery, Tor Vergata University of Rome, Rome, Italy*
[s] *Department of Urology, University of Medicine and Pharmacy Iuliu Haţieganu, Cluj-Napoca, Romania*
[t] *Department of Urology, University of Catania, Catania, Italy*
[u] *Division of Urology, Department of Oncology, School of Medicine, San Luigi Hospital, University of Turin, Orbassano, Turin, Italy*
[v] *Department of Urology, Rush University Medical Center, Chicago, IL*

[1]Shared co-first authorship.
[2]Shared co-senior authorship.
*Corresponding author. Tel.: 0871388415; fax: 0871387756.
E-mail address: mic.marchioni@gmail.com (M. Marchioni).

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[w] I.O.S.U.D., George Emil Palade University of Medicine, Pharmacy, Sciences and Technology from Târgu Mureș, Târgu Mureș, Romania
[x] Department of Neurosciences, Science of Reproduction and Odontostomatology, University of Naples Federico II, 80131 Naples, Italy

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Abstract

Background: In patients affected by high-risk nonmuscle invasive bladder cancer (HR-NMIBC) progression to muscle invasive status is considered as the main indicator of local treatment failure. We aimed to investigate the effect of progression and time to progression on overall survival (OS) and to investigate their validity as surrogate endpoints.

Methods: A total of 1,510 patients from 18 different institutions treated for T1 high grade NMIBC, followed by a secondary transurethral resection and BCG intravesical instillation. We relied on random survival forest (RSF) to rank covariates based on OS prediction. Cox's regression models were used to quantify the effect of covariates on mortality.

Results: During a median follow-up of 49.0 months, 485 (32.1%) patients progressed to MIBC, while 163 (10.8%) patients died. The median time to progression was 82 (95%CI: 78.0−93.0) months. In RSF time-to-progression and age were the most predictive covariates of OS. The survival tree defined 5 groups of risk. In multivariable Cox's regression models accounting for progression status as time-dependent covariate, shorter time to progression (as continuous covariate) was associated with longer OS (HR: 9.0, 95%CI: 3.0−6.7; $P < 0.001$). Virtually same results after time to progression stratification (time to progression ≥10.5 months as reference).

Conclusion: Time to progression is the main predictor of OS in patients with high risk NMIBC treated with BCG and might be considered a coprimary endpoint. In addition, models including time to progression could be considered for patients' stratification in clinical practice and at the time of clinical trials design.

Keywords: High risk nonmuscle invasive bladder cancer; Progression-free survival; Overall survival; Bacillus of Calmette-Guerin; Surrogate endpoint

Abbreviations: BCG, Bacillus of Calmette-Guerin; BMI, body mass index; CI, confidential interval; CIS, carcinoma in situ; CPR, C-reactive protein; HR, hazard ratio; HR-NMIBC, high-risk nonmuscle invasive bladder cancer patients; IBS, integrated brier score; LMR, lymphocyte to monocyte ratio; MIBC, muscle-invasive bladder cancer; mpGPS, modified Pathologic Glasgow Prognostic Score; NLR, neutrophil to lymphocyte ratio; OM, overall mortality; OS, overall survival; PFS, progression-free survival; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; reTURB, secondary transurethral resection of bladder tumor; RSF, random survival forest; SE, standard error; TURB, transurethral resection of bladder tumor; VIMP, variable importance method

1. Introduction

Nonmuscle invasive bladder cancer (NMIBC) treatment paradigm includes endoscopic resection and, in intermediate and high-risk patients, adjuvant treatments through intravesical instillation with Bacillus of Calmette-Guerin (BCG) [1,2]. Unfortunately, up to 50% of patients treated with BCG might experience recurrence and up to 30% of them will progress to muscle-invasive bladder cancer (MIBC). [3].

Progression or recurrence after BCG failure is associated with high overall mortality (OM) and cancer-specific mortality rate, up to 50% at 5-year [4], also depending on the different histologic subtype [5]. Thus, several randomized clinical trials are testing the effectiveness of new immunotherapeutic agents for treating BCG failure patients with promising results [6−8]. Still a not negligible proportion of patients, even if treated with new agents, will need radical cystectomy [6].

In clinical trials, observed OS difference represents the relevant clinical benefit of any experimental treatment [9]. Still, OS use might be limited by several factors [10], including the effect of noncancer deaths in a population of patients often composed of the elderly [11] or the relatively low events rate. To overcome such limitations, progression and time to progression are often used as surrogate endpoints in clinical trials exploring treatment benefits for bladder cancer [12]. Furthermore, the current paradigm based on cisplatin neoadjuvant treatment in MIBC might be challenged by introducing new agents currently under investigation [13].

However, not all patients who progress to MIBC status might need the same treatment, and the association of chemotherapy and immunotherapy could be reserved for those with more aggressive features. We aimed to test the effect of progression and time to progression on OS in patients treated for NMIBC with BCG. Moreover, we evaluated the validity of such surrogate endpoints within future randomized clinical trials.

2. Patients and methods

2.1. Study population

Patients treated at 18 different tertiary institutions for histologically proven T1 high risk NMIBC (HR-NMIBC) were included. All the procedures were performed between January 2002 and December 2012. All patients underwent secondary transurethral resection of bladder tumor (reTURB) within 4 to 6 weeks after the primary TURB to confirm NMIBC status. After reTURB all patients

underwent BCG intravesical instillation with a schedule including an induction and a maintenance phase. The induction phase consisted of 1 instillation per week for 6 weeks. During the maintenance phase, instillation was administered for 3 weeks at 3, 6, 12, 18, 24, 30, 36 months from therapy start. Such schedule represents the standard of care according to current guidelines [14]. Only data about patients with full information about BCG schedule administration were collected [3]. Those who experienced mild side effects for BCG administration were rechallenged, while those not eligible for BCG treatment were excluded. In addition, patients with missing information about main covariates of interest were excluded.

2.2. Follow-up and progression definition

Follow-up consisted of cystoscopy and urine cytology every 3 months during the first 2 years, if negative cystoscopy were repeated every 6 months up to fifth year and then yearly. In case of suspect recurrence all patients underwent secondary transurethral resection of bladder tumor (TURB). Abdomen CT-scan was performed based on each center preference or at the time of progression. Progression was defined as presence of MIBC at histological specimen obtained during follow-up (TURB or cystectomy). Time to progression was defined as the time interval between the first TURB to any pathologically proven MIBC progression. Those who experienced high grade and/or T1 bladder cancer recurrence were treated by mean of radical cystectomy or new instillation cycles based on physician and patients' preferences.

2.3. Covariates of interest

Patients related covariates of interest were age, gender, statin use, smoking history, body mass index (BMI) and prognostic nutritional index (PNI) [15]. Tumor related covariates of interest were tumor size, presence of lymph vascular invasion at TURB or at reTURB, focality (single or multiple), high grade tumor at reTURB, concomitant carcinoma in situ (CIS) and modified Pathologic Glasgow Prognostic Score (mpGPS) [16]. Other covariates of interest were C-reactive protein (CPR), neutrophil to lymphocyte ratio (NLR) [17], platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR) [18]. Other covariates of interest included BCG schedule completeness and subsequent treatments (namely mitomycin or other chemotherapy treatments).

2.4. Follow-up and outcomes definition

Primary outcome of interest was OS. The follow-up was defined as the time interval between first TURB and death for any cause. For patients in whom no death was recorded the follow-up time interval was defined as the period from first TURB to the last follow-up visit.

2.5. Statistical analysis

Descriptive analysis was carried out using median (q1 = first quartile, q3 = third quartile), for the continuous variables and percentages values for the categorical ones. Correlation between progression and OM was tested by Kendall rank correlation test [19]. The Cox-proportional hazards regression model (Cox model) is a default choice in analyzing right-censored time-to-event data. A semiparametric method is a restrictive proportional hazards assumption that is always not met in applications. In addition, since it is not a data-driven method, it does not provide a ranking of covariates, but it is up to the clinician to understand and choose covariates considering only the clinical meaning and not the nature of the data.

The Random Survival Forest (RSF) is a nonparametric and nonlinear machine learning technique for right-censored time-to-even data [20]. RSF algorithm draws B bootstrap generate from the original data and with Bagging generates B new training sets with replacement. Thus, this procedure excluded for each bootstrap sample, N subject called out-of-bag data. At each node of the tree, randomly select M features for splitting, the F split is made using the candidate feature and its cut-off point that maximizes the survival differences between daughter nodes under a predetermined split rule. Survival function and patient status were treated as response variables in each tree. The choice parameters for RSF were the number of growing trees, the splitting rule, the number of predictors randomly selected at each split, and the predicted error [20]. For RSF the dataset was divided into the training set using 80% of the original sample and the test set using the remaining 20%.

There are several splitting rules for RSF [21]. The most used method for splitting is the log-rank that splits nodes by maximization of the log-rank test statistic, a log-rank score splitting rule that splits nodes by maximization of a standardized log-rank score statistic, conservation of events splitting rule that splits nodes by finding daughters closest to the conservation-of-events principle, a random log-rank splitting rule that splits nodes by the variable with maximum log-rank [21]. We used prediction error based on the Integrated Brier score (IBS) and 1-C statistics to measure the prediction accuracy and prediction error. The smaller the IBS value the greater the prediction. For both, the confidence interval was found by the bootstrap resampling method. The importance of each of the covariates was determined by the variable importance method (VIMP) and Minimal depth. The larger the VIMP, the more predictive the variable. A VIMP close to zero indicates that the variable makes a low contribution to predictive accuracy and a negative value indicates that the predictive accuracy is improved by omission of the variable. Minimal depth indicates the impact of the covariates on the prediction. The smaller the Minimal depth, the more predictive the covariates. Ranking the VIMP (VIMP RANK) from 1 to n where

n is the number of predictors, the predictor with larger rank is the lowest important.

After variable selection, the survival tree data mining technique was used to obtain homogeneous classes of individuals regarding the time-dependent variable of interest, based on recursive partitioning, by handling interactions between the most important covariates. Thus, the survival curves estimated by the Kaplan-Meier method were drawn corresponding to the leaves of the tree and the Cox analyses of patterns identified were used to estimate the hazard ratio (HR) for each leave, taking as a reference the one in which the risk of dying was the highest.

Moreover, Cox regression models with time-dependent covariate were applied to test the effect of time on progression after adjusting for age and progression status. The latter was modeled as a time-dependent covariate. Landmark analyses at 12 and 60 months were also performed in order to further control immortal-time bias [22,23].

Sample size estimation was based on our results to estimate how many patients could be avoided to be enrolled in a study evaluating a new treatment showing a relative hazard of 0.9 with 0.2 beta, 0.05 alpha and a median follow-up of 5 years [24]. All statistical analyses were performed using R Statistical Software (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Overall, 1,740 patients were screened, and 1,510 (86.8%) patients were included after application of exclusion criteria. The median age was 71.0 (IQR: 65.0−78.0) years; most of the patients were male (80.9%) with a smoking history (55.4%). Moreover, patients more frequently harbored unifocal tumors (55.7%) without CIS (84.7%). However, tumors were more frequently larger than 3 cm (64.1%, Table 1). Overall, 357 (23.6%) patients had previous early instillation with mitomycin. Moreover, 128 (8.35%) patients had an incomplete BCG administration. All of them were treated with mitomycin. In addition, 138 (9.1%) patients received mitomycin after complete BCG schedule. Other intravesical chemotherapy regimens were used in 39 (2.6%) patients.

During a median follow up of 49.0 (IQR: 40.0−73.0) months, 485 (32.1%) patients progressed to MIBC, while 163 (10.8%) patients died. The 5- and 7-years OS rates were 90.4% (standard error [SE]: ±1.0%) and 78.2% (SE: ±1.7%), respectively. The median time to progression 82 (95% confidential interval [CI]: 78.0−93.0) months. The 5- and 7-years progression-free survival rates were 61.4% (SE: ±1.7%) and 48.0% (SE: ±2.1%), respectively. Kendall's correlation test showed a statistically significant correlation between progression and mortality (tau: 0.29, 95% CI: 0.19−0.32; $P < 0.001$).

In RSF, out of 21 covariates tested, time to progression and age are the most important according to both VIMP and Minimal Depth methods (Fig. 1). RSF models showed a good performance over time according to the Brier score both in the training and validation sets (Fig. 2). C-index results to be 0.814 (0.792−0.842) on the training set and 0.726 (0.700−0.793) on the test set. IBS result to be 0.060 (0.060−0.061) for training and 0.092 (0.091−0.093).

Table 1
Main patients and tumor's characteristics.

Variables	Overall ($N = 1,510$)
Age (years)	71.0 (65.0−78.0)
Gender (male)	1,222 (80.93%)
Smoking history	837 (55.43%)
Statin use	402 (26.62%)
BMI (kg/m^2)	27.0 (24.0−29.0)
Prognostic nutritional index	51.0 (48.0−56.0)
C-reactive protein (mg/l)	2.0 (0.0−11.0)
Neutrophil to lymphocyte ratio	3.0 (2.0−4.0)
Platelet to lymphocyte ratio	121.0 (88.0−165.0)
Lymphocyte to monocyte ratio	3.0 (2.0−4.0)
Lymphovascular invasion	225 (14.90%)
Multifocal tumors	669 (44.30%)
Tumor size >3 cm	968 (64.11%)
mGPS (1−2)	429 (28.41%)
Carcinoma in situ	231 (15.30%)
High grade tumor at reTURB	376 (24.90%)
Lymph vascular invasion at reTURB	85 (5.63%)

Values are expressed as median and interquartile ranges (IQR) and absolute frequency (*n*) and column percentage (%) for categorical.

The survival tree-derived algorithm defined 5 risk groups (terminal nodes) based on time to progression and age at the time of diagnosis as shown in Fig. 3. The 5-year OS rate were 99.9% (SE: ±0.0), 99.9% (SE: ±0.00), 88.6% (SE: ±1.8)%, 78.3% (SE: ±5.9), and 75.6% (SE: ±4.0) for group 1 (time to progression ≥62.5 months and age <77.5 years); group 2 (time to progression ≥62.5 months and age ≥77.5 years), group 3 (age <79.5 years and time to progression between 10.5 and 62.5 months), group 4 (age <79.5 years and time to progression <10.5 months) and group 5 (time to progression <62.5 months and age ≥79.5 years); respectively.

The 7-year OS rate were 98.2% (SE: ±1.1), 96.1% (SE = ±2.7), 74.2% (SE: ±3.5)%, 45.4% (SE: ±13.8), and 29.9% (SE: ±5.6) for group 1 (time to progression ≥62.5 months and age <77.5 years); group 2 (time to progression ≥62.5 months and age ≥77.5 years), group 3 (age <79.5 years and time to progression between 10.5 and 62.5 months), group 4 (age <79.5 years and time to progression <10.5 months) and group 5 (time to progression <62.5 months and age ≥79.5 years); respectively.

Compared to group 1 all groups defined according to the survival tree showed shorter OS (Table 2). Landmark analyses yielded virtually the same results (Table 3). In multivariable Cox's regression models accounting for progression status as time-dependent covariate, shorter time to

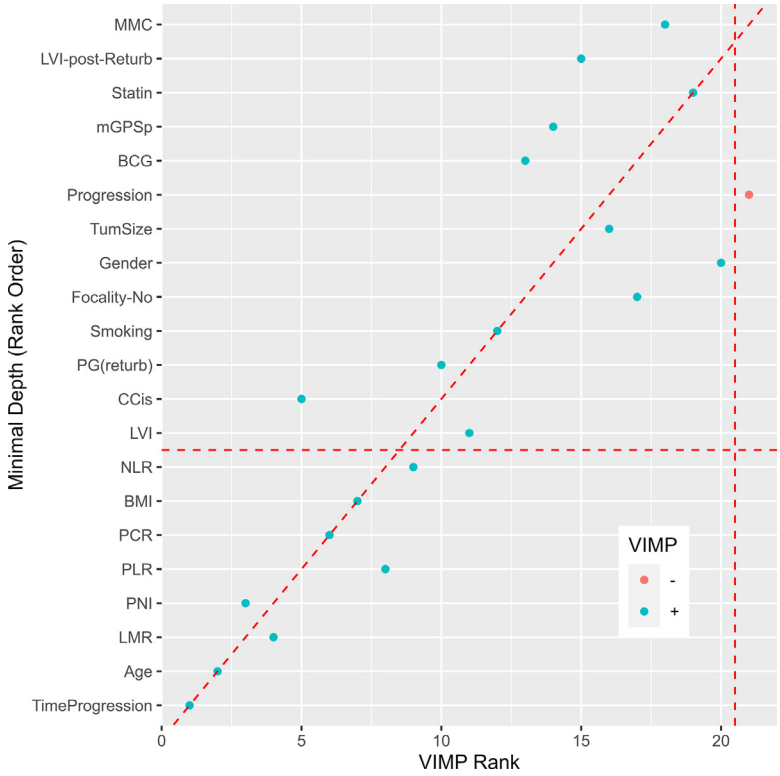

Fig. 1. The minimal depth and VIMP rankings for covariate selection by Random Survival Forest method using OS outcome. The importance of the variables, as measured by both ordered VIMP (VIMP RANK) and minimal depth are depicted. The dashed diagonal indicates perfect agreement between the importance measures.

progression (as continuous covariate) was associated with longer OS (HR: 9.0, 95%CI: 3.0−6.7; P < 0.001). Multivariable Cox regression models confirmed that the strongest predictor of OS was time to progression even after adjusting for age (Table 4). Based on our results and assuming a censoring rate of 5 unit/y, the sample size needed using OS as primary outcome was 9,156 patients. Instead, sample size estimation based on progression was about 5,298 patients.

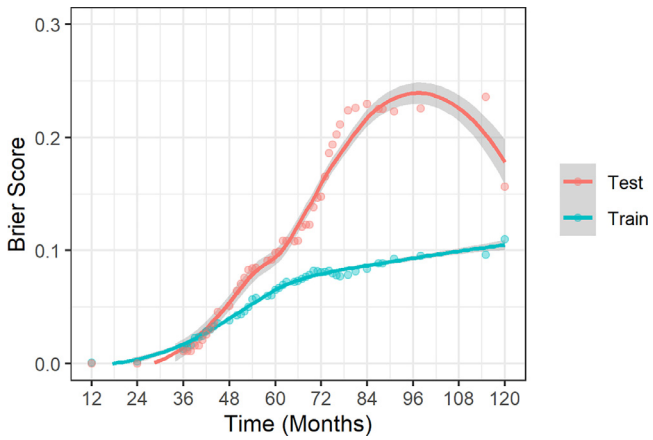

Fig. 2. Brier score for classification performance in training and test cohorts.

4. Discussion

Our study showed that time to progression represents the main predictor of mortality in patients with HR-NMIBC. In addition, we showed a statistically significant correlation between progression and mortality. Our results showed that time to progression should be considered as one of the main indicator of treatments failure in patients with HR-NMIB. Indeed, even if progression by itself is confirmed as correlated with mortality, its effect should be critically ascertained, based on patients' characteristics, such as age, and the time to progression. Furthermore, our results suggest the validity of time to progression and progression as possible surrogate endpoints. Important points of discussion have been raised.

First, the use of time-to progression as co-primary outcome in NMIBC allows to plan shorter trials compared to OS. In our experience, a clinical trial drawn based on the current study results would need double of the patients if OS is used for sample size calculation instead of time to progression. Such results corroborate the use of time to progression as primary outcome when planning clinical trials, like previously stated [25]. It is of note, that in our cohort time to progression was quite shorter than reported in previous studies, such as the CUETO trial with progression rates lower than 20% at 5-year vs. about 40% in our experience [26]. Thus, a larger cohort or longer observation might be needed when such criteria are applied to other populations. As previously

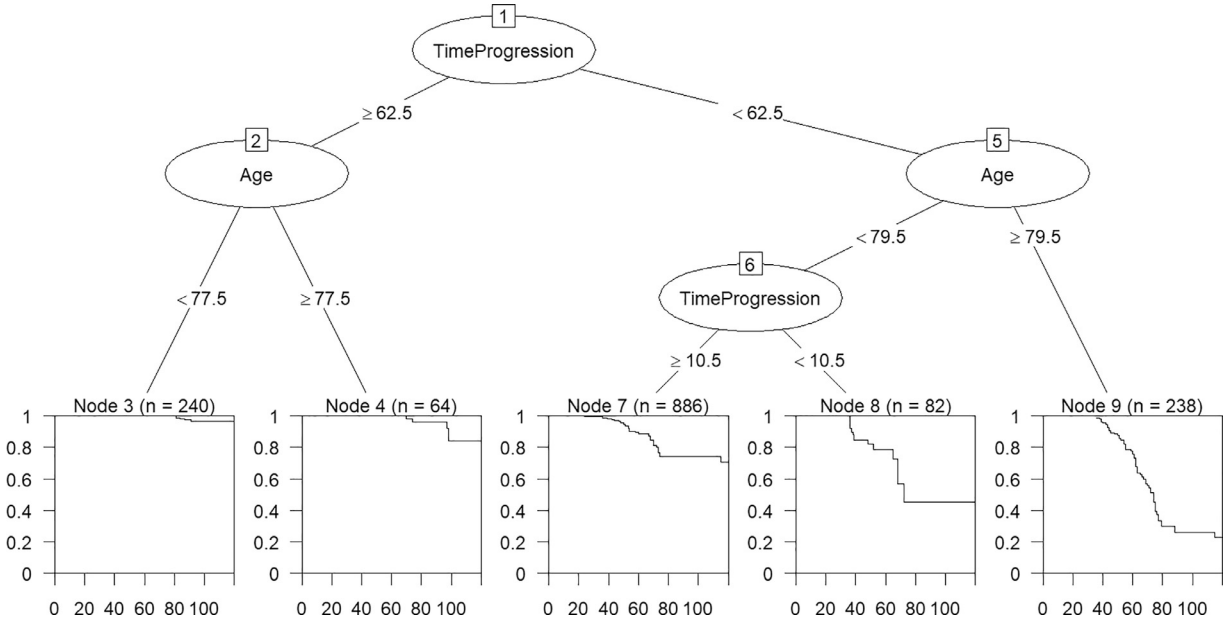

Fig. 3. Survival tree for the probability of OS events in the cohort. Squares represent terminal nodes; numbers (n) in squares denote sample size (topline), and curves inside the squares show the Kaplan-Meier estimated survival of subpopulations. Circles represent the most important variables based on the SRF. The optimal cut-off is based on the log-rank test (LRT). The terminal nodes specify a combination of predictors and their cut-off values leading to a terminal node forming an interaction pattern. Each interaction pattern specifies a subgroup of individuals with similar survival probability.

pointed out, the use of time to progression could be limited by the relatively small number of events that could be expected [25]. However, even if complete response has been suggested as a primary outcome for trial design and sample size calculation, the inclusion of time to progression as coprimary endpoint could be more informative about the OS probability. Actually, OS should still be considered the most important measure of patient clinical benefit [9].

Second, we provided a new classification based on 2 easy collected features, namely time to progression and age. We were able to identify 5 risk groups with statistically significant and clinically meaningful differences in

Table 2
Cox's proportional hazard model analyses estimated risk of death for groups defined by time to progression and age, identified at terminal node of survival tree.

Risk groups	5-year overall survival (±standard error)	7-year overall survival (±standard error)	Hazard ratio (95% confidence interval; *P* value)
Time to progression ≥ 62.5, Age <77.5	99.9 (±0.0)	98.2 (±1.1)	Reference
Time to progression ≥ 62.5, Age ≥ 77.5	99.9 (±0.0)	96.1 (±2.7)	9.0 (3.0−26.7; $P < 0.001$)
10.5 ≤ Time to progression <62.5, Age <79.5	88.6 (±1.8)	74.2 (±3.5)	14.3 (5.7−36.1; $P < 0.001$)
Time to progression <10.5, Age <79.5	78.3 (±5.9)	45.4 (±13.8)	44.9 (15.0−135.0; $P < 0.001$)
Time to progression <62.5, Age ≥79.5	75.6 (±4.0)	29.9 (±5.6)	58.7 (23.4−147.0; $P < 0.001$)

The estimated risk reported.

Table 3
Cox's proportional hazard model analyses for OS estimated risk of death for groups defined by time to progression and age, identified at terminal node of survival tree within subset population for those followed at least until landmark time. The estimated risk reported as hazard ratio (95% confidence interval).

Risk groups	Landmark analysis at 12 months[a]	Landmark analysis at 60 months[a]
Time to progression ≥62.5, Age <77.5	Reference	Reference
Time to progression ≥ 62.5, Age ≥ 77.5	8.89 (2.96−26.7, $P < 0.001$)	8.89 (2.96−26.7, $P < 0.001$)
Time to progression <62.5, Age ≥77.5	14.3 (5.70−36.1, $P < 0.001$)	8.69 (3.29−23.0, $P < 0.001$)
10.5 ≤ Time to progression <62.5, Age <79.5	44.9 (15.0−135.0, $P < 0.001$)	26.6 (7.04−101.0, $P < 0.001$)
Time to progression <62.5, Age ≥79.5	58.7 (23.4−147.0, $P < 0.001$)	45.7 (17.9−117.0, $P < 0.001$)

[a] Subset population for those followed at least until landmark time.

Table 4
Cox's proportional hazard models including progression status modeled as a time-dependent covariate predicting risk of overall mortality.

Covariates	Hazard ratio (± standard error)	*P* value
Time to progression <10.5 months	Reference	
10.5≤ and <62.5 months	0.4 (±0.3)	<0.001
≥62.5 months	0.1 (±0.5)	<0.001
Progression (yes vs. no)	1.6 (±0.2)	0.053
Age (years)	1.1 (±0.01)	<0.001

The estimated risk reported as hazard ratio (±standard error).

terms of survival. Such risk groups could be used in clinical practice to plan treatment intensification in those who are at higher risk. To date, new biomarkers are being proposed [27]. Unfortunately, their use in clinical practice is limited by the scarce availability, the high costs and the high complexity of the analytical process [27]. Recently an interesting debate is ongoing about the use of bladder sparing treatments in patients candidate to radical cystectomy [28]. However, some concerns have been raised about patients' selection criteria used [29] and to date no consensus about those who might benefit more of such new treatments have been reached. A model also considering time to progression could be helpful for future studies planning.

Our study is not devoid of limitations, first since almost all patients received the same treatment we could not test the effect of different approaches on both progression-free survival and overall mortality as was done in previous works aiming to evaluate other surrogate endpoints [19]. However, we could verify the existence of a statistically significant correlation between progression and mortality at patient-level analyses. Even if we were not able to formally test the hypothesis of surrogacy between progression-free survival and overall survival our results are of great interest and represent a benchmark for future studies aiming to validate the use of progression-free survival as surrogate endpoint. Such studies should include trial-level surrogacy testing [30].

In addition, due to its retrospective nature, our database lacks significant information, such as completeness of TURB, tumor location within the bladder, presence of tumor into bladder diverticula, benign prostatic hyperplasia that limits tumor's accessibility. For instance, our database lack of systematic information about the treatment option used in those with high grade recurrences. Several different treatments are available, while radical cystectomy is considered the best option in terms of oncological outcomes, in selected patients a bladder-sparing approach could be suitable [31]. Even if these patients represent only a small proportion of our cohort, subsequent treatments might have an unmeasurable effect on bladder cancer progression that could not be controlled in our analyses. In future the introduction of new treatment regimens, based on immunotherapy in association to BCG or alone, might deeply change the current treatment paradigm. However, to date no strong evidence is available about the effectiveness of such treatments in patients with high risk NMIB [32]. Our study lacks central pathological and imaging review, and the assessment of progression was based on each center evaluation. Moreover, due to the retrospective multi-institutional nature of the study reporting biases and differences in follow-up assessment or treatment schedules could not be controlled as in other studies with a similar design. Also, the effect of subsequent treatments, after radical cystectomy or at the time of metastases, could not be evaluated in our study due to the lack of such information in our database.

Finally, immortal-time bias could affect the results of our study. Indeed, those with longer time to recurrence must experience a longer survival. However, we relied on 2 different sets of analyses to control for such bias, namely time-dependent Cox's regression, and landmark analyses [22,23]. In both sets of analyses time to progression and risk groups defined based on time to progression showed the strongest effect on OS, corroborating that the observed effect was not affected by immortal-time bias. Our analyses also showed that velocity of progression is more important than progression by itself allowing a tailored treatment before radical cystectomy or definitive treatments in those who need. Such observation could be of great importance when planning future studies comparing bladder sparing treatments vs. radical cystectomy.

5. Conclusion

Time to progression is the main predictor of OS in patients with high risk NMIBC treated with BCG and might be considered as a coprimary endpoint. In addition, models including time to progression could be considered for patients' stratification in clinical practice and at the time of clinical trials design.

Declaration of competing interest

Each of the authors certify that the manuscript represents original and valid work that has not been previously published and is not currently under consideration by any other journal. Additionally, all the authors: have given final approval of the submitted manuscript approved the contents of this paper and have participated sufficiently in the work to take public responsibility for all content.

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