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Prognostic Factors of Long-Term Survival in Non-Muscle-Invasive Bladder Cancer: An 18-Year Retrospective Study from Real-Life Practice

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Abbreviations:
NMIBC: Non-Muscle- Invasive Bladder Cancer;
BCG: *Bacillus Calmette- Guérin*;
HIVEC: Hyperthermic Intravesical Chemotherapy;
EAU: European Association of Urology;
COVID-19: Coronavirus Disease 2019;
TAR-200: Target Adjustable Release 200;
GDPR: General Data Protection Regulation;
TURBT: Transurethral Resection of Bladder Tumor;
EORTC: European Organization for Research and Treatment of Cancer;
CI: Confidence Interval;
EMA: European Medicines Agency;
WHO: World Health Organization;
CIS: Carcinoma in situ;
TNM: Tumor-Node-Metastasis;
RecScore: Recurrence Score;
ProgScore: Progression Score;
IQR: Interquartile Range.

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Rezumat

Factori de prognostic pentru supraviețuirea pe termen lung în cancerul vezical non-invaziv muscular (NMIBC): un studiu retrospectiv de 18 ani bazat pe practica clinică reală

Introducere: Cancerul vezical non-invaziv muscular (NMIBC) este frecvent şi heterogen, necesitând strategii terapeutice adaptate riscului. BCG rămâne tratamentul standard pentru formele cu risc intermediar şi înalt, însă eficiența sa este influențată de accesul limitat, toleranța variabilă, rezistența la tratament şi disfuncționalitățile sistemului de sănătate.
Material şi metodă: Acest studiu retrospectiv a avut ca obiectiv identificarea factorilor de prognostic pentru supraviețuire, cu o abordare ipotetică suplimentară a influenței pandemiei COVID-19. Deşi nu am putut evalua direct impactul pandemiei COVID-19 din cauza lipsei unor variabile înregistrate, presupunem că aceasta ar fi putut contribui la eficiența limitată a terapiei BCG în contextul nostru clinic. Au fost incluşi 100 de pacienți, selectați dintr-un grup inițial de 297 diagnosticați în Clinica de Urologie din Târgu Mureş între 2006–2008, urmăriți până în 2024. Analiza prognostică a inclus variabile clinice, iar scorurile RecScore şi ProgScore au fost calculate folosind calculatorul de risc EORTC. Nu s-au aplicat praguri specifice; scorurile au fost analizate ca variabile continue.
Rezultate: Vârsta peste 70 de ani şi multiplicitatea tumorală s-au asociat semnificativ cu o mortalitate crescută. RecScore a fost semnificativ corelat cu riscul de recidivă (p=0.0464). ProgScore a arătat o asociere marginală cu mortalitatea în analiza univariată (p=0.0561), dar nu a fost semnificativ în modelele multivariate (p=0,9159). Terapia BCG a avut un efect protector marginal, dar nu a influențat semnificativ supraviețuirea. Deşi nu am putut evalua direct impactul pandemiei COVID-19, presupunem că aceasta ar fi putut contribui la întreruperi ale tratamentului în cohorta noastră reală.

Concluzii: Rezultatele susțin necesitatea unor strategii personalizate, bazate pe risc, şi subliniază importanța integrării datelor din practica reală în managementul NMIBC, în special în contexte de disfunctionalitați ale sistemului de sănătate.

Cuvinte cheie: NMIBC, BCG, recidivă, factori de prognostic, supraviețuire, terapie intravezicală

Abstract

Introduction: Non-muscle-invasive bladder cancer (NMIBC) is common and heterogeneous, requiring risk-adapted therapeutic strategies. BCG remains standard for intermediate- and high-risk forms, but its effectiveness is influenced by limited access, variable tolerance, treatment resistance, and healthcare system disruptions.
Material and Methods: This retrospective study aimed to identify prognostic factors for survival with an additional assessment of the influence of the COVID-19 pandemic. Although we could not directly evaluate the effect of COVID-19 pandemic due to lack of recorded variables, we hypothesize it may have contributed to the limited impact of BCG therapy in our real-world setting. One hundred patients were selected from an initial group of 297 diagnosed in the Urology Clinic of Tg. Mureș between 2006–2008, followed up until 2024. Prognostic analysis included clinical variables, RecScore and ProgScore were calculated using the EORTC risk calculator. No specific cut-offs were applied; the scores were analyzed as continuous variables.
Results: Age over 70 and tumor multiplicity were significantly associated with increased mortality. RecScore was significantly correlated with the risk of relapse (p=0.0464). ProgScore showed a marginal association with mortality in univariate analysis (p=0.0561) but was not significant in multivariate models (p=0,9159). BCG therapy had a marginal protective effect, but did not significantly influence survival. Although we could not directly evaluate the effect of COVID-19 pandemic due to lack of recorded variables, we hypothesize that it may have contributed to treatment discontinuities in this real-life cohort.
Conclusions: The results support the need for personalized, risk-based strategies and underline the importance of integrating real-world data into NMIBC management, especially in the context of systemic disruptions.

Keywords: NMIBC, BCG, recurrence, prognostic factors, survival, intravesical therapy

Introduction

Bladder cancer ranks among the ten most frequent malignancies globally, with more than 570,000 new cases reported each year (1). Non-muscle-invasive bladder cancer (NMIBC), encompassing stages Ta, T1, and carcinoma *in situ* (CIS), accounts for approximately 75% of bladder cancer cases (2). Despite its generally favorable prognosis compared to muscle-invasive forms, NMIBC is associated with high recurrence and progression rates, necessitating long-term clinical vigilance (3,4).

According to the European Association of Urology (EAU), risk stratification – based on tumor size, multifocality, grade, and recurrence history – is essential for guiding treatment decisions (5). In intermediate- and high-risk cases, intravesical *Bacillus Calmette-Guérin* (BCG) therapy post-complete resection remains the standard of care, although patient response remains difficult to predict (6). However, real-world data underscore significant outcome variability, especially during systemic disruptions such as the COVID-19 pandemic. Resistance to BCG and its limitations have accelerated interest in neoadjuvant strategies, including novel or optimized regimens and alternative intravesical chemotherapeutic agents with distinct mechanisms of action designed to address current therapeutic gaps in NMIBC management (1,7). Several novel intravesical chemotherapeutic strategies have emerged, targeting specific mechanisms to overcome BCG resistance and improve clinical outcomes in NMIBC. These include: cytotoxic synergy, as observed with the combination of gemcitabine and docetaxel (8,9); enhanced bladder wall adhesion and sustained release, such as epirubicin delivered via thermosensitive hydrogels, and hyperthermia-induced cytotoxicity through HIVEC technology (10); biodegradable drug delivery systems enabling continuous agent release, exemplified by TAR-200 (11); and agents targeting apoptotic pathways, such as valrubicin (12,13). Additionally, immune modulation using non-virulent bacteria

(e.g., *Mycobacterium phlei*) mimics BCG-like immune responses with potentially fewer adverse effects.

This study retrospectively analyzes a 16-18-year cohort of NMIBC patients treated at the Urology Clinic of Târgu Mureş, aiming to identify key prognostic factors for long-term survival – specifically age, tumor grade, multifocality, and treatment modality.

Material and Methods

Study Design

This study is retrospective, observational, unicentric, conducted in the Urology Clinic of the Mureş, County Clinical Hospital, and was conducted in accordance with the ethical standards of the Institutional Research Committee following the guidelines outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Târgu Mureş County Clinical Hospital (No. 845/28/05/2023). To minimize bias, data were extracted using standardized selection forms, and all histopathological diagnoses were independently verified.

Participants and Procedure

Patient data were anonymized and processed in accordance with the regulations in force regarding the protection of personal data (GDPR). The initial group included 297 patients hospitalized between January 2006 and December 2008, diagnosed with bladder cancer. Of these, 197 were excluded due to failure to meet strict eligibility criteria, so the final analysis was performed on a sample of 100 patients diagnosed with non-muscle invasive bladder cancer (NMIBC). The selection of eligible patients was carried out based on a standardized electronic form "Patient Selection Form-NMIBC Study 2006-2024" which includes established selection criteria, namely.

Inclusion criteria:

- Histopathologically confirmed diagnosis (Ta, T1, CIS);
- Tumor stage and grade confirmed according to TNM 2002 and WHO 1973;
- Initial treatment performed between 2006-2008 in the study center, namely administration of intravesical instillations with BCG (complete or partial);
- Patient included based on an approved protocol with anonymized data;
- Clinical data and RecScore/ProgScore scores available;
- Documented follow-up until 2024.

Exclusion criteria:

- Muscle-invasive tumor (T2 or more advanced at diagnosis);
- Major comorbidities that compromise survival analysis (e.g., non-oncological terminal diseases);
- Presence of another synchronous malignancy on diagnosis;
- Lack of essential clinical, pathological, or therapeutic data;
- Patient refusal to undergo recommended treatment;
- Incomplete follow-up (<5 years of available data).
- All patients underwent transurethral resection of bladder tumor (TURBT). Tumors were stratified by number (solitary vs. multiple) and size (≤ 3 cm vs. > 3 cm).

All histopathological diagnoses were confirmed by accredited pathologists, and tumor staging was based on the 2002 TNM classification. Grading followed the 1973 WHO classification for uniformity, and tumors were stratified by size (threshold > 3 cm) and number (single vs. multiple). For patients with NMIBC the standard diagnostic and therapeutic approach involves (TURBT), typically complemented by intravesical chemotherapy.

BCG Therapy and Follow-up

BCG therapy was administered according to EAU guidelines, consisting of an induction phase followed by maintenance. Data were collected from electronic medical records, histopathology bulletin registers and follow-up medical observation sheets. Recurrence (RecScore) and progression (ProgScore) scores were calculated using validated tools. Significance in statistical testing was defined by cut-off of $p<0.05$.

Intravesical BCG therapy followed the Lamm protocol (weekly instillations for six consecutive weeks, followed by three weekly maintenance instillations every three to six months for up to three years), in accordance with the 2006-2008 European Association of Urology (EAU) guidelines and institutional practice. Patients were followed

from the time of initial diagnosis until December 2024, resulting in a follow-up duration of 16 to 18 years. Clinical information, histopathology reports, and follow-up data were extracted from archived medical records and hospital registers. Risk scores for recurrence and progression (RecScore and ProgScore) were calculated using the EORTC validated tool (15).

Statistical Analysis

The statistical analysis was performed according to a rigorous protocol, including elements of descriptive statistics (frequency, percentage, mean, median, standard deviation) and elements of inferential statistics. The Shapiro-Wilk test was applied to determine the distribution of the analyzed data series. The Mann-Whitney test, a non-parametric test used to compare medians in the case of a non-Gaussian distribution, was applied to compare two data sets. The Chi-square and Fisher tests were used to evaluate the association between qualitative variables. The Kaplan–Meier method was applied for survival analysis, and the log-rank test (Log Rank Mantel-Cox) was used for univariate comparisons. Multivariate Cox proportional hazards regression was applied to identify independent predictors of recurrence. Multivariate Cox proportional hazards regression was performed to identify independent predictors of overall mortality using follow-up time in months. This method allowed for time-to-event modeling, accounting for censored data. Relative risks (RR), 95% confidence intervals (CI) and median survival times were also calculated. The significance threshold chosen for the p value was 0.05. Statistical analysis was performed using the GraphPad Prism v.9.0 trial version and the SPSS 26.0 trial version.

The RecScore is a recurrence risk score calculated using the EORTC risk tables for non-muscle invasive bladder cancer (NMIBC). It estimates the probability of tumor recurrence based on several clinical and pathological features:

- Number of tumors (single vs. multiple);
- Tumor diameter (>3 cm);
- Prior recurrence rate;
- Tumor stage (Ta vs. T1);
- Tumor grade (low vs. high);
- Presence of concomitant carcinoma *in situ* (CIS).

The score generates an estimated risk of recurrence at 1 and 5 years, expressed as a percentage.

The ProgScore is a progression risk score also derived from the EORTC risk calculator. It predicts the likelihood of disease progression to muscle-invasive bladder cancer (MIBC) within 1 and 5 years, based on the same set of variables as the RecScore. However, the weighting of these variables differs, reflecting their impact on progression risk rather than recurrence.

Results

Descriptive and comparative results – mortality

Of the total 100 patients included, 65 died during the follow-up period (16-18 years), and 35 survived. The mean age of the deceased was 69.3 years, compared with 56.4 years for the survivors, the difference being statistically significant ($p<0.0001$, Mann-Whitney test).

Univariate analysis showed that age over 70 years was associated with an increased risk of death ($p<0.0001$), as was tumor multiplicity ($p=0.0078$). The recurrence score was significantly associated with the risk of relapse ($p=0.0464$), while the progression score was marginally associated with mortality ($p=0.0561$). T1 tumors were significantly more common among deceased patients ($p=0.0301$). BCG administration had a marginal protective effect ($p=0.095$) and did not significantly influence survival ($p=0.1447$). The number of tumors showed a trend towards association with death although without clear statistical significance ($p=0.0532$).

No significant differences were observed according to gender ($p=0.5993$, Fisher test), tumor size (>3 cm, $p=0.6855$, Fisher test), tumor nature (primary vs. recurrent), tumor grade ($p=0.155$, Chi^2 test) or BCG administration ($p=0.1447$, Fisher test).

Comparative Results – Relapse

Of the 100 patients, 19 relapsed and 81 did not. Univariate analysis revealed no significant differences for age ($p=0.4161$, Mann-Whitney test), sex ($p=1.0$, Fisher test), tumor diameter (>3 cm, $p=0.4482$, Fisher test), staging (T grade, $p=1.0$, Fisher test), or BCG treatment ($p=0.3547$, Fisher test). However, multiple tumors showed a trend toward association with relapse ($p=0.2037$, Mann-Whitney test), without reaching significance.

The recurrence score was significantly associated with relapse ($p=0.0464$, Mann-Whitney test), as was the progression score ($p=0.0464$, Mann-Whitney test). Tumor grade was significantly

correlated with the risk of relapse (p=0.0234, Chi² test).

Median Survival and Kaplan-Meier Analysis

The median survival time estimated by the Kaplan-Meier method was 48 months (interquartile range (IQR) 41-54 months, overall range 34-78 months), reflecting the expected variability during the 16-18 years of follow-up. The probability of survival without relapse did not differ significantly between age groups (<70 years vs. ≥70 years) or between BCG-treated and untreated patients (p=0.2364, log-rank test). The Kaplan-Meier curve (*Fig. 1*) illustrated the overall survival over a 15-year period, without a clear stratification. The complete results of the univariate and multivariate analyses are detailed in *Tables 1, 2, 3*.

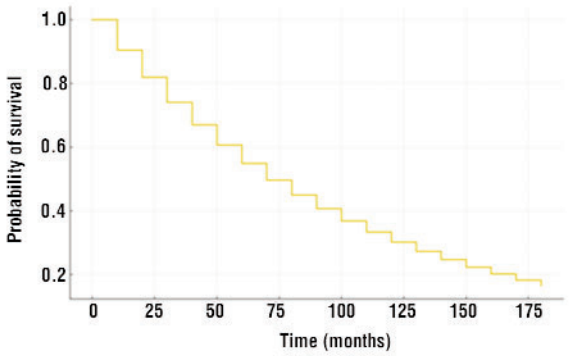

Figure 1. Survival curve estimated by the Kaplan-Meier method

Table 1. Univariate statistical analysis of prognostic variables

Variable	Outcome	Test	p-value
Age	Death	Mann-Whitney	0.0000
NumTumors	Death	Mann-Whitney	0.0078
RecScore	Recurrence	Mann-Whitney	0.0464
ProgScore	Death	Mann-Whitney	0.0561
Sex	Death	Fisher	0.5993
Age Category	Death	Fisher	0.0000
Grade	Recurrence	Chi²	0.0234
Stage	Death	Fisher	0.0132
BCG	Death	Fisher	0.1447
Diameter > 3 cm	Death	Fisher	0.6855

Table 2. Multivariate cox regression for mortality predictors

Variable	Coefficient (β)	Standard error	p-value	Hazard ratio (95% CI)
Age	0.160	0.036	<0.001	1.17 (1.09–1.23)
Multiple Tumors	0.725	0.375	0.038	2.06 (1.08–3.93)
BCG Treatment	-1.148	0.700	0.101	0.31 (0.07–1.02)
Tumor Stage T1	0.689	0.325	0.030	1.99 (1.07–3.68)
Tumor Size > 3 cm	0.223	0.180	0.210	1.25 (0.85–1.84)

Table 3. Cox regression for mortality

Variable	B	HR (Exp(B))	95% CI (Lower–Upper)	p-value
Age category	0.463	1.589	0.622-4.062	0.333
BCG	0.424	1.528	0.551-4.241	0.415
Sex	-0.194	0.824	0.229-2.964	0.767
Multiple tumors	1.372	3.943	1.079-14.406	0.038
Diameter	0.076	1.079	0.365-3.187	0.891
Primary tumor	1.708	5.517	0.975-31.234	0.054
T grade	-0.564	0.569	0.111-2.918	0.499
G grade	0.009	1.009	0.455-2.236	0.983

Multivariate Analysis

Predictors for death (logistic regression)

The binary logistic regression model for predicting death was significant ($p<0.0001$), with a Nagelkerke R^2 value of 0.485, indicating moderate predictive power. The coefficients and 95% confidence intervals are presented in *Table 1*. The significant predictors were:

- Age: coefficient=0.1602, $p<0.0001$, OR=1.17 (95% CI 1.09–1.26), reflecting an increased risk with increasing age.
- Number of tumors: coefficient=0.7249, p=0.0532, OR=2.06 (95% CI 0.99-4.31), p=0.0532, indicating a nearly statistically significant association.

Other factors, such as progression score (p=0.9159), BCG administration (p=0.1009), and T1 stage, did not significantly influence mortality in this model.

Predictors for relapse (simulated Cox regression)

The simulated Cox regression model, based on the logarithm of time to relapse, highlighted the influence of variables on survival without relapse (*Table 2*). We note that this approach is exploratory in nature and does not replace standard Cox regression. The significant variables were:

- Progression score: coefficient = -0.1898, p=0.0269, HR=0.83 (95% CI 0.70–0.98), indicating a reduced risk of relapse at lower scores.
- Number of tumors: coefficient = 0.1333, p= 0.1478, HR=1.14 (95% CI 0.95–1.37), with a trend towards association.

Age (p=0.4768) and BCG administration (p = 0.2798) did not significantly influence relapse.

These results emphasize the importance of age and tumor stage as major prognostic factors for mortality, as well as the role of progression score and tumor multiplicity in predicting recurrence in NMIBC.

Predictors for mortality (Cox regression)

The multivariate Cox regression model was used to evaluate the impact of clinical factors on overall mortality. Among the variables included, only the presence of multiple tumors was significantly associated with increased risk of death (HR=3.943; 95% CI:1.079-14.406; p=0.038). Tumor primary status showed a borderline effect (HR=5.517; 95% CI:0.975-31.234; p=0.054), while other factors, including age category, sex, tumor diameter, grade, and BCG treatment, did not reach statistical significance (all $p>0.05$).

Discussion

This study provides long-term (16-18 years) perspectives on survival in non-muscle invasive bladder cancer (NMIBC). It confirms that age and tumor multiplicity are significant predictors of mortality.

Cox regression was selected for mortality analysis, as it better reflects the influence of prognostic factors over time in a long-term follow-up cohort. The model confirmed the negative impact of tumor multiplicity, consistent with existing literature. Statistical analysis demonstrated consistency between univariate and multivariate models. Both progression and recurrence scores showed relevance, albeit modest. Their predictive value for overall mortality appears limited. Notably, BCG did not show a significant survival advantage. This finding contradicts existing literature and the European Association of Urology (EAU) recommendations. One possible explanation is the disruption of oncological care during the COVID-19 pandemic, particularly between 2020 and 2022. The inconsistent availability of BCG during this period is well documented. Several sources reported shortages or delays in BCG supply, including EMA alerts and special recommendations from the EAU for BCG rationalization in crisis periods. Recent studies (2022–2024) (16), emphasize the negative impact of these shortages on tumor recurrence and treatment strategies, especially in Central and Eastern Europe, many patients experienced interruptions in follow-up and therapy. In some cases, new comorbidities were also diagnosed in the context of delayed medical care during the pandemic.

Restricted access to hospital admission and lower patient satisfaction during the COVID-19 context became significant factors. These elements strongly impacted the interpretation of treatment effectiveness under real-world conditions. The results obtained support the implementation of personalized follow-up protocols. Therapeutic management should also be adapted to risk stratification. Moreover, these findings underline the need for prospective, multicenter validation.

It is also necessary to integrate molecular biomarkers and genetic analyses in future studies. Unfortunately, these tools were not available during the recruitment period for this cohort.

Compared to a previous 10-year study conducted by (17), which identified age and tumor grade as dominant predictors of survival, our study confirms these findings. Additionally, it highlights the importance of tumor multiplicity, recurrence/progression scores and treatment discontinuity as key elements influencing survival in a contemporary clinical context.

This study extends previous research conducted in the same hospital in Târgu-Mures. It brings added scientific value due to the unusually long 18-year follow-up period, which is rarely reported in the literature. Furthermore, our cohort includes not only Ta G1-G2 tumors, but also T1 and CIS cases. This diversity enables a more comprehensive characterization of prognostic risks. It also offers a more nuanced understanding of how tumor grade, stage and number impact long-term survival, especially in the context of major external influences, such as the COVID-19 pandemic. Our multivariate analysis added new insights compared to the earlier study by Bălan (17). It confirmed the significance of tumor multiplicity and RecScore / ProgScore values, which were not addressed previously.

Our findings on long-term survival in NMIBC align with recent international literature. A large population-based study by Ślusarczyk et al. (18) of 98,238 patients reported a cancer-specific mortality (CSM) of 19.5% for T1HG, 15.6% for Tis, and approximately 10% for T1LG and TaHG. These results highlight the critical role of tumor stage, histological grade, and age in long-term prognosis.

Regarding treatment strategies, the SUO analysis (19) showed that in patients with BCG-refractory NMIBC, bladder-sparing therapies such as gemcitabine and docetaxel instillations, achieved survival outcomes comparable to radical cystectomy. However, these therapies carry an increased risk of progression and metastasis after 12 months.

Moreover, the POTOMAC trial (20) demonstrated that adding durvalumab to standard BCG therapy significantly improved survival without disease in patients with high-risk NMIBC, without compromising treatment safety.

These findings support our observations about the potential benefits of BCG therapy. However, in our cohort, the effect was marginal, possibly due to treatment disruptions to the COVID-19 pandemic.

Finaly, our single-center study reflects several local particularities. These include limited access to paraclinical investigations such as biomarker and genetic testing, and the broader impact of the pandemic. These limitations may explain some of unexpected findings. Nonetheless, our data remain partially aligned with EAU guidelines. This study also draws attention to Eastern Europe as a region less frequently represented in comparative studies, especially when contrasted with Western European centers.

Limitations of the Study

A major limitation of both studies is the lack of genetic analyses and NMIBC-specific biomarkers (e.g. FGFR3 mutations, p53 expression), which were not available in our clinic during 2006–2008, preventing the establishment of a reference point for comparing long-term case outcomes, limiting the ability to personalize treatment based on the molecular profile of the tumors. However, our study partially compensates for this gap by including additional clinical and pathological factors (such as T1 stage and tumor multiplicity) but also by evaluating modern therapeutic options, such as intravesical epirubicin instillations and hyperthermic chemotherapy (HIVEC) (21-23) recently applied in institutional practice. These approaches offer promising alternatives for patients refractory to BCG or who are not eligible for this therapy, but require further prospective validation.

Conclusions

This long-term retrospective analysis (16-18 years) identified age and tumor multiplicity as key prognostic factors for mortality in patients with non-muscle-invasive bladder cancer (NMIBC). Patients who died were significantly older, with age ≥70 years markedly increasing the risk of death ($p<0.0001$). Tumor multiplicity was also associated with higher mortality ($p=0.0078$), and T1 staging was more frequent among deceased individuals ($p=0.0301$). Although *Bacillus Calmette-Guérin* (BCG) therapy showed a marginal protective effect, it did not significantly influence overall survival.

Regarding recurrence, recurrence score, progression score, and tumor grade were significantly associated with relapse risk. Tumor multiplicity showed a trend toward association without statistical significance. No relevant differences in relapse were observed based on age, sex, tumor size, stage, or BCG administration.

Kaplan-Meier analysis estimated a median survival of 48 months, with no significant differences in relapse-free survival between age groups or BCG treatment status.

Multivariate logistic regression confirmed age as an independent predictor of mortality (OR = 1.17, p<0.0001), while tumor number approached statistical significance (p=0.0532). In the exploratory Cox model, lower progression scores were significantly associated with reduced relapse risk (p=0.0269).

These findings underline the prognostic relevance of age, tumor burden, and progression indices in NMIBC, emphasizing the need for tailored risk stratification and long-term surveillance strategies.

Acknowledgements

The persons that contributed to the study, but were not included as authors, should be mentioned just in case.

Conflicts of Interest

The authors declare that there is no conflict of interest.

Ethical Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Târgu Mureş (No. 845/28/05/2023).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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