# ADVANCED TREATMENT OF Ta NON-MUSCLE INVASIVE BLADDER TUMORS

Theses of doctoral (PhD) dissertation

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# ABBREVIATIONS

BCG - Bacillus Calmette Guerin

BC - Bladder Cancer

TNM - Tumor, Lymph Node, Metastasis

EORTC - European Organization for Research and Treatment of Cancer

LG - Low Grade

HG - High Grade

CIS - In-situ carcinoma

TURBT - Transurethral resection of bladder tumor

NMIBC- Non-muscle invasive bladder tumors

MIBC - Muscle-invasive bladder tumors

MMC– Mitomycin C

WHO - World Health Organization

PUNLMP - Papillary urothelial neoplasia with low malignancy potential

CT - Computed tomography

NLR - Neutrophil and lymphocyte ratio

CUETO - Spanish Urology Oncology Group (Club Urológico Espanol de Tratamiento Oncológico)

OS - Overall Survival

SD - Standard Deviation

SI – Single Immediate intravesical instillation

RFS - Recurrence-free survival

# GENERAL AIMS

1. The main goal of the PhD dissertation is to analyze the biological evolution of Ta non-muscle invasive bladder tumors.

2. Identification of clinical, paraclinical, and histological parameters that affect disease management of Ta non-muscle invasive bladder tumors.

3. Analysis of recurrence, progression, cancer-specific survival, and overall survival in non-muscle-invasive bladder tumors in the light of clinical, paraclinical, and histological parameters.

4. The role of Neutrophil and Lymphocyte Ratio (NLR) biomarker in clinical decision making: treatment, follow-up, and management.

5. Identification of differences in Ta G1 and Ta G2 non-muscle invasive bladder tumors that require a personalized therapy.

# INTRODUCTION

Bladder cancer is one of the most common urinary tract tumors, ranking second after prostate cancer. About half of these newly diagnosed tumors are low-grade malignancies (LG) and> 70% are non-muscle invasive bladder cancers (NMIBC).

The basic pillar for the diagnosis and treatment of non-invasive bladder cancer is transurethral resection of the bladder tumor (TURBT) and the latest version of the European Association of Urology guidelines, "we recommend immediate chemotherapeutic instillation in tumors suspected of low or moderate risk." We speak of low-risk tumors with primary, unique, TaG1 (low malignant potential papillary urothelial neoplasia, LG) and <3 cm, as well as non-associated in-situ carcinoma (CIS). Medium-risk tumors are those that do not fit into the low category or any of the following: T1 tumor, G3 (high grade [HG]) tumor, and CIS; or recurrent and large (> 3 cm) TaG1G2 / LG tumors (all traits should be present).

Although NMIBC is a non-muscle invasive tumor, the risk of recurrence and progression is well known. The European Organization for Research and Treatment of Cancer (EORTC) has introduced a scoring system to calculate the likelihood of recurrence and progression of the disease.

To the best of our knowledge, a long-term comparison of well-differentiated (G1) and moderately well-differentiated (G2) Ta tumors (according to the 1973 World Health Organization (WHO) system) has not been released for overall survival (OS). In a number of large case-control studies analyzing the long-term survival of NMIBC patients, usually after TURBT and intravesical chemotherapy, the survival range varies between studies, but is mostly higher than in muscle-invasive bladder cancer (MIBC).

# AIMS OF THE STUDY

The main aim of the study was to compare the long-term survival rate between well-differentiated (G1) and moderately well-differentiated (G2) type Ta bladder cancer patients after transurethral resection of the bladder tumor. The secondary objective was to examine the clinical and pathological prognostic factors of patients from the perspective of overall survival rate.

## MATERIAL AND METHODS

Our study included 243 Ta non-muscle invasive bladder cancer patients who underwent transurethral resection of bladder tumor at the Târgu Mureş Urology Department over a period of 3 years, between January 2006 and December 2008. We received ethical approval from the Ethics Committee of Mureş County Hospital.

The inclusion criteria were as follows: primary Ta, G1, and G2 tumors not associated with in-situ carcinoma (these can be classified as low to moderate tumors according to the guidelines of the European Association of Urology). Exclusion criteria were: all recurrent or advanced cancers, any T1 and / or G3 / HG tumors, any concomitant CIS, and lost follow-up. EORTC risk scores were calculated for all patients; the EORTC risk tables allow the calculation of the probability of recurrence and progression, taking into account the number of tumors, tumor size, previous recurrence rate, T-category, concomitant CIS, and classification.

Histological classification was performed according to the 1973 World Health Organization (WHO) classification. Recurrence was defined as relapse of disease after more than 3 months postoperatively and progression was defined as the appearance of T1 or muscle invasive bladder cancer (MIBCs).

According to the guidelines of the European Association of Urology, Bacillus Calmette-Guerin (BCG) intravesical immunotherapy was used to treat moderate-risk Ta tumors following the Lamm system: 1 instillation per week for 6 weeks and then 3-week instillation for 3 or 6 months.

Follow-up was performed by clinical examination and cystoscopy every 3 months for the first 2 years and by cystoscopy every 6 months for the next 3 years and annually thereafter. The first endpoint was the time to first recurrence; second endpoint is time to progression and third endpoint is death from any trigger (from the National Health Insurance Registry).

## RESULTS

A total of 243 patients were analyzed for G1 and G2 Ta tumors and 164 met the inclusion criteria. Seventy-nine patients were excluded from our study due to the presence of concomitant in-situ carcinoma (1 patient) (108), high-grade G3 / HG tumors (47 patients), loss of follow-up, and incomplete data (31 patients) for 10-year survival. The mean follow-up of patients was 109 months (IQR 70-121 months). The mean age at the time of diagnosis was 63.3 years (21–89) and 135 (82.3%) were male patients. In 78 cases (47.6%) multiple tumors were observed, in 86 (52.4%) cases the tumor diameter was> 3 cm, G2 tumors were observed in 105 (64%) patients. Intravesical immunotherapy with BCG was administered to 32 (19.5%) patients

according to the guidelines in force at the time (moderate-risk Ta tumors). Most patients had EORTC recurrence rates ranging from 1 to 4: 99 patients (60.4%). The EORTC progression score ranged from 1 to 6 in 107 patients (65.2%). Recurrence was observed in 26 patients (15.8%) and progression in 5 (3%) patients. A total of 102 patients (62.2%) survived 10 years after diagnosis (Table 1).

Table 1: Characteristics of 164 patients with low and moderate Ta bladder tumors at the time of diagnosis

| Patients characteristics | No patients, % | G1 | G2 | *P* |
|---|---|---|---|---|
| Age | | | | |
| Mean | 63.3 y | 62.9 y | 63.6 y | .71 |
| Gender | | | | |
| Male | 135 (82.3%) | 45 (76.3%) | 90 (85.7%) | .12 |
| Female | 29 (17.7%) | 14 (23.7%) | 15 (14.3%) | |
| Tu diameter | | | | |
| <3 cm | 78 (47.6%) | 34 (57.6%) | 44 (41.9%) | .053 |
| >3 cm | 86 (52.4%) | 25 (42.4%) | 61 (58.1%) | |
| No tumors | | | | |
| Single | 86 (52.4%) | 32 (54.2%) | 54 (51.4%) | .73 |
| Multiple (2–7) | 78 (47.6%) | 27 (45.8%) | 51 (48.6%) | |
| Grade | | | | |
| G1 | 59 (36%) | – | – | – |
| G2 | 105 (64%) | – | – | – |
| BCG treatment | | | | |
| No | 132 (80.5%) | 45 (76.3%) | 87 (82.8%) | .30 |
| Yes | 32 (19.5%) | 14 (23.7%) | 18 (17.2%) | |
| Rec EORTC score | | | | |
| 0 | 26 (15.8%) | 26 (44.1%) | 0 | <.001* |
| 1–4 | 99 (60.4%) | 17 (28.8%) | 82 (78.1%) | |
| 5–9 | 39 (23.8%) | 16 (27.1%) | 23 (21.9%) | |
| Prog EORTC score | | | | |
| 0 | 57 (34.8%) | 26 (44%) | 31 (29.5%) | .06 |
| 1–6 | 107 (65.2%) | 33 (56%) | 74 (70.5%) | |
| Recurrence | 26 (15.8%) | 13 (22%) | 13 (12.4%) | .10 |
| Progression | 5 (3%) | 3 (5%) | 2 (1.9%) | .25 |
| Deaths | 62 (37.8%) | 19 (32.2%) | 43 (41%) | .26 |

BCG = Bacillus Calmette–Guerin, CI = confidence interval, EORTC = The European Organization for Research and Treatment of Cancer, HR = hazard ratio.

Table 2 shows the relationship between clinicopathological features and overall survival in the study group. In the study of deaths, at the time of diagnosis, advanced age was

associated with a lower overall survival: 69 mean age, compared with a mean age of 59.8 for survivors (P <.001). Mortality was higher in men (38.5%) than in women (34.3%), but we did not find a statistically significant correlation (P = .68). Even if no statistically significant correlation was found, the survival rate in G1 (67.8%) was higher compared to G2 (59%) patients (P = .26). BCG treatment was associated with a higher overall survival of 84.4% compared with 56.8% of patients who did not receive BCG therapy, P = 0.004.

Table 2: Comparison of clinical-pathological factors with overall survival

| | Death | | |
|---|---|---|---|
| **Patients characteristics** | **No (102 patients)** | **Yes (62 patients)** | ***P*** |
| Age mean | 59.8 y | 69 y | **<.001*** |
| Gender male (no/%) | 83 (61.5) | 52 (38.5) | .68 |
| Female | 19 (65.5) | 10 (34.5) | |
| Tu diameter <3 cm (no/%) | 51 (65.4) | 27 (34.6) | .42 |
| >3 cm | 51 (59.3) | 35 (40.3) | |
| No tumors single (no/%) | 57 (66.3) | 29 (33.7) | .25 |
| 2–7 (no/%) | 45 (57.7) | 33 (42.3) | |
| Grade G1 (no/%) | 40 (67.8) | 19 (32.2) | .26 |
| G2 (no/%) | 62 (59) | 43 (41) | |
| BCG treatment no (no/%) | 75 (56.8) | 57 (43.2) | **.004*** |
| Yes (no/%) | 27 (84.4) | 5 (15.6) | |
| Recurrence EORTC score 0 (no/%) | 17 (65.4) | 9 (34.6) | .93 |
| 1–4 (no/%) | 61 (61.6) | 38 (38.4) | |
| 5–9 (no/%) | 24 (61.5) | 15 (38.5) | |
| Progression EORTC score 0 (no/%) | 40 (70.3) | 17 (29.8) | .12 |
| 1–6 (no/%) | 62 (57.9) | 45 (42.1) | |
| Recurrence no (no/%) | 87 (63) | 51 (37) | .6 |
| Yes (no/%) | 15 (57.7) | 11 (42.3) | |
| Progression no (no/%) | 101 (63.5) | 58 (36.5) | **.04*** |
| Yes (no/%) | 1 (20) | 4 (80) | |

BCG = Bacillus Calmette–Guerin, EORTC = The European Organization for Research and Treatment of Cancer.

Univariate Cox analysis showed that the negative prognostic factors for overall survival were: advanced age, risk ratio (HR) 1.07; BCG treatment lack HR 0.30 and progression during follow-

up HR 5.25. Multivariate Cox analysis showed that independent predictors of overall survival were: age (HR 1.07); EORTC recurrence score from 1 to 4 (HR 0.23); EORTC recurrence score 5-9 (HR 0.17); and progression (HR 5.18) (Table 3).

Table 3: Univariate and multivariate Cox regression analyzes to predict the overall survival of 164 low- and moderate Ta bladder cancer patients.

| | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| **Prognostic factor** | **HR** | **95% CI** | ***P*** | **HR** | **95% CI** | ***P*** |
| Age cont | 1.07 | 1.04–1.10 | **<.001*** | 1.07 | 1.03–1.10 | **<.001*** |
| Gender | 0.93 | 0.47–1.83 | .84 | 0.82 | 0.40–1.68 | .60 |
| Multifocality | 1.29 | 0.78–2.13 | .31 | 1.90 | 0.81–4.43 | .13 |
| Diameter | 1.26 | 0.76–2.08 | .36 | 1.18 | 0.49–2.81 | .70 |
| Grade | 1.31 | 0.76–2.25 | .32 | 1.75 | 0.79–3.83 | .16 |
| EORTC rec | | | Ref. | | | |
| 1–4 score | 1.08 | 0.52–2.24 | .82 | 0.23 | 0.06–0.91 | **.036*** |
| 4–9 score | 1.06 | 0.46–2.42 | .89 | 0.17 | 0.03–0.76 | **.02*** |
| EORTC prog 1–6 score | 1.52 | 0.87–2.67 | .13 | 1.85 | 0.52–6.56 | .33 |
| BCG treatment (no treat) | 0.3 | 0.12- 0.79 | **.01*** | 0.40 | 0.15–1.05 | .063 |
| Recurrence | 1.28 | 0.67–2.46 | .44 | 1.16 | 0.48–2.77 | .72 |
| Progression | 5.25 | 1.89–14.57 | **<.001*** | 5.18 | 1.33–20.18 | **.018*** |

BCG = Bacillus Calmette–Guerin, CI = confidence interval, EORTC = The European Organization for Research and Treatment of Cancer, HR = hazard ratio.

Univariate and multivariate logistic regression analysis highlighted that advanced age (HR 1.10) and lack of BCG treatments (HR 0.24 and 0.29) are independent predictors of mortality in the 10 years after diagnosis (Table 4).

Table 4: Univariate and multivariate logistic regression predicting the overall survival of 164 patients with low and moderate Ta bladder cancer.

| | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| **Prognostic factor** | **HR** | **95% CI** | ***P*** | **HR** | **95% CI** | ***P*** |
| Age cont | 1.10 | 1.05–1.14 | **<.001*** | 1.10 | 1.05–1.15 | **<.001*** |
| Gender | 0.84 | 0.36–1.94 | .68 | 0.73 | 0.27–1.98 | .54 |
| Multifocality | 1.44 | 0.76–2.71 | .25 | 2.46 | 0.66–9.16 | .17 |
| Diameter | 1.29 | 0.68–2.44 | .42 | 0.94 | 0.23–3.77 | .94 |
| Grade | 1.46 | 0.74–2.85 | .26 | 1.84 | 0.67–5.00 | .23 |
| EORTC rec | | | Ref | | | |
| 1 | 1.17 | 0.47–2.90 | .72 | 0.30 | 0.05–1.56 | .15 |
| 2 | 1.18 | 0.41–3.31 | .75 | 0.21 | 0.02–1.53 | .12 |
| EORTC prog | 1.70 | 0.86–3.38 | .12 | 2.04 | 0.32–12.79 | .44 |
| BCG treatment | 0.24 | 0.08–0.67 | **.006*** | 0.29 | 0.09–0.90 | **.03*** |

BCG = Bacillus Calmette–Guerin, CI = confidence interval, EORTC = The European Organization for Research and Treatment of Cancer, HR = hazard ratio.

The Kaplan-Meier survival analysis showed an 8% difference in survival between grades G1 and G2, but no statistically significant difference was found. The five-year survival of G1

patients was 86.4% (CI 74.7–93), while that of G2 patients was 84.7% (CI 76.3–90.3). Overall 10-year survival was 67.8% (CI 54.3-78.1) in G1 patients and 59% (CI 49-67.3) in G2 patients.

BCG therapy was effective in terms of overall survival, with 5-year survival in 82.6% (CI 74.9-88) in patients not receiving BCG therapy and 96.8% (CI 79.8-99) in patients receiving BCG therapy. 10-year survival in patients not receiving BCG therapy was 56.8% (CI 47.9–64.7), while 10-year survival in patients receiving BCG was 84.4% (CI 66.4–93.1). , P = 0.006.

## DISCUSSION

The long-term survival of 164 Ta G1-G2 non-muscle invasive bladder cancer (NMIBC) patients was assessed in a center with a mean follow-up of 109 months. Ten years after the time of diagnosis, 62% of patients were survivors. At diagnosis, advanced age was associated with worse overall survival between TaG1 and TaG2 patients in terms of 10-year overall survival. More interesting is the statistically significant relationship we found between BCG treatment and longer overall survival.

In our study, we also demonstrated that advanced age is an independent prognostic factor. At 5-year follow-up, 27% of patients older than 70 years were cancer-free, compared with 27% of patients younger than 70 years (37%), including high-risk NMIBC patients.

Data on long-term (at least 10 years) overall survival after the initial diagnosis of Ta bladder tumors are lacking in the literature. In a large multicenter group of TaG1 patients, the estimated overall survival at 5 years was 86% (similar to our study, where the overall survival at TaG1 at 5 years was 86.4%), but more than half of the patients received immediate postoperative intravesical chemotherapy.

Our study has several limitations. First, retrospective analysis needs further confirmation in future research. Second, patients did not receive immediate postoperative intravesical chemotherapy, although patients at moderate risk received adjuvant therapy. Third, we did not perform a central pathological examination of the samples and did not redistribute the samples to the most recent WHO classification. Furthermore, there were no data on the smoking status of patients, which is a well-known prognostic factor for urothelial carcinomas. In addition, specific tumor survival should have been a primary target, but unfortunately we did not have access to patients ’death certificates. Despite these limiting factors, this study met its goal of comparing the overall survival of newly diagnosed G1 and G2 Ta bladder cancer patients 10 years after diagnosis.

## CONCLUSION

Patients with well-differentiated (G1) and moderately well-differentiated (G2) Ta tumors showed similar long-term overall survival after diagnosis. Bacillus Calmette Guerin treatment leads to longer overall survival, even in moderate-risk bladder tumors.

# THE ROLE OF NEUTROPHIL TO LYMPHOCYTE RATIO IN PATIENTS WITH PTA NON-MUSCLE INVASIVE BLADDER CANCER

## INTRODUCTION

In neoplasms, a significant amount of immune cells accumulate in the microenvironment of tumor cells, which is maintained by the cytokines and inflammatory mediators produced by the tumor itself or by the tumor-associated stroma. Inflammatory factors promote tumor formation and progression.

Elevated laboratory values due to inflammatory processes may be predictors of tumor extent and aggression. One such biological marker is the neutrophil-lymphocyte ratio (NLR), which has a prognostic role in the prognosis of pancreatic, breast, and colon tumors in addition to urological tumors such as renal cell carcinoma and upper urinary tract urothelial carcinomas. Several studies demonstrate the importance of neutrophil-lymphocyte ratio (NLR), including in determining the prognosis of bladder tumors.

The use of biomarkers with predictive and prognostic roles is essential in determining the evolution of tumors. It is important that these are part of everyday practice, easily accessible and cost-effective.

## AIM OF THE STUDY

The aim of the study was to investigate the role of NLR as a prognostic biomarker for disease recurrence, progression and survival of pTa NMIBC.

## MATERIAL AND METHODS

In a retrospective study, we enrolled 54 histologically confirmed patients with stage Ta BC who underwent transurethral resection of the bladder tumor (TURBT) between January 2007 and December 2008 (mean follow-up 106 months (IQT 68-116)) at the Urology Clinic in Târgu Mureş. Selection criteria were: primary tumor, low degree of differentiation, NLR determination before resection; NLR was assessed as pathological if it exceeded a value above 3.

Statistical analysis was performed using the STATA 11 Statistical Program. Histopathological classification was performed according to the 1973 guidelines of the World Health Organization.

Clinical follow-up was based on cystoscopy, every three months for the first two years, every six months for the following three years, and annually thereafter. Follow-up CT imaging was performed according to the guidelines of the then EAU (European Association of Urology) in clinically justified cases. Differences between non-parametric variables (expressed in median) were analyzed by Mann – Whitney U test.

Survival analysis was performed as follows: the Kaplan – Meyer method and the long-rank test were used for univariate comparisons. Univariate and multivariate Cox regression models investigated the association of prognostic factors with overall survival after TURBT. All P values were two-sided and defined as statistically significant $P < 0.05$. Statistical analyzes were performed using Stata 11.0 statistical software (Stata Corp., College Station, TX).

## RESULTS

The mean age of the patients in the study was 63 years (IQR 55-72). A significant proportion of patients had an NLR <3 (37 patients / 68.51%). The mean recurrence EORTC score was 4 (IQR 1-6) and the progression EORTC score was 3 (IQR 0-6). Overall, recurrence occurred in 8 (14.81%) patients and 2 (3.70%) patients were identified with T2 or higher progression during the follow-up period (29, IQR 25–36 months).

No statistically significant association was found between NLR> 3 and other clinical or pathological factors, however, all patients with progression were in the NLR> 3 group (Table 1). Kaplan-Meier analysis of Progression-free survival (PFS) showed lower PFS in the NLR> 3 group: 94.12% vs. 100%, $p = 0.04$. Recurrence was found in 4 (10.8%) patients in the low NLR group; similarly, 4 (23.5%) patients from the high NLR group presented recurrence.

Based on multivariate Cox regression analyzes, NLR was found to be a prognostic factor for recurrence (HR = 1.09, p = 0.01) (Table 2).

Kaplan Meier's analysis of recurrence-free survival (RFS) showed no statistical significance among NLR groups: 82.67% vs. 64.12%, p = 0.26, however, multivariate Cox regression analysis demonstrates that NLR as a continuous variable is an independent prognostic factor for RFS.

During follow-up (106 months), 18 patients died, of whom 7 (41.2%) were from the NLR> 3 group. The Kaplan-Meier overall survival curve showed a 10-year overall survival of 70.27% in the low NLR group, compared with 58.82% overall survival in the high NLR group, p = 0.45. In the multivariate analysis, age at the time of diagnosis proved to be a predictive factor, while NLR showed no statistically significant association (HR 1.03, Cl 0.98-1.08, p = 0.22) (Table 3).

Table 1. Characteristics of the 54 patients with pTa bladder cancer at diagnosis according to NLR value

| Patients characteristics | All patients | NLR<3 | NLR>3 | P value |
|---|---|---|---|---|
| Total, n (%) | 54 | 37 | 17 | |
| Gender male | 10 (18.5 %) | 6 (162%) | 4 (235%) | 0.52 |
| female | 44 (81.5 %) | 31 (83.8%) | 13 (76.5%) | |
| Tu. Diameter <3 cm | 21 (38.9 %) | 12 (32.4%) | 9 (52.9%) | 0.15 |
| >3 cm | 33 (61.1 %) | 25 (67.5%) | 8 (47.1%) | |
| No. tumors single | 24 (44.4 %) | 17 (45.9%) | 7 (41.2%) | 0.74 |
| Multiple (2-7) | 30 (55.5 %) | 20 (54.0%) | 10 (58.8%) | |
| Grade G1 | 22 (40.7 %) | 16 (43.2%) | 6 (35.3%) | 0.58 |
| G2 | 32 (59.3 %) | 21 (56.7%) | 11 (64.7) | |

| | | | | |
|---|---|---|---|---|
| Recurrence | 8 (15.8 %) | 4 (10.8%) | 4 (23.5 %) | 0.22 |
| Progression | 2 (3.7 %) | 0 | 2 (11.7%) | **0.03** |
| Deaths | 18 (33.3 %) | 11 (29.7%) | 7 (41.2%) | 0.40 |

Table 2. Multivariable Cox regression analyses predicting recurrence of 54 patients with Ta bladder cancer.

| Prognostic factor | Multivariable | | |
|---|---|---|---|
| | HR | 95 % CI | p value |
| NLR | 1.09 | 1.02-1.16 | **0.01** |
| Gender Male vs Female | 0.99 | 0.17-5.58 | 0.99 |
| Age cont. | 0.98 | 0.91-1.06 | 0.73 |
| Diameter<3cm vs >3 cm | 8.23 | 0.77-87.45 | 0.08 |
| Grade G1vs G2 | 0.17 | 0.02-1.01 | 0.052 |
| Multifocality Single vs Multiple | 0.35 | 0.04-3.01 | 0.34 |

CI: confidence interval, HR: hazard ratio

*NLR cat: HR 4.81, 95 % CI: 0.86-26.72, p value : 0.07

Table 3. Multivariable Cox regression analyses predicting survival of 54 patients with Ta bladder cancer.

| Prognostic factor | Multivariable | | |
|---|---|---|---|
| | HR | 95 % CI | p value |
| NLR | 1.03 | 0.98-1.08 | 0.22 |
| Gender Male vs Female | 1.02 | 0.32-3.25 | 0.96 |
| Age cont. | 1.06 | 1-1.12 | **0.03** |
| Diameter<3cm vs >3 cm | 1.8 | 0.42-7.7 | 0.42 |
| Grade G1vs G2 | 1.02 | 0.35-2.98 | 0.96 |
| Multifocality Single vs Multiple | 0.72 | 0.18-2.85 | 0.64 |

CI: confidence interval, HR: hazard ratio

*NLR cat: HR 1.17 , 95 % CI: 0.42-3.24, p value : 0.76

## DISCUSSION

The use of biomarkers that play a predictive and prognostic role is essential for tumor evolution. The integration of these markers into daily practice is extremely important, and they should be easily accessible and cost-effective.

In this regard, we demonstrated that NLR as a continuous variable is a prognostic factor for recurrence in Ta NMIBC. As a categorical variable, NLR> 3 was not statistically significant (HR 4.81, p = 0.007). However, a reference value is important in clinical practice and, since NLR> 3 has been validated for high-risk NMIBC, it can be used as a low-risk NMIBC threshold.

In recent years, great importance has been attached to the prognostic role of biomarkers in the blood in determining the evolution / outcome of tumors.

# CONCLUSION

Among the limitations of our study we have to mention its retrospective nature; our patient follow-up extended for almost 10 years after TURBT. In addition, the sample size was an additional limitation, but considering the long follow-up and previous results for the high-grade NMIBC (those also from the monocentric cohort and further validated in a multi-institutional cohort), our results can be considered reliable. . Of course, these findings need to be externally verified in a multi-institutional study.

In the group analyzed in our study, high NLR is considered a statistically significant value and an independent prognostic factor for poor prognosis of stage Ta bladder tumors. In low-risk, non-muscle-invasive bladder cancer, NLR may be a reliable biomarker in clinical decision-making regarding follow-up schedule.

# GENERAL CONCLUSIONS

1. Treatment of patients with non-invasive bladder cancer should be individualized.

2. Assessment of prognostic factors is mandatory in the individualized treatment of non-invasive bladder cancer patients.

3. Patients should be grouped according to a risk protocol developed by the European Organization for Research and Treatment of Cancer (EORTC).

4. Postoperative follow-up and treatment of patients with Ta non-invasive bladder cancer should be based on the risk of recurrence and progression.

5. The need for adjuvant treatment is unquestionable.

6. Biomarkers with new prognostic factors can radically change clinical decision-making.

7. The Neturophil and Lymphocyte Ratio (NLR) is an available biomarker that could be widely used in clinical practice and has a prognostic role.

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