

A mathematical model for predicting tumor recurrence within 24 months following surgery in patients with T1 high-grade bladder cancer treated with BCG immunotherapy

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Abbreviations used: T1HG, T1 high-grade; BCG, Bacillus Calmette-Guerin; BC, bladder cancer; NMIBC, non-muscle invasive bladder cancer; NLR, neutrophils-to-lymphocytes ratio; MLP, multi-layer perceptron; KNN, K-nearest neighbors; DT, decision tree; BZ, Bnai-Zion Medical Center; RC, Rabin Medical Center.

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ABSTRACT

OBJECTIVES: Aggressive bladder cancer has a high rate of recurrence and progression. Treatment of T1 high-grade (T1HG) bladder cancer lesions is challenging. Current prognostic models reasonably predict progression; however, additional prognostic markers are required to accurately predict recurrence. The aim of the study was to develop a prediction model for risk of recurrence in individual patients with T1HG bladder cancer treated with intravesical BCG.

PATIENTS AND METHODS: Medical records of 115 patients with T1HG bladder cancer treated with adjuvant intravesical BCG immunotherapy from two different hospitals were reviewed. Mathematical algorithms were applied to identify parameters that could accurately predict recurrence within 24 months after surgery.

RESULTS: Overall recurrence rate at 24 months after surgery was 49%. Of all clinical and pathological parameters evaluated, the best predictor of recurrence within 24 months after surgery was neutrophils-to-lymphocytes ratio. This ratio predicted recurrence with 86% sensitivity and 62% specificity in the whole database. The main limitations of our study are its retrospective nature and the small patient number.

CONCLUSIONS: Neutrophils-to-lymphocytes ratio was found to be superior to traditional parameters for the prediction of recurrence within 24 months following surgery in patients with T1HG bladder cancer treated with intravesical BCG immunotherapy. Stratifying patients using risk factors can help determine the appropriate follow-up and treatment for each individual patient.

Keywords: bladder cancer; decision tree model; neutrophils-to-lymphocytes ratio

INTRODUCTION

Bladder cancer (BC) is the most common cancer of the urinary tract. The age-standardized rate in the European Union is 27 and 6 per 100,000 in men and women, respectively [1]. Most patients with BC (~80%) are diagnosed with non-muscle invasive bladder cancer (NMIBC) [2].

High-grade urothelial carcinoma invading the lamina propria (T1HG) is a challenging subgroup of BC. Although defined a NMIBC, it carries a 78% and 45% risk for recurrence and progression in 5 yrs, respectively [3]. Treatment options include adjuvant intravesical therapy or radical

cystectomy [4]. While giving the best oncological control, cystectomy carries significant morbidity and mortality.

Current models, including EORTC and CUETO, reliably predict progression but poorly predict recurrence [5]. The use of mathematical algorithms may lead to identifying novel predictors of outcome within this group of patients.

The aim of the study was to develop a mathematical model that can predict the risk of recurrence within 24 months after TURBT in an individual patient with T1HG BC following intravesical Bacillus Calmette-Guerin (BCG) immunotherapy based on patient data.

PATIENTS AND METHODS

After approval from the institutional ethics committees, we retrospectively reviewed 266 consecutive patients diagnosed with non-muscle invasive urothelial carcinoma of the bladder between 2003 and 2009, in two urology departments: Bnai-Zion Medical Center (BZ), Haifa, Israel and Rabin Medical Center (RC), Petach Tikva, Israel. Patients with T1HG tumors who received BCG treatment and had a recurrence or had no recurrence during at least 24 months of follow-up were included. Since BCG treatment is known to delay the onset of recurrence [6], patients who didn't receive BCG were excluded. Overall, 115 patients were included, 45 from BZ and 70 from RC.

Patients underwent a complete TURBT and resected specimens were reviewed by a genitourinary pathologist who confirmed the diagnosis. Tumors were graded and staged according to the 2004 WHO grading system [7] and the 2002 American Joint Committee on Cancer TNM staging system [8]. All patients underwent second-look TUR-BT and treated with intravesical BCG. Both hospitals used the same protocol for intravesical BCG treatment, consisting of 1 vial of OncoTICE (MSD, Hertfordshire, UK) diluted in 50 ml saline per week for 6 consecutive weeks. Patients keep the instilled solution for 2 hours without voiding. Follow-up consisted of cystoscopy, urine cytology and upper-tract imaging. Disease recurrence was defined as the first pathologically confirmed tumor relapse in the bladder, regardless of the tumor stage.

Data collected included age, sex, co-morbidities, other malignancies, smoking status, creatinine level, complete blood count, neutrophils-to-lymphocytes ratio (NLR), urine cytology, and pathological parameters (number and size of tumors) and follow-up data including recurrence. Blood tests were taken prior to initiation of treatment. Standard statistical tools in addition to machine-learning algorithms were used in order to identify best predictors for recurrence. In a parallel study [9], we showed a correlation between NLR and progression of NMIBC. The present study focuses on recurrence in a subset of patients with T1HG BC treated with BCG. We were interested in identifying predictors for 2-year recurrence, we also sought to identify the time-period with the highest risk of recurrence and time period with the most aggressive treatment.

The common practice in medical analysis is to seek significant correlations between two parameters, thus proving a relation between them. We went beyond that and used machine-learning algorithms to make practical predictions. We applied a few well-known algorithms such as Multi-Layer Perceptron (MLP) and K-Nearest Neighbors (KNN) [10,11] but eventually we used the Decision Tree (DT) algorithm [12]. In this algorithm one constructs a tree-like network, where at each node the input vector is "inquired" on some property of it. For example, a node might inquire whether the tumor size is greater or smaller than 5 mm, whether the age is above or below 70 yrs, etc. Typically, a tree consists of a sequence of inquiries on different features of a given patient, resulting in a decision (termed a *leaf* in the tree), which in our case is whether or not the tumor will recur within 24 months after surgery. The actual tree (the sequence of inquiries) is obtained by a process in which an optimal tree is fitted to a given dataset such that the tree gives the best correct partition of the patient population into subsets. After a tree is constructed, it can be examined for inquiries that contributed little to the correct conclusion. Branches associated with such inquiries are then 'pruned'.

Though all three algorithms gave comparable results, there are

advantages to the DT: it relates directly to the data, it is intuitive to apply because important predicting features are transparent, and the pruning process leaves out only the truly determining features. Using a DT algorithm allowed us to use a "mushy zone" which is an interval of indecision.

RESULTS

The study cohort included 115 T1HG BC patients treated with intravesical BCG from two different medical centers. One database (BZ45) consisted of 45 patients from Bnai-Zion Medical center (35 men and 10 women; mean age 70.7 yrs; mean number of tumors 3.1; mean size of largest tumor 27.7mm). The second database (RC70) consisted of 70 patients from Rabin Medical Center (62 men and 8 women; mean age 70.7 yrs; mean number of tumors 1.8; mean size of largest tumor 26.4 mm).

Table 1 shows the values of NLR for each database and the correlation between 2-year recurrence rate and four parameters: NLR, age, number of tumors, and size of largest tumor. There was a significant correlation between age and 2-year recurrence rate in BZ45 database but not for RC70 database. None of the other parameters had statistically significant correlation. Not surprisingly, all three machine-learning algorithms failed to give adequate predictions when trained on either of these two databases.

Table 1. Mean and standard deviation of NLR values for each of the two databases BZ45 and RC70, and P-values of the correlation between recurrence within 24 months and each of these four parameters: NLR value, number of tumors, size of the largest tumor and age.

Data-base	NLR (mean ± SD)	P-value			
		NLR	No. of tumors	Size of tumor	Age
BZ45	4.1 ± 2.8	0.25	0.78	0.28	0.03
RC70	3.2 ± 2	0.18	0.34	0.28	0.38

Being an indication of systemic inflammatory response, NLR can be affected by several blood disorders or non-bladder tumors. Therefore, we excluded patients with blood disorders, non-bladder malignancy or extreme lymphocytes count. We analyzed only patients with lymphocytes count between 12%–40% of while blood count.

We ended up with 73 patients: 26 patients in BZ26 database (21 men and 5 women; mean age 69 yrs; mean number of tumors 3.1; mean size of largest tumor 25.3 mm), and 47 patients in RC47 database (39 men and 8 women; mean age 70 yrs; mean number of tumors 1.9; mean size of largest tumor 29.3 mm). **Table 2** summarizes statistical analysis of these databases.

From this analysis, we see that NLR and age were significantly correlated with recurrence in 24 months for patients in BZ26 database ($P = 0.01$); however, only NLR had significant correlation with recurrence in 24 months in RC47 database ($P = 0.04$). These results were similar across the two other algorithms (MLP and KNN).

There are several ways to construct a DT that give rise to slightly different trees. A typical result is provided in **Figure 1**. The tree pre-

sented in **Figure 1** was trained by BZ26 database, and the results are given separately for each database, and also for the combined database. The tree has a total of 3 leaves. The root of the tree inquires about the NLR value, with a cutoff of 2.42, which is comparable with the value reported in ref [13]. A NLR value above 2.42 is marked with T (true) that leads to a leaf marked R (recurrence), predicting recurrence within 24 months following surgery. A negative answer to the inquiry $NLR > 2.42$ is marked as F (false) which leads to the second inquiry which in turn asks if the patient's age is over 78 yrs. Positive answer leads to a leaf R, and a negative (F) answer leads to a leaf N (no recurrence) that means no recurrence in 24 months. Near each leaf we list 3 sets of numbers. The first set is for BZ26 database, the second set is for the RC47 database and the third set is for the combined database. The numbers marked for each database are the total number of patients that reach this leaf of the tree, and the false identifications. For instance, the notation (17/3) in **Figure 1** means that 17 patients in the BZ26 database are associated with this leaf and in 3 out of them the prediction of recurrence is correct. **Table 3** shows the sensitivity and specificity of the tree shown in **Figure 1**.

Table 2. Mean and standard deviation for NLR values for each of the two databases BZ26 and RC47, and P-values of the correlation between recurrence under 24 months and four parameters: NLR value, number of tumors, size of the largest tumor and age.

Data-base	NLR (mean ± SD)	P-value			
		NLR	No. of tumors	Size of tumor	Age
BZ26	3.5 ± 1.6	0.012	0.76	0.31	0.011
RC47	2.6 ± 1	0.04	0.3	0.4	0.45

Table 3. Sensitivity and specificity of the predictions made by the decision tree shown in figure 1. Numbers in brackets are the total number of patients with recurrence. First row for BZ database; second row for RC database; third row for the combined database.

Database	Sensitivity	Specificity
BZ26 (positive = 16)	100%	70%
RC47 (positive = 20)	80%	44%
Combined (positive = 36)	89%	51%

Table 4. Sensitivity and specificity values of the predictions made by the decision tree algorithm shown in figure 2. First row for BZ database; second row for RC database; third row for the combined databases.

Database	Sensitivity	Specificity
BZ26	100%	75%
RC47	74%	61%
Combined	84%	65%

A drawback of the tree shown in **Figure 1** is the rigidity of the cutoff value. Since the database consists of clinical parameters that are naturally measured up to some accuracy, and since a decision might

have serious clinical implications, we upgraded the DT algorithm to include a mushy zone around the cutoff point $NLR = 2.4$; thus, we included an interval of values where no decision is made on recurrence. It remains to find the length of the mushy zone. In general, this can be achieved by seeking the DT that maximizes sensitivity and specificity, without losing too many patients into the mushy zone. However, in our case we employed a different approach. We assumed that the relative error in WBC count is about 5% [14]. Therefore, the expected error of NLR is approximately. Hence, for $NLR \sim 2.4$, the expected error is approximately 0.2. This motivated us to define a mushy zone of size 0.2. Therefore, we defined the mushy zone as the interval between 2.3–2.5. Thus, our model predicts no recurrence within 24 months for patients with $NLR < 2.3$, and recurrence within 24 months for patients with $NLR > 2.5$. Patients with NLR in the mushy zone $2.5 > NLR > 2.3$ are left undetermined. The DT is depicted in **Figure 2**. The results of this decision tree, including mushy zone algorithm, are given in **Table 4**. The mushy zone contained 5 (19%) patients from BZ26 database and 5 (11%) patients in the RC database. The sensitivity of the DT with mushy zone is similar to the DT shown in **Figure 1**, but the specificity is improved.

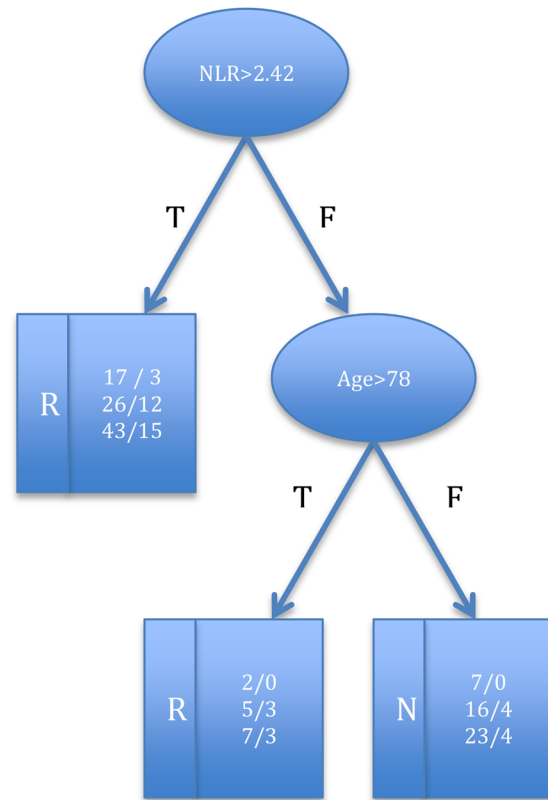


Figure 1. Decision-tree algorithm for NLR and age. R, recurrence; F, false; T, true; N, no recurrence. First row for BZ database, second row for RC database and the third row for the combined databases. The number on the left side is the total number of patients from the specific database that applies to the inquiry, and the second one is the number of patients that the algorithm was wrong for them.

The main drawback of a DT with mushy zone is that some patients are left undecided. While the algorithm may be upgraded to include a penalty for too many undecided patients, an alternative approach is

to apply clinical criteria other than NLR to reach a decision for such patients. Along this line, we constructed an optimal tree that is depicted in **Figure 3**. In this DT, the patients in the mushy zone are further classified according to their age, with a cutoff of 76 yrs. The results of this DT are given in table 5. The sensitivity and specificity of this DT is comparable to that of the mushy zone DT; however, in this DT, all patients are classified.

Table 5. Sensitivity and specificity values of the predictions made by the decision tree algorithm shown in figure 3. First row for BZ database; second row for RC database; third row for the combined databases.

Database	Sensitivity	Specificity
BZ26	100%	80%
RC47	75%	56%
Combined	86%	62%

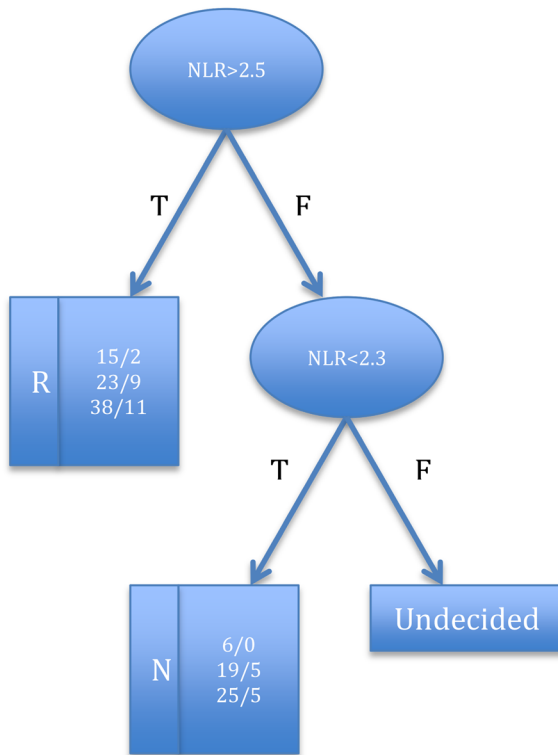


Figure 2. Decision-tree algorithm including the mushy zone. R, recurrence; F, false; T, true; N, no recurrence. First row for BZ database, second row for RC database and the third row for the combined database. The number on the left side is the total number of patients from the specific database that applies to the inquiry, and the second one is the number of patients that the algorithm was wrong for them.

DISCUSSION

The management of T1HG urothelial cancer is challenging. Although non-muscle invasive, it harbors the potential for recurrence and progression [1]. Two major options are available for the management of patients with T1HG tumors: TURBT followed by intravesical therapy,

or immediate radical cystectomy. Immediate cystectomy may give the advantage of long term cancer cure; however, it is considered an over-treatment in several cases [15] and carries serious impairment on patient’s quality of life, in addition to high morbidity and mortality rates, not less than cystectomy done for invasive disease [16]. Considering survival, Kulkarni *et al.* estimated that a healthy 60 years-old patient undergoing cystectomy for high risk non-muscle invasive disease has a life expectancy of 14.29 yrs compared to 13.63 yrs in similar patient undergoing conservative management [17]. Although avoiding complex surgery and its complications, conservative treatment should give similar cancer control rates to surgical approach. Presently we lack algorithms that can reliably predict recurrence in the individual patient to support choosing the right decision.

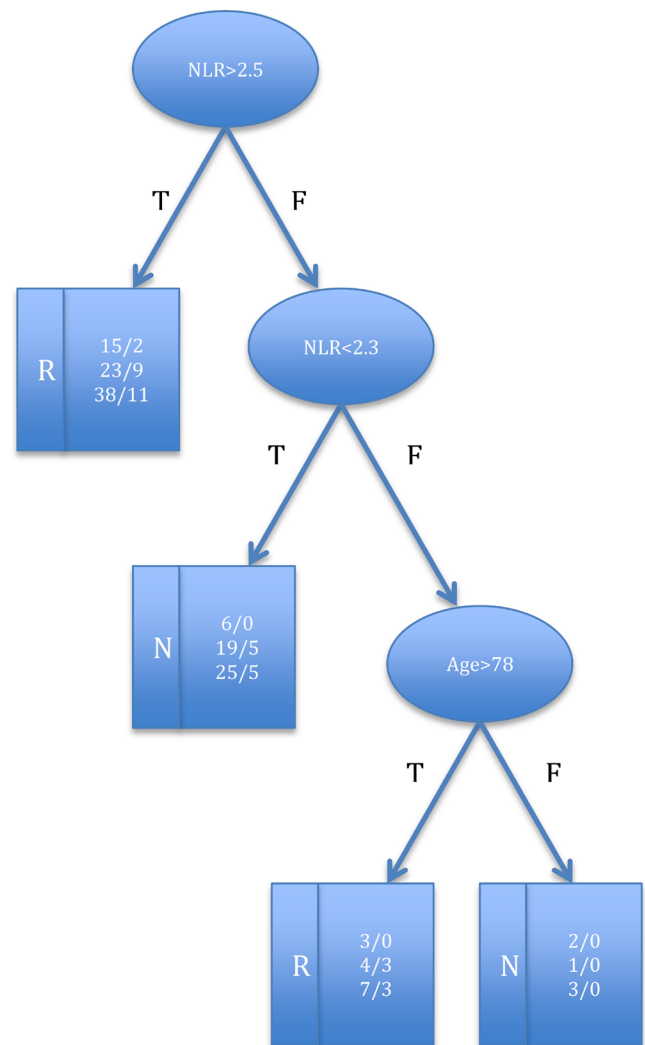


Figure 3. A final decision-tree algorithm including LNR, mushy zone and age. R, recurrence; F, false; T, true; N, no recurrence. First row for BZ database, second row for RC database and the third row for the combined database. The number on the left side is the total number of patients from the specific database that applies to the inquiry, and the second one is the number of patients that the algorithm was wrong for them.

It has already been proved that elevated levels of NLR are associated with poor prognosis in a number of malignancies [18]. In patients

who underwent radical cystectomy for bladder cancer, elevated NLR values were associated with low survival rate [19–21]. Current theories claim that the systemic inflammatory response triggered by cancer includes relative neutrophilia and lymphocytopenia, which may lead to an elevated excretion of pro-angiogenic factors, growth factors, and anti-apoptotic markers by neutrophils, and a decreased intratumoral T-cell activity, leading to tumor growth and progression. Therefore, an elevated NLR may represent a pro-tumor inflammatory state associated with more advanced stage cancer and worse outcome [22].

Consistent with these theories, pre-treatment NLR has been shown to correlate with treatment outcomes in kidney and invasive bladder cancer [23,24]. Krane *et al.* found that patients with a NLR > 2.5 had a significantly higher likelihood of extravesical bladder cancer at radical cystectomy, suggesting they may benefit from neoadjuvant chemotherapy [20]. Temraz *et al.* showed a correlation between higher pre-operative NLR and overall survival and shorter time to recurrence in patients with muscle invasive bladder cancer undergoing cystectomy [25].

By using machine-learning algorithms, we found that in patients with T1HG BC who underwent TURBT, who has no other malignancies or blood disorders, and treated with intravesical BCG, NLR has a better potential to predict recurrence in 24 months compared to conventional clinical parameters. In a former study, we showed that NLR was superior to conventional scores in predicting progression in all stages and grades of NMIBC [9]. On multivariate analysis, NLR > 2.4 was a significant predictor of progression after adjusting for the risk of disease progression according to the EORTC risk tables. These findings, obtained using mathematical models rather than standard statistical methods, further support the role of NLR in predicting recurrence in this selected group of patients.

The main limitation of our study is its retrospective nature. This required us to reduce the initial database to a much smaller patient cohort that met all the requirements set above. Another drawback of using a retrospective database is that data collection was different in the two hospitals, particularly so in collecting blood samples. This might be a main reason for the different results in the two hospitals. Nevertheless, our findings are consistent with previous publications, suggesting that NLR may aid in optimizing treatment for NMIBC patients in equivocal cases, especially in those who harbor a T1HG tumor. Further prospective studies are required to evaluate whether incorporating pre-treatment NLR to current risk stratification tools may improve treatment outcome in this group of patients. In addition, studies aimed at understanding the mechanism underlying the association between NLR and treatment outcome should be encouraged.

CONCLUSIONS

NLR can better predict the risk of recurrence within 24 months following surgery in patients with T1HG bladder cancer treated with intravesical BCG. By using NLR for patients' stratification, we could better choose the right treatment option for individual patients.

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