Factors predicting recurrence in non-muscle invasive bladder cancers

● Sezgin Okçelik[1], ● Halil Kızılöz[2], ● Muhammed Cihan Temel[2], ● Ramazan Acar[3]

[1]Afyonkarahisar State Hospital, Clinic of Urology, Afyonkarahisar, Turkey

[2]Nevsehir State Hospital, Clinic of Urology, Nevsehir, Turkey

[3]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Medical Oncology, Ankara, Turkey

ABSTRACT

Aims: We aimed to assess patients with non-muscle invasive bladder cancer (NMIBC) to find out the factors affecting recurrence after initial treatment.

Methods: In this retrospective cohort study, we investigated patients who underwent transurethral bladder tumor resection (TURB) between January 2014 and April 2020. Patients' age, gender, initial symptoms, time from the initial symptoms to hospital admission, history of systemic diseases, smoking history, pathological features, intra-vesical treatment records and information about recurrence were recorded. Recurrence was considered as any tumor development other than the aforementioned residual tumor.

Results: A total of 103 patients (mean±SD age: 68.5±9.1 years; 93 men and 10 women) were evaluated. The mean diameter of the tumors was 3±1.6 cm. Following the initial TURB and/or re-TURB, 28 (27.1%) patients underwent induction chemotherapy or BCG therapy. Residual tumor was detected in 35 (34%) patients who were either detected within the first three months following the TURB, without receiving any intravesical therapy, or in re-TURB performed for the purpose of resection of the residual visible bulky lesions following an incomplete initial resection. Eleven patients (10.6%) recurred within a median of 18 months of follow-up. The median recurrence-free survival was 25 months (95% confidence interval (CI): 16.5-33.4). The presence of carcinoma *in situ* (CIS) [Hazard ratio (HR): 3.00, 95% CI: 1.2-7.6, p=0.03], female gender (HR: 2.38, 95% CI: 1.03-5.4, p=0.03) and age >70 years (HR: 1.87, 95% CI: 1.02-3.41, p=0.03) were significantly associated with recurrence.

Conclusions: The present study showed that the presence of CIS, female gender, and age >70 years were independently associated with the recurrence of NMIBC.

Introduction

Bladder cancer is the 7th most common cancer among men and 11th among women in the world. The annual incidence of bladder cancer is 9/100,000 in males and 2.2/100,000 in females (1). Every year, 110,500 new cases in men and 70,000 new cases in women are diagnosed (2). Approximately 75% of the cases are non-muscle-invasive bladder cancer (NMIBC) at diagnosis (2). As an imaging method, ultrasonography is used with high sensitivity and specificity, and cystoscopy is still the gold standard (3,4). Owing to the high incidence of the disease and thereby of NMIBC, a precise algorithm is needed

in diagnosis, treatment and follow-up of this disease. Up to 50-70% of NMIBC subsequently recur mostly within two years following the initial interventions and 10-20% of them progress to muscle invasive bladder cancer (MIBC) (5). In order to prevent the recurrence and progression, patients are followed up at short intervals of cystoscopy and administered adjuvant intravesical chemotherapy or immunotherapy when necessary (6). Intra vesical chemotherapy/immunotherapy applications reduce recurrence and progression but cause some local and systemic side effects (7). Prediction of tumor recurrence is crucial in the follow-up period of this disease. Factors including

age, tumor grade, tumor number, tumor size, presence of carcinoma *in situ* (CIS), hematuria, and intravesical therapy have been investigated for being predictors of recurrence in NMIBC in a number of studies (8-10). However, a number of possible relapse-related factors are not investigated well and are still equivocal in their link to recurrence.

In this study, we aimed to assess a six-year follow-up and treatment outcomes of patients diagnosed with NMIBC. We also examined the potential factors associated with recurrence following initial treatment.

Methods

This retrospective study was performed at Nevsehir State Hospital. Hospital records of patients who underwent transurethral bladder tumor resection (TURB) surgery between January 2014 and April 2020 were evaluated. The main inclusion criterion was the pathological diagnosis of urothelial carcinoma or transitional cell carcinoma. Patients with benign pathologies, adenocarcinoma, paraganglioma, and signed ring cell carcinoma were excluded. Since all subjects were operated in the same unit, all surgeries were performed with a 24 Fr endoscopy using bipolar energy. Recorded variables were age, gender, smoking, complaints on admission, physical findings on admission, the time between the initial complaints and hospitalization, comorbid diseases, pathology reports of the first and recurrent disease, intravesical treatment, recurrence or progression data, and disease-related oncological and functional endpoints. NMIBC was defined as papillary tumors confined to the mucosa and invading the lamina propria, and flat, high grade tumors confined to the mucosa, named as CIS (Tis). Tumor recurrence was defined as immediate failure of intravesical treatment or tumor growth at the 3th month surveillance cystoscopy in patients who did not receive induction intravesical treatment. If tumor recurrence was detected within the first three months following the first surgery, these recurrences were evaluated as residual tumors and completion surgeries were named as re-TURB. The study was approved by the Nevsehir Haci Bektas University Institutional Review Board.

Ethical issues of this study were approved by the Nevsehir Haci Bektas University Local Ethics Committee (protocol number: E.683, date: 18.06.2020).

All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistical Analysis

Statistical Package for the Social Sciences (15.0, Chicago, IL, USA) was used for statistical analysis. Statistical evaluation results were reported as mean±standard deviation (minimum-maximum values) or median-interquartile range (IQR) according to the normal distribution of variables. The distribution of continuous variables was evaluated by the Shapiro-Wilk test. The Student's t-test, Wilcoxon rank test and the Mann-Whitney U test were used to compare the data as appropriate. Cut-off values, sensitivity and specificity of baseline tumor size in the prediction of disease recurrence were calculated using receiver operating curves (ROC) analysis. The Kaplan-Meier survival curves were computed to display disease-specific survival. Factors associated with survival were investigated by the Cox regression analysis. p<0.05 was considered statistically significant in all analyses.

Results

Between January 2014 and May 2020, 150 patients underwent TURB surgery at Nevsehir State Hospital. Of these patients, 103 were included in the current analysis. The mean age of the patients was 68.5±9.1 years. The mean diameter of the tumors was 3±1.6 cm. The initial symptoms were hematuria in 93 (90.2%) patients, dysuria in four (3.88%) patients, nocturia in two (1.94%) patients, flank pain in one (0.97%) patient, incontinence in one (0.97%) patient, and lower urinary tract symptoms in two (1.94%) patients. Clinical and pathological features of the first TUR and re-TUR of the patients (if performed) are summarized in Table 1. The median follow-up time was 18 (IQR: 9-35) months.

After the first TURB or re-TURB, 28 (27.1%) patients underwent induction chemotherapy or Bacillus Calmette-Guérin (BCG) therapy. Tumor recurrence was detected in 35 (34%) of the patients within the first three months in re-TURB surgery. The characteristics of residual tumors in the first three months are summarized in Table 2.

Patients with muscle invasive cancer (pT2) or more advanced cancer detected in follow-up surveys within the first three months following the initial TURB without intravesical induction therapy or TURB before the intravesical induction treatment were excluded from further recurrence analyses. Subsequent surveys revealed recurrence in 11 (10.67%) patients. All recurrences were in non-invasive (pTa) stage with 10 (9.7%) low grade types and 1 (0.97%) high grade type. The median number of recurrences within 18 months was 2 (IQR: 1-3). The recurrence-free survival rate at 12 months was 69.4% and the median recurrence-free survival time was 25 months [95% confidence interval (CI): 16.5-33.4]. The initial tumor size in patients with vs. without subsequent recurrence was similar (mean/median 3.3±1.7/3 vs. 2.8±1.4/3, p=0.11).

Tumor size was greater than 3 cm in 53 (51.45%) patients. ROC analysis showed that initial cut-off tumor size of 3.75 cm might be a predictor of recurrence, being the best cut-off size with the highest diagnostic accuracy on ROC table (sensitivity: 70.2%, specificity: 39.3%; area under curve: 0.573). However, the

Table 1. Demographic, clinical and pathological features at diagnosis and initial interventions (n=103)

Age* (mean±SD) (year)	68.5±9.1
Gender	
Male, n (%)	93 (90.3)
Female, n (%)	10 (9.7)
Median duration time of symptom (IQR) (day)	14 (7-20)
Comorbidities (overall), n (%)	**81 (78.6)**
Diabetes mellitus, n (%)	26 (21.31)
Hypertension, n (%)	41 (33.60)
Coronary artery disease, n (%)	30 (24.59)
Asthma, n (%)	12 (9.83)
Others, n (%)	13 (10.65)
Tumor grade **	
Low grade, n (%)	73 (70.9)
High grade, n (%)	30 (29.1)
Tumor stage **	
pTa, n (%)	78 (75.7)
pT1, n (%)	25 (24.3)
CIS **	
Yes, n (%)	9 (8.7)
No, n (%)	94 (91.3)
Early intravesical chemotherapy	
Present, n (%)	20 (19.4)
Absent, n (%)	83 (80.6)

*Age at the time of diagnosis.
**Pathological features including tumor stage, tumor grade and presence of CIS are noted based on the higher occurrence if there was a pathologic upgrading in TURBs performed within the first three months in those who did not receive any intravesical induction therapy or before the intravesical therapy following one or more course of TURBs until the visible bulky lesions are all resected.
CIS: Carcinoma *in situ*, IQR: Interquartile range, TURB: Transurethral bladder tumor resection, SD: Standard deviation

Table 2. Patient characteristics and tumor features of residual tumors in the first three months (n=35)

Age (mean±SD) (year)	70±9.8
Gender	
Male, n (%)	30 (85.7)
Female, n (%)	5 (14.3)
Tumor grade	
Low grade, n (%)	18 (51)
High grade, n (%)	17 (49)
Tumor stage	
pTa, n (%)	21 (60)
pT1, n (%)	7 (20)
pT2, n (%)	6 (17.1)
pT4a, n (%)	1 (2.9)
Presence of CIS	
Yes, n (%)	3 (8.5)
No, n (%)	32 (91.5)

CIS: Carcinoma *in situ*, SD: Standard deviation

initial tumor size was not associated with recurrence (p=0.78). Similarly, the pathological stage and grade had also no association with recurrence (p=0.47 and p=0.45, respectively). On the other hand, CIS and female gender were significantly associated with the tumor recurrence. The presence of CIS (HR: 3.00, 95% CI: 1.2-7.6, p=0.03), female gender [Hazard ratio (HR): 2.38, 95% CI: 1.03-5.4, p=0.03] and age >70 years (HR: 1.87, 95% CI: 1.02-3.41, p=0.03) were significantly associated with recurrence.

However, the time from initial symptom to hospital admission (HR: 1.28, 95% CI: 0.7-2.28, p=0.39) and the presence of comorbidities (HR: 1.49, 95% CI: 0.74-2.96, p=0.24) did not increase overall recurrence. Age >70 years at the diagnosis (HR: 1.87, 95% CI: 1.02-3.41, p=0.03) was significantly associated with disease recurrence. Survival plots in Figures 1-3 and Table 3 show the changes in survival outcomes in different subgroups.
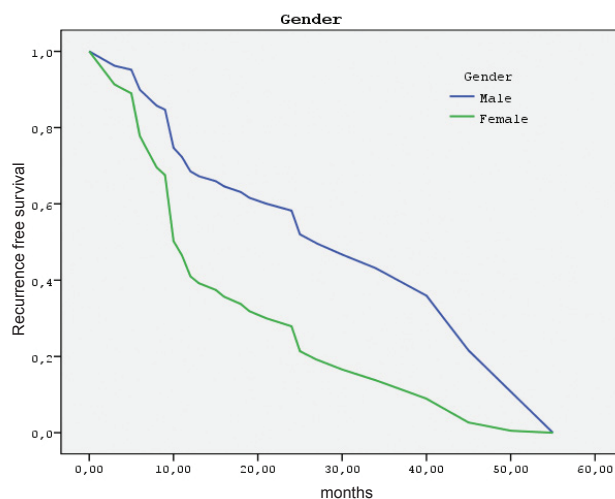

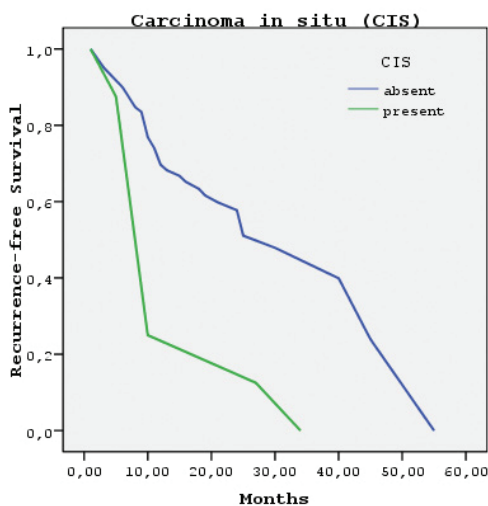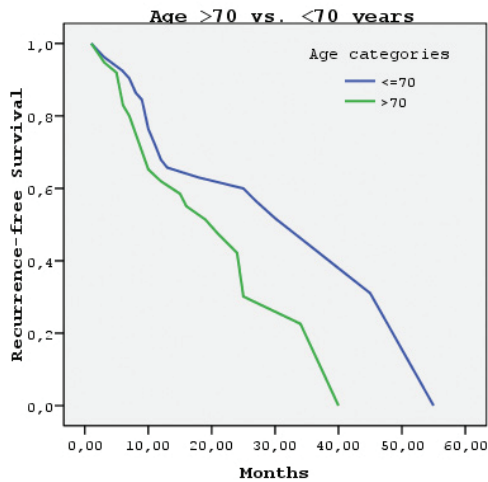**Figure 1.** Recurrence-free survival according to gender

Figure 2. Recurrence-free survival according to carcinoma *in situ* presence

Figure 3. Recurrence-free survival according to age

Intravesical induction chemotherapy or BCG administration following initial and complementary TURB showed a weak/borderline association with disease recurrence (HR: 1.67, 95% CI: 0.9-3.1, p=0.09). This factor was not studied in Ta vs. T1 tumors and HG vs. LG tumors owing to the limited number of patients. Interestingly, history of smoking tended to show a slightly longer recurrence-free survival, which was not statistically significant (p=0.07).

Discussion

It is important to detect and treat NMIBC recurrences early and predict patients who will progress (11). The European Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder 2017 suggest surveillance cystoscopy and if necessary, intravesical treatments according to the risk classification (6). In addition, re-TURB is recommended two or six weeks after the first TURB in medium and high-risk tumors (11). Clinical and pathological features can be used to predict recurrence and progression. Several factors that may affect recurrence and progression have been proposed so far and some nomograms have been developed (12).

Previous research has indicated age, tumor grade, number of tumors, tumor size and the number of past recurrences as the risk factors for the new recurrence in NMIBC (9). However, we did not observe any association of these variables with recurrence except for age. In another study, tumor grade and the presence of CIS component were identified as the predictors of recurrence (8). Our study confirms the value of CIS component on the same outcome, but we did not observe any association with baseline tumor grade and subsequent recurrences. Kim et al. (10) showed that age, macroscopic hematuria, presence of upper urinary tract tumor, higher tumor stage and tumor grade, presence of CIS, greater tumor size and tumor number, and intravesical treatment were associated with tumor recurrence.

We found similar results in terms of age and the presence of CIS. Although many factors have been previously evaluated in this regard, number of previous recurrences, greater number of tumors, and tumor size come forward (13). Sylvester et al. (12) established a risk calculation system for the European Organisation for Research and Treatment of Cancer, consisting of 6 factors including tumor number, tumor size, time of tumor recurrence, tumour stage, tumor grade, and presence of CIS.

Female gender has previously been reported as a risk factor for shortening T1G3 bladder tumor recurrence time (14). The Club Urologico Español De Tratamiento Oncológico study also reported that men had a longer recurrence period than women. Similarly, in our study, female sex showed a direct correlation with recurrence rates. Mungan et al. (15) reported females had a worse prognosis in bladder tumor than males, but the clinicopathologic explanation of this phenomenon has not been made so far.

Luján et al. (9) reported higher age as a negative risk factor for recurrence-free survival while Gontero et al. (16) reported that solely age was a risk factor for recurrence in T1G3 tumors. In our study, age over 70 years was associated with shorter recurrence-free survival.

Many authors have indicated a link between smoking, bladder tumor and higher recurrence. Ucpinar et al. (17) demonstrated rapid tumor recurrence in patients with a smoking history. Soria et al. (18) also showed that smoking increased bladder tumor incidence and recurrence. Recurrences were more frequent in patients who continued smoking after the diagnosis of bladder cancer in another study (19). Interestingly, we observed less recurrence in patients who smoked, with a borderline significance (p=0.07). Nevertheless, the overall number of patients with recurrence was low.

Based on our data, it is crucial to closely monitor females, patients who are over the age of 70 years and patients with an initial diagnosis of CIS. Classification of risk can be done using various nomograms other than the previously mentioned risk factors that are associated with tumor recurrence. Accordingly, alongside CIS, which is a widely-published and known indicator of cancer recurrence, factors such as age and female gender can also be identified as leading to a poor prognosis in clinical practice. Moreover, intravesical induction chemotherapy or immunotherapy treatment may prevent tumor recurrence and even progression in this group of patients, even if they have been classified as low risk and not in need of adjuvant therapy following TURB in current clinical practice.

Our study has some limitations. The most prominent one is its being a retrospective cohort study. Another one is its being conducted on a relatively small number of patients. Owing to this, we could not study the subgroup analysis of intravesical chemotherapy and BCG. Studies with larger populations are needed to confirm these results.

Table 3. Factors evaluated for possible association with tumor recurrence and recurrence-free survival (n=96)

			HR	p
The duration from initial symptoms to hospital admission	Longer than 14 days	Shorter than 14 days		
Tumor-free survival at 12 months, (%)	66.1	72.4		
Median recurrence-free survival	25 mo (95% CI: 7-42.9)	25 mo (95% CI: 16.6-33.3)	1.28	0.39
Initial tumor size	Greater than 3.75 cm	Smaller than 3.75 cm		
Tumor-free survival at 12 months, (%)	70.3	69		
Median recurrence-free survival	25 mo (95% CI: 19.4-29.1)	25 mo (95% CI: 22.4-33.2)	1.09	0.51
Initial tumor stage	pTa	pT1		
Tumor-free survival at 12 months, (%)	71	63.9		
Median recurrence-free survival	27 mo (95% CI: 19.9-34)	25 mo (95% CI: 4.1-45.8)	1.26	0.47
Initial tumor grade	Low grade	High grade		
Tumor-free survival at 12 months, (%)	70.3	67.1		
Median recurrence-free survival	30 mo (95% CI: 17.3-42.6)	25 mo (95% CI: 2.4-47.5)	1.25	0.45
CIS	Present	Absent		
Tumor-free survival at 12 months, (%)	25	74.1		
Median recurrence-free survival	10 mo (95% CI: 7.6-12.4)	30 mo (95% CI: 18-41.9)	3	0.03
Gender	Male	Female		
Tumor-free survival at 12 months, (%)	72.3	45		
Median recurrence-free survival	30 mo (95% CI: 18.7-41.2)	10 mo (95% CI: 9-10.9)	2.38	0.03
Age	≤70	>70		
Tumor-free survival at 12 months, (%)	72.3	65.2		
Median recurrence-free survival	45 mo (95% CI: 27.7-62.2)	21 mo (95% CI: 10-31.9)	1.87	0.03
History of smoking	Yes	No		
Tumor-free survival at 12 months, (%)	70.9	50		
Median recurrence-free survival	27 mo (95% CI: 16.2-37.7)	10 mo (95% CI: 7.6-12.4)	3	0.07
Other systemic diseases	Yes	No		
Tumor-free survival at 12 months, (%)	72.6	58.1		
Median recurrence-free survival	27 mo (95% CI: 16.9-37)	18 mo (95% CI: 6.5-29.4)	1.49	0.24
Intravesical induction therapy	Yes	No		
Tumor-free survival at 12 months, (%)	61.5	72.8		
Median recurrence-free survival	16 mo (95% CI: 3-32.8)	40 mo (95% CI: 18.4-61.5)	1.67	0.09

HR: Hazard ratio, CI: Confidence interval, mo: Months, CIS: Carcinoma *in situ*, SD: Standard deviation

Conclusion

In conclusion, the current study showed that risk of recurrence in NMIBC is not low. Women, patients older than 70 years, and those with CIS might be candidates of a more aggressive adjuvant treatment and surveillance protocols following the initial TURB.

Ethics

Ethics Committee Approval: This study was approved by the Nevsehir Haci Bektas University Local Ethics Committee (protocol number: E.683, date: 18.06.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.O., M.C.T., R.A., Concept: S.O., H.K., M.C.T., R.A., Design: S.O., Data Collection or Processing: S.O., Analysis or Interpretation: S.O., H.K., M.C.T., R.A., Literature Search: S.O., M.C.T., R.A., Writing: S.O., H.K., M.C.T.

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