

ORIGINAL ARTICLE

Prediction of recurrence in non-muscle invasive bladder cancer patients. Do patient characteristics matter?

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Summary

Purpose: To evaluate patients, diagnosed with non-muscle invasive bladder cancer, according to patient specific parameters including hemoglobin level, estimated glomerular filtration rate (eGFR), body mass index (BMI) and cigarette smoking and to identify if any of these parameters matters in terms of recurrence prediction.

Methods: 231 patients who have undergone transurethral resection of the bladder (TURB) between January 2015 and January 2018 and diagnosed with non-muscle invasive bladder cancer (NMIBC) were included. Patient demographic characteristics including age, sex, BMI and cigarette smoking were assessed. Hemoglobin, creatinine and eGFR values were recorded. Follow-up was performed according to the European Association of Urology (EAU) guidelines' recommendations. Recurrence and progression during follow-up were recorded.

Results: 231 patients were included in the study. Median pa-

tient BMI, Hb levels, and eGFR values were 26.51 kg/m² (IQR 5.48), 14,2 g/dL (IQR 2.50), and 83.25 ml/min/1.73m² (IQR 27.83), respectively. Among all patients, 105 (45%) were ex-smokers and 78 (33%) were current smokers, 41 had anemia (17.7%), 37 (16%) patients were obese; 104 (45%) had mildly impaired renal function and 34 (14.7%) had impaired renal function. During follow-up, 67 (29%) patients had disease recurrence and 21 (9.1%) had disease progression (9.1%). Univariate and multivariate analyses revealed significant relationship between recurrence and obesity, impaired renal function and cigarette smoking.

Conclusions: Recurrence is a commonly encountered unfortunate consequence of NMIBC, and obesity, renal failure, history of smoking and anemia seem to increase the rate of recurrence among bladder cancer patients.

Key words: bladder cancer, patient characteristics, progression, recurrence

Introduction

Bladder cancer is the 11th most commonly encountered malignancy worldwide and a possible cause of mortality in high risk bladder cancer patients. Nearly 75% of diagnosed bladder cancer cases are non-muscle invasive in nature. However, recurrence or progression of these lesions are commonly encountered. Probability of recurrence at 5 years ranges from 31 to 78% [1]. To prevent this unfortunate consequence, risk stratification and

routine follow-up of patients are planned. Follow-up periods, intravesical instillation therapies are planned and the risk of recurrence and progression is predicted according to the grade and stage of disease and the risk stratification nomograms. European Organization for Research and Treatment of Cancer (EORTC) nomogram is one of the most commonly used nomograms, which evaluates the patients according to the size, number, grade

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and stage of their tumors, the number of previous recurrences and presence or absence of concomitant carcinoma *in situ* [2]. Another commonly used nomogram is the 'Club Urologico Espanol de Tratamiento Oncologico' (CUETO) nomogram, which evaluates patients who have received intravesical bacillus Calmette-Guerin (BCG) treatment. CUETO nomogram does not take tumor size into account, however it additionally evaluates the age and gender of the patients [3].

Patients' demographic characteristics and laboratory values are not fully taken into account while patients are being stratified. Routinely used nomograms do not evaluate the hemoglobin level, estimated glomerular filtration rate (eGFR), body mass index (BMI) and cigarette smoking habits of the patients, which might all have an effect on the nature and aggressiveness of bladder cancer. There are studies in the literature that have evaluated certain laboratory parameters and demographic characteristics of non-muscle invasive bladder cancer (NMIBC) patients and found positive and negative impacts of these parameters on recurrence and progression [4-10]. In this study, we aimed to evaluate our patients according to these parameters and to identify if any of them matters in terms of recurrence prediction.

Methods

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

We retrospectively evaluated 302 patients who had undergone transurethral resection of the bladder (TURB) between January 2015 and January 2018. Patients who were diagnosed with NMIBC were included into our study, after approval from the Institutional Internal Review Board. Patients who were initially diagnosed with muscle invasive disease, patients who were lost on follow-up and patients whose follow-up schedule was not compliant with the recent guidelines due to patients' incompetence, were excluded from the study. Additionally, patients with concomitant upper tract urothelial carcinoma or renal cell carcinoma were excluded from the study (Figure 1). Demographic characteristics including age, sex, body mass index (BMI) and cigarette smoking were noted before the first TURB. Laboratory parameters including hemoglobin, creatinine and eGFR values were recorded as well.

Follow-up was performed according to the European Association of Urology (EAU) guidelines' recommendations [1]. Patients who were initially diagnosed

with low grade, non-invasive urothelial carcinoma were followed up by cystoscopy in the 3rd and 12th month following TURB and annually thereafter. Patients who were initially diagnosed with high grade urothelial carcinoma were undergone a re-TURB, 2-6 weeks after the initial operation. Following re-TURB, patients were treated with intravesical instillations of BCG, according to surgeon's choice and patient compliance and in case of availability of BCG regimens. Patients were also followed by routine cystoscopy, every 3 months in the first 2 years and every 6 months in following 2 years, and annually thereafter. Recurrence was defined as any detection of a newly formed mass after first TURB during follow-up. Progression was defined as upgrading of the stage or grade during routine follow-up. Any recurrence was treated with resection of the newly diagnosed mass. Cytology was obtained during cystoscopy in high risk patients. If cytology results were positive or suspicious in case of a normal cystoscopic examination, biopsies from the bladder and prostate were obtained, in addition to upper urinary tract imaging. Patients with benign recurrences were not classified under the recurrence group. Patients with progression to muscle invasive disease were treated either with cystectomy and urinary diversion or with multimodal treatment. Time to recurrence and progression were assessed as well.

Follow-up duration was calculated beginning from the initial TURB operation at our institution, until January 2018. Anemia was defined as hemoglobin (Hb) values lower than 11 mg/dl for female and 12 mg/dl for male patients. Estimated GFR (eGFR) values were calculated according to National Kidney Foundation's CKD-EPI Creatinine Equation. Renal functions were categorized as normal (eGFR>90 ml/min/1.73m²), mildly impaired (eGFR between 60-90 ml/min/1.73m²) and impaired (eGFR<60 ml/min/1.73m²) according to the 'National Kidney Foundation, Kidney Disease Outcomes Quality Initiative' (NKF KDOQI) stages. Obesity was defined as BMI 30 kg/m² or greater, based on National Institute of Health (NIH) guidelines. Smoking status of patients was categorized as never-smokers, former smokers (quitted before the first admission) and current smokers (smokers who were smoking at the time of admission).

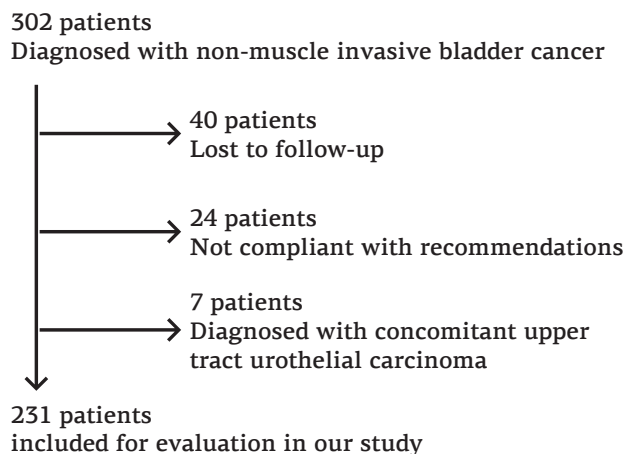


Figure 1. Flow chart of patients according to inclusion and exclusion criteria.

Statistics

Chi-square (χ^2) test or Fisher’s exact test (when χ^2 test assumptions did not hold due to low expected cell counts) were used to compare categorical variables and Mann-Whitney U test was used to compare the differences in continuous variables. The Kaplan-Meier method was used to calculate recurrence free survival. The effects of obesity, smoking, preoperative anemia and renal function on recurrence free survival were separately estimated by log rank test. Obesity, smoking, preoperative anemia and renal function variables were further entered into Cox multivariate regression analysis, with backward selection, to determine independent predictors of tumor recurrence. The proportional hazards assumption and model fit were assessed by means of residual (Schoenfeld and Martingale) analysis. Statistical analyses were performed using SPSS software version 21. P values represent two-sided statistical tests with statistical significance at $p < 0.05$.

Results

A total number of 231 patients (208 male;90% and 23 female;10%), were included in the study. Their median age was 64 years (IQR 15). Median follow up time was 24 months (IQR 27). Median patient BMI, Hb levels, and eGFR values were 26.51 kg/m² (IQR 5.48), 14.2 g/dL (IQR 2.50), and

83.25 ml/min/1.73m² (IQR 27.83), respectively. Among all patients, 105 (45%) were former smokers and 78 (33%) were current smokers at the time of initial admission. Forty-one (17.7%) patients had anemia, 37 (16%) were obese; 104 (45%) had mildly impaired renal function and 34 (14.7%) had impaired renal function. During follow-up, 67 (29%) patients had disease recurrence and 21 (9.1%) had disease progression. Median time to recurrence was 18 months (IQR 24) and median time to progression was 23 months (IQR 25). On univariate analysis, no significant difference was observed between patients with recurrent and non-recurrent tumors in terms of sex and post-op mitomycin therapy ($p > 0.05$, for each variable) (Table 1). Progression to muscle invasive disease was observed in 6 (0.25%) patients and 3 of them were treated with cystectomy, while the other 3 received multimodal treatment due to their existing comorbidities. Death occurred in 2 (0.08%) patients during follow-up.

Anemia and bladder cancer recurrence

On univariate analysis, significant differences were observed between patients with recurrent (20 patients, 29%) and non-recurrent (21 patients, 12%) tumors regarding preoperative anemia ($p = 0.002$)

Table 1. Preoperative demographics and results of univariate analysis in terms of recurrence

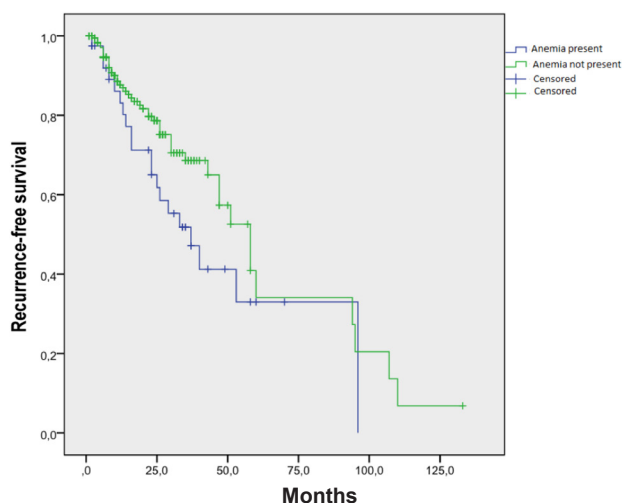
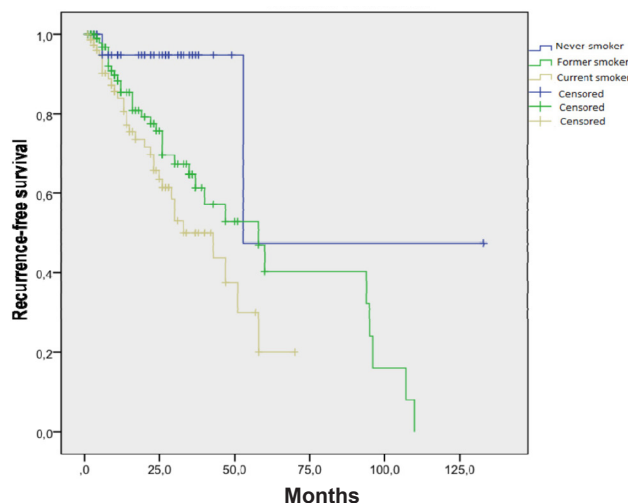
Demographics	Overall n (%)	Recurrent tumor n (%)	Non-recurrent tumor n (%)	Univariate p value
Median age (IQR)	65 (15)	64 (15)	68 (17)	0.005
Gender				0.745
Male	208 (90)	61 (91)	147 (89.9)	
Female	23 (10)	6 (9)	17 (10.1)	
Postoperative mitomycin				0.38
Yes	52 (22)	18 (26.7)	34 (20.7)	
No	179 (77.5)	49 (73.1)	130 (79.3)	
Obesity				<0.001
Yes	37 (16)	19 (28.4)	18 (11)	
No	194 (84)	48 (71.6)	146 (89)	
Preoperative anemia				0.002
Yes	41 (17.7)	20 (29.9)	21 (12.8)	
No	190 (82.3)	47 (70.1)	143 (87.2)	
Renal function				<0.001
Normal	93 (40.3)	12 (17.9)	81 (49.4)	
Mildly impaired	104 (45)	42 (62.7)	62 (37.8)	
Impaired	34 (14.7)	13 (19.4)	21 (12.8)	
Smoking				<0.001
Never	48 (20.8)	3 (4.5)	45 (27.4)	
Former	105 (45.5)	33 (49.3)	72 (43.9)	
Current	78 (33.8)	31 (46.3)	47 (28.7)	

Boldface numbers show statistical significance

Table 2. Multivariate Cox regression analysis for the prediction of recurrence of bladder cancer among 231 individuals

Variables	Recurrence-free survival		
	HR	95% CI	p
Age (continuous)	1.02	0.99-1.05	0.18
Female sex	0.87	0.34-2.19	0.77
Preoperative anemia	1.44	0.82-2.51	0.19
Renal function (ref. normal)			
Mildly impaired	2.18	1.08-4.34	0.027
Impaired renal function	1.41	0.55-3.62	0.46
Obesity	1.83	1.05-3.28	0.038
Postoperative mitomycin	1.17	0.63-2.17	0.61
Smoking (ref.: never smoker)			
Former smoker	4.02	1.12-13.79	0.024
Active smoker	6.62	1.19-22.76	0.002

Boldface numbers show statistical significance

**Figure 2.** Kaplan-Meier analysis of patient recurrence-free survival with anemia as variable (p=0.19).**Figure 3.** Kaplan-Meier analysis of the recurrence-free survival of patients, with smoking as variable (p=0.024).

(Table 1). No association was identified between the time to first recurrence and presence of anemia (log-rank, p=0.74). On multivariate Cox regression analysis, preoperative anemia was not associated with tumor recurrence (p=0.19, HR 1.44, 95%CI 0.82-2.51) (Table 2 and Figure 2).

Smoking and bladder cancer recurrence

On univariate analysis, significant differences were observed between patients with recurrent and non-recurrent tumors regarding smoking status (p<0.001) (Table 1). Being former smoker and being current smoker were both associated with shorter time to first recurrence compared to never-smokers (log-rank p=0.005 and p>0.001 respectively) (Figure 3). On multivariate Cox regression analysis, a significant difference was observed in the rate of

tumor recurrence with former smokers and smokers at the time of admission, compared to never smokers (p=0.029 and p=0.004) (Table 2).

Obesity and bladder cancer recurrence

On univariate analysis, a significant difference was observed between patients with recurrent (19 patients, 28.4%) and non-recurrent tumors (18 patients, 11%), regarding obesity (p<0.001) (Table 2). Obesity was associated with shorter time to first recurrence (log-rank p=0.17) (Figure 4). On multivariate Cox regression analysis, obesity was independently associated with tumor recurrence (p=0.038) (Table 2).

Renal function and bladder cancer recurrence

On univariate analysis, a significant differ-

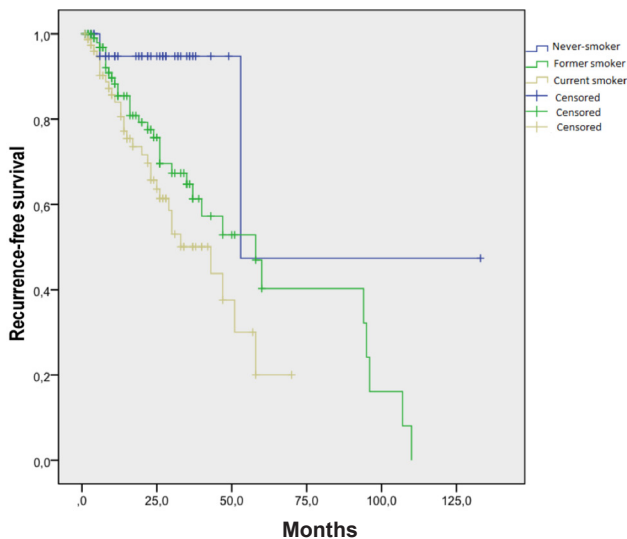


Figure 4. Kaplan-Meier analysis of the recurrence-free survival of patients, with smoking as variable ($p=0.058$).

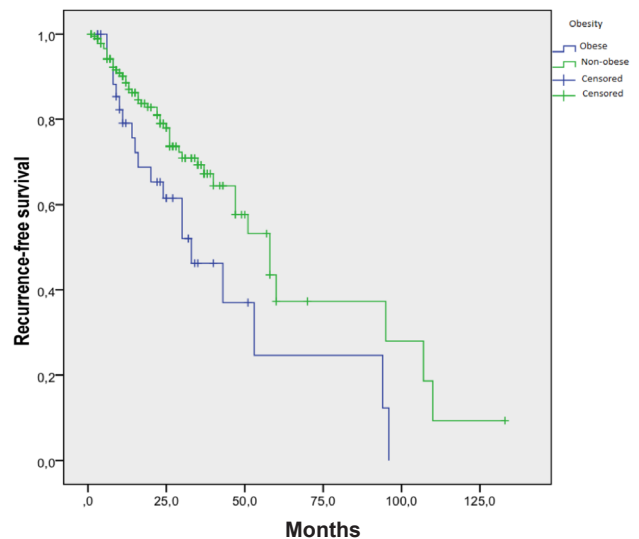


Figure 5. Kaplan-Meier analysis of the recurrence-free survival of patients, with obesity as variable ($p<0.001$).

ence was observed between patients with recurrent and non-recurrent tumors regarding renal function ($p<0.001$) (Table 1). Both mildly impaired and impaired renal function were associated with shorter time to first recurrence (log-rank $p<0.001$ and $p=0.037$ respectively) (Figure 5). On multivariate Cox regression analysis, mild renal functional impairment was independently associated with tumor recurrence, yet no significant association was observed regarding impaired renal function ($p=0.027$ and $p=0.46$) (Table 2 and Figure 5).

Discussion

Bladder cancer is a commonly encountered disease, especially due to high prevalence of smoking addiction in the community. Invasiveness and grade of bladder cancer are the main determinants for treatment and follow-up strategies. Non-muscle invasive bladder cancer is the predominant type and nearly 75% of diagnosed cases are not infiltrating beyond the lamina propria layer of the bladder [1]. However, recurrence and progression of bladder cancer can be encountered and patients should be followed closely. Follow-up strategies are mainly determined by the stage and grade of the tumor. EORTC and CUETO nomograms are the main tools for the prediction of disease recurrence and progression [2,3]. These nomograms evaluate the characteristics of the tumor, but do not evaluate the characteristics and demographics of patients in detail. Each patient has his own course and nature of the disease and recurrence and progression can not be foreseen solely according to the characteristics of the tumor. Thereby, we aimed to evaluate our patients with NMIBC, according to their demo-

graphic and laboratory parameters and their course of disease recurrence and progression.

There are various studies in the literature, which have separately evaluated the relationship between different demographic parameters and recurrence. Presence of anemia, obesity, eGFR value, smoking status and other related parameters were evaluated, which may all have an impact on tumors' nature and aggressiveness. Soria et al. conducted a multicenter study and evaluated 1117 patients with non-muscle invasive bladder cancer in relation to preoperative anemia (PA) on recurrence and progression [4]. The authors concluded that PA was associated with poor oncological outcomes and had negative effects on recurrence-free and progression-free survival. In accordance with their study, we have also concluded that tumor recurrence was more common among patients with preoperative anemia. However, presence of anemia was not associated with the duration of time between first diagnosis to tumor recurrence. Anemia reflects the lack of bone marrow production and ineffective oxygenation of tissues, and thereby, patients generate a weaker immune response, particularly in effective clearance of toxic metabolites and lysis of tumor cells. Another hypothesis could be the aggressiveness of the tumor which leads to 'anemia of chronic disease' and this might be an underlying cause of preoperative anemia. However, the underlying mechanism behind these hypotheses needs evaluation by further studies.

Cigarette smoking is a proven underlying cause of bladder cancer and its effect on recurrence has been evaluated in multiple studies. Soria et al. evaluated the effect of cigarette smoking and cessation status on bladder cancer incidence and

recurrence in a review they have conducted recently [5]. They have analysed 9 different studies and concluded that smoking is associated with a higher risk of bladder cancer recurrence and cessation of smoking decreases the risk of bladder cancer. Conversely, Li et al. collected the data of 484 patients with non-muscle invasive bladder cancer and on multivariate analysis they found that smoking status did not have an influence on tumor recurrence [6]. However, when current and former smokers were compared, cumulative smoking exposure was associated with higher, and >10 years of cessation was associated with lower risk of tumor recurrence. In a similar study, which was conducted by Ogihara et al., 634 patients were evaluated, which were diagnosed with NMIBC [7]. They have found that, being a current or former smoker was associated with higher recurrence rates, when compared with non-smokers. Additionally, they have stated that cessation of smoking more than 15 years significantly decreases the risk of tumor recurrence, regardless of the intensity or duration of smoking. In our study, we have detected a shorter duration to recurrence in current and former smokers, and increased recurrence rates when compared with never-smokers. We have emphasized that, exposure to tobacco-containing products increases the aggressiveness, and thereby recurrence rates of the bladder cancer.

The relationship between other parameters and recurrence have been evaluated by multiple studies in the literature. As an example, Cao et al. evaluated 242 patients with non-muscle invasive bladder cancer and investigated the effect of impaired eGFR, areca nut chewing and smoking status on recurrence rates [8]. Recurrence was observed in 140 patients (57.9%) and the authors concluded that heavy areca nut chewing, being a current smoker, presence of impaired eGFR, and higher tumor grade are independent factors which have an influence on bladder cancer recurrence. In our study, we have detected a shorter time to recurrence in patients with renal functional impairment and renal failure. Lenis et al. recently evaluated the effect of metabolic syndrome on recurrence of bladder cancer in patients who were treated with intravesical BCG therapy [9], and they have concluded that elevated BMI is strongly associated with recurrence and progression. Kluth et al. also investigated the

effect of obesity on T1 high grade bladder cancer patients [10]. They included 892 patients to their study and on univariate and multivariate analysis they found that obesity was associated with worse outcomes including higher possibility of tumor recurrence, progression, cancer specific mortality and general mortality. In terms of obesity, our study revealed that obese patients have shorter time to recurrence and on multivariate analysis obesity was independently associated with tumor recurrence. However, these results were inconclusive in multivariate analysis. Association between these parameters with tumor aggressiveness and recurrence rates needs further evaluation and underlying causes are not well understood.

Our study has some limitations. First of all, our study has a relatively small patient number and has a retrospective design. A prospective study with larger patient numbers would have reveal more clear and trustworthy results. Additionally, we could not evaluate the effect of different variables on tumor progression and mortality rates. Larger patient numbers were needed in order to statistically analyze these parameters. The relationship between age and recurrence was also evaluated. However, the results were not compliant with the results in the literature. Also, effective BCG treatment and immediate postoperative mitomycin instillation could not applied to every patient due to shortage in BCG and mitomycin regimens and patient incompetence during BCG treatment.

Conclusions

In conclusion, recurrence is a commonly encountered unfortunate consequence of NMIBC and obesity, renal failure, history of smoking and anemia seem to increase the rate of recurrence among bladder cancer patients. These groups of patients should be informed about their possibly increased risk of recurrence and strict follow-up should be applied. However, these conclusions need further verification by prospective studies, with larger patient numbers.

Conflict of interests

The authors declare no conflict of interests.

References

1. Babjuk M, Burger M, Compérat E et al. EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS). European Association of Urology Guidelines, 2018.

2. Sylvester RJ, van der Meijden AP, Oosterlinck W et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49:466-5; discussion 475-7.
3. Rosevear HM, Lightfoot AJ, Nepple KG, O'Donnell MA. Usefulness of the Spanish Urological Club for Oncological Treatment scoring model to predict non-muscle invasive bladder cancer recurrence in patients treated with intravesical bacillus Calmette-Guérin plus interferon- α . *J Urol* 2011;185:67-71.
4. Soria F, Moschini M, Abufaraj M et al. Preoperative anemia is associated with disease recurrence and progression in patients with non-muscle-invasive bladder cancer. *Urol Oncol* 2017;35:113.e9-113.e14.
5. Soria F, Marra G, Čapoun O, Soukup V, Gontero P. Prevention of bladder cancer incidence and recurrence: tobacco use. *Curr Opin Urol* 2018;28:80-7.
6. Li HM, Azhati B, Rexiati M et al. Impact of smoking status and cumulative smoking exposure on tumor recurrence of non-muscle-invasive bladder cancer. *Int Urol Nephrol* 2017;49:69-76.
7. Ogihara K, Kikuchi E, Yuge K et al. Refraining from Smoking for 15 Years or More Reduced the Risk of Tumor Recurrence in Non-muscle Invasive Bladder Cancer Patients. *Ann Surg Oncol* 2016;23:1752-9.
8. Cao J, Xu R, Zhao X et al. Areca Nut Chewing and an Impaired Estimated Glomerular Filtration Rate as Significant Risk Factors for Non-Muscle-Invasive Bladder Cancer Recurrence. *Sci Rep* 2016;6:29466.
9. Lenis AT, Asanad K, Blaibel M, Donin NM, Chamie K. Association between Metabolic Syndrome and Recurrence of Nonmuscle Invasive Bladder Cancer following bacillus Calmette-Guérin Treatment. *Urol Pract* 2018;5:132-8.
10. Kluth LA, Xylinas E, Crivelli JJ et al. Obesity is associated with worse outcomes in patients with T1 high grade urothelial carcinoma of the bladder. *J Urol* 2013;190:480-6.