Administration of Renin-Angiotensin System Inhibitor Affects Tumor Recurrence and Progression in Non-Muscle Invasive Bladder Cancer Patients

Saran Maneesuwansin, M.D., Chalairat Suk-ouichai, M.D., Patkawat Ramart, M.D., Siros Jitpraphai, M.D., Kittipong Phinthusophon, M.D., Ekkarin Chotikawanich, M.D., Teerapon Amornvesukit, M.D., Tawatchai Taweemonkongsap, M.D., Bansithi Chaiyaprasithi, M.D., Sunai Leewansangtong, M.D., Sittiporn Srinualnad, M.D., Chaiyong Nualyong, M.D.

Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: To evaluate the effects of renin-angiotensin system inhibitors (RASIs) on tumor-recurrence and disease-progression in non-muscle invasive bladder cancer (NMIBC) patients.

Methods: From 2006-2015, 348 NMIBC patients at Siriraj Hospital were recruited for this study. Tumor-recurrence was identified after the transurethral resection of bladder cancer (TUR-BT) and pathological confirmation of NMIBC, while stage-progression was defined as muscularis-propria invasion after pathological review or metastases. Cox proportional hazards models were used to assess the recurrence-free survival (RFS) and progression-free survival (PFS) rates.

Results: Of the 348 patients, 86 (24.7%) received RASIs at the first TUR-BT. The median age was 68 years, and it was significantly older for the RASI cohort. No differences in the tumor characteristics of the groups were found. The median follow-up periods for tumor-recurrence and stage-progression were 2.3 and 3.7 years, respectively. Forty percent of the patients experienced tumor-recurrence, with the no-RASI cohort experiencing a significantly higher tumor-recurrence rate (46% versus 22%, $p<0.001$). The 5-year RFS rates were 54% and 78% for the no-RASI and RASI cohorts, respectively ($p=0.001$). Stage-progression was observed in 6% of the patients. The 5-year PFS rates were 87% and 97% for the no-RASI and RASI cohorts, respectively. On univariate and multivariate analyses, a tumor size ≥3 cm and tumor multifocality were associated with recurrent bladder cancer ($p<0.02$). On the other hand, the administration of RASIs was associated with a reduced recurrence ($p\leq0.002$).

Conclusion: Our study suggests that RASI administration might be a potential factor to prevent bladder cancer recurrence. Further study is needed to evaluate the effects of RASIs.

Keywords: Non-muscle invasive bladder cancer; renin-angiotensin system inhibitors; tumor recurrence; stage progression (Siriraj Med J 2019;71: 31-37)

Abbreviations

AJCC	= American Joint Committee on Cancer
Ang II	= Angiotensin II
AT1R	= Angiotensin type 1 receptor
BCG	= Bacillus Calmette–Guerin
CI	= Confidence interval

Corresponding author: Chalairat Suk-ouichai
Email: chalairat.suk@mahidol.ac.th
Received 6 February 2018 Revised 15 March 2018 Accepted 21 March 2018
ORCID ID: 0000-0003-3175-0886
http://dx.doi.org/10.33192/Smj.2019.06

EORTC = European Organization for Research and Treatment of Cancer
HR = Hazard ratio
IQR = Interquartile range
MIBC = Muscle invasive bladder cancer
MMC = Mitomycin C
MP = Muscularis propria
NMIBC = Non-muscle invasive bladder cancer
OR = Odd ratio
PFS = Progression-free survival
RASI = Renin-angiotensin system inhibitor
RFS = Recurrence-free survival
RR = Relative risk
TUR-BT = Transurethral resection of bladder tumor

INTRODUCTION

Bladder cancer is the second most common urologic malignancy and the eighth most common overall malignancy in Thailand.[1] Most patients present with gross hematuria, and 75% of patients have non-muscle invasive bladder cancer (NMIBC) stages Ta, T1, and Tis.[2-4] Transurethral resection of bladder tumor (TUR-BT) is the standard treatment and the diagnostic procedure.[2-4] Up to 50% of NMIBC patients experience tumor recurrence, and 6% -17% progress to muscle invasive bladder cancer (MIBC).[4] The use of adjuvant agents after a TUR-BT has been introduced to reduce the risk of tumor recurrence and progression.[2-4]

Adjuvant intravesical therapy, such as Bacillus Calmette–Guerin (BCG) and mitomycin C (MMC), has been utilized in current practice to decrease the incidences of recurrent NMIBCs and disease progression.[2-6] A recent meta-analysis demonstrated that adjuvant intravesical BCG as immunotherapy was associated with reduced recurrent NMIBC (RR 0.56, 95% CI 0.43-0.71).[5] Additionally, intravesical chemotherapy such as MMC, doxorubicin, and epirubicin have also been associated with a decreased risk of bladder cancer recurrence (RR 0.68, 95% CI 0.55 - 0.83; RR 0.80, 95% CI 0.72 - 0.88; and RR 0.63, 95% CI 0.53 - 0.75, respectively). As to tumor progression, only adjuvant intravesical BCG has been associated with a reduced risk of progression (RR 0.39, 95% CI 0.24 - 0.64). Given its potential role in both reduced tumor recurrence and progression, immunotherapy such as checkpoint blockade has also been studied as an option for the treatment of NMIBC patients.[7] However, all agents are adjuvant treatments after the TUR-BT.

Angiotensin II (Ang II) is a key biological peptide in renin-angiotensin systems. Ang II is involved in the regulation of blood pressure, water, and sodium homeostasis, and in the control of other neurohumoral systems. It also leads to the excessive production of reactive oxygen species, and to the hypertrophy, proliferation, migration, and apoptosis of vascular cells.[8] Angiotensin type 1 receptors (AT1Rs) are expressed in various malignancies, including bladder cancer, and are significantly involved in tumor growth, metastasis, and angiogenesis.[9] Ang II-AT1R signaling leads to the potent induction of vascular endothelial growth factors.[10] Recent publications have outlined that renin-angiotensin system inhibitors (RASIs) have an antiangiogenic effect on bladder cancer.[11–12]

Our primary objective was to determine the effects of RASIs on tumor recurrence and disease progression in NMIBC patients.

MATERIALS AND METHODS

After receiving Siriraj Institutional Review Board approval (Si 708/2015), patients diagnosed with NMIBC at Siriraj Hospital between 2006 and 2015 were recruited for the study. Excluded were those patients who were followed up for less than 1 year, underwent a cystectomy due to unresectable lesions, took RASIs after the initial TUR-BT, or had concurrent upper urinary tract tumors. A total of 348 patients were ultimately available for the study.

The patient and tumor characteristics were collected retrospectively. The RASIs had been prescribed by physicians as anti-hypertensive drugs or for other indications, such as cardiac or renal disorders. The pathological reports were in accord with the guidelines of the American Joint Committee on Cancer (AJCC) current during that period. NMIBCs were defined as Ta, TI or Tis. Regarding the past records, some tumors were reported pathologically as NMIBC by non-muscularis propria invasion (Tu). MIBCs had been confirmed by histological muscularis propria invasion (T2-T4). Tumor-recurrence had been identified after the TUR-BT and pathological confirmation of NMIBC. Stage-progression was identified as MIBC or

lymph nodes or distant metastases. Tumor multifocality was defined as the presence of 2 or more tumors. The surveillance schedules had followed the standard guidelines for each NMIBC risk group. The TUR-BT technique and the administration of intravesical therapy depended upon the preferences of the attending staff.

Continuous variables were shown as medians and interquartile ranges (IQRs), and they were compared with the Mann–Whitney U test. Categorical variables were presented as numbers (percent) and compared with the Chi-square or Fisher's exact tests. Cox proportional hazards models were employed to assess the recurrence-free survival (RFS) and progression-free survival (PFS) rates. The RFS curve was generated using the Kaplan-Meier method and compared with the log rank test. Variables with $p<0.05$ were considered significant. The analyses were performed using SPSS Statistics for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Overall, 348 patients were analyzed. Their median age was 68 years. The patient and tumor characteristics are listed in Table 1. Of those patients, 86 (25%) were taking RASIs at the time of the first TUR-BT. The types of RASI are listed in Table 2. Male gender was predominant in both cohorts. The smoking histories, tumor sizes, grades, and multifocality of the cohorts were similar. One hundred and eighty-one patients (29%) had never smoked, 101 (52%) used to smoke, and 66 (19%) were current smokers. The tumor size was less than 3 cm in 233 patients (67%), while it was equal to, or greater than, 3 cm in 115 patients (33%). Ta was found in 95 patients (27.3%), T1 and Tis in 43 patients (12.4%), and Tu in 210 patients (60.3%). One hundred and sixty-eights patients (48%) had high grade tumors, with 119 and 49 patients in the no-RASI and RASI cohorts, respectively. Multifocal tumors were found in 170 patients (49%), with 130 and 40 patients in the no-RASI and RASI cohorts, respectively. MMC was administrated after the TUR-BT in 50 patients (14.4%), while 113 patients (32.5%) received BCG therapy, and a further 25 (7.2%) received both agents.

The median follow-up times for tumor recurrence and stage progression were 2.3 years (IQR 1.1-4.2) and 3.7 years (IQR 2.0-5.8), respectively. One hundred and forty patients (40%) experienced tumor recurrence, with patients in the RASI cohort having a significantly lower rate of tumor-recurrence (22% versus 46%, $p<0.001$), as shown in Table 3. The 5-year recurrence-free survival (RFS) rates were 54% and 78% for the no-RASI and RASI cohorts, respectively ($p=0.001$). The RFS between the 2 cohorts was demonstrated with Kaplan–Meier curves (Fig 1). Stage progression was observed in 19 patients (6%), with 3 and 16 patients in the RASI and no-RASI cohorts, respectively ($p=0.5$). The 5-year PFS rates were 87% and 97% for the no-RASI and RASI cohorts, respectively.

On univariate and multivariate analyses (Table 4), a tumor size equal to or greater than 3 cm, tumor multifocality, and patients without RASIs were associated with recurrent bladder cancer (all $p<0.02$). However, there was no significant association between RASI administration and decreased disease progression in both the univariate and multivariate analyses.

DISCUSSION

In Thailand, bladder cancer is the second most common urologic malignancy and the eighth most common overall malignancy, with a prevalence of 4.5/100,000 in males and of 1.2/100,000 in females.[1] NMIBC is the most common presentation, and a variety of adjuvant treatments have been investigated to prevent tumor recurrence and disease progression.[2-7] In a recent meta-analysis, only intravesical BCG demonstrated an association with reduced bladder cancer recurrence and progression in NMIBC patients.[5] In contrast, adjuvant chemotherapy has been solely associated with decreased tumor recurrence, not progression.[5] However, the adverse effects of intravesical BCG are still a concern. Targeted therapies such as checkpoint inhibitors, which function as immunotherapy, have been explored for their substantial effects.[7] In addition, the AT1R has been found in various cancer cells and been shown to be involved in tumor growth and angiogenesis.[9-10] Shirotake and colleagues, who studied the AT1R of bladder cancer patients, reported that it was an independent predictor of the RFS rate on multivariate analysis.[9] As such, RASIs, which are prescribed as anti-hypertensive drugs, may have a potential role in diminishing the risks of tumor recurrence and progression.

The AT1R has been found in bladder cancer specimens and has been significantly associated with intramural neovascularization.[9] AT1R could therefore be a potential factor to identify patients with a high risk of tumor recurrence. Ang II-AT1R also has an impact on tumor microenvironments and thus promotes tumor growth, survival, invasive behavior, and tumor cell migration.[10] This suggests that RASIs, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockages, which are prescribed as anti-hypertensives, might have substantial roles. Blocking the AT1R might reduce tumor growth and angiogenesis and, in turn, inhibit tumor proliferation.[9,10] Previous studies from Yuge et al. and Blute et al. showed that the administration of RASIs was

TABLE 1. Patient and tumor characteristics.

	All patients (n=348)	No-RASIs (n = 262)	RASIs (n = 86)	*p Value*
Age , years, median (IQR)	68.2 (30.9-93.2)			0.03
< 65 years, *n* (%)	127 (36.5)	104 (39.7)	23 (26.7)	
≥ 65 years, *n* (%)	221 (63.5)	158 (60.3)	63 (73.3)	
Gender, *n* (%)				0.89
Male	261 (75.0)	196 (74.8)	65 (75.6)	
Female	87 (25.0)	66 (25.2)	21 (24.4)	
Smoking, *n* (%)				0.10
Never	181 (29.0)	135 (51.5)	46 (53.5)	
Former	101 (52.0)	71 (27.1)	30 (34.9)	
Current	66 (19.0)	56 (21.4)	10 (11.6)	
Tumor size, *n* (%)				0.37
< 3 cm	233 (67.0)	172 (65.6)	61 (70.9)	
≥ 3 cm	115 (33.0)	90 (34.4)	25 (29.1)	
Tumor stage, *n* (%)				0.04
Ta	95 (27.3)	68 (26.0)	27 (31.4)	
T1+Tis	43 (12.4)	27 (10.3)	16 (18.6)	
Tu	210 (60.3)	167 (63.7)	43 (50.0)	
Tumor grade, *n* (%)				0.06
Low	180 (51.7)	143 (54.6)	37 (43.0)	
High	168 (48.3)	119 (45.4)	49 (57.0)	
Tumor multifocality, *n* (%)				0.62
No	178 (51.1)	132 (50.4)	46 (53.5)	
Yes	170 (48.9)	130 (49.6)	40 (46.5)	
Presence of MP in specimen, *n* (%)				0.22
No	208 (59.8)	141 (53.8)	67 (77.9)	
Yes	140 (40.2)	121 (46.2)	19 (22.1)	
Intravesical agents, *n* (%)				0.50
None	160 (46.0)	124 (47.3)	36 (41.9)	
MMC	50 (14.4)	40 (15.3)	10 (11.6)	
BCG	113 (32.5)	80 (30.5)	33 (38.4)	

Abbreviations: BCG = Bacillus Calmette-Guerin; IQR = interquartile range; MMC = mitomycin C; MP = muscularis propria; RASI = renin-angiotensin system inhibitor

TABLE 2. Types of renin-angiotensin system inhibitors.

Renin-angiotensin system inhibitors	n = 86
Angiotensin-converting enzyme inhibitor, n (%)	38 (44.2)
Enalapril	32 (37.2)
Imidapril	1 (1.2)
Nootropril	1 (1.2)
Peridopril	1 (1.2)
Quinapril	3 (3.5)
Angiotensin II receptor blockers, n (%)	48 (55.8)
Irbesartan	5 (5.8)
Losartan	28 (32.6)
Olmesartan	1 (1.2)
Telmisartan	2 (2.3)
Valsartan	12 (14)

TABLE 3. Tumor recurrence and stage progression.

	All patients (n=348)	No-RASIs (n = 262)	RASIs (n = 86)	*p-Value*
Tumor recurrence	140 (40.2)	121 (46.2)	19 (22.1)	<0.001
Stage progression	19 (5.5)	16 (5.67)	3 (3.5)	0.46

Abbreviations: RASI = renin-angiotensin system inhibitor

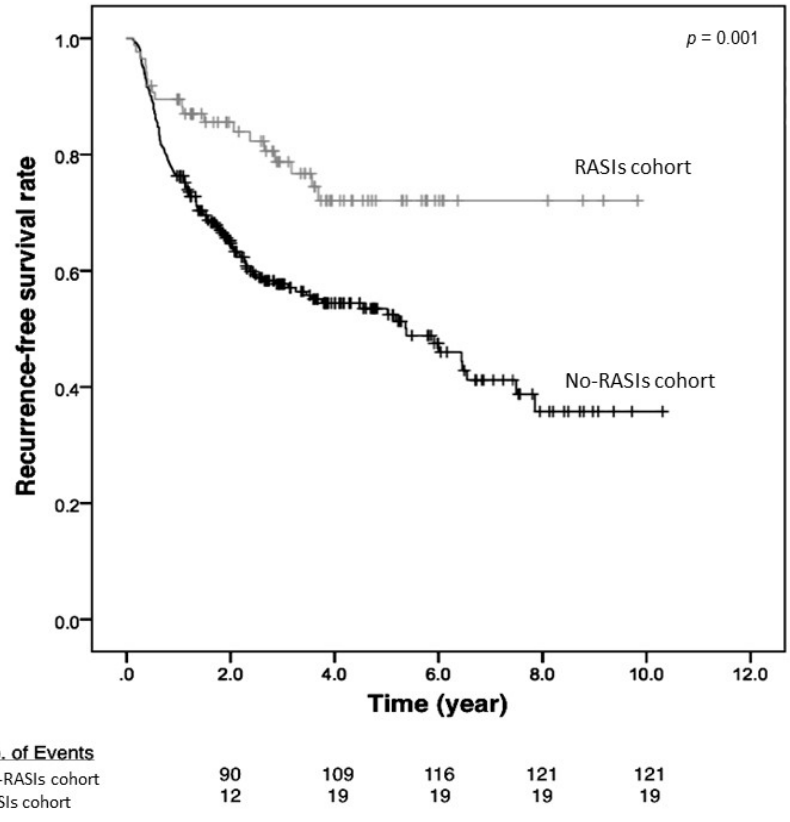

Fig 1. Kaplan-Meier curves demonstrates recurrence-free survival between 2 cohorts of patients: RASIs (gray) and no-RASIs (black).

TABLE 4. Univariate and multivariate analyses for factors associated with tumor recurrence.

	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*p-Value*	HR (95 % CI)	*p-Value*
Age ≥ 65 years	1.25 (0.88-1.78)	0.22		
Female	0.92 (0.63-1.36)	0.69		
Smoking		0.31		
Former	0.92 (0.63-1.34)			
Current	0.69 (0.43-1.12)			
Intravesical		0.26		
MMC	1.12 (0.70-1.81)			
BCG	0.83 (0.57-1.21)			
MMC+BCG	0.55 (0.25-1.20)			
High grade	1.16 (0.83-1.61)	0.39		
Tumor size ≥ 3 cm	1.56 (1.12-2.19)	0.009	1.50 (1.07-2.10)	0.018
Tumor multifocality	1.53 (1.10-2.14)	0.012	1.49 (1.07-2.09)	0.019
Administration of RASIs	0.45 (0.28-0.73)	0.001	0.46 (0.29-0.75)	0.002

Abbreviations: BCG = Bacillus Calmette-Guerin, CI = confidence interval, HR = hazard ratio, IQR = interquartile range, MMC = mitomycin C, RASI = renin-angiotensin system inhibitor

associated with reduced risks of tumor recurrence and disease progression in NMIBC patients.[11,12]

Of the 348 patients in the present study, 140 (40%) and 19 (6%) patients experienced tumor recurrence and progression, respectively. The incidences in our study were similar to those in research by Yuge et al., which demonstrated that 39% of patients had tumor recurrence and 5% had stage progression.[11] On multivariate analysis, RASI administration was significantly associated with a reduced risk of tumor recurrence in our study as well as in the work of Yuge et al. and Blute et al.[11,12] Nevertheless, none of the studies showed that RASIs were associated with disease progression. In our study, the RASI cohort had a significantly greater 5-year RFS rate than that of the no-RASI cohort (78% versus 54%, p=0.001). This was comparable to the 5-year RFS rates of the study by Yuge et al., which were 78% and 53% for the RASI and no-RASI cohorts, respectively, (p=0.01).[11]

Patients with NMIBC after a TUR-BT are classified based on the risk stratification of recurrence and progression.[2-4] Different further management strategies are employed for each group of NMIBC patients. As to the European Organization for Research and Treatment of Cancer (EORTC) risk table, patients with multiple or large tumors are at high risk for bladder cancer recurrence and stage progression.[2–4,13–15] Our study revealed that tumor multifocality and a tumor size greater than 3 cm were associated with an increased risk of tumor recurrence. Millán-Rodríguez et al. studied a cohort of 1,529 patients with NMIBC; their Kaplan–Meier analysis demonstrated that tumor recurrence was statistically significant for multiple tumors and a large tumor size (p<0.001). On multivariate analysis, multifocality and a large tumor were also associated with an increased risk of tumor recurrence (OR 2.0, 95% CI 1.6–2.4; and OR 1.7, 95% CI 1.3–2.0, respectively).[13] It has been suggested that high-risk NMIBC patients should receive intravesical BCG to prevent recurrence and progression.[2-4,13-15]

Previous meta-analyses have shown that intravesical therapies significantly decrease the risk of recurrence in NMIBC patients.[5] The type of intravesical therapy used depended on the risk profile of each patient. BCG therapy showed better outcomes in terms of a reduction in tumor recurrence than a TUR-BT alone or intravesical chemotherapy.[5] Nonetheless, some patients could not tolerate its adverse effects, and some tumors still refracted or relapsed after treatment.[6,16] In our study, intravesical therapy, including BCG and MMC, was not associated with tumor recurrence and disease progression. The number of patients recruited for the study could be the

explanation, given that the role of the RASIs was our primary outcome.

The major limitation of our study was its retrospective design with intermediate follow-up. As to the historic data, the tumor stages and grades differed slightly from the current classifications. While patients given intravesical BCG in other studies showed a reduced risk of tumor recurrence and progression, our study had too limited a number of patients to show similar outcomes. In addition, supplies of intravesical BCG were unavailable in Thailand during several periods, thereby precluding the utilization of BCG based upon patient risk classifications. Nevertheless, there was a sufficient number of patients in our study to demonstrate the impact of RASIs on bladder cancer recurrence. To our knowledge, this is the first study to reveal the impact of RASIs on NMIBCs in Thailand. A prospective study will be needed to further evaluate the effectiveness of RASIs in decreasing NMIBC recurrence and stage progression.

CONCLUSION

Our study suggests that RASI administration in patients with NMIBC might be a potential factor to prevent bladder cancer recurrence. To the best of our knowledge, this is the first study in Thailand to address the benefits of RASIs for NMIBC patients. Further study is needed to evaluate the effects of RASIs on NMIBC patients.

REFERENCES

1. Lojanapiwat B. Urologic cancer in Thailand. Jpn J Clin Oncol. 2015;45(11):1007-15.
2. Babjuk M, Bohle A, Burger M, Capoun O, Cohen D, Comperat EM, et al. EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol. 2017;71(3): 447-61.
3. Woldu SL, Bagrodia A, Lotan Y. Guideline of guidelines: non-muscle-invasive bladder cancer. BJU Int. 2017;119(3):371-80.
4. Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. J Urol. 2016;196(4): 1021-9.
5. Chou R, Selph S, Buckley DI, Fu R, Griffin JC, Grusing S, et al. Intravesical Therapy for the Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis. J Urol. 2017;197(5):1189-99.
6. Cambier S, Sylvester RJ, Collette L, Gontero P, Brausi MA, van Andel G, et al. EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guerin. Eur Urol. 2016;69(1):60-69.
7. Siefker-Radtke AO, Apolo AB, Bivalacqua TJ, Spiess PE, Black PC. Immunotherapy With Checkpoint Blockade in the Treatment of Urothelial Carcinoma. J Urol. 2018;199(5):1129-42.
8. Sparks MA, Crowley SD, Gurley SB, Mirotsou M, Coffman TM. Classical Renin-Angiotensin system in kidney physiology. Compr Physiol. 2014;4(3):1201-28.
9. Shirotake S, Miyajima A, Kosaka T, Tanaka N, Maeda T, Kikuchi E, et al. Angiotensin II type 1 receptor expression and microvessel density in human bladder cancer. Urology. 2011;77(4):1009 e19-25.
10. Tanaka N, Miyajima A, Kosaka T, Miyazaki Y, Shirotake S, Shirakawa H, et al. Acquired platinum resistance enhances tumour angiogenesis through angiotensin II type 1 receptor in bladder cancer. Br J Cancer. 2011;105(9):1331-7.
11. Yuge K, Miyajima A, Tanaka N, Shirotake S, Kosaka T, Kikuchi E, et al. Prognostic value of renin-angiotensin system blockade in non-muscle-invasive bladder cancer. Ann Surg Oncol. 2012; 19(12):3987-93.
12. Blute ML, Jr., Rushmer TJ, Shi F, Fuller BJ, Abel EJ, Jarrard DF, et al. Renin-Angiotensin Inhibitors Decrease Recurrence after Transurethral Resection of Bladder Tumor in Patients with Nonmuscle Invasive Bladder Cancer. J Urol. 2015;194(5): 1214-9.
13. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J, Vicente-Rodriguez J. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. J Urol. 2000;163(1):73-78.
14. Rodriguez Faba O, Palou J. Predictive factors for recurrence progression and cancer specific survival in high-risk bladder cancer. Curr Opin Urol. 2012;22(5):415-20.
15. Sexton WJ, Wiegand LR, Correa JJ, Politis C, Dickinson SI, Kang LC. Bladder cancer: a review of non-muscle invasive disease. Cancer Control. 2010;17(4):256-68.
16. Sfakianos JP, Kim PH, Hakimi AA, Herr HW. The effect of restaging transurethral resection on recurrence and progression rates in patients with nonmuscle invasive bladder cancer treated with intravesical bacillus Calmette–Guerin. J Urol. 2014;191(2): 341-5.