ORIGINAL ARTICLE

Bladder cancer in southwestern Iran: Histopathologic and clinical features

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ABSTRACT

Background: Bladder cancer (BC) is one of the leading causes of cancer death. However, there is little knowledge on the histopathologic features of BC in Iran. In line with our previous report, the aim of this study was to investigate the epidemiologic, histopathologic and clinical features of BC in southwestern Iran 2009-2015.
Methods: Data were retrieved from Nemazee and Faghihi cancer registries. Data were cleaned and prepared to statistical analysis. Data were described using descriptive statistics and more explored to test some of our hypotheses. Univariate and multivariate logistic regression were done.
Results: A total of 756 patients with a mean age of 64.51±12.99 years were enrolled. Male: female ratio was a 3.97 and consistent across age groups. Among both genders, initial presentation of 79% of patients was painless hematuria. 94.7% of tumors were transitional cell carcinoma, 43.1% were muscle invasive, 26.2% were metastatic and 50.7% were high grade tumors. 86% of none-muscle- invasive and 44.0% of invasive tumors were managed by transurethral resection of bladder. Recurrence was seen in 436 (57.7%) of patients and was associated with hookah tobacco smoking (Adjusted Odds ratio: 1.44, 95% CI: 1.01- 2.1) and history of hypertension (1.36, 1.00-1.86).
Conclusions: Delayed diagnosis, younger ages at diagnosis and a similar share of advanced tumors between males and females were remarkable differences of epidemiologic features of BC in southwestern Iran compared with western countries. While management of non- muscle invasive tumors meet the recommended standards of care but it does not for muscle invasive tumors.
Keywords: Disease management, epidemiology, histology, pathology, urinary bladderneoplasms

INTRODUCTION

Bladder cancer (BC) is the 9th leading cause of cancer related deaths in the world. According to the GLOBOCAN 2012, annual number of new cases of and deaths due to BC were estimated at 430000 and 165000, respectively[1,2]. However, its incidence and mortality rates are highly variable throughout the world. As about 59 percent of BCs cases were reported from developed countries.(3) The highest incidence of BC has been reported from Northern America and Europe; and the lowest incidence from Latin America, the Caribbean, and Asia[2].

In the Eastern Mediterranean Region (EMRO), BC is the fifth most common cancer and the second in males. A similar pattern with an increasing incidence trend has been reported for Iran[4,5].

Abovementioned markedly geographical variations in incidence and mortality rates of BC are mainly due to different epidemiological patterns regarding its major risk factors including male gender, older ages, smoking, opium consumption, disinfected drinking water, using several drugs (e.g. cyclophosphamide) and exposure with arsenic and aromatic amines[6,7,8].

Accordingly, there are also some geographical variations in histopathologic features of BC, globally, i.e. WhileTransitional cell carcinoma (TCC) has been reported as the most common type of BC (almost 95% of new cases), Squamous cell carcinoma has been documented as the most common (60%) type of it in Egypt, parts of Africa, and the Middle East[9,10,11].

In concordance with the lack of reliable cancer epidemiological data from countries in Middle Eastern region, as we know, there is little knowledge on the histopathological features of BC in Iran. This lack of evidences occurs while, in Iran, BC accounts for about 9% of all cancers and increasing trends were reported regarding its incidence and mortality[12,13].

In line with our previous report on the epidemiology of BC in Fars province in 2007-2009, to provide an updated and more detailed data on the epidemiology and clinicopathology of BC in southern Iran 2009-2015.

MATERIAL AND METHODS

This retrospective study was conducted in Shiraz, the capital of Fars province, Iran. Fars province has an area of 122,600 km² and is located at south of Iran. According to the national statistical center of Iran, this province had a population of more than 4.82 million people (less than 7% of Iran population), 67.6% of urbanization and an 86.3% of literacy rate by 2016[14].

To retrieve a representative sample, multiple accessible data sources were searched for BC cases. Data were retrieved mostly from Nemazee hospital-based cancer registry, and archives of medical records of Nemazee and Faghihi hospitals affiliated to Shiraz University of Medical Sciences. From March, 2009 until September 2015, totally data of 756 patients gathered that 463 of them were related

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to Nemazee and 293 of them were about Faghihi hospital patients. We also cross checked patients' data with reportsavailable from archives of Pathological laboratoryofeach of hospitals,only for cases that had incomplete data.Department of Urology (especially Onco-urology ward) that was placed in Nemazee and Faghihi hospitals of Shiraz University of Medical Sciences is the main referral center for urological cancers in Southwestern Iran which cover almost all patients from Fars province, and a considerable proportion (more than 50%) of the patients come from neighboring provinces including Bushehr, Hormozgan and Kohgiluyeh and Boyer-Ahmad.

Data sources were searched for patients who had a pathologically confirmed diagnosisof BC (ICD-O-3 code: C67)and undergone surgical operation for BC. The patients whohad diagnosed before 2009 and came to hospital (in the study period) for recurrence were excluded.

Data were collected using a pre-designed form for use in the current study. Demographic data (gender, age at diagnosis),date of diagnosis, initial presentation(hematuria, dysuria , both or none), type of operation(transurethral resection of bladder[TURB], partial cystectomy, radical cystectomy), histologic type(Transitional cell carcinoma [TCC], adenocarcinoma, squamous cell carcinoma), grade of tumor pathology(according to the World Health Organization and International Society of Urological Pathology grading system[WHO/ISUP]: high or low grade), history of smoking and hookah and opium consumption(yes or no), past history of systemic diseases (hypertension, diabetes mellitus, benign prostatic hyperplasia[BPH])according to patients self-reports , tumor metastasis and muscle invasion were collected.Data on the tumor recurrence was also gathered.Different reports available for each casewere sorted by date, and after removing duplicated reports, cases with recurrence were identified and registered as recurrent cases.

Data were cleaned and prepared for statistical analysis according to recommended procedures[15]. Duplicatedreports were identified using software techniques.To do this, reports were sorted by date and merged in to the last report.

Data were described using mean± standard deviation (SD) and relative frequencies by different variables.Then we explored the data for statistical associations which were clinically meaningful, using chi- squared, two independent sample t-tests and logistic regression modeling.As missing rate was less than 2%, we excluded missing data from analyses.

A logistic regression model was fitted to identify predictor variables of recurrence. We applied backward elimination approach for variable selection for multivariable modeling. Crude odds ratios (95% Confidence intervals) were also estimated as well as adjusted odds ratios. P-values less than 0.05 were considered statistically significant. Statistical analyses were done by SPSS software (version 20).

The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (Code IR.sums.med.rec.1396.s02).

RESULTS

Data from a total of 756 patients with a mean age of 64.51±12.99 years (Median: 65, range: 23-92 years) were analyzed. The most of patients were male 604(79.9%) (Fig. 1).

Male/female ratio was estimated at 3.97. This ratio was not statistically different across all age groups (i.e., less than 40, 40-49, 50-59, 60-69, equal with or more than70; P-value= 0.12; Figure 1).

The most common initial presentation was painless hematuria 598(79.2%; among males, 79.3%; among females, 78.9%), while only 29 (3.8%) patients had history of dysuria without hematuria as their main presentation. Twelve patients (1.6%) had no significant urinary sign or symptom and their bladder cancer was diagnosed accidentally or during the evaluation of other cancers.

Based on the surgical information, transurethral resection of bladder (TURB) was performed for 504 (67.8%), radical cystectomy in 226 (30.5%), and partial cystectomy in 13(1.7%) patients. From those who underwent radical cystectomy, 86.3% (n=195 out of 226) had high grade tumorsand fromwhomanaged with TURB, 35.7% (n=180 out of 504) had high grade tumors (P-value> 0.001). The most of non-muscle –invasive tumors were managed applying TURB (363 out of 423, 86%), while around half of muscle invasive tumors were managed by radical cystectomy (174 out of 320, 54%).

History of cigarette and hookah smoking was positive in 331(43.8%) and 187(24.8%) cases, respectively.Smoking was more common in males than females (40.7% vs. 3.2%, p<0.001). Almost 21.2% of patients including 153 males and 6 females had a positive history of opium consumption (Table 1).

The share of muscle invasive tumors was estimated at 43.1%, which was 43.7% among males and 40.3% among female patients (P=0.440). Mean of age of patients at diagnosis in invasive and non-invasive cases were 65.86±11.7 and 63.53±13.8 years, respectively (P=0.016). There was no significant association between muscle invasion and primary clinical presentation of disease (P=0.102). A number of 195 cases were metastatic (26.2%). Proportions of metastatic tumors among males and females were estimated at 25.6% (152 out of 594) and 28.9 %(43 out of 149), respectively (P=0.411). Patients with metastatic tumor were older than others (P=0.015).

About half of patients (n= 361) had high grade TCC. The most of patients 286(79.2%) with high grade TCC were male. The proportion of high grade TCC in male and female patients were not statistically different (51% of male patients vs. 52% of females;P-value =0.78; Table 2).

Recurrence was seen in 436 (57.7%) of patients, 336(77%) of them were male and 100 (23%) were female. There was a significant difference in the recurrence rate of bladder cancer between males and females (p= 0.02). Based on the best fitted logistic regression to identify associated factors with tumor recurrence, gender (Adjusted OR: 1.46, 95% CI: 0.99- 2.15), metastasis (Adjusted OR:1.80, 95% CI: 1.24-2.62), muscle invasion (Adjusted OR:1.91, 95% CI: 1.39- 2.63), hookah consumption (Adjusted OR:1.44, 95% CI: 1.01- 2.1) and hypertension (Adjusted OR:1.36, 95% CI: 1.00- 1.86) were associated with recurrence of Bladder cancer (Table 3).

Fig.1. Age and gender distribution of Bladder cancer cases in Shiraz, 2009-2015

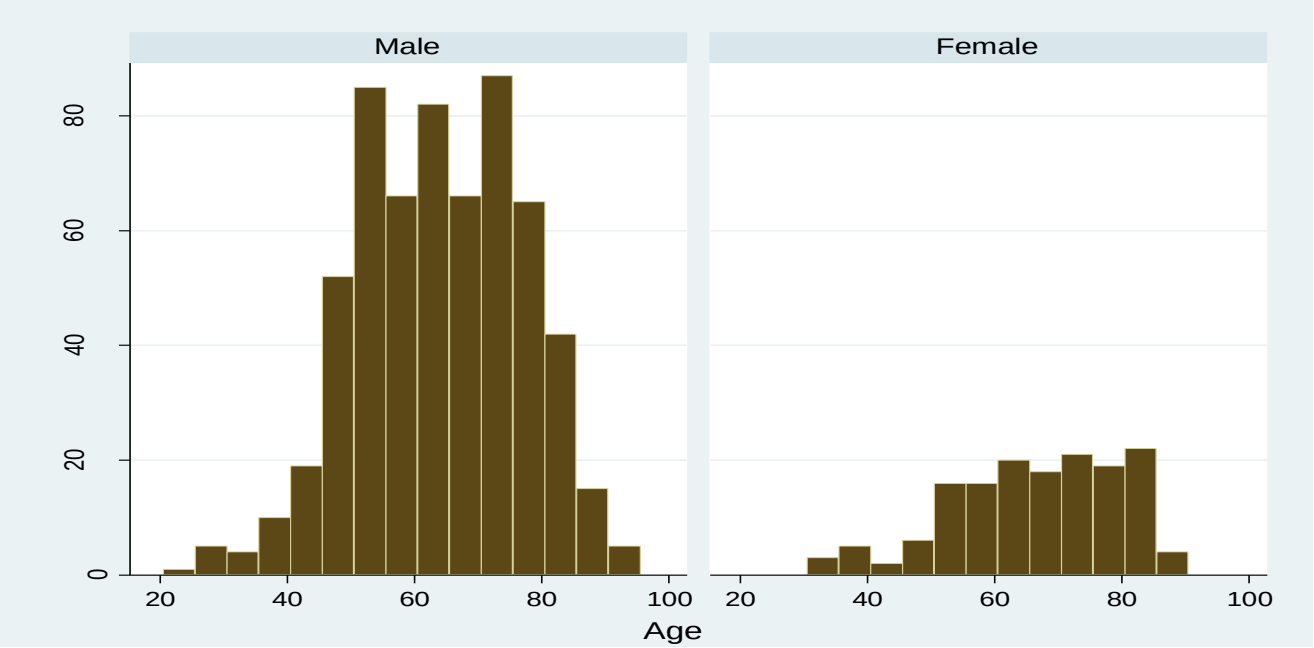

Table 1: Characteristics of patients with bladder cancer in Shiraz, 2009-2015, by gender; (n=756*)

Characteristic	Stratum			
		Male (n=604)	Female (n=152)	P-value
Age group	<40	15(2.5)	6(3.9)	0.12
	40-49	58(9.6)	8(5.3)	
	50-59	157(26.0)	34(22.4)	
	60-69	151(25.0)	35(23.0)	
	>70	223(36.9)	69(45.4)	
Cigarrete Smoking	No	296(49.1)	128(84.2)	<0.001
	yes	307(50.9)	24(15.8)	
Hookah consumption	No	447(74.1)	121(79.6)	0.16
	yes	156(25.9)	31(20.4)	
Opium consumption	No	450(74.6)	146(96.0)	<0.001
	yes	153(25.4)	6(4.0)	
History of DM	No	542(89.9)	129(84.9)	0.079
	Yes	61(10.1)	23(15.1)	
History of HTN	no	340(56.4)	57(37.5)	<0.001
	Yes	263(43.6)	95(62.5)	
History of BPH	No	451(74.8)	152(100)	-
	Yes	152(25.2)	0(0)	

*missing data were excluded from analyses.

Table 2.Histopathological characteristics of bladder tumors in Shiraz, 2009-2015

		Grade	Overall	Male	Female	P-Value
Histopathology	TCC	Low	351(49.2)	281 (49.6)	70 (48.3)	0.78
		High	361(50.7)	286 (50.4)	75 (51.7)	
	SCC	Low	2 (20)	1(14.3)	1(33.3)	0.49
		High	8 (80)	6(85.7)	2(66.7)	
	Adenocarcinoma	Low	4(28.6)	4(30.8)	0(0)	0.51
		High	10(71.4)	9(69.2)	1(100)	
	Mixed	Low	2(28.6)	2(28.6)	0(0)	-
		High	5(71.4)	5(71.4)	0(0)	
Muscle invasion	No		423 (56.9)	334(56.2)	89(59.7)	0.440
	Yes		320 (43.1)	260(43.8)	60(40.3)	
Metastasis	No		548 (73.8)	442(74.4)	106(71.1)	0.411
	Yes		195 (26.2)	152(25.6)	43(28.9)	
Recurrence	No		320 (42.3)	268 (44.4)	52 (34.2)	0.02
	Yes		436 (57.7)	336 (55.6)	100(65.8)	

Table 3: Associated factors with recurrence of bladder cancer in Shiraz, 2009-2015

Factor	Crude OR (95% CI)	Adjusted OR (95% CI)
Gender (Ref. Male)	1.53(1.06- 2.22)	1.46(0.99- 2.15)
Metastasis (Ref. No)	2.22(1.56- 3.17)	1.80(1.24- 2.62)
Hookah consumption (Ref. No)	1.39(0.99- 1.96)	1.44(1.01- 2.1)
Muscle invasion (Ref. No)	2.22(1.64- 3.00)	1.91(1.39- 2.63)
Hypertension (Ref. No)	1.35(1.00- 1.81)	1.36(1.00- 1.86)

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; Ref., Reference category

DISCUSSION:

In this study we investigated the histopathological and clinical features of bladder cancer in southwestern Iran. An updated presentation of distribution of bladder cancer was provided,focusing on the patient's age and gender, first clinical presentation and major approaches for clinical management of disease, histology, differentiation, metastases, muscle invasion and recurrence of tumor, as well as self- reported history of consumption of opium, hookah andcigarrete smoking, and history of hypertension, type 2 diabetes and benign prostate hyperplasia.

Study findings revealed that half of patients were younger than 65 years old. According to available evidence, age at diagnosis of BC for more than half of patients is 75[16,17,18], which is around ten years older than observed median in our study. In addition, it is expected that only one out of 10 patients were younger than 55 years[17]. In this study we observed that more than 20 percent of patients were younger than 55 years. Previous studies from middle eastern region had also shown that mean of age of BC patients at diagnosis were equal or even younger than what that we observed in the current study[17,18]. Younger ages at diagnosis may be a hint for future researches to investigate different causal profile of BC in this region.

Estimated Male: Female ratio in our study was around 4:1, which was higher than what that reported for United Kingdom i.e. 2.7:1 and equal with what that reported for United States of America[17]. Although this ratio varies highly across geographical parts of the world, but it is well documented that throughout the world, males have a higher risk of incidence of BC at least 2 times more than females. A recent review has shown that the higher risk in males is independent of their higher risk exposure[19]. Although higher risk of BC in males may be highly related to disparate molecular mechanisms and also sex steroid hormones pathways between males and females, it may be also due to different risk exposure profiles[19,20].

Based on the study results, painless hematuria was the most common (more than 79%) initial presentationof disease. In line withprevious reports, we observed that there is no gender differenceregarding initial presentation of the BC[21]. However, there is a body of evidence have revealed that in a considerable share of female cases with hematuria, it is incorrectly attributed to conditions such as urinary tract infections[22,23]. It consequently leads to a probable wrong or delayed diagnosis of BC among them[16]. More researches to investigate effects of higher proportion of further urological evaluation of patients with hematuria on the more timely diagnosis of BC especially among females may be valuable[24].

The most common type of surgery was transurethral resection of bladder (TURB), which used to remove the tumor in more than 67% of cases. In line with current standards of care, TURB was applied to manage a proportion of 86% of none-muscle- invasive tumors. However, it was also applied for tumor management in more than 44% of muscle invasive tumors, what that seems to be different from standards of care for muscle invasive cases[25]. It may be due to lack of patients' consent for radical cystectomy or clinical considerations regarding patients' characteristics. However, further studies are needed to investigate it in more details in Iran.

Despite of expectation for more advanced tumors among females[20], there was no statistically significant difference between males and females regarding muscle invasion, metastasis and high grade. It may be due to delayed diagnosesin both of males and females, as a proportion of more than 40.0% of cases in both of males and females were muscle invasive, a more than 50% of tumors had high grade in both genders, and also among both of males and females more than 25% of cases were metastatic. However, there was a 46% of higher risk of recurrence among females compared with males (OR= 1.46, 95% CI: 0.99- 2.15).

With regard totumor recurrence, positive history of consumption of hookah (waterpipe tobacco smoking) was associated with higher risk of recurrence (OR= 1.44, 95% CI: 1.01- 2.1). Despite of previously showed association between cancer occurrence and consumption of hookah, as well as smoking and incidence of BC but, we could not able to find any reliable study which has been investigated the association of recurrence of BC with hookah consumption[26]. Accordingly, future studies should be considering the consumption of hookah as a correlated factor of recurrence of BC.

Another associated factor with recurrence of BC was a self-reported positive history of hypertension (OR= 1.36, 95% CI: 1.00- 1.86). Although this finding is consistent with some previous studies but, there is a controversy regarding the association of hypertension and incidence or prognosis of BC[27,28].

Although in this study we explored data from a relatively high sample size of BC from a developing country gathered during 7 years, but our study suffers from some limitations. This study was a secondary data analysis of available data.We have no data on the patients' outcome. Therefore, no survival or outcome analysis was done, while it is one of the missing pieces of puzzle of BC in the developing countries.

In conclusion despite of delayed diagnosis of BCs in southwestern Iran, patients in this region are younger than western countries. Although man are at higher risk of BC but they have not less advanced tumors than females.Future studies are highly recommended to investigate these findings.

Although management of non- muscle invasive tumors meet the recommended standards of care but it

does not for less than half of muscle invasive tumors. Again, future studies are appreciated to investigate the role of evidence based clinical management of BC in Iran.

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REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M. GLOBOCAN, cancer incidence and mortality worldwide: IARC cancer base no. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. 2012.
2. Malats N, Real FX. Epidemiology of bladder cancer. Hematology/oncology clinics of North America. 2015;29(2):177-89, vii.
3. Stewart B, Wild CP. International Agency for Research on Cancer, WHO. (2014) World Cancer Report 2014 [Online] 2014 [Available from: http://www.thehealthwell.info/node/725845.
4. Shafi H, Ali Ramaji A, Akbarzadeh Pasha A, Yousefnia Pasha YR, Kasayan AA, Aghajanimir M, et al. A Survey on 175 Cases of Bladder Cancer in the Patients Who Referred to the Hospitals Affiliated to Babol University of Medical Sciences, Iran (2001-2011). Journal of Babol University Of Medical Sciences. 2013;15(2 %U http://jbums.org/article-1-4357-en.html):116-22 %& %! %9 Research %L A-10-1370-876 %+.
5. Rezaianzadeh A, Mohammadbeigi A, Mobaleghi J, Mohammadsalehi N. Survival analysis of patients with bladder cancer, life table approach. Journal of mid-life health. 2012;3(2):88-92.
6. Chavan S, Bray F, Lortet-Tieulent J, Goodman M, Jemal A. International variations in bladder cancer incidence and mortality. European urology. 2014;66(1):59-73 %@ 0302-2838.
7. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. Jama. 2011;306(7):737-45 %@ 0098-7484.
8. Bachir BG, Kassouf W. Cause–effect? Understanding the risk factors associated with bladder cancer. Expert review of anticancer therapy. 2012;12(12):1499-502 %@ 73-7140.
9. Konety BR, Carroll PR. Urothelial carcinoma: cancers of the bladder, ureter, & renal pelvis. Smith and Tanagho's General Urology. 18 ed. New York: Mc Graw-Hill Companies; 2013. p. 308-27.
10. da Costa LAV, Wroclawski ML, Machado MT, Pompeo ACL, Wroclawski ER. Non-occupational risk factors for bladder cancer.
11. Salem HK, Mahfouz S. Changing patterns (age, incidence, and pathologic types) of schistosoma-associated bladder cancer in Egypt in the past decade. Urology. 2012;79(2):379-83 %@ 0090-4295.
12. Ahmadi M, Ranjbaran H, Amiri MM, Nozari J, Mirzajani MR, Azadbakht M, et al. Epidemiologic and socioeconomic status of bladder cancer in Mazandaran Province, northern Iran. Asian Pacific Journal of Cancer Prevention. 2012;13(10):5053-6 %@ 1513-7368.
13. Salehi A, Khezri A-a, Malekmakan L, Aminsharifi A. Epidemiologic status of bladder cancer in Shiraz, southern Iran. Asian Pac J Cancer Prev. 2011;12(5):1323-7.
14. Iran Sco. Statistical center of Iran: Statistical center of Iran 2017 [Available from: https://www.amar.org.ir/english/Databases-Systems/Time-Series/agentType/ViewType/PropertyTypeID/306).
15. Molavi Vardajani H, Haghdoost AA, Shahravan A, Rad M. Cleansing and preparation of data for statistical analysis: A step necessary in oral health sciences research. Journal of Oral Health and Oral Epidemiology. 2016;5(4).
16. Shariat SF, Sfakianos JP, Droller MJ, Karakiewicz PI, Meryn S, Bochner BH. The effect of age and gender on bladder cancer: a critical review of the literature. BJU international. 2010;105(3):300-8.
17. Bladder Cancer Risk Factors, USA: American Cancer Society; 2017 [Available from: https://www.cancer.org/cancer/bladder-cancer/causes-risks-prevention/risk-factors.html.
18. Risks and causes London, UK: Cancer Research UK [updated 20 Jul 2015. Available from: http://www.cancerresearchuk.org/about-cancer/bladder-cancer/risks-causes.
19. Dobruch J, Daneshmand S, Fisch M, Lotan Y, Noon AP, Resnick MJ, et al. Gender and bladder cancer: a collaborative review of etiology, biology, and outcomes. European urology. 2016;69(2):300-10.
20. Thorstenson A, Hagberg O, Ljungberg B, Liedberg F, Jancke G, Holmäng S, et al. Gender-related differences in urothelial carcinoma of the bladder: a population-based study from the Swedish National Registry of Urinary Bladder Cancer. Scandinavian journal of urology. 2016;50(4):292-7.
21. Henning A, Wehrberger M, Madersbacher S, Pycha A, Martini T, Comploj E, et al. Do differences in clinical symptoms and referral patterns contribute to the gender gap in bladder cancer? BJU international. 2013;112(1):68-73.
22. Johnson EK, Daignault S, Zhang Y, Lee CT. Patterns of hematuria referral to urologists: does a gender disparity exist? Urology. 2008;72(3):498-502.
23. Fajkovic H, Halpern JA, Cha EK, Bahadori A, Chromecki TF, Karakiewicz PI, et al. Impact of gender on bladder cancer incidence, staging, and prognosis. World journal of urology. 2011;29(4):457-63.
24. Moyer VA. Screening for bladder cancer: US Preventive Services Task Force recommendation statement. Annals of internal medicine. 2011;155(4):246-51.
25. Griffiths TL. Current perspectives in bladder cancer management. International journal of clinical practice. 2013;67(5):435-48.
26. Montazeri Z, Nyiraneza C, El-Katerji H, Little J. Waterpipe smoking and cancer: systematic review and meta-analysis. Tobacco control. 2016:tobaccocontrol-2015-052758.
27. Dal Moro F, Bovo A, Crestani A, Vettor R, Gardiman MP, Zattoni F. Effect of hypertension on outcomes of high-risk patients after BCG-treated bladder cancer: a single-institution long follow-up cohort study. Medicine. 2015;94(9):e589.
28. Jiang X, Castelao JE, Yuan J-M, Groshen S, Stern MC, Conti DV, et al. Hypertension, diuretics and antihypertensives in relation to bladder cancer. Carcinogenesis. 2010;31(11):1964-71.