Impact of Smoking Status on the Recurrence of Superficial Urinary Bladder Cancer

Abdullah Rababa'ah, MD*, Mohammad Serhan, MD*, Firas Khori, MD*, Ahmad Alhiary, MD*, Anees Hjazeen, RN*

ABSTRACT

Objectives: The objectives of this study were to assess the association between smoking and the primary characteristics of superficial bladder cancer (SBC) and to investigate the effect of smoking and smoking cessation on the recurrence rate of SBC.

Methods: This was a descriptive comparative study involving 200 patients with Ta or T1 superficial (non-muscle-invasive) urinary bladder cancer who underwent transurethral resection of bladder tumor (TURBT) and surveillance cystoscopy at Prince Hussein Bin Abdullah II Center for Urology and Organ Transplantation between April 2014 and May 2020. The original smoking status for each patient at the time of diagnosis was recorded, and cystoscopic findings along with histopathologic tumor characteristics were compared between smokers and non-smokers. Subsequently, the patients were categorized into the following three subgroups: non-smokers, persistent smokers, and quitters who stopped smoking within three months of the initial diagnosis of urinary bladder cancer. Finally, the recurrence rate of bladder cancer in the surveillance cystoscopy program for each patient was calculated and compared between the different groups.

Results: One hundred seventy-four males and 26 females were included in the study. We found that smoking was only associated with tumor multicentricity. One hundred ninety-one patients completed the 5-year study period. Non-smokers had the lowest recurrence rate and the best recurrence-free survival throughout the study. While persistent smokers and quitters had similar early recurrence rates, smoking cessation was found to reduce late recurrences. The median cumulative 5-year recurrence-free survival for non-smokers, quitters, and persistent smokers was 48, 40, and 35 months, respectively.

Conclusion: Since improved late recurrence rates were found in patients who quit smoking, in addition to the negative effects of smoking on general health, smokers with SBC should be thoroughly counseled, encouraged and persuaded regarding smoking cessation to enjoy a better quality of life.

Keywords: superficial bladder cancer (SBC), smoking status, surveillance cystoscopy, recurrence

RMS August 2022; 29 (2): 10.12816/0061169

INTRODUCTION

Bladder cancer (BC) is the second most common cancer of the genitourinary system [1] and the ninth most frequent cancer worldwide, with approximately 400,000 newly diagnosed cases per year [2]. In addition, BC ranks as the ninth leading cause of cancer-related deaths worldwide, according to the International Agency for Research on Cancer [3].

From the Department of:
* Urology, Prince Hussein Bin Abdullah II Center for Urology and Organ Transplantation, Correspondence should be addressed to Dr. A. Rababa'ah, E-mail: arababaah@gmail.com
Submission date:3 May 2021 , Acceptance date :25 Feb 2021, Publication date :1 Aug 2022

Compared to other cancers, mortality rates are generally lower for BC [2] since the majority of newly diagnosed BCs (70% in one study [4]) are superficial bladder cancers (SBCs), also known as non-muscle-invasive bladder cancers (NMIBCs) [5]. The cancer-specific survival of high-grade SBC ranges from 70–85% at 10 years, and rates are even higher among those with low-grade disease [6].

However, SBC often recurs after transurethral resection [7] and, hence, may adversely affect the quality of life of the patients [8] and generate high disease-management costs [9]. Some studies have reported that the recurrence rate varies significantly from patient to patient. In one study, for example, the 5-year probability of recurrence ranged from 31% to 78% depending on the clinical and pathological severity [10].

While smoking is a well-known risk factor for the development of BC [11–14], its effects have been investigated less frequently in relation to the prognostic factors of BC, including recurrence [15–18]. Moreover, although many studies have investigated the effectiveness of treatment for SBC with regard to recurrence, progression, and mortality, most studies have not investigated the effect of smoking, or other factors that are modifiable by patients, on BC prognosis [19], especially prospectively [20].
The recurrence of BC can be associated with high costs. According to one study, in 2000 alone, urology clinics received almost half a million outpatient visits by patients with BC [21]. Given the chronicity of SBC, its negative effects on the quality of life of patients, and the associated high management costs, it is essential to elucidate preventable factors that may reduce the risk of recurrence. We investigated the role of smoking as one of these factors.

METHODS

This was a descriptive comparative study done at Prince Hussein Bin Abdullah II Center for Urology and Organ Transplantation between April 2014 and May 2020. The study was launched in October 2016. We retrospectively reviewed the files of 200 patients with SBC who accomplished the initial inclusion criteria. Then, prospectively from that point on, we continued recording the results of their surveillance cystoscopy program for a total of 5 years of follow up for each patient.

All enrolled patients underwent transurethral resection of the bladder tumor (TURBT) and were diagnosed with SBC, either stage Ta or T1, in the period between April 2014 and April 2105. The CIS stage was an exclusion criterion since it is an independent risk factor for recurrence. Should a second session TURBT was needed for the completion of tumor resection; it was considered the primary TURBT to eliminate the risk of considering residual tumor as an early recurrence. Cystoscopic and pathologic criteria of the primary tumor were recorded and compared among smokers and non-smokers at the time of diagnosis to assess the association, if any, between smoking and the size, number, stage, and grade of the tumor.

Next, the patients were divided into the following three groups according to their smoking status: non-smokers, including those who never smoked or ex-smokers who stopped smoking at least 5 years before the diagnosis; persistent smokers who continued to smoke or resumed smoking after quitting for a short period after the diagnosis; and quitters who stopped smoking within 3 months after the diagnosis and did not resume smoking thereafter. In fact, our initial intention was to further divide patients according to the 2004 WHO [22] tumor grading into high or low grades to check if there was a difference in the effect of smoking cessation on the recurrence rate between the two

groups. However, due to the small sample of non-smokers who had high-grade tumors (n=7), we decided not to use this subdivision and instead combined the two groups together.

All enrolled patients followed the same surveillance cystoscopy program according to the American Urological Association (AUA) guidelines. The number of tumor recurrences for each patient in the three groups was recorded, the annual recurrence rate was measured, and the recurrence-free survival was analyzed and compared between the three groups over the 5-year study period. Any patient who received intravesical BCG or chemotherapy in the course of follow up was excluded from the study in an attempt to eliminate other confounding factors that may affect recurrence.

Data gathering

Patients' clinical data, data regarding the primary tumors pathologic characteristics, and the results of the first few cystoscopy operations before we launched the study were derived from patient files. Thereafter, patients were briefly interviewed by a specialist in the preoperative area on the day of surgery - one day after the preoperative assessment in the clinic - and questioned about their smoking status, any specific treatment they might have received, any complications, and the counseling they had received in the preoperative assessment clinic the day before. A statement of ethics approval was obtained from the Ethical Committee of the Royal Medical Services.

Statistical analysis

Categorical data was expressed as frequencies, and percentage scale data was expressed as the mean ± standard deviation (SD). Chi-square analysis of independence was used to reveal the association between categorical data. Cumulative recurrence-free survival was measured using the Kaplan–Meier survival analysis. The Mantel–Cox log-rank test was used for pairwise comparisons. A P value of 0.05 was considered statistically significant. IBM SPSS version 25 was used for the statistical analysis.

RESULTS

Of the 200 patients enrolled at the beginning of the study, 174 patients were males and 26 females. Around 40% of the patients could identify smoking as a risk factor of BC. Eighty-one percent of the female patients and 84% of the male patients were smokers at the time of diagnosis. While most of the patients admitted that they received clear counseling about the association between smoking and BC at the time of diagnosis, only 32% of the patients reported that doctors frequently encouraged them to quit smoking during late follow-up clinic visits.

Seventeen patients required a second session of TURBT, with 9 for tumor resection completion and 8 for restaging of the T1 high-grade tumor. The associations between smoking and the primary tumor characteristics for all 200 patients initially enrolled in the study are shown in Table I. There was a statistically significant association only between smoking and the number of tumors (i.e., multicentricity) (p value of <0.001), while size, stage, and grade had no statistically significant association.

One hundred ninety-one patients completed the five-year protocol of surveillance: two patients had a radical cystectomy operation, two patients were lost in follow up, and five patients received BCG. Table II shows the clinical and pathological characteristics and the number of recurrences for patients in the three groups (non-smokers, persistent smokers, and quitters). Noticeably, 80% of females who were smokers at the time of diagnosis quit smoking within 3 months after the diagnosis, while only 40% of the males were able to do the same.

A total of 107 recurrence events occurred over the 5-year study period. Fifty-nine percent of non-smokers with tumor recurrence had only one or two recurrence events, in comparison with 51% and 64% of quitters and persistent smokers with tumor recurrence, respectively, who had 3 or more recurrence events. The 5-year recurrence-free survivals for the three groups are shown in Figure 1. The median recurrence-free survival was 48 months for non-smokers, 40 months for quitters, and 35 months for persistent smokers. The log-rank test and pairwise comparison showed that there was a statistically significant difference in the 5-year recurrence-free survival between non-smokers and persistent smokers, in favor of non-smokers ($p<0.001$), with a hazard ratio (HR) of 2.83 and 95% confidence interval (95% CI) of 1.720–4.653, while there was no statistically significant difference between quitters and non-smokers ($p=0.150$), (HR, 1.162; 95% CI, 0.946–1.382) and persistent smokers and quitters ($p=0.420$), (HR, 1.121; 95% CI, 0.913–1.342). Figure 2 illustrates the annual recurrence rate for all groups. The recurrence rates for quitters and persistent smokers were close to each other in the first 3 years (51% vs. 50% in the second year, respectively). However, in the fourth and fifth years, the decline in recurrence rate was more pronounced for quitters than persistent smokers (26% vs 40%, respectively, in the fifth year). Non-smokers had the lowest recurrence rates in the study period, which were 40% and 22% in the second and fifth years, respectively, in comparison.

Table I. Pathologic characteristics of the primary tumor in all patients initially enrolled in the study in relation to smoking status at the time of diagnosis.

n=200	**Non-smokers (n=34)**	**Smokers at diagnosis* (n=166)**	**P value**
Stage			
Ta	29	141	0.958
T1	5	25	
Grade			
Low	26	126	0.994
High	8	40	
Number of tumors			
Single	25	41	<0.001
Multiple	9	125	
Size of tumor			
≤3 cm	15	87	0.378
>3 cm	19	79	

*All patients in both the persistent smoker and quitter groups.

Table II. The clinical and pathological characteristics and the number of recurrences for patients who completed the 5-year surveillance cystoscopy protocol.

n=191	Non-smoker (n=33)	Persistent smokers (n=87)	Quitters (n=71)	Overall
Gender				
Male	28 (85%)	83 (95%)	55 (77%)	166 (87%)
Female	5 (15%)	4 (5%)	16 (23%)	25 (13%)
Age (years)	62 (34–76)	59 (38–74)	63 (43–71)	61 (34–76)
Primary tumor				
Stage				
Ta	28 (85%)	76 (87%)	64 (90%)	168 (88%)
T1	5 (15%)	11 (13%)	7 (10%)	23 (12%)
Grade				
Low	26 (79%)	68 (78%)	57 (80%)	151 (79%)
High	7 (21%)	19 (22%)	14 (20%)	40 (21%)
Number of tumors				
Single	25 (76%)	21 (24%)	19 (27%)	59 (31%)
Multiple	8 (34%)	66 (76%)	52 (73%)	132 (69%)
Size of tumor				
≤3 cm	15 (45%)	47 (54%)	38 (54%)	100 (52%)
>3 cm	18 (55%)	40 (46%)	33 (46%)	91 (48%)
Number of recurrences				
1	6 (35%)	9 (17%)	8 (22%)	23 (25%)
2	4 (24%)	10 (19%)	10 (27%)	24 (25%)
≥3	7 (41%)	34 (64%)	19 (51%)	60 (50%)

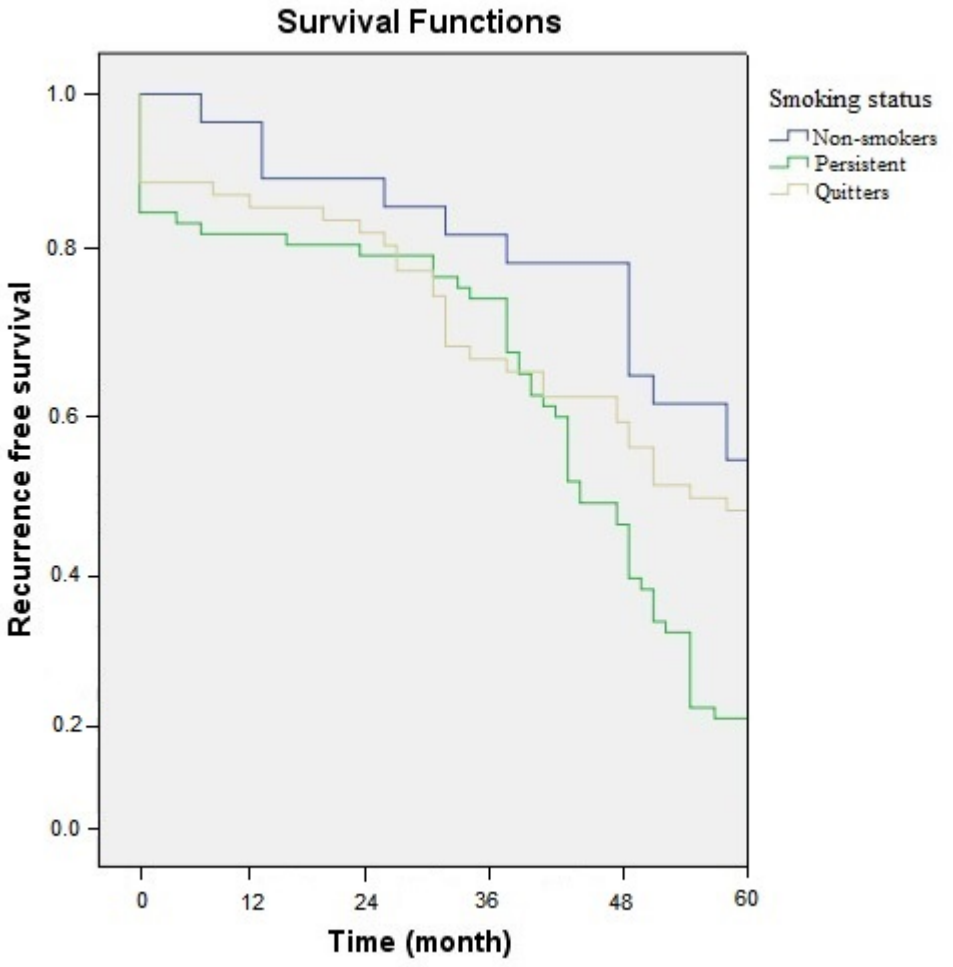
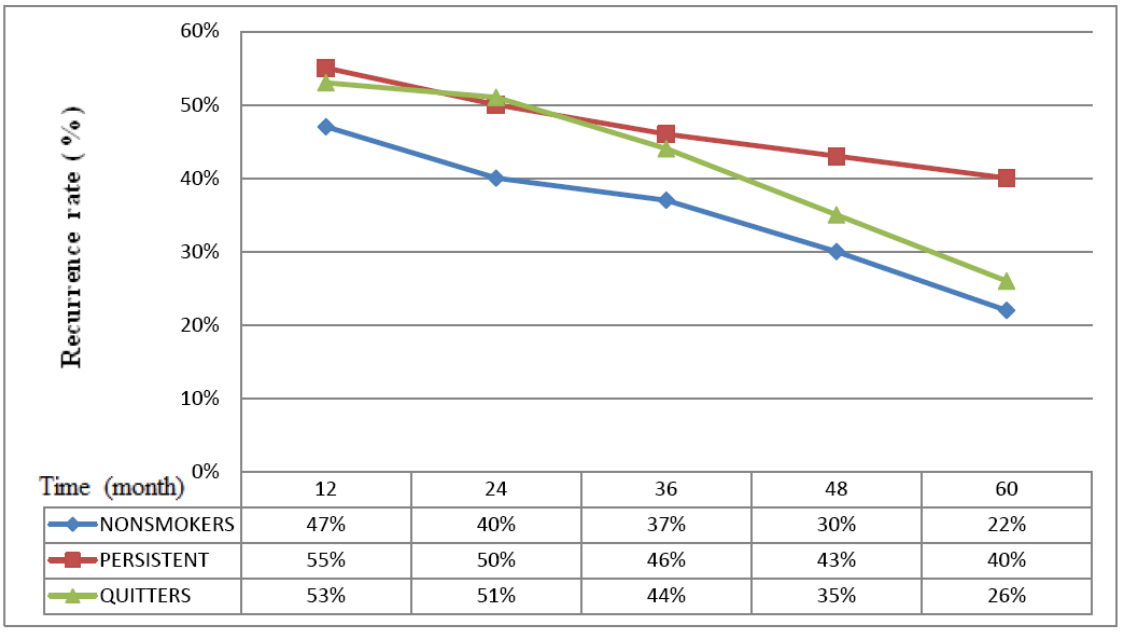


Figure 1. Kaplan–Meier cumulative recurrence-free survival analysis. Sixty percent of persistent smokers and quitters achieved three-year recurrence-free survival. However, only 20% of persistent smokers achieved 5-year recurrence-free survival compared to around 50% of quitters, who remained recurrence free for the whole 5-year study period.



Time (month)	12	24	36	48	60
NONSMOKERS	47%	40%	37%	30%	22%
PERSISTENT	55%	50%	46%	43%	40%
QUITTERS	53%	51%	44%	35%	26%

Figure 2. Annual recurrence rates. The beneficial effects of smoking cessation appear after 36 months.

DISCUSSION

We showed that smoking is associated with tumor multicentricity rather than grade, stage, or size. In comparison, Barbosa et al. reported that there was only a weak association between smoking intensity and increased risk of these characteristics in a previous cohort involving 323 patients with BC [23].

We also showed that non-smokers had the lowest recurrence rates when compared to both quitters and persistent smokers. A similar finding was reported in a meta-analysis done by van Osch et al. [18]. The meta-analysis included 11 studies and showed a slightly increased risk of recurrence among persistent smokers compared to nonsmokers (HR, 1.27; 95% CI, 1.09–1.46). The risk for former smokers relative to those who never smoked was, however, relatively weak (HR, 1.13; 95% CI, 1.00–1.25). A larger meta-analysis of 15 studies of 10,192 patients with SBC reported an increased risk of recurrence in both persistent (summary relative risk estimate [SSRE], 1.23; 95% CI, 1.05–1.45) and former smokers (SSRE, 1.22; 95% CI, 1.09–1.37) compared to non- smokers [15].

Smoking cessation seems to improve recurrence-free survival. Two previous studies concluded that quitting smoking at the time of diagnosis appears to be an effective step in preventing the recurrence of the disease [24,25]. Fleshner et al. examined the effect of quitting smoking on the short-term recurrence of SBC, reporting a slight reduction in the risk of recurrence [26]. Chen et al. found that persistent smokers had a 2.2-fold increase in the risk of disease recurrence compared with patients who quit smoking at the time of diagnosis [27]. The 3-year recurrence-free rate for non-smokers, quitters, and persistent smokers was 57%, 62%, and 45%, respectively. In our study, however, quitting smoking had no effect on early recurrence of the tumor (i.e., in the first 3 years), which can explain why there was no statistically significant improvement in the cumulative 5-year recurrence-free survival in quitters versus persistent smokers. In comparison, we found a progressive improvement in the recurrence rate and the recurrence-free survival later in the fourth and fifth years of the study. Similarly, other studies have reported that only long-term smoking cessation is associated with reduced recurrence compared to persistent smoking [16,28,29].

In light of the relatively long latency period between smoking exposure and the development of BC [5], it is understandable that the impact of changing smoking habits after diagnosis on the probability of tumor recurrence will need years to be appreciated. Moreover, epidemiological studies suggest that short-term smoking cessation before diagnosis does not immediately reduce the risk of BC occurrence [30], further indicating that a longer period than few years is needed before the effect of smoking cessation on recurrence becomes obvious. In addition, it is well established that a first recurrence is in most cases due to incomplete resection and/or tumor cell re-implantation, whereas new independent tumor formation in new locations has a more important role in late recurrences [31]. Finally, the theory of "field change" proposes that premalignant cell transformation has already occurred at the time of diagnosis at different sites across the bladder urothelium, justifying why smoking cessation will not have a large early impact on disease recurrence [32].

Although not included in the scope of our study, other studies have quantitatively investigated the effect of smoking on the recurrence of SBC. In a retrospective international cohort study of 2,043 patients with SBC, Rink et al. reported a significantly reduced risk of recurrence among light (≤19 cigarettes per day) short-term smokers compared to long-term heavy smokers. The authors also found that patients who stopped smoking more than 10 years prior to the diagnosis had a reduced risk of recurrence [28]. In addition, based on the alterations observed at the molecular level involving COX-2 and BAX regulations related to the degree of smoking, Mitra et al. concluded that both the quantity and duration of cigarette smoking were associated with a worse outcome of BC [33].

As the relationship between smoking and the course of the disease is well documented, SBC recurrence is now accepted as a preventable condition [34,35]. However, Nieder et al. found that only 36% of patients with urothelial cancer identified smoking as a risk factor of their disease [36], compared to lung cancer patients, of whom 97.4% could recognize smoking as an important factor [37].

In addition to the increased risk of SBC recurrence, persistent smoking might lead to the development of a second smoking-related cancer in patients who had previous urinary bladder cancer (HR=3.67) [38]. Unfortunately, while other researchers have reported that almost half of the patients who were current smokers at the time of diagnosis of BC were able to quit smoking permanently [39], only 45% of current smokers at diagnosis stopped smoking in our study, while around 14% returned back to smoking briefly after they had initially stopped.

The important question is the following: are urologists doing enough regarding the counseling of patients about the above mentioned risks of persistent smoking?

We found that only 32% of the patients in our study reported that their urologist tried to persuade them about smoking cessation during late follow-up visits. Likewise, Guzzo et al. reported that only 10.4% of the respondents in their study population were offered specific cessation aids by their urologist [35]. On the contrary, several studies reported that patients diagnosed with BC were more likely to quit smoking if they received adequate counseling [39,40].

Considering the results of our study and similar evidence from other studies indicating the beneficial effect of smoking cessation on the outcomes of SBC, in addition to the negative effects of smoking-related diseases on the overall survival of BC patients [41], it is obvious that smoking cessation should be encouraged for every patient with SBC at the time of diagnosis and that patients should be counseled regarding the delayed benefits of recurrent rate reduction.

Limitations of the study

Our study has some limitations. Firstly, the smoking status and the type of counseling patients received from the urologist were derived subjectively from the patients. Secondly, the study did not differentiate smokers based on quantitative measures. The possible need for follow-up times of longer than 5 years to better assess the effect of smoking cessation is another limitation.

REFERENCES

1. **Siegel RL, Miller KD, Jemal A.** Cancer statistics, 2019. CA: Cancer J Clin 2019;69(1):7–34.
2. **Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F.** Bladder cancer incidence and mortality: a global overview and recent trends. Eur Urol 2017;71:96–108.
3. **Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A.** Global cancer statistics, 2012. CA: Cancer J Clin 2015;65:87–108.
4. **Kirkali Z, Chan T, Manoharan M, Algaba F, Busch C, Cheng L, *et al*.** Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology 2005;66(6, Supplement 1):4–34.
5. **Bryan RT, Zeegers MP, van Roekel EH, Bird D, Grant MR, Dunn JA, *et al*.** A comparison of patient and tumour characteristics in two UK bladder cancer cohorts separated by 20 years. BJU Int 2013;112:169–75.
6. **Palou J, Sylvester RJ, Faba OR, Parada R, Pena JA, Algaba F, *et al*.** Female gender and carcinoma in situ in the prostatic urethra are prognostic factors for recurrence, progression, and disease-specific mortality in T1G3 bladder cancer patients treated with bacillus Calmette-Guerin. Eur Urol 2012;62(1):118–25.
7. **Yan Y, Andriole GL, Humphrey PA, Kibel AS.** Patterns of multiple recurrences of superficial (Ta/T1) transitional cell carcinoma of bladder and effects of clinicopathologic and biochemical factors. Cancer 2002;95:1239–46.
8. **Roychowdhury DF, Hayden A, Liepa AM.** Health-related quality-of-life parameters as independent prognostic factors in advanced or metastatic bladder cancer. J Clin Oncol 2003;21:673–8.
9. **Svatek RS, Hollenbeck BK, Holmںng S, Lee R, Kim SP, Stenzl A, *et al*.** The economics of bladder cancer: costs and considerations of caring for this disease. Eur Urol 2014;66:253–62.
10. **Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, *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(3):466–77.
11. **Jiang X, Castelao JE, Yuan JM, Stern MC, Conti DV, Cortessis VK, *et al*.** Cigarette smoking and subtypes of bladder cancer. Int J Cancer 2012;130:896–901.
12. **Garcia-Closas M, Rothman N, Figueroa JD, Prokunina-Olsson L, Han SS, Baris D, *et al*.** Common genetic polymorphisms modify the effect of smoking on absolute risk of bladder cancer. Cancer Res 2013;73:2211–20.
13. **Ghadimi T, Gheitasi B, Nili S, Karimi M, Ghaderi E.** Occupation, smoking, opium, and bladder cancer: a case-control study. South Asian J Cancer 2015;4:111–4.
14. **Masaoka H, Matsuo K, Ito H, Wakai K, Nagata C, Nakayama T, *et al*.** Research group for the development and evaluation of cancer prevention strategies in Japan. Cigarette smoking and bladder cancer risk: an evaluation based on a systematic review of epidemiologic evidence in the Japanese population. Jpn J Clin Oncol 2016;46:273–83.

15. **Hou L, Hong X, Dai M, Chen P, Zhao H, Wei Q, *et al*.** Association of smoking status with prognosis in bladder cancer: a meta-analysis. Oncotarget 2017;8(1):1278–89.
16. **Li HM, Azhati B, Rexiati M, Wang WG, Li XD, Liu Q, *et al*.** Impact of smoking status and cumulative smoking exposure on tumor recurrence of non-muscle-invasive bladder cancer. Int Urol Nephrol 2017;49(1):69–76.
17. **Wilcox AN, Silverman DT, Friesen MC, Locke SJ, Russ DE, Hyun N, *et al*.** Smoking status, usual adult occupation, and risk of recurrent urothelial bladder carcinoma: data from The Cancer Genome Atlas (TCGA) Project. Cancer Causes Control 2016 27:1429–35.
18. **van Osch FHM, Jochems SHJ, van Schooten FJ, Bryan RT, Zeegers MP.** Significant role of lifetime cigarette smoking in worsening bladder cancer and upper tract urothelial carcinoma prognosis: a meta-analysis. J Urol 2016;195:872–9.
19. **Gritz ER, Dresler C, Sarna L.** Smoking, the missing drug interaction in clinical trials: ignoring the obvious. Cancer Epidemiol Biomark Prev 2005;14:2287–93.
20. **Crivelli JJ, Xylinas E, Kluth LA, Rieken M, Rink M, Shariat SF** (2014) Effect of smoking on outcomes of urothelial carcinoma: a systematic review of the literature. Eur Urol 65:742–754.
21. **Konety BR, Joyce GF, Wise M.** Bladder and upper tract urothelial cancer. J Urol 2007;177:1636–45.
22. **Eble JN, Sauter G, Epstein JI, Sesterhenn IA.** World Health Organization classification of tumours. Pathology and genetics of tumours of the urinary system and male genital organs. Lyon, France: IARC Press; 2004.
23. **Barbosa ALA, Vermeulen SHHM, Aben KK, Grotenhuis AJ, Vrieling A, Kiemeney LA.** Smoking intensity and bladder cancer aggressiveness at diagnosis. PLOS ONE 2018;13:e0194039.
24. **Simonis K, Shariat SF, Rink M.** Urothelial Cancer Working Group of the Young Academic Urologists (YAU) Working Party of the European Association of Urology (EAU). Smoking and smoking cessation effects on oncological outcomes in nonmuscle invasive bladder cancer. Curr Opin Urol 2014;24:492–9.
25. **Ogihara K, Kikuchi E, Yuge K, Ito Y, Tanaka N, Matsumoto 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.
26. **Fleshner N, Garland J, Moadel A, Herr H, Ostroff J, Trambert R, *et al*.** Influence of smoking status on the disease-related outcomes of patients with tobacco-associated superficial transitional cell carcinoma of the bladder. Cancer 1998;86:2337–45.
27. **Chen CH, Shun CT, Huang KH, Huang CY, Tsai YC, Yu HJ, *et al*.** Stopping smoking might reduce tumour recurrence in nonmuscle-invasive bladder cancer. BJU Int 2007;100:281–6.
28. **Rink M, Furberg H, Zabor EC, Xylinas E, Babjuk M, Pycha A, *et al*.** Impact of smoking and smoking cessation on oncologic outcomes in primary non-muscleinvasive bladder cancer. Eur Urol 2013;63(4):724–32.
29. **Rink M, Xylinas E, Babjuk M, Hansen J, Pycha A, Comploj E, *et al*.** Impact of smoking on outcomes of patients with a history of recurrent nonmuscle invasive bladder cancer. J Urol 2012;188(6):2120–7.
30. **van Osch FH, Jochems SH, van Schooten F-J, Bryan RT, Zeegers MP.** Quantified relations between exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies. Int J Epidemiol 2016;45:857–70.
31. **Bryan RT, Collins SI, Daykin MC, Zeegers MP, Cheng K, Wallace DMA, *et al*.** Mechanisms of recurrence of Ta/T1 bladder cancer. Ann R Coll Surg Engl 2010;92:519–24.
32. **Braakhuis BJM, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH.** A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res 2003;63:1727–30.

33. **Mitra AP, Castelao JE, Hawes D, Tsao-Wei DD, Jiang X, Shi SR, *et al*.** Combination of molecular alterations and smoking intensity predicts bladder cancer outcome: a report from the Los Angeles Cancer Surveillance Program. Cancer 2013;119:756–65.
34. **Figueroa JD, Han SS, Garcia-Closas M, Baris D, Jacobs EJ, Kogevinas M, *et al*.** Genome-wide interaction study of smoking and bladder cancer risk. Carcinogenesis 2014;35:1737–44.
35. **Guzzo TJ, Hockenberry MS, Mucksavage P, Bivalacqua TJ, Schoenberg MP.** Smoking knowledge assessment and cessation trends in patients with bladder cancer presenting to a tertiary referral center. Urology 2012;79:166–71.
36. **Nieder AM, John S, Messina CR, Granek IA, Adler HL.** Are patients aware of the association between smoking and bladder cancer? J Urol 2006;176(6 Pt 1):2405–8.
37. **Johnson B, Abouassaly R, Ghiculete D, Stewart RJ.** Evaluating the effectiveness of a smoking warning label on raising patient awareness of smoking and bladder cancer. J Urol 2013;190:475–9.
38. **Shiels MS, Gibson T, Sampson J, Albanes D, Andreotti G, Beane Freeman L, *et al*.** Cigarette smoking prior to first cancer and risk of second smoking-associated cancers among survivors of bladder, kidney, head and neck, and stage I lung cancers. J Clin Oncol 2014;32:3989–95.
39. **Bassett JC, Gore JL, Chi AC, Kwan L, McCarthy W, Chamie K, *et al*.** Impact of a bladder cancer diagnosis on smoking behavior. J Clin Oncol 2012;30:1871–8.
40. **Ostroff J, Garland J, Moadel A, Fleshner N, Hay J, Cramer L, *et al*.** Cigarette smoking patterns in patients after treatment of bladder cancer. J Cancer Educ 2002;15:86–90.
41. **Piccirillo JF, Tierney RM, Costas I, Grove L, Edward L, Spitznagel J, French AR, *et al*.** Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA 2004;291:2441.