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Review Article

Impact of Smoking on Prognosis and Survival of Patients with Bladder Cancer

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Abstract

Cigarette smoking is the established risk factor for the development of urothelial carcinoma of bladder (UCB). However, the impact of smoking on the outcomes of urothelial carcinoma patients remains poorly investigated. Current evidence proves that cigarette smoking increases the risk of disease recurrence and potentially disease progression in patients with urothelial carcinoma of bladder. Current and heavy long-term smokers seem to be at the greatest risk. The majority of retrospective studies found an association between smoking status as well as cumulative exposure and disease recurrence in patients treated with TURB. The evidence for association with disease progression was less abundant. There are insufficient data investigating the impact on cancer-specific and overall survival in patients with bladder cancer. The impact of smoking with outcomes of T1 UCB or high risk disease, patients receiving intravesical therapies is limited because of a lack of data and controversial findings. Long-term smoking cessation seems to mitigate the detrimental effects of smoking in non-muscle-invasive and muscle-invasive bladder cancer.

Keywords: Bladder cancer; Smoking; Smoking cessation; Prognosis recurrence; Progression; Survival; Urothelial carcinoma

1. Introduction

Bladder carcinoma is the sixth most common cancer in both sexes with an estimated 72,570 new cases and 15210 deaths in 2013 in the USA [1]. Tobacco smoking is the most important risk factor for bladder cancer. The risk of

bladder cancer is directly related to the intensity and duration of smoking, while quitting smoking reduces the risk of bladder cancer. At diagnosis, approximately 75% of patients presented with non-muscle invasive bladder cancer (NMIBC) and were treated with transurethral resection of bladder tumor (TURBt) followed by intravesical therapy [2]. In contrast, most patients with muscle-invasive (T2-4,n-) bladder cancer were treated with radical cystectomy. However, NMIBC is the single most expensive cancer per patients due to its high recurrence rate in patients [3].

Today, there is convincing evidence that cigarette smoking is an established risk factor for bladder cancer [4]. Cigarette smoking compromise half of the bladder cancer and considerably increases the risk of urothelial carcinoma of bladder incidence by smoking pattern four to six-fold [5].The risk of bladder cancer development is inversely proportional with the age at first exposure and cessation of cigarette smoking[5]. According to the recent patterns, about 50% of young men and 10% of young women are smokers and only comparatively few of them quit again [6]. Although there is close link between cigarette smoking and the development of bladder cancer, the affect of smoking on the course of disease and its outcomes has no firm conclusion drawn yet. We learn that other malignancies, such as lungs or oropharyngeal cancer, when continuing smoking after diagnosis negatively affects oncological outcomes [7]. In addition, smoking cessation obviously decreases the risk of UCB development; thus it is an important role in attempt of smoking cessation in reducing the burden of the disease [8]. However, smoking cessation and time of smoking cessation beneficially influence oncological outcomes in bladder carcinoma remains unclear. The involvement of smoking in the role of UCB prognosis could have a significant impact on the clinical management of the patients. In this review article, we illustrate and summarize the most current evidence regarding the effects of smoking and smoking cessation on oncological outcomes of patients with bladder carcinoma.

2. Source of Evidence

We search a literature from PubMed/Medline to identify original articles, review articles, and editorials regarding smoking and smoking cessation in bladder cancer. MeSH-terms included in this article are urothelial carcinoma, bladder carcinoma, smoking, smoking cessation, recurrence, progression, survival, outcome, and prognosis. This review article had no time limits, but focused on the most significant findings from the past few years.

3. Tobacco Smoke Involved in Bladder Carcinoma

A class of aromatic amines, 4-aminobiphenyl (ABP) has important role in the mechanism of bladder carcinogenesis. A genotoxic mode of action of 4-ABP that involves the induction of DNA adducts and mutation [9]. 4-ABP requires metabolic activation to exert its genotoxic effects. The biotransformation of 4-ABP consists of N-oxidation catalyzed primarily by the cytochrome P-450 1A2. The resulting hydroxyarylamine may undergo detoxification through N-acetylation or conjugation with acetate, sulfate, or glucoronate [10-12]. The acetate and sulfate O-conjugate can interact with DNA or proteins, whereas the glucuronate O-conjugate circulate in the body and reach to the urinary tract, where it undergoes hydrolysis at the acidic pH of urine [11, 12]. The resultant electrophilic nitrenium cation can bind directly the DNA of uroepithelial cells and form covalent adducts, mainly at the C8 position of guanine, N-(deoxyguanosine-8-yl)-4-ABP (known as 4-ABP-DNA adduct). It is known that persistent 4-

ABP-DNA adducts and similar adducts from the family of aromatic amines that involved in the genesis of bladder cancer [9].

4. Impact of Smoking on Outcomes

The impact of smoking on the prognosis in patients with UCB became a topic of interest over the past few years. To summarize the available evidence, we selected 16 studies that met the inclusion criteria for this review article. The association of smoking with disease recurrence, disease progression and cancer-specific mortality, the three most important disease outcomes in bladder cancer is summarized in Table 1 [13-28]. Though there are minor variations in disease outcome definitions among studies, the definitions were sufficiently similar to allow for evidence synthesis. For the patients with UCB treated with TURBt, disease recurrence was defined as a relapse in the bladder but disease progression was defined as a muscle-invasive recurrence in the bladder cancer.

Here, we selected 16 studies that evaluate the impact of smoking on outcomes of patients treated with TURB for UCB (n=5739) [13-28]. Study characteristics, patient characteristics and outcomes are presented in Table 1. Among the 16 studies, there was marked variation in patient age, pathologic characteristics (ie,stage and grade), and follow-up time. There is also variation in the use of intravesical therapy. The association of smoking with an outcome following categories of smoking status was reported: nonsmokers or never smokers (a negligible number of lifetime cigarette smoked), smokers (a non-negligible number of lifetime cigarettes smoked), former smokers (stopped smoking prior to diagnosis), and current smokers (smoked at the time of diagnosis). Similarly, there is quitter category, former smokers who quitted smoking >1 yr prior to diagnosis, and quitters who stopped smoking between 1 yr before and 3 months after diagnosis.

The exact estimation of smoking exposure with disease outcome is difficult to understand, as there is no consistent way of reporting this variable in the article. In general, the smoking exposure categorizations depends on smoking quantity (cigarettes or packs smoked per day), smoking duration (years of smoking), and cumulative smoking exposure accounting for both quantity and duration[8]. Cumulative smoking exposure was reported as pack-years (means average number of packs smoked per day multiplied by the number of years of smoking). The influence of cumulative smoking exposure on disease recurrence was only evaluated in four studies [15, 16, 21, 22]. In addition, a high cumulative exposure results in disease recurrence The low prevalence of disease progression in NMIBC results in low number of events, thus, limitation in explanation for a lack of significance in some studies. In most studies there was mixed patients with recurrent NMIBC. Rink et al. [15] investigated the impact of smoking with history of recurrent NMIBC. They found no difference in the risk of disease recurrence and progression among current, former, and never smokers.

The risk of disease progression was increased on the outcomes of high-grade T1 urothelial carcinoma of bladder. There are two selected studies [14, 20] investigating the patients (n=361) treated with TURB with or without adjuvant therapy. The effect of smoking status on the risk of disease progression was not statistically significant in

both studies. So, these studies neither work for controlling the smoking exposure nor examine any other end point such as disease recurrence, cancer-specific mortality, or overall mortality. There was no statistically significant association of smoking status with cancer-specific mortality or overall mortality with bladder cancer. In contrast, an increasing smoking exposure was inversly associated with reduced overall survival [16].

5. Impact of Smoking on the Effectiveness of Intravesical Therapy

Adjuvant intravesical chemotherapy or immunotherapy is indicated for patients with intermediate risk and high risk bladder cancer [2]. In general, intravesical Bacillus Calmette-Guerin (BCG) therapy is the most effective adjuvant treatment in UCB that reducing the risk of both disease recurrence and prognosis, respectively [2, 29]. BCG instillations in bladder induce secretion of cytokines and chemokines, and presentation of BCG and/or cancer cell antigens to cells of the immune system, and immune system cells that play important role in BCG therapy include CD4(+) and CD8(+) lymphocyte, natural killer cells, granulocytes, macrophages, and dendritic cells. Bladder cancer cells are killed through direct cytotoxicity by secretion of soluble factor such as TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) and to some extent, by the direct action of BCG [30]. The results are summarized in Table 1. There was mixed evidence for an effect of smoking on the response to intravesical therapy. Some studies found that smokers who treated with BCG were at increased risk compared with nonsmokers treated with BCG for disease recurrence[15, 22, 23, 25, 31]. Similarly, current smokers seemed to be at greatest risk for failure of immunotherapy compared with never smokers. There was no difference between former smokers and nonsmokers smokers in two studies [16, 31]. Here, Sfakianos et al. [19] found there is no association of smoking status with disease recurrence, disease progression, cancer specific mortality, or any-cause mortality in a cohort of patients received BCG therapy. Similarly, Ajili et al. [24] also detected there is no association of smoking status with disease recurrence. But, Gee et al. [18] reported that the risk of disease recurrence was significantly lower in current smokers compared with former smokers (HR: 0.27, p=0.03]. Here, Gangawar et al. [25] reported that smokers were more likely to experience disease recurrence compared to never smokers (HR: 2.84, p=0.005; however, no association was detected for disease progression. Generally, most studies did not analyse the end points of disease progression, cancer specific mortality, or overall mortality, mainly due to small sample sizes which resulting in low number of events. In those studies, there was no association found while investigating the effects of smoking on disease progression. Rink et al. [15] also did not find any association on disease progression.

The effect of smoking on patients treated with intravesical chemotherapy was analyzed by the two studies are as follows. Lammers et al. [22] reported that nonsmokers treated with adjuvant intravesical epirubicin chemotherapy had better recurrence-free survival compared with smokers (HR:1.47, p=0.048). Whereas, Serreta et al. [23] reported that smokers had an increased risk of disease recurrence compared with nonsmokers (HR: 1.60, p=0.04).

								Outcome			
	Study and patient characteristics							Disease Recurrence		Disease Progression	
Study	Duration	Sample size	Median age	Pathologic stage %	Pathologic grade%	Median follow-up	Intravesical therapy %	Smoking status	Smoking exposure	Smoking status	Smoking exposure
Allard et al. [17]	1990-1992	368	65.1	Ta ,78.8 T1,21.2	G1, 34.2 G2, 53.8 G3, 12.0	23.7	BCG, 17.4; Chemo, 2.2	HR:1.28 HR:1.45	-	-	-
Fleshner et al. [13]	1985-1995	286	61.2	Ta, 52.4 Tis,16.8 T1, 30.8	G1, 33.6 G2, 31.1 G3, 35.3	57.3	BCG, 22.7; Chemo, NR	HR:0.99 P=0.89[2] HR:1.40 P=0.03[3]	-	-	-
Cheng et al. [14]	1987-1992	83	72	T1,1oo	LG, 72.5 HG,27.5	64.8	BCG, 13.3; Chemo, 19.3	-	-	P=0.22[1]	-
Gee et al. [18]	1991-2003	43	67	NR	NR	NR	BCG, 100; Chemo, NR	HR:3.20 P=0.05[11] HR:0.27 P=0.03[3]	-	-	-
Gangawar et al. [25]	2006-2008	135	57.1	NR	G1, 50.4 G2/G3, 49.6	14	BCG, 54.8; Chemo, 0.0	HR:1.86 P=0.02[11]	-	HR:1.96 P=0.39[11]	-
Lammers et al. [22]	1998-2004	718	66.5	Ta, 78.7 T1, 21.3	G1, 42.1 G2, 47.0 G3, 10.9	30	BCG, NR Chemo, 100	HR:1.47 P=0.048[11]	P=0.30[12] P=0.25[13] P=0.06[14]	-	-

Sfakianos et al. [19]	1994-2008	623	76	Ta, 35.2 Tis,30.3 T1, 34.5	LG, 9.6 HG, 90.4	80.9	-	HR:1.05 P=0.68[11] HR:1.05 P=0.65[15] HR:1.04 P=0.81[10]	-	HR:1.02 P=0.93[11] HR:1.00 P=0.99[15] HR:1.16 P=0.61[10]	-
Ajali et al. [24]	2000-2007	112	63.9	Ta, 60.7 T1, 39.3	G1, 39.3 G2, 43.8 G3, 17.0	NR	BCG, 100; Chemo, NR	HR:0.49 P=0.05	-	-	-
Segal et al. [20]	1995-2005	278	72.8	T1,100	HG, 100	36	BCG, 35.6; Chemo, NR	-	-	HR:1.15 P=0.51[11]	-
Rink [15]	1987-2007	390	67	Ta, 67.9 Tis, 1.5 T1, 30.5	G1, 36.9 G2, 28.7 G3, 34.4	66	BCG, 15.4; Chemo, 3.3	P=0.5[15] P=0.4[10] P=0.7[3]	P=0.02[16] P<0.001[17] HR:2.08 P=0.006[18] HR:4.31 P<0.001[19]	P=0.7[15] P=0.2[10] P=0.2[3]	P<0.001[16] P<0.001[17] P=0.003[20]
Chen CH [21]	1997-2005	265	67	Ta, 62.4 T1, 37.6	LG, 72.5 HG, 27.5	38	BCG, 18.9; Chemo, 57.7	HR:2.2 P=0.03[4] HR:1.4 P=0.35[5] HR:2.2 P=0.01[6]	HR:1.01 P=0.98[7] HR:1.5 P=0.27[8] HR:2.1 P=0.02[9]	P=0.43[3] P=0.29[10] P=0.02[6]	-
Serretta [23]	2002-2003	395	68	Ta, 36.5 T1, 63.5	G1, 35.9 G2, 64.1	48	BCG, NR Chemo, 100	HR:1.6 P=0.04[11]	-	-	-
Rink [16]	1987-2007	2043	67	Ta, 61.0 T1, 39.0	G1, 23.6 G2, 33.8 G3, 42.6	49	BCG, 16.1; Chemo, 3.8	HR:1.12[15] HR:1.22[10]	HR:0.43[21] HR:0.91[22] HR:0.35[23]	HR:1.29[15] HR:2.09[10]	HR:0.12[21] HR:0.43[22] HR:0.05[23]

Grotenhuis et al. [27]	1995-2012	963	64	Ta, 70.0; Tis, 3.8 T1, 26.2	LG, 61.8; HG, 38.2	44	BCG, 22.0; Chemo, 33.0	HR=1.06 P=0.68 P=0.47	P=0.62 P=0.61	HR=1.85 P=0.25 P=0.54	P=0.95 P=0.15
Kashif khan et al. [26]	2008-2012	64	59.9	NR	NR	28.4	BCG, 100; Chemo, NR	NS	-	OR=4.02 P=0.04	-
Wyszynski et al. [28]	1994-2001	726	NR	Ta\T1, 93.7; Tis, 6.3	LG, 73.1; HG, 25.9	67.2	BCG, NR Chemo, NR	HR=1.61 P=0.003 HR=1.51 P=0.02	-	-	-

G1= grade1; G2= grade2; G3= grade3; BCG= bacillus calmette-Guerin; NR= not reported; LG= low grade; HG= high grade; HR=hazard ratio; Arabic numerals denote the followings: 1, current smokers compared with former smokers compared with never smokers; 2, quitters compared with former smokers; 3,current smokers compared with former smokers; 4, never smokers compared with quitters; 5, former smokers compared with quitters; 6, current smokers compared with quitters; 7, 20-39 compared with 1-19 pack-years; 8, 40-59 compared with 1-19 pack-years; 9, 60 or more compared with 1-19 pack-years; 10, current smokers compared with never smokers; 11, smokers compared with nonsmokers; 12, number of cigarette par day; 13, number of years of smoking; 14, number of pack-years; 15, former smokers compared with never smokers; 16, 20 or more compared with less than 20 cigarettes/day; 17, 20 or more compared with less than 20 years of smoking; 18, moderate smokers compared with light short-term smokers; 19, heavy long-term smokers compared with light short-term smokers; 20, heavy long-term smokers compared with moderate smokers compared with light short-term smokers; 21, heavy short-term smokers compared with heavy long-term smokers; 22, light long-term smokers compared with heavy long-term smokers; 23, light short-term smokers compared with heavy long-term smokers.

Table 1: Studies evaluating association of smoking and outcomes of patients with urothelial carcinoma of the bladder treated with transurethral resection of the bladder.

6. Gender-Specific Effect of Smoking

We identified three studies of gender-specific differential effects of smoking in patients with UCB treated with TURBt (n=2134). In the cohort of 286 patients Fleshner et al. [13] determined that men with continued smoking were associated with diminished time to recurrence (HR: 1.40; 95% confidence interval, 1.03-1.91) and with diminished survival free of adverse events (p=0.14). In contrast, a cohort of 1549 ever smoking patients with NMIBC, Rink et al. [15] found that both sexes had similar risks of disease recurrence and disease progression but women smokers were less likely to experience any-cause mortality compared with their male counterparts (HR: 0.65; p=0.004). Finally, in a cohort of 299 ever smokers with recurrent urothelial NMIBC treated with TURBt with or without intravesical therapy, Rink et al[16]reported that women smokers did not have an altered risk of disease recurrence comparison with men, but they did have an increased risk of disease progression (HR: 1.95; p=0.03). Clearly, these finding suggest that there is no clear evidence that effects of smoking on patient outcomes after TUTBt are more prone in one sex compared with the other.

7. Impact on Smoking Cessation

Smoking cessation seems to mitigate the detrimental effects on outcome of both disease recurrence and disease progression in patients with bladder cancer. Fleshner et al. [13] reported that there was no any difference in disease recurrence when patients who quit smoking between 1 year before and 3 months after diagnosis were compared with patients who quit between 10 years before and 1 year before diagnosis. However, continued smokers recur faster (median time to recurrence is 8.9 months , 13 months and 12 months for continued, quitters and exsmokers, respectively). Sfakianos et al. [19] found no associations of smoking cessation with disease recurrence, disease progression, cancer-specific mortality, or any-cause mortality. Similarly, Lammers et al. [22] also did not find any association with smoking cessation.

On the other hand, Cheng et al. [14] reported that both current and former smokers did not have an increase risk of disease recurrence in relation with patients who quit $\geq$ 1 year before diagnosis, but patients who quit smoking between 1 year before and 3 months after diagnosis had an increased risk (HR:2.2, p=0.01, and HR: 2.2, p=0.03, respectively). In a cohort of 2043 patients with primary NMIBC, Rink et al. [15] determined that patients who quit smoking $\geq$ 10 years prior to diagnosis had a 0.66 times (95%CI, 0.52-0.84) reduced risk of disease recurrence and 0.42 times (95%CI, 0.22-0.83) reduced risk of disease progression. In general, we can say smoking cessation at least 10 years in former smokers was significantly associated with better outcomes (disease recurrence and disease progression) compared with current smokers. Similarly, in a cohort of patients with recurrent NMIBC, Rink et al. [16] found that former smokers, patients who stopped smoking $\geq$ 10 years ago before diagnosis had a decreased risk of disease recurrence (HR: 0.40, p<0.001) than former smokers, who stopped smoking <10 years ago.

In summary, though the finding are contradictory, most of the studies determine that an increased time between smoking cessation and disease diagnosis is related to improved prognosis. Thus, it is possible that quitting smoking at diagnosis also alters the course of disease. Interestingly, the cutoff $\geq$ 10 years prior to diagnosis is associated with

a reduced risk of disease recurrence and disease progression. Therefore, the studies addressing the influence of smoking cessation on outcomes of UCB indicating quitting smoking reduces the risk of disease recurrence, disease progression, or both.

8. Discussion

Bladder cancer is one of the most common cancers worldwide, with the highest incidence due to smoking. There is also growing evidence that smoking not only cause development of bladder cancer but also influences outcomes. Over past few years there is a lots of research groups investigating the course of disease which is associated with smoking over bladder cancer. According to the available evidence regarding the impact of smoking on outcomes of UCB, we found that smoking status and cumulative smoking exposure both influence disease prognosis. There are selected 16 studies evaluated smoking and outcomes of patients with UCB treated with TURBt [13-28]. Most studies found that current smokers those with substantial cumulative exposure had increased risk of disease recurrence [13, 16, 22, 23, 31]. In addition, there was some evidence for an association of smoking with disease progression, although this evidence was not plentiful to support this. There is also lack of conclusive evidence to support the relationship of smoking with cancer-specific mortality or any-cause mortality. Three studies only investigated these end points in patients receiving TURB [18, 19, 22-25, 31].

Due to immune modulative function of tobacco smoke on immune cells, two studies found that smokers who received BCG were at increased risk for disease recurrence [32]. And it is also note that smokers who treated with adjuvant intravesical chemotherapy is also at greatest risk for disease recurrence. The findings regarding the influence of smoking cessation on outcomes of bladder cancer were partly conflicting, but a long-term cessation seems to reduce the harmful effects of smoking [21].The evidence found regarding gender-specific effects of smoking are contradictory. Future intervention is needed to clarify between the genders related to smoking and UCB outcomes. Although no any studies specifically analyzing the sex-specific effects of smoking in bladder cancer, the evidence from different subgroup did not stress an inferior smoking-related outcome of any sex over the other. Most of the studies determined that influence of smoking cessation on outcomes of UCB treated with TURB, quitting smoking reduces the risk of disease recurrence, disease progression, or both. Similarly, in numerous studies it is reported that increased time between smoking cessation and diagnosis was related to improved prognosis. But, point to be noted that quitting at diagnosis also alters the course of the disease. While most studies examine the impact of cigarette smoking, other tobacco products (e.g., cigars, bidis, water pipes, and tobacco chewing) and different forms of tobacco exposure (e.g., second-hand smoking and occupational exposure) are excluded. In addition, it is difficult to compare findings from studies, which is conducted by different group or in different patient populations, because of problem in the correct quantification of tobacco exposure [6]. To calculate cumulative cigarette smoking exposure, the medical profession has approved pack-year (the average number of packs smoked per day multiplied by the number of years of smoking). However, that measure assumes that duration and intensity (pack per day) have equivalent effects. The recent findings on smoking and UC prognosis involve substantial challenged. The evidence which is gained by prospective, randomized controlled studies, but the reported results from the past few years

derived from retrospective studies resulting in limitations. The role for research on smoking is that smoking status and smoking exposure were mostly self-reported and these data were subject to recall bias. Additionally, if current smokers reported themselves as former smokers, the associations of smoking and outcomes would be biased towards the null, especially if such patients could not successfully quit smoking following diagnosis. Biochemical verification of smoking status may be a goal for future investigations. Recently published studies in different cancer entities including muscle invasive bladder cancer found clear dose-response relationships between smoking amount and smoking duration as well as inverse relationships with time since smoking cessation [16].

Several risk factors have been identified and for risk stratification and patient counselling, two established models are frequently used, the risk tables of the European Organization for Research and Treatment of cancer (EORTC) and Club Urologico Espanol de Tratamiento Oncologico (Spanish Urological Oncology Group) (CUETO) [2]. Recently published studies have challenged the accuracy and clinical utility of these models because of insufficient discrimination [33]. In fact, both models do not adjust for the impact of the best established individually modifiable risk factor, which may improve outcome predictions. There are different variety of decision making tools like blood, tissue, and\or urine biomarkers may help in patient selection regarding multimodal therapies and also help in selection of patient of muscle invasive who is at high risk for disease progression and need early radical cystectomy [34]. It was confirmed that smoking information and tissue markers status improve prognostication of UCB outcomes in MIBC patients treated with radical cystectomy, when the combination of markers and smoking features reached the highest level of discrimination [35]. Generally, there are several questions regarding the associations of smoking and oncological outcomes in bladder cancer still remain unanswered. The association between smoking and UCB is not as well-known as that of lung cancer in our patients [36]. For many patients, cancer diagnosis represents a teachable moment and drives them to successfully quit smoking. However, in addition to improve the lifestyle of urologic disease patients and understand the biological mechanisms behind smoking-related disease growths that affects oncological outcomes, cancer diagnosis represents a teachable moment in many patients by successfully quitting smoking. Urological patients are willing to stop smoking by getting some education and taking a help from their physicians [37]. Although, continuing smoking after diagnosis may cause poor outcomes rather than smoking cessation at the time of diagnosis. . The role of all urologists regarding smoking cessation must be top priorities and goal must be to help patients stop smoking as soon as possible. Also, counsel their patients regarding the detrimental effects of smoking and also help them in cessation of smoking attempts.

9. Conclusion

Smoking not only affects the development of urothelial carcinoma but also affect the prognosis and survival of bladder carcinoma. It also strongly suggests that smoking status and cumulative exposure affect disease recurrence, disease progression and survival. Although, studies have demonstrated that long-term smoking cessation improves prognosis, the current evidence lacks prospective evaluation of this relationship. Therefore, urologists must need to counsel their patients regarding the harmful effects of smoking on bladder cancer development and their outcomes

and the beneficial effect of smoking cessation. Further research regarding impact of smoking needs to continue to improve our understanding, as well as the impact of smoking cessation strategies, are needed.

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