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Seminar article

The role of the urologist in smoking cessation: Why is it important?

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Abstract

Introduction: Tobacco use is the most preventable cause of death in the world today. Smoking is a well-known risk factor for various cancers, including urothelial carcinoma, and bladder cancer (BCa) is a leading global cause of cancer mortality in men.

Objective: To review the epidemiology of BCa as a tobacco-related disease, the association between smoking and BCa risk, and the potential smoking cessation interventions that urologists can perform in their medical practice.

Methods: A search of recent literature was conducted using the MEDLINE database and the Internet, as well as resources from well-known health, cancer, and tobacco control organizations.

Results: Smoking is well described as a risk factor of BCa. The risk correlates with the number of cigarettes smoked daily and the duration of smoking. Moreover, smoking worsens BCa treatment outcomes and prognosis. However, smoking cessation substantially prolongs life at every stage, and brief medical interventions can be performed by urologists that can result in the patient ceasing to smoke. Patient education is critical, especially if the patient is unaware that smoking increases the risk of BCa.

Conclusion: Urologists may play an essential role in helping their patients cease smoking, subsequently decreasing the smoking-related risk of BCa. Their cessation efforts should be focused on brief interventions and collaboration with specialized smoking cessation resources.

Keywords: Smoking; Bladder cancer; Smoking cessation; Brief intervention

Introduction

Currently, 1.2 billion people use tobacco worldwide, and this epidemic is increasing in developing countries, particularly among men [1]. The World Health Organization estimates that, during the 20th century, more than 100 million people died of smoking-attributable diseases. If the current patterns and trends of tobacco use continue, the number of smoking-attributable deaths will increase worldwide to more than 8 million per year by 2030 [2].

Estimates also show that smoking is responsible for approximately 30% of all cancer deaths [3]. In 2005, the total number of smoking-attributable cancer mortalities in developed countries was estimated to be more than 700,000 [4]. Although most of these mortalities are attributed to lung cancer (500,000), which is almost exclusively caused by smoking, bladder cancer (BCa) is also well recognized as a smoking-attributable disease [4]. BCa is the most common malignancy of the urinary tract, the seventh most common cancer in men, and the second most common neoplasm of the urogenital tract, occurring slightly less than prostate cancer. The global age-standardized BCa mortality rate is 3 per 100,000 for men and 1 per 100,000 for women [5].

We review the available literature that addresses the association between smoking and BCa, as well as the potential interventions that urologists can perform to encourage smoking cessation. Brief interventions by physicians are thought to be sufficient to increase the patient's awareness of smoking as a risk factor for cancer and decreased health, subsequently motivating the patient to make a serious attempt to cease smoking [6,7]. In a number of countries, both general practitioners and medical specialists, including pulmonologists, cardiologists, and oncologists, have advised their patients to quit smoking, although this practice is not widespread [8].

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Smoking and the risk of BCa

Cigarette smoking has been well documented as a risk factor for BCa, through both clinical and epidemiological studies [3]. The first epidemiological observations regarding the relationship between tobacco smoking and the development of BCa date back to the 1950s [9]. The first monograph from the International Agency for Research on Cancer regarding tobacco smoking as a carcinogenic risk for humans, released in 1986, also reported that cigarette smoking causes BCa [10]. In the next International Agency for Research on Cancer monograph from 2004, cancer experts reported that there was enough scientific evidence to consider cigarette smoking as a causative factor both BCa and ureter cancer [11]. Since then, much epidemiological research has been conducted, which confirms a 2- to 3-fold higher risk of BCa in smokers compared with nonsmokers.

In a recent meta-analysis, which analyzed the results of 21 studies, the magnitude of the risk of lower urinary tract cancer, and specifically BCa, was estimated from 36 partial measurements of risk [12]. The results indicate that the combined risk of these cancers in current smokers was higher (risk ratio [RR] = 2.80, 95% CI: 2.0–3.92) compared with nonsmokers, and the risk was comparable to that reported in cohort and case-control studies. In another pooled analysis study, which included 8,316 cases, the odds ratios (OR) for current smokers compared with nonsmokers were 3.9 (95% CI: 3.5–4.3) for men and 3.6 (95% CI: 3.1–4.1) for women [13]. In another meta-analysis of 43 epidemiological studies (8 cohort and 35 case-control studies), current cigarette smokers had an approximately 3 times higher risk of urinary tract cancer than nonsmokers did [14]. The summary OR adjusted for current cigarette smokers compared with nonsmokers were 3.18 (95% CI: 2.35–4.29) for studies with men, 2.90 (95% CI: 2.01–4.19) for studies with women, and 3.33 (95% CI: 2.63–4.21) for studies with men and women combined. In 2007, the results of a long-term cohort study were published, which assessed the influence of active smoking on subsequent BCa risk [15]. The study subjects included patients from 2 cohorts, recruited in 1963 and 1975. The study results indicated that current smokers had an elevated risk of BCa in both the 1963 cohort (RR = 2.7, 95% CI: 1.6–4.7) and the 1975 cohort (RR = 2.6, 95% CI: 1.7–3.9), after adjusting for age, education, and marital status.

Dose-response effect

Besides smoking status, the frequency and duration of cigarette smoking by patients seem to noticeably increase the risk of BCa. In a recently published study, Brennan et al. [16] reported the results of a combined analysis of 11 case-control studies, measuring the relationship between cigarette smoking and BCa. Information regarding smoking was collected from 2,600 male patients with BCa and 5,524 male controls, and included the patient's duration of smoking habit, number of cigarettes smoked per day, and time from smoking cessation. A dose-response effect was observed between the number of cigarettes smoked per day and the risk of BCa, up to a threshold limit of 15 to 20 cigarettes per day (OR = 54.50, 95% CI: 3.81–5.33), after which no increased risk was observed.

As well, most studies indicate a linear positive association between risk of BCa and increasing duration of smoking [5,11,16], even in patients with a relatively short duration of smoking. The results reported by Brennan et al. [16] found a linear increasing risk of BCa with increasing duration of smoking, ranging from an OR of 1.96 after 20 years of smoking (95% CI: 1.48–2.61) to 5.57 after 60 years (95% CI: 4.18–7.44). In a recent, large, hospital-based case-comparison study, the authors evaluated the association between smoking, clinical characteristics, and diagnosis of BCa [17]. In total, 1,544 adult patients with BCa were recruited from participating hospitals in the West Midlands, England, between 2005 and 2011. After adjusting for age and sex, it was noted that current smokers were on an average 4.0 years younger at diagnosis (95% CI: 25.9–22.0), had larger tumors (mean difference = 0.48 cm, 95% CI: 0.04–0.91), had higher T category (mean difference = 0.25, 95% CI: 0.08–0.41), and had a slightly higher grade (mean difference = 0.15, 95% CI: 0.002–0.30), compared with nonsmokers [17]. Similar results were obtained in a Japanese study, in which current smokers were also found to be diagnosed at an earlier age, have higher T category and grade, and have larger tumor size at diagnosis, compared with those in nonsmokers [18]. Given their results, van Roekel et al. [17] recently suggested that clinicians should be made aware of the possible relationship between smoking and severity of BCa. In addition, they suggest that smoking patients could have a higher risk of more malignant phenotypes of BCa at diagnosis (larger tumors, higher T categories, and higher tumor grades) compared with nonsmokers. These results could indicate that a thorough resection is critical among smokers, even including the detrusor muscle, to determine muscle-invasiveness of the tumor [17].

Cigarette smoking as a risk factor for reduced effect of BCa treatment

Another important effect of cigarette smoking is the effect on BCa treatment, with most studies clearly indicating worse BCa treatment outcomes in smoking patients compared with nonsmokers [19]. In a retrospective cohort study using The Memorial Sloan-Kettering Cancer Center Tumor Registry, Fleshner et al. [20] analyzed cases of non–muscle-invasive BCa (NMIBC) (n = 1,632) between 1985 and 1995. After exclusions, 286 cases of tobacco-related NMIBC were divided into 3 groups, according to tobacco exposure (127 exsmokers, 51 who had recently quit, and

108 current smokers). Exsmokers tended to develop NMIBC at a later age, which suggests that limiting carcinogen exposure, even in late stages, of cancer might retard the progression of preneoplastic epithelium into frank carcinoma. Univariate analysis of smoking suggested no overall difference in recurrence-free survival (RFS, $P = 0.23$), although current smokers tended to have faster recurrence (median time to recurrence = 8.9 mo vs. 13 and 12 mo in those who had recently quit and exsmokers, respectively). Multivariate analyses revealed lower RFS for current smokers compared with those who had recently quit or exsmokers, and that male sex and smoking continuation were associated with diminished time to recurrence (RR = 1.40, 95% CI: 1.03–1.91). However, there was no significant difference observed between the exsmokers and those who had recently quit. In a multivariate assessment of adverse events (mostly defined as progression to muscle-invasive transitional cell carcinoma), a trend was observed where smokers experienced adverse events faster (RR = 1.46; 95% CI: 0.98–2.14; $P = 0.06$) [20]. Lammers et al. conducted a prospective study in patients with NMIBC, undergoing transurethral treatment followed by intravesical chemotherapy, and assessed the role of smoking status on the clinical outcome (RFS). After a mean follow-up of 2.5 years, 284 cases of recurrence were detected (39.6% of patients studied). After univariate and multivariate analyses, RFS (and other well-defined parameters) was much more frequent among nonsmokers (62.3%), compared with exsmokers and current smokers (46.8%) ($P = 0.005$). In this study, number of cigarette pack-years (≥ 35) also significantly influenced RFS ($P = 0.057$). Based on their study results and review of the literature, the authors stated that more attention should focus on encouraging patients to cease smoking after an initial diagnosis of NMIBC. They also concluded that these patients should be treated more aggressively and be kept under closer follow-up schedules [21]. Rink et al. [22] analyzed data obtained from 2,043 patients with primary NMIBC that were treated with transurethral resection of the bladder, with or without intravesical instillation therapy. They observed that continuous smoking was associated with poor treatment outcomes among patients with primary NMIBC and that there was a significant dose-response relationship between cumulative smoking exposure, which combines quantity and duration of smoking, and the patients' clinical outcomes. Smoking status was significantly associated with the cumulative incidence of disease recurrence ($P = 0.044$) and progression ($P < 0.001$), with current smokers having the highest incidence for both end points. There was no difference between current and former smokers with respect to disease recurrence, and no difference between former and nonsmokers regarding disease progression. Among ever smokers, cumulative smoking exposure was vividly associated with disease recurrence ($P < 0.001$), progression ($P < 0.001$), and overall survival (OS) ($P < 0.001$). Heavy long-term smokers had the worst outcomes and were followed by light long-term smokers, heavy short-term smokers, and light short-term smokers. In multivariable analyses, adjusted for the effects of standard clinical-pathologic factors, smoking status was not associated with disease recurrence ($P = 0.120$), but was associated with disease progression ($P = 0.003$). In comparison with nonsmokers, current smokers had a 2.09-fold (95% CI: 1.29–3.39) higher risk of disease progression. The lack of independent association between smoking status and disease recurrence might be affected by the use of adjuvant intravesical therapy, which has been proven to modify the risk of disease recurrence [23]. Other important results from this study were that smoking cessation, more than 10 years before diagnosis of NMIBC, lowered the risk of disease recurrence and progression by statistically and clinically significant margins. The associations between cumulative smoking exposure and disease recurrence, progression, and mortality were similar for current smokers, former smokers who had stopped more than 10 years before NMIBC diagnosis, and former smokers who had stopped smoking for at least 10 years ($P > 0.05$ for each group). The health benefits of long-term smoking cessation might therefore be the result of a decrease in systemic damage, improved repair mechanisms, or recovery of defensive mechanisms [22,24,25]. Sylvester et al. [26] also found a significant detrimental effect of smoking on the recurrence rate in their analysis of patients with NMIBC. Although former smokers and nonsmokers had a similar risk of disease recurrence after bacillus Calmette-Guérin (BCG) immunotherapy, current smokers had a reduced BCG response, after adjusting for the effects of standard clinical and pathologic factors. Intravesical BCG instillations induce a cytokine-dependent immune response, leading to enhanced apoptosis in the tissues [27]. It is suggested that active cigarette smoking impairs cytokine activity, B- and T-cell responses, and natural killer cell activation, which might explain the reduced response to BCG therapy among current smokers [28].

Bostrom et al. [29] have evaluated the effect of smoking on outcomes in a large cystectomy series, using a database of 564 patients (64% smokers and 36% nonsmokers) who were treated with radical cystectomy. A significant difference was observed in the 10-year disease-specific survival (DSS) of nonsmokers (66%) and current smokers (52%) ($P = 0.039$). The difference was even more pronounced when the 10-year OS was analyzed (62% vs. 37%, $P = 0.015$). Survival was further analyzed using Cox proportional hazard models for DSS and OS, and smoking was found to be associated with a 1.4-fold higher risk of both BCa-specific (95% CI: 1.0–1.9) and overall mortality rates (95% CI: 1.1–1.8) in univariate analyses. When the same univariate analyses were carried out in the male and female cohorts, a significant increase in BCa-specific mortality was noted among men (hazard ratio [HR] = 1.7; 95% CI: 1.1–2.5; $P = 0.013$). The authors note that, as in most BCa cohorts, women were in a minority (22% of the cohort) and were less frequently smokers (51% vs. 68% of men), which

may explain the difference between the sexes' mortality rates. The results of this study carry important implications for BCa screening protocols. Smokers appear to be ideally suited for early detection of aggressive tumors, and appear to benefit more from screening [29]. Other authors who have assessed the influence of cigarette smoking on patients who underwent radical cystectomy have obtained similar results. Hafron et al. [30] used multivariate analysis to show that smoking was inversely correlated with OS (smokers vs. nonsmokers, HR = 0.71, $P = 0.40$). Another multivariate analysis, conducted by Yafi et al. [31], indicated that cigarette smoking was associated with lower rates of cancer-specific survival (HR = 1.30; 95% CI: 1.005–1.691; $P = 0.046$) and overall mortality (HR = 1.31; 95% CI: 1.049–1.628; $P = 0.017$).

Rink et al. [32] retrospectively collected data regarding smoking, clinical, and pathologic variables, including smoking status, number of cigarettes per day, duration in years, and time since smoking cessation, from 1,506 patients treated with radical cystectomy for BCa. Smoking status was associated with the cumulative incidence of disease recurrence ($P = 0.004$) and cancer-specific mortality ($P = 0.016$) in univariate analyses, as well as with disease recurrence in multivariable analysis ($P = 0.02$). Among current smokers, and after adjusting for standard characteristics, multivariate analysis found that cumulative smoking exposure was associated with advanced tumor stage ($P < 0.001$), lymph node metastasis ($P = 0.002$), disease recurrence ($P < 0.001$), cancer-specific mortality ($P = 0.001$), and overall mortality ($P = 0.037$) [32].

Potential effect of smoking cessation on BCa risk and treatment

There is no doubt that smoking cessation substantially prolongs life. Long-term prospective studies conducted among British physicians by Doll et al. [33] estimate that cessation of smoking at 50 years of age can halve the risk of premature, smoking-attributable death, while ceasing smoking at 30 years of age completely eliminates the risk. Compared with nonsmokers, on an average cigarette smokers died 10 years younger. Thankfully, cessation of smoking was beneficial at every stage of life, as ceasing smoking at 60, 50, 40, or 30 years of age, increased life expectancy by approximately 3, 6, 9, or 10 years, respectively, compared with those who continued smoking [33].

However, we questioned whether the benefits of smoking cessation also applied to patients diagnosed and treated for BCa. If so, should cessation be encouraged at all costs among patients already diagnosed with BCa? Does evoking the additional stress of cessation in patients with cancer have a medical basis? Unfortunately, the studies regarding this issue are few, and their results are somewhat divergent.

With respect to NMIBC, Fleshner et al. [20] determined that there was no difference in recurrence when patients who quit smoking (from 1 y before to 3 mo after diagnosis) were compared with patients who quit earlier (from 10–1 y before diagnosis). Consistent with this finding, Lammers et al. [21] reported that there was no difference in RFS on comparison of those who quit smoking ≥15 years before diagnosis with current smokers. Sfakianos et al. [28] found no associations between smoking cessation and disease recurrence, disease progression, cancer-specific mortality, or any-cause mortality, using cessation categories of ≥10 years before diagnosis, 0.1 to 10 years before diagnosis, and at diagnosis. Rink et al. found that patients with primary NMIBC who stopped smoking at least 10 years before diagnosis experienced reduced risk of disease recurrence (HR = 0.66, 95% CI: 0.52–0.84) and disease progression (HR = 0.42, 95% CI: 0.22–0.83), but not any-cause mortality, when compared with current smokers. In addition, patients who quit smoking more than 10 years before diagnosis did not experience more favorable outcomes than current smokers did [22]. Finally, in a cohort of patients with recurrent NMIBC, Rink et al. [34] determined that compared with current smokers, patients who stopped smoking at least 10 years before diagnosis had a decreased risk of disease recurrence (HR = 0.40, $P < 0.001$) but not of disease progression (Table).

With respect to cystectomy, Lee et al. [35] observed that quitting smoking before diagnosis (≥10.1, 5.1–10, 1.1–5, and 0.1–1 y) did not influence OS or DSS when compared with nonsmokers. However, Rink et al. [32] reported a reduced risk of disease recurrence (HR = 0.44, 95% CI: 0.31–0.62), cancer-specific mortality (HR = 0.42, 95% CI: 0.29–0.63), and any-cause mortality (HR = 0.69, 95% CI: 0.52–0.91) for patients who quit smoking at least 10 years before diagnosis, compared with current smokers. In a study, which examined the effect of smoking cessation on the results of BCa treatment, it was concluded that quitting smoking reduces the risk of disease recurrence, disease progression, or both, after transurethral resection of bladder tumor [19,32]. In another study, the authors also concluded that quitting smoking reduced the risk of disease recurrence, cancer-specific mortality, and any-cause mortality for cystectomized patients with muscle-invasive BCa. Therefore, smoking cessation programs for patients with BCa, led by urologists, should be a priority in BCa management, given the poor public awareness that smoking increases the risk of BCa [36–38] (Table).

Since studies suggest that there is a significant effect when patients stop smoking 10 years before diagnosis, and bearing in mind that the peak incidence of BCa occurs in the sixth decade of life, it is unclear whether we should begin advocating for cessation as early as possible [21,34,35]. Although we have presented the currently available data, we are still lacking conclusive evidence regarding reduced recurrence or cancer-specific mortality after smoking cessation. Such evidence would likely be

Table
Studies evaluating the outcomes of smoking cessation in patients with bladder cancer treated with transurethral resection or radical cystectomy

References	Years of study	Number of patients (*n*)	Median age (y)	Pathological stage (%)	Pathological grade (%)	Median follow-up (mo)	Outcome(s) of smoking cessation
Transurethral resection of the bladder							
Fleshner et al. [20]	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	No difference in recurrence for quitting smoking <1 y before diagnosis to <3 mo after diagnosis vs. >1 to <10 y before diagnosis
Chen et al. [25]	1997–2005	265	67	Ta 62.4 T1 37.6	LG 72.5 HG 27.5	38	Increased risk of recurrence for current and former smokers vs. those who quit <1 y before to <3 mo after diagnosis (HR = 2.2, P = 0.01 and HR = 2.2, P = 0.03, respectively)
Lammers et al. [21]	1998–2004	718	66.5	Ta 78.7 T1 21.3	G1 42.1 G2 47.0 G3 10.9	30	No difference in recurrence-free survival for quitting smoking >15 vs. <15 y before diagnosis
Sfakianos et al. [28]	1994–2008	623	76	Ta 35.2 Tis 30.3 T1 34.5	LG 9.6 HG 90.4	80.9	No differences in recurrence-free survival, progression or cancer-specific mortality for quitting smoking >10 y and 0, 1–10 y before diagnosis vs. at the diagnosis
Rink et al. [34]	1987–2007	390	67	Ta 67.9 Tis 1.5 T1 30.5	G1 36.9 G2 28.7 G3 34.4	66	Reduced risk of recurrence for quitting smoking <10 y before diagnosis vs. current smokers (HR = 0.40, P < 0.001)
Rink et al. [22]	1987–2007	2,043	67	Ta 61.0 T1 39.0	G1 23.6 G2 33.8 G3 42.6	49	Reduced risk of recurrence and progression for quitting smoking <10 vs. >10 y before diagnosis (HR = 0.66, 95% CI: 0.52–0.84)
Radical cystectomy							
Lee et al. [35]	1989–2008	602	62.2	T0–T2 56.8 T3-T4 43.2	G1–G2 15.6 G3 84.4	56	No difference in recurrence and cancer-specific survival for quitting smoking >10.1, 5.1–10.0, 1.1–5, and 0.1–1.0 y before diagnosis vs. nonsmokers
Rink et al. [32]	2000–2008	1,506	66.4	T0 5.2 Ta 4.1 Tis 11.2 T1 11.3 T2 26.6 T3 30.5 T4 11.2	None 5.2 LG 1.9 HG 92.9	34.3	Reduced risk of recurrence, cancer-specific mortality, and any-cause mortality for quitting smoking >10 y before diagnosis vs. current smokers (HR = 0.44, 95% CI: 0.31–0.62; HR = 0.42, 95% CI: 0.29–0.63; HR = 0.69, 95% CI: 0.52–0.91)

G1 = grade 1; G2 = grade 2; G3 = grade 3; HG = high grade; LG = low grade; T0 = no tumor; Ta–T4 = T categories; Tis = carcinoma in situ.

provided by a randomized clinical trial where smokers with newly diagnosed BCa were, or were not, assisted with smoking cessation. Unfortunately, there are currently no prospective studies assessing the effect of smoking cessation at the time of diagnosis, or the optimal design of smoking cessation programs for patients with BCa.

An alternative would be to conduct a further observational study that examines the relationship between smoking and recurrence or prognosis, with a special emphasis on examining dose-response relations and the time since cessation. If such a study produced strong evidence of the effect of cessation on improvement in BCa recurrence or prognosis, we would still need to determine the cost-effectiveness of interventions performed by urologists.

The role of the urologist in smoking cessation

Despite the fact that there are clear indications regarding the substantial negative effect of smoking on the risk of BCa, physicians still do not incorporate smoking cessation into their daily practice when treating at-risk patients [20,39]. Previous studies among general practitioners (e.g., in the Nordic countries, where physicians typically agree that smoking cessation should be an integral part of the health care system) often ignore the subject, owing to time constraints [40]. Subsequently, when referring patients who want to quit to smoking, cessation specialists are typically suggested.

General practitioners in England vary in their belief in the effectiveness of medical interventions for smoking and also in their use of such interventions [41]. According to the 2000 US National Health Interview Survey, only 50% of regular smokers who visited their physician reported receiving advice to quit [8]. Urologists tend to be even worse in recommending cessation counseling, as is shown by a large study examining the practice patterns of 601 American urologists, especially regarding smoking cessation assistance for patients with BCa [42]. More than half (55.6%) of urologists never discussed smoking cessation,

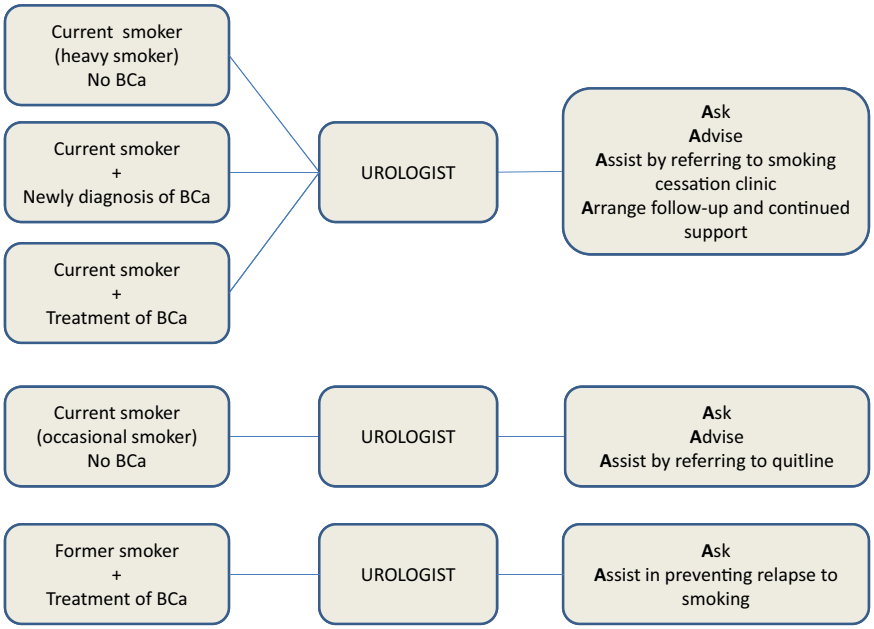

Fig. Role of urologists in the smoking cessation process. (Color version of figure is available online.)

whereas only 19.8% always discussed smoking cessation with their patients with BCa. Of the 55.6% of urologists who never discussed smoking cessation, 40.7% believed smoking cessation will not alter the course or outcome of the disease, and 37.7% did not feel qualified to give smoking cessation advice. Of the urologists who rarely provide smoking cessation counseling, behavioral support programs (9.1%), written materials on smoking cessation (5.3%), and prescribe nonprescription and prescription medications (6.4% and 0.7%, respectively) were recommended. Only 5.7% of urologists have received formal training regarding how to assist patients with smoking cessation. Those urologists were more likely to recommend smoking cessation, prescribe medications or over-the-counter nicotine replacement therapy, suggest behavioral support programs, and provide written materials, compared with those without training (20.6% vs. 6.0%, $P = 0.0011$) [42]. Similar results were reported in a study conducted in the United Kingdom, where only 7% of patients with BCa reported being advised to quit smoking by their urologist [41].

A number of patients visit their urologists regularly, some as often as they visit their primary care physician. Therefore, urologists who treat smoking patients with any urological disorder (not necessarily cancer) should include smoking cessation in their medical practice. Even short discussions with the patient regarding cessation, followed by referrals to quitlines, have been shown to be effective [43]. Brief smoking cessation advice, offered by a urologist at an outpatient clinic, could be a basic intervention, and this method has recently been reported as highly effective. Bjurlin et al. [44] performed yearly observations of patients, who were assessed using the Fagerström test for nicotine dependence and a questionnaire regarding their readiness to quit, between 2009 and 2011 [45]. In total, 100 patients received a 5-minute smoking cessation intervention, 41 the intervention plus nicotine replacement therapy, and 38 received regular medical care. The 1-year cessation rate in the brief intervention group was 12.1% compared with 2.6% in the regular care group (HR $= 4.44$, $P = 0.163$) Adding nicotine replacement therapy increased the cessation rate to 19.5% (HR $= 9.91$, $P = 0.039$, vs. regular care). Patients who received the brief intervention were significantly more likely to attempt to quit (HR $= 2.31$, $P = 0.038$), and increased readiness to quit scores were associated with an increased cessation rate and increased cessation attempts. The authors highlight that there is ample room for urologists to provide smoking cessation assistance and underline the significant effect of brief, simple advice regarding cessation on the patient cessation rates [44].

The general concept of brief interventions, used by physicians to support smoking cessation, is consistent with the 4As or 5As [46,47], which include *asking* patient whether he/she smokes, *advising* him/her to stop smoking, a*ssisting* the patient to quit smoking, and *arranging* follow-up visits to monitor the patient's smoking status [46]. Some smoking cessation guidelines also recommend adding *assessing* patient's motivation for smoking cessation, although this activity is typically used in smoking cessation clinics or when calling phone counselors [47].

Urologists who want to implement brief interventions in their everyday practice must take into account the patient's attitude toward smoking and willingness to quit. Depending on the situation, the urologist's role may adapt slightly. In all cases, when the urologist first meets the patient, or follows up after a long absence, the patient's smoking status should be assessed and recorded (Fig.). If the patient

smokes, it should be specified whether they are smoking on daily basis, how many cigarettes they smoke a day, and for how long they have been smoking. Special attention should be paid to patients who smoke heavily (more than 20 cigarettes a day) or for an extended period of time (more than 20 y).

The next step should be to authoritatively encourage the patient to cease smoking. For example, physicians might use the sentence, "As your physician (urologist), I must advise you that smoking is risky for your health, and it is important for you to stop" [47,48]. Such encouragement should be reinforced with a description of the benefits of smoking cessation, for both the genitourinary system and health in general. The next step should be to refer heavy smokers to a professional support team (e.g., smoking cessation clinic or phone "quitlines"), especially for patients who have newly diagnosed BCa (treatment naive) or have already been treated (Fig.), since these patients generally require immediate professional assistance for the treatment of tobacco dependence. When meeting occasional smokers, urologists should evaluate the patient's smoking status, encourage them to cease smoking, and refer them to a quitline or behavioral support specialist. If the urologist feels competent, he/she may perform the entire process alone (ask, advise, and assist) (Fig.). However, this requires both motivation and prior training in this specialized area. To ensure the brief interventions are effective, urologists should repeat the 4As or 5As at all meetings with the patient, particularly for patients who have attempted to quit and have been successful for some time. In these cases, the urologist should support the patient in the cessation for as long as possible, which may require regular contact with both the patient and other health care providers who are supporting the patient's cessation [48].

We should also bear in mind that involvement of the urologist in the process of quitting smoking reduces the risk of not only BCa but also other cancers of the urinary tract. There is also a clear association between smoking and the risk of other cancers, including lung cancer, cancer of larynx, esophagus, stomach, and pancreas. Smokers who are treated for BCa are also at the risk of cardiovascular and respiratory diseases, including myocardial infarction, aortic aneurysm, or chronic obstructive pulmonary disease, which limits the chance of BCa recurrence [49]. Reducing the risk of these diseases has a beneficial effect on the treatment process of BCa [19]. We should also remember that some urological diseases are long-term diseases and require periodic visits in urologist's office, which can be used to monitor and reinforce the smoking cessation process [50]. Given that an immediate decrease in the risk of BCa is observed among patients who gave up smoking (40%–60% from 1–4 y to 25 y of abstinence), and that smoking cessation for 10 years before the diagnosis of BCa improves the treatment results, we should make a special effort to encourage patients to cease smoking at the earliest age [16]. In this situation, the urologist's ability to intervene may be limited, as there are generally no symptoms of BCa or other tobacco-dependent diseases when interventions are performed early.

Unfortunately, patients are not normally aware that smoking is a risk factor of BCa, and urologists rarely provide this information. Of patients having BCa, only 22% realized that smoking was a risk factor for BCa [41]. Nieder et al. [36] evaluated the social awareness of smoking as a risk factor for developing bladder, renal, or lung cancer, and found that although 98% of respondents were aware of the risk of lung cancer, only 36% and 32% were aware of the risk of bladder and renal cancer, respectively. The awareness of smoking as a risk factor for BCa was significantly associated with higher education level and sex. Highly educated respondents were more than 5 times as likely to perceive smoking as a risk factor for BCa, compared with the under-educated. Moreover, women were more than 2 times more likely to perceive this association, compared with men [36].

In the study published by Bassett et al. [51], patients were more likely to associate tobacco use with the lung, head, and neck cancer, as well as heart and lung disease, rather than with their own malignant diagnosis, revealing poor social awareness of tobacco's role in BCa. Respondents' awareness of the relationship between smoking and BCa was largely dependent on their interaction with their urologist, and was greater when the urologist was the respondent's source of information. Active smokers were the most reliant on their urologist for education and were the most likely to identify tobacco use as a risk factor for BCa. For many active smokers, the BCa diagnosis represented a teachable moment, as 48% reported successful cessation following diagnosis. The diagnosis of BCa was the most often cited reason for cessation, followed by the advice of the urologist. Among recent exsmokers, 76% cited the diagnosis of BCa as a reason for cessation. Also, the urologist's advice was reported more often than the advice of the primary care provider (55% vs. 28%, $P = 0.03$). Smokers with a new diagnosis of BCa were approximately 5 times more likely to quit smoking than smokers in the general population (48% vs. 10%, $P < 0.001$); and therefore, the authors conclude that patient education plays a pivotal part in the urologist's health-promoting role [51].

Smoking cessation resources

Smoking cessation is recommended as part of many government cancer control programs or strategies. The European Code Against Cancer [52] sums up the steps, which have to be taken to provide early detection, and provides 11 recommendations for cancer prevention. The first 7 recommendations address patient's lifestyle (primary cancer prevention), whereas the other 4 address population-based early cancer diagnoses methods (secondary cancer prevention). First recommendation of the Cancer Code

explicitly states, "Do not smoke; if you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers." The first recommendation also provides an explanation why patients who smoke, and would like to avoid or treat cancer, should not continue to smoke. At a national level, the European Code Against Cancer is often published in several versions addressed to health professionals and patients. In many countries, local health authorities or medical associations also publish guidelines on smoking cessation or treatment of tobacco dependence [53,54]. Typically, these guidelines are founded on an evidence-based approach and are targeted to a wide variety of health professionals. Some guidelines are also created specifically for targeted audience, including general physicians, cardiologists, pulmonologists, gynecologists, oncologists, and psychiatrists. Some guidelines focus on brief interventions for smoking cessation, whereas others focus on long-term intensive treatment for tobacco dependence [47].

A well-organized network of smoking cessation clinics might effectively strengthen tobacco control programs at the population level [55]. Typically, basic support for smoking cessation is provided in primary health care settings, whereas more advanced support is provided in outpatient clinics located in hospitals or health institutes. Most smoking cessation guidelines describe how smoking cessation should be planned and organized within this framework [47]. Unfortunately, in most countries, the number of smoking cessation clinics is not sufficient to treat all smokers for tobacco dependence, and thus the role of trained general practitioners and medical specialists, including urologists, would appear to be crucial for effective large-scale smoking cessation programs. Randomized, controlled trials have shown that telephone counseling (quitlines) significantly increase short- and long-term cessation rates, which further improve if counseling is multisession, proactive, and tailored to the patient's needs. In several countries, evidence-based quitlines have been used, owing to their cost-effectiveness and wide availability [56], as most services act as toll-free help line [6]. In many countries, quitline numbers appear on cigarette packs alongside health warnings. In addition to medical treatment, quitlines may also help support physicians who are treating patients for tobacco dependence. For example, a quitline specialist can encourage the patient to maintain cessation between physician visits and undertake the more time-consuming support that some patients may require to achieve long-term cessation.

Both brief interventions and long-term intensive treatment of tobacco dependence require advanced training, conducted by specialized and certified institutions or organizations. In the United Kingdom, experts from the Health Development Agency established standards for training in smoking cessation treatments [57]. According to their recommendations, "Smoking cessation training standard has been informed by the practical experience of those currently delivering smoking cessation interventions, those running the specialist NHS cessation services, as well as by reviews of research evidence and of existing training programmes, together with consultation with academics, trainers, medical and policy advisers" [57]. In the United Kingdom, where the smoking cessation system is well organized, these training programs cover knowledge and skills for brief interventions, as well as intensive one-to-one support and group intervention. Both trainers and advisers must be accredited by the appropriate health care authorities.

Population-based smoking cessation programs, which are broadly organized in many countries, can also provide support to both patients and urologists [58]. There are many effective global, national, and regional smoking cessation activities that are organized annually at the population level. Some of the most effective programs include the *Great American Smoke-out*, UK's *No Smoking Day,* Poland's *Let's Stop Smoking Together*, and the World Health Organization's *World No Tobacco Day* [59–62]. Some campaigns motivate smokers to attempt to quit and build their capacity to abstain for as long as possible, whereas other events focus on raising awareness in smokers (and the general public) of the health consequences of smoking, and the benefits of quitting. In the past decades, 2 large European Union events have been developed for smokers who want to quit: *Help—for a life without tobacco* and *Ex-smokers are unstoppable* [63,64]. Media campaigns have also been organized at an international level to support smokers who wish to quit, including *Every cigarette is doing you damage* or *Cigarettes are eating you and your baby alive* [65].

Summary and conclusions

Currently, 1.2 billion people use tobacco worldwide, and this epidemic is increasing in the developing countries, especially among men. Tobacco use is the single most preventable cause of death in the world, killing up to half of tobacco users prematurely. Currently, the annual global number of tobacco-related deaths is approximately 5.2 million, and the number of smoking-attributable cancer mortalities in developed countries is estimated at more than 700,000 cases.

BCa is the most common malignancy of the urinary tract, the seventh most common cancer in men worldwide, and eighth most frequent cause of cancer-specific mortality in Europe. Smoking has been well documented as a risk factor for BCa, with the risk correlating with the number of cigarettes smoked in a day and the duration of smoking. Moreover, smoking worsens BCa treatment outcomes and prognosis.

Urologists may play an essential role in assisting patients to cease smoking, thereby decreasing the risk of BCa other tobacco-related diseases. Urologists should be focused on brief interventions, as well as collaboration with specialized smoking cessation resources. To support urologists in their brief interventions, we recommend the following steps: adaptation of cancer prevention and smoking cessation

guidelines for urologists' daily practice and offering urologists certified training programs for the treatment of tobacco dependence. Urological patients can be supported by referrals to smoking cessation clinics and quitlines, as well as population-based cessation.

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