Review Article

Review on gender differences in non-muscle invasive bladder cancer

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Abstract: Differences in the epidemiology, diagnosis and outcomes according to gender in patients diagnosed with non-muscle invasive bladder cancer (NMIBC) has been widely reported. In this article we present gender-specific differences in NMIBC in terms of epidemiology, risk factors, first clinical presentation, management and clinical outcomes based on systematically review evidence of existing literature. A literature search of English-language publications that included an analysis of the association of gender differences in patients with NMIBC was performed using PubMed. Sixty-four studies were selected for analysis with consensus of all authors. The incidence and mortality for urothelial bladder cancer (UBC) are higher in men, whereas cancer specific mortality to incidence ratio is significantly lower for men than for women. This phenomenon could be partially explained by differences in exposure to bladder cancer carcinogens. However female gender is associated with higher stage at presentation. Thirteen studies with a total of 11,069 patients diagnosed with NMIBC were included for analysis according to outcomes. In studies that found statistically significant differences in outcomes between sexes, female gender was reported as risk factor for disease recurrence, progression or cancer specific mortality. None of included studies found worse outcomes in men when compared to women with NMIBC. Results of our review suggest that female gender in patients diagnosed with NMIBC is associated—though inconsistently—with higher stage at presentation and poorer outcomes. Numerous factors may influence gender gap in incidence rate, clinical management and reported outcomes. Consensus on comparable data collection in routine practice and prospective trials including clinical outcomes are required to identify gender-specific differences in patients diagnosed with NMIBC.

Keywords: Bladder cancer; gender; non-muscle invasive bladder cancer (NMIBC)

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Introduction

Sex-specific discrepancies in epidemiology, diagnosis, and clinical outcomes of most of non-gender specific cancers have been reported (1,2). The most common malignancy of the urinary tract is urothelial bladder cancer (UBC). In 2016 alone, UBC was diagnosed in 437,000 cases and 186,000 patients succumbed to the disease (3). It remains the 9th commonest diagnosed cancer and the 13th most common cause of death globally. A sex-related differences are observed in the epidemiology of UBC, with about 3-fold higher incidence in men compared to women (4). However, the ratio of cancer-specific mortality (CSM) to incidence in UBC is significantly lower among men than women,

indicating that female gender is associated with higher risk of CSM in UBC (4). Moreover, women are more often diagnosed with locally advanced disease and possess greater proportion of nonurothelial cell types at presentation when compared to their male counterparts (5). Furthermore, in the retrospective analysis by Horstmann *et al.* UBC was diagnosed at a significantly younger age in men than in women (mean age: 62 *vs.* 67 years) (6). Regardless of the stage, female gender has been shown in number of studies to be dismal prognostic factor among patients diagnosed with UBC (7-9). According to WHO, bladder cancer specific mortality is greater in women when compared with men in the majority of analyzed countries, with only two exceptions of worse outcomes in males. Higher UBC specific morality in men compared with women in Eastern Europe and Russia could be presumably caused by regional differences in exposures to carcinogens, especially tobacco smoking, between gender, contributing to differences in the incidence of aggressive form of UBC (10). Overall, female gender is associated with loosing greater proportion of life expectancy years due to UBC (11).

At presentation, about 75% of UBC is confined to the mucosa [non-muscle invasive bladder cancer (NMIBC)], while in the remaining 25%, cancer infiltrates muscle layer of the bladder wall [muscle invasive bladder cancer (MIBC)] or already formed metastases (12). Age-specific incidence of NMIBC cancer increased from 5.52 to 9.09 per 100,000 from 1998 to 2006, as reported in population-based study on US population (13). Interestingly, the incidence rise of UBC in this population was 25% faster among men compared to women (14). NMIBC is a heterogeneous disease and high-grade lesions invading subepithelial tissue (T1HG) and/or carcinoma in situ (CIS) are known risk factors of progression. Therefore, subgroups of NMIBC were recognized including low, intermediate and high-risk lesions. High-risk NMIBC remains potentially lethal disease with the risk of death ranging from 5% to even 38% (15). In several studies that included patients diagnosed with NMIBC female gender was related with higher risk of disease recurrence and progression, but data is inconsistent (16). Numerous explanations for the observed gender discrepancies have been introduced, including delayed diagnosis, disparate quality of medical care and diverse response to conservative therapy.

The aim of this systematic review is to present gender-related differences in epidemiology, clinical management and outcomes in patients diagnosed with NMIBC.

Evidence acquisition

Systematic search through PubMed database to identify articles devoted to gender diversities in bladder cancer published from 1980 to 2018 in English language was performed. The review was carried out according to the Preferred Reported Items for Systematic Reviews and Meta-analysis guidelines (PRISMA, www.prisma-statement.org) (*Figure 1*). The following phrases were used during the search: urothelial cancer or bladder cancer, sex, gender, males and females, men and women combined with several groups of keywords relevant to the discussed sections. These included: biology, etiology, management and outcomes with specific attention to non-muscle invasive disease. Clinical series, review articles and editorials were identified and all abstracts were reviewed but only the most significant papers were completely analyzed and used as the references. Eligible studies were approved by every co-author. Additional unique records were identified through the discussions with the supervising, senior author (J Dobruch). In order to store publications and remove duplicates Mendeley Desktop version 1.17.9 (© 2008-2016 Mendeley Ltd.) was used.

Evidence synthesis

Although gender is widely known risk factor used as a covariate in numerous studies, number of investigators have searched the explanations to unravel gender diversities in bladder cancer. The phenomenon should be presented in the focus of variety of elements including differences in exposures to risk factors and potential gender related mechanisms of chemical compounds metabolism, delayed diagnosis and uneven management of corresponding stages and grades of the disease and diverse biology of the cancer itself as well.

Results

Gender differences and risk factors

Potential risk factors of UBC have been widely investigated. The most common and well established one is cigarette smoking. People, who have ever smoked tobacco are at 2.5-fold greater risk of developing UBC compared to nonsmokers (17-21). According to several observational studies, cigarette smoking was reported as a cause of 50% of all UBC new cases and 40% of all UBC deaths

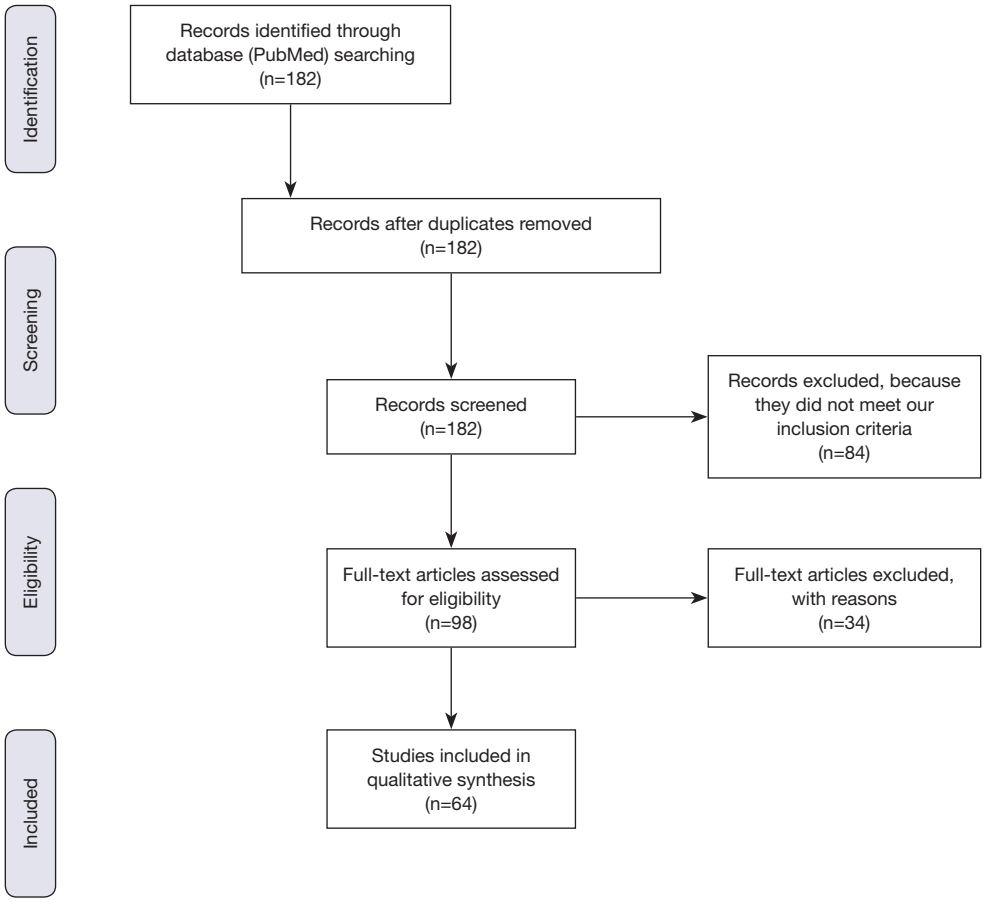

Figure 1 Flow chart of the study inclusion process according to PRISMA.

(22-24). Since 1980s, large decrease in the spread of tobacco smoking was noticed for both genders, but on the other hand the quantity of people who smoke increased due to population growth. From 1980 to 2012 significant decrease of cigarette smoking prevalence was observed in the male and female population (41.2% to 31.1% and 10.6% to 6.2%, respectively) (25). Despite significant male predominance in smoking prevalence, data extracted from The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) and National Lung Screening Trial (NLST) to stratify risk of UBC according to sex, age, smoking status showed that gender gap in epidemiology of UBC cannot be fully explained according to differences in daily smoking prevalence between genders (26). The gender-related disparity in incidence of UBC in men and women with similar exposures to tobacco was also reported in previous studies (17,27). Environmental exposure to aromatic amines, polycyclic aromatic hydrocarbons, chlorinated hydrocarbons, arsenic at drinking water is another significant causative agent for UBC (28-30). Several studies report that that hairdressers and barbers may have increased risk of developing UBC due to occupational exposure, but the data are conflicting (31,32). Interestingly, among women using permanent hair dyes compared to never users of dye, who had NAT2 (N-acetyltransferase 2) slow acetylation phenotype, higher risk of UBC was found, on the other hand further analyses did not find correlation between hair dye exposure and increased risk of UBC (31,32). The metabolism of UBC carcinogens and the impact of sex hormone are disputed, emphasizing the theory that observed sex related UBC risk could be consequence of sex hormones cooperation with the hepatic biotransformation of carcinogens, with androgens and estrogens exerting opposing effects (33). In particular, at the molecular level, gender-specific expression patterns of UGTs (uridine 50-diphosphoglucuronosyl transferase), which participate in aromatic liver biotransformation was observed (34). GSTM1 (glutathione-S-transferase M1), another liver enzyme that participate in metabolism of

bladder carcinogens by ligating glutathione, could partially explain gender gap in UBC incidence. Indeed, greater risk of UBC related with GSTM1 null genotype was found in women (OR 1.7; 95% CI: 1.0–3.0), but not in male group (OR 0.9; 95% CI: 0.7–1.3). Interestingly, women with the GSTM1 null genotype, increased risk of UBC was observed only among smokers (OR 2.3; 95% CI: 1.1–4.5 in smokers versus OR 0.9; 95% CI: 0.3–2.5 in non-smokers) (35).

Gender gap in diagnosis

Female gender is associated with more advanced disease at the time of diagnosis with UBC. According to Surveillance, Epidemiology and End Results (SEER) database, women are more often diagnosed with MIBC at presentation (22% *vs.* 25% in Caucasian and 30% *vs.* 43% in African-American respectively, P<0.001) (9). Data from more than 20,000 patients from the Netherlands Cancer Registry revealed statistically significant sex-related differences in stage distribution (Ta *vs.* T1) at presentation for NMIBC, with women presenting more often with T1 disease (9). Gender gap in stage at presentation and outcomes could be due to biologic differences as well as diagnostic delay in women. Indeed, there is data reporting no differences in clinical symptoms between sexes, while primary diagnostic approach as shown in numerous studies differ. It was reported that gender gap in evaluation of hematuria exist. Female gender was associated with higher risk of receiving symptomatic treatment for hematuria, without further evaluation (36). The retrospective data of 926 patients revealed 65% greater likelihood of specialized investigation of first or recurrent episode of hematuria (37). Interestingly, the analysis of data from 343 patients with confirmed UBC found among women time-delay from clinical symptoms suggestive for UBC to definitive diagnosis (38). Delay in UBC diagnosis might be responsible for higher stage at presentation and worse outcomes in women compared to men.

Outcomes

Patients treated with organ-preserving therapy

Abundant number of studies revealed female gender as a risk factor for disease recurrence or progression in patients treated with transurethral resection of the bladder tumor (TURBT) with adjuvant intravesical immunotherapy with however controversial conclusions. Seven studies with a total of 5,904 patients were included for analysis in this respect. In one single-institution retrospective study of 146 patients with T1HG UBC treated with BCG, the variable "*CIS in the prostatic urethra or female gender*" was associated on multivariate analysis with significantly increased risks of recurrence [hazard ratio (HR) 2.53; P=0.0003], progression (HR 3.59; P=0.001), and death from bladder cancer (HR 3.53; P=0.004) (7). It is worth to emphasize that patients did not undergo repeat transurethral resection (reTUR) nor maintenance bacillus Calmette-Guérin (BCG) was adopted, so conclusions are still uncertain. Similarly, Noon *et al.* using a population-based cancer registry, also detected a significantly increased CSM among women *vs.* men with NMIBC (39), while Alanee and colleagues noted in the SEER database that female gender was independently associated with higher risk of CSM among patients diagnosed with CIS (HR 1.69) (40). On the other hand, in retrospective analysis of data from 916 patients diagnosed with T1 UBC, women were in significantly greater risk of disease recurrence in the overall cohort. Interestingly in this series, among patients treated additionally with BCG authors did not reveal correlation between gender and risk of disease recurrence (41). Furthermore, in another study with 1,021 patients (756 men and 265 women) who received induction BCG for NMIBC, Boorjian *et al.* did not report an association between sexes and disease recurrence or progression (42). However, restaging TUR was performed in every case in the latter series, whereas in the former one restaging TUR was not uniformly implemented. At the same time, a meta-analysis of 15,215 patient diagnosed with high-grade T1 NMIBC determined female sex as risk factor for disease progression, but not for recurrence or CSM (43). In conclusion, we found that in one study female gender was associated with increased risk of disease progression as well as recurrence, in two studies, authors reported increased risk for disease recurrence, but not for disease progression. In four analyzed studies, authors did not report correlation between gender and risk of disease progression, recurrence or disease-specific mortality (*Table 1*).

Patients treated with RC

When diagnosed with MIBC, radical cystectomy (RC) is the standard of care, whereas in patients diagnosed with NMIBC RC could be an option in selected subgroups of high-risk disease. Six studies with a total of 16,389 patients including 5,165 patients with ≤ pT1 were considered for analysis. In a few series of patients treated with RC for NMIBC, gender was the independent risk factor for CSM

Table 1 Gender-specific outcomes in patients diagnosed with NMIBC treated with organ-preserving therapy

Study	Number of pts	Gender distribution [%]	Stage distribution [%]	Median follow-up (years)	Restaging TUR	BCG therapy	Impact of female gender on progression risk (F:M HR, P)	Impact of female gender on recurrence risk (F:M HR, P)	Impact of female gender on DSM risk (F:M HR, P)
Palou *et al.* (7)	146	F: 18 [12]; M: 128 [88]	Ta: 0 [0]; T1: 146 [100]; CIS: 0 [0]; cCIS: 95 [65]	8.7	No	Induction only	↑ (HR 3.59, P=0.001, 95% CI: 1.64–7.88)	↑ (HR 2.53 P=0.0003, 95% CI: 1.50–4.25)	↑ (HR 3.53, P=0.004, 95% CI: 1.40–8.89)
Fernandez *et al.* (8)	1,062	F: 111 (10.5); M: 951 (89.5)	Ta: 214 [20]; T1: 848 [80]; CIS: 0 [0]; cCIS: 80 [8]	5.75	No	Induction only	↔ (HR 1.007, P=0.98, 95% CI: 0.578–1.757)	↑ (HR 1.801 P=0.0001, 95% CI: 1.331–2.436)	NR
Boorijan *et al.* (42)	1,021	F: 265 [26]; M: 756 [74]	Ta: 612 [60]; T1: 409 [40]; CIS: 0 [0]; cCIS: 629 [62]	>5	Yes	Induction only	↔ (HR 1.01, P=0.35, 95% CI: 0.79–1.11)	↔ (HR 1.01, P=0.95, 95% CI: 0.85–1.63)	NR
Kluth *et al.* (41)	916	F: 190 [21]; M: 726 [79]	Ta: 0 [0]; T1: 916 [100]; CIS: 0 [0]; cCIS: 53 [6]	3.6	No	Induction only: 234 [26]	↔ (HR 1.247 P=0.32, 95% CI: 0.798–1.947)	↑ (HR 1.312, P=0.026, 95% CI: 1.033–1.668)	↔ (HR 1.137 P=0.677, 95% CI: 0.622–2.078)
Gontero *et al.* (44)	2,451	F: 439 [18]; M: 2,012 [82]	Ta: 0 [0]; T1: 2,451 [100]; CIS: 0 [0]; cCIS: 599 [24]	5.2	Yes: 935 [38]	Induction only	↔ (HR 1.31 P=0.015, 95% CI: 1.05–1.64)	↔ (HR 1.07 P=0.32, 95% CI: 0.93–1.24)	↔ (HR 1.10, P=0.56, 95% CI: 0.74–1.13)
Takenaka *et al.* (45)	185	F: 30 [16]; M: 155 [84]	Ta: 14 [8]; T1: 46 [25]; CIS: 125 [68]; cCIS: 185 [100]	3.1	No	Induction only	↔ (HR 0.143, P=0.085, 95% CI: 0.024–1.323)	NR	NR
Holz *et al.* (46)	123	F: 14 [11]; M: 109 [89]	Ta: 21 [17]; T1: 102 [83]; CIS: 0 [0]; cCIS: 48 [39]	4.7	Yes: 27 [22]	Induction + Maintenance	↔ (HR 0.87, 95% CI: 0.22–3.49)	↔ (HR 0.75, 95% CI: 0.3–1.9)	NR

↑, increased risk; ↔, no impact. NR, not reported; HR, hazard ratio; CI, confidence interval; P, probability value; M, male; F, female; CIS, carcinoma in situ; cCIS, concomitant carcinoma in situ; TUR, transurethral resection; BCG, bacillus Calmette-Guérin.

Table 2 Gender-specific outcomes in patients diagnosed with NMIBC treated with RC

Study	Number of pts overall	Number of pts with ≤ T1		Follow-up (years)	Impact of female fender on CSM risk (F:M HR, P)
		M (%)	F (%)		
Tilki *et al.* (50)	243	243 (NR)		3.17	↑, HR =2.45, P=0.03
Otto *et al.* (54)	2,483	583 (75.3)	125 (24.7)	3.5	↑, HR =1.26, P=0.01
Kluth *et al.* (47)	8,102	2,435 (84.1)	459 (15.9)	3.4	↑, HR =1.17, P<0.01
Messer *et al.* (48)	4,216	1,064 (80.6)	256 (19.4)	2.7	↑, HR =1.27, P<0.01
Soave *et al.* (52)	517	156 [84]	30 [16]	10.4	↔, NR
Mitra *et al.* (53)	828	146 [50]	146 [50]	3.7	↔, NR

↑, increased risk; ↔, no impact. NR, not reported; P, probability value; M, male; F, female; HR, hazard ratio; NMIBC, non-muscle invasive bladder cancer; RC, radical cystectomy; CSM, cancer-specific mortality.

as well as for early complications (47-49). In a group of patients with CIS resistant to TURBT complemented with intravesical BCG therapy treated with RC, female sex was an independent risk factor for increased CSM (P=0.029) (50). Similar conclusions have been revealed in cohorts treated with RC, which had no evidence of disease (pT0N0) following RC (51). On the other hand the data published by Soave *et al.* and Mitra *et al.* showed no difference in survival among gender treated with RC for NMIBC (52,53). It is worth to emphasize that cohort of patients were heterogenous according to administration of neoadjuvant chemotherapy and no detailed information on its usage can be provided. To sum up in four included studies, authors found that female gender was associated with increased risk of cancer specific morality. In two analyzed studies correlation between gender and cancer specific mortality was not statistically significant (*Table 2*). Potential explanations of these divergent outcomes in females and males diagnosed with NMIBC cancer include that: female gender is associated with worse response to BCG immunotherapy (22), female bladders may be worse staged at primary TURBT (female bladders are typically thinner and so more prone to understaging MIBC) (55) or there is delay in the time to diagnosis for female patients (as irritative bladder symptoms or hematuria in female patients are initially treated as infections or detrusor overactivity, before complete evaluation) (37).

Molecular profiles of male and female bladder cancer

According to The Cancer Genome Atlas (TCGA) majority of NMIBC have FGFR3 (fibroblast growth factor receptor 3) mutations, Ras activation, and wild-type TP53 (56,57). There are number of UBC biomarkers implemented to clinical practice. Genetic sex related discrepancies according to UBC may lead to different disease biology among women and remains to be confirmed in well-designed prospective studies (58). Recently, published studies found possible correlation with BCG failure and ARID1A (AT-rich interactive domain 1A) (59). The progression of high-risk NMIBC at molecular level has not been fully understood. Some evidence revealed that p16/P53/RB1 signaling axis promotes progression of high-risk NMIBC (60), but there is lack of investigations showing possible differences at molecular level according to gender, that could explain clinical observed gender gap.

Androgen axis dependence in UBC induction and progression could partially explain the gender discrepancy in epidemiology and outcomes (61). Empirical studies show that estrogens may protect against UBC development, but afterwards support UBC progression (62,63). On the other hand, androgens, may initiate and promote progression of bladder cancer with its receptor playing a principal role (64). It could be assumed that, in females, due to the altered androgen levels, hormone-dependent mechanisms in progression of bladder cancer may impact inferior survival compared to males.

Conclusions

Gender differences in epidemiology, diagnosis, management and outcomes among patients diagnosed with NMIBC are pronounced. Both genetic and environmental factors are believed to play roles in gender differences in bladder cancer. Number of authors reported gender-related

differences, when evaluating hematuria. By understanding sex-related discrepancies in NMIBC, gender-specific strategies for diagnosing and treatment, could be adopted to improve outcomes and reduce CSM. The present review does not find clear conclusions according to gender gap in NMIBC. Continued, especially prospective trials are thus required.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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