

Comparative Analysis of Gender-Related Differences in Symptoms and Referral Patterns prior to Initial Diagnosis of Urothelial Carcinoma of the Bladder: A Prospective Cohort Study

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Key Words

Urinary bladder neoplasms · Carcinoma · Transitional cell · Sex characteristics · Referrals

Abstract

Objective: To analyze gender-specific differences regarding clinical symptoms, referral patterns and tumor biology prior to initial diagnosis of urothelial carcinoma of the bladder (UCB). **Methods:** A consecutive series of patients with an initial diagnosis of UCB was included. All patients completed a questionnaire on demographics, clinical symptoms and referral patterns. **Results:** In total, 68 patients (50 men, 18 women) with newly diagnosed UCB at admission for transurethral resection of bladder tumors were recruited. Dysuria was more often observed in women (55.6 vs. 38.0%, $p = 0.001$). Direct consultation of the urologist was conducted by 84.0% of males and 66.7% of females ($p = 0.120$). One third of the women saw their general practitioner and/or gynecologist once or twice ($p = 0.120$) before referral to the urologist. Furthermore, women were significantly more often treated for urinary tract infections than men (61.1 vs. 20.0%, $p = 0.005$). Cystoscopy at first presentation to the

urologist was more often performed in men than women (88.0 vs. 66.7%, $p = 0.068$), with a more favorable tumor detection rate at first cystoscopy in men (96.0 vs. 50.0%, $p < 0.001$). **Conclusions:** Delayed referral patterns might lead to deferred diagnosis of UCB and consequently to adverse outcome. Thus, primary care physicians might consider referring patients with bladder complaints to specialized care earlier.

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Introduction

The impact of female gender on outcome in urothelial carcinoma of the bladder (UCB) is a controversial matter. Although UCB is more frequent in men, women are more likely to suffer from an adverse survival outcome [1, 2].

Various factors have been suggested to account for the sex differences of UCB, namely disparities in health care, environmental exposure to carcinogens, genetics, anatomy, hormone balance, tumor biology and social life [2]. Furthermore, delayed diagnosis of UCB due to misinterpretation of its early signs might also result in advanced

tumor stages in female patients upon initial diagnosis of UCB [3–6].

Therefore, the aim of our study was to validate the findings of a previously presented questionnaire-based study incorporating a comparative analysis of gender-associated differences in terms of symptoms, referral patterns and therapy before initial diagnosis of UCB within a prospective, double-center study [5].

Patients and Methods

Patient Selection

The present prospective cohort study comprised a total of 68 consecutive patients undergoing transurethral resection of bladder tumor (TUR-BT) for newly diagnosed UCB at two tertiary referral centers from 2010 to 2013. After obtaining informed consent for surgery and study participation, all of the patients received a questionnaire before TUR-BT. The data from the Bolzano patients ($n = 46$), which have already been published in Henning et al.'s study [5], were excluded prior to analysis within the present study.

Questionnaire

The five-page questionnaire was identical to the previously published questionnaire developed by Henning et al. [5] (fig. 1). Information was collected on smoking habits and profession. The presence of clinical symptoms was evaluated, specifically hematuria, dysuria and/or bladder pain and treatment of urinary tract infection (UTI) within a 12-month period prior to the initial diagnosis of UCB. Furthermore, nocturia and urgency within 4 weeks prior to the diagnosis of UCB were also assessed. The other items addressed consultation and treatment before referral to the urologist. Our study group was questioned regarding the frequency of visiting their general practitioner (GP) and/or gynecologist due to bladder complaints prior to referral to the urologist. In addition, we assessed the frequency of urological consultations before cystoscopy was conducted and whether a tumor was observed at initial cystoscopy.

Pathologic Evaluation

All of the specimens were analyzed according to standard pathologic procedures at each institution. Tumors were staged according to the 2010 American Joint Committee on Cancer TNM classification and tumor grading was assessed according to the 2004 WHO classification [6].

Statistical Analysis

The Kolmogorov-Smirnov test was used to evaluate the normal distribution of continuous variables. Continuous variables are presented as mean values with standard deviations (SD) or as a median with interquartile ranges (IQR), according to the type of distribution. The Wilcoxon rank sum test (Mann-Whitney U; two categories) and the Kruskal-Wallis test (three or more categories) was utilized for non-normally distributed variables. Comparison between categorical variables was performed using Fisher's exact and χ^2 test. Statistical analyses were conducted with SPSS Statistics® 20 (SPSS, IBM Corp., Armonk, N.Y., USA). The reported p values are two-sided with the statistical significance level set at $p < 0.05$.

Results

Patient Characteristics

A total of 50 male patients (73.5%) and 18 female patients (26.5%) with a respective median age of 68 (IQR 58.8) and 69 (IQR 63.8) years entered this prospective cohort study. In the male cohort, 36.0% were non-smokers, 26.0% active smokers and 38.0% former smokers ($p = 0.425$). In contrast, 27.8% of the female patients were non-smokers, 16.7% were active smokers and 55.6% were former smokers ($p = 0.425$). In terms of profession, 32.4% of our population were office workers, of whom 32.0% were male and 33.3% female ($p = 0.001$). Table 1 gives a detailed summary of the descriptive characteristics of our cohort.

Clinical Symptoms

Gross hematuria within 12 months prior to UCB diagnosis was observed in 70.0% of men and 61.1% of women ($p > 0.05$). The mean time interval between the incidence of gross hematuria and diagnosis of UCB was 11.3 (SD 4.5) months in men and 10.3 (SD 6.7) months in women ($p > 0.05$). Dysuria and/or bladder pain within 4 weeks before initial diagnosis was reported in 38.0% of the male and 55.6% of the female patients ($p > 0.05$). Nocturia 4 weeks prior to UCB diagnosis was reported in 62.0% of the males and 50.0% of the females ($p > 0.05$). Urgency was monitored in 62.0% of the men and 61.1% of the women ($p > 0.05$) (table 1, fig. 2).

Referral Patterns

Direct consultation of a urologist was initiated by 84.0% of the men vs. 66.7% of the women. 16.0% of the men and 33.4% of the women saw their GP and/or gynecologist once or twice before referral to the urologist ($p = 0.120$). Symptomatic treatment by the GP and/or gynecologist was administered once or more in 38.0% of the men and in 44.5% of the women ($p = 0.868$). Treatment of UTI within 12 months prior to initial UCB diagnosis was given to 20.0% of the men and to 61.1% of the women ($p = 0.005$). At first urological consultation, cystoscopy was performed in 88.0% of the men vs. 66.7% of women ($p = 0.07$). Detection of bladder tumor at initial cystoscopy was observed in 96.0% of the men and in 50.0% of the women ($p < 0.001$) (table 1).

Tumor Stage Distribution in Men and Women

Men significantly more often presented with pTa (58.0 vs. 33.3%), pT1 (16.0 vs. 5.6%) and \geq pT2 (18.0 vs. 11.1%) than women, while women were significantly more likely

Name:
Date of birth:

Section I. (To be completed by the treating urologist)

Date of interview:
Date of TUR-BT:
Histopathology: pT []
Low grade [] High grade []
Concomitant CIS Yes [] No []

Section II. (To be completed by the patient)

Smoking habits

- [] I am a non-smoker.
[] I am a smoker. I have been smoking since ____ (year) around ____ cigarettes per day.
[] I am an ex-smoker, I stopped smoking in ____ (year). Prior to that, I smoked around ____ cigarettes per day.

Profession

- Which profession(s) did you have in the last 20 – 30 years of your working life? (multiple choices are possible)
[] Office work
[] Painter/limer/varnisher
[] Hairdresser
[] Dye industry
[] Motor mechanic
[] Housewife
[] Other _____

Symptoms

- (1) Within the last 12 months, did you notice visible blood in your urine?
Yes [] No []
If yes, when was the first time of occurrence of visible blood in your urine?
____ months ago
- (2) Within the last 12 months, did you experience episodes of bladder pain and/or a burning sensation when passing urine?
Yes [] No []
- (3) Within the last 4 weeks, did you experience episodes of permanent or recurring unpleasant urge to pass urine?
Yes [] No []
- (4) Within the last 4 weeks, did you have to get up more often than twice a night to pass urine?
Yes [] No []

Consultations and treatments

- (5) How often did you consult a general practitioner and/or a gynecologist regarding your complaints before you were referred to a urologist for further evaluation?
[] Never, I directly consulted a urologist
[] Once or twice
[] Three times or more often
- (6) How often did you receive symptomatic treatment (e.g. pain medication) regarding your complaints before you were referred to a urologist for further evaluation?
[] Never, I was directly referred to a urologist
[] Once or twice
[] Three times or more often

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(Continued on next page.)

- (7) How often did you receive treatment for bladder infections from your general practitioner and/or gynecologist before you were referred to a urologist for further evaluation?
 Never
 Once or twice
 Three times or more often
- (8) Did the urologist perform a cystoscopy at the first consultation?
 Yes No
- (9) Was the bladder tumor discovered at the first cystoscopy performed?
 Yes No

Fig. 1. Questionnaire.

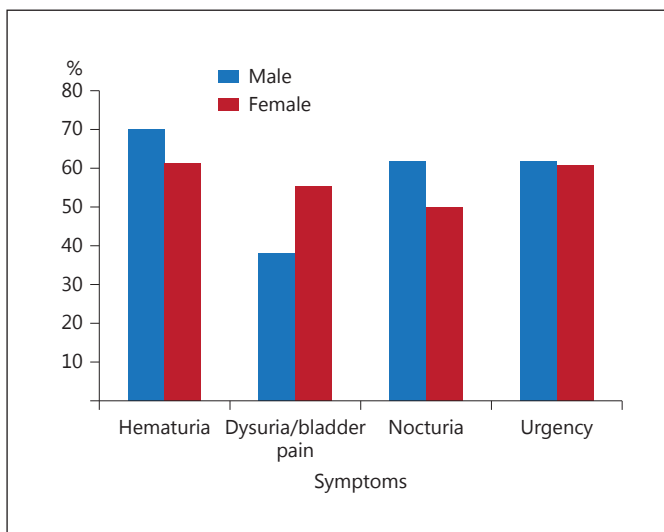


Fig. 2. Clinical symptoms within 12 months prior to initial diagnosis of UCB.

than men to be associated with carcinoma in situ (CIS) only (50.0 vs. 8.0%, $p = 0.002$ for all). High-grade tumor distribution was 64.0% in men vs. 61.1% in women ($p > 0.05$). Tumor stage distribution in detail can be seen in table 2.

Discussion

Data on gender-associated differences in referral patterns at the time of initial UCB diagnosis are rare. The current study revealed several disparities in clinical symptoms, referral patterns, tumor stages and grading between both sexes. In terms of clinical symptoms, gross hematu-

ria was more frequently observed in men than women; women suffered more often from dysuria and/or bladder pain, while nocturia was more prevalent in men. Furthermore, female patients were more often treated for voiding disorders or presumed UTIs without further examination or prompt referral to specialized care by the urologist compared to men. In addition, tumor detection by the urologist was more often observed at second cystoscopy in females, while in the vast majority of the male population, bladder tumors were detected during first cystoscopy.

The findings of the present study are largely congruent with the findings of Henning et al. [5]. The authors presented a questionnaire-based study in which they also found that women were more likely to be treated by their GP or gynecologist for voiding complaints and UTIs instead of being directly referred to a urologist. In terms of gender-related differences in clinical symptoms, their results are mostly in line with our findings with respect to dysuria and/or bladder pain and urgency. The differences between the results in the present and Henning et al.'s cohort refer to the frequency of hematuria and nocturia, which both were more frequently observed in men than women in our study population and conversely in Henning et al.'s study. Furthermore, women in Henning et al.'s cohort more often presented with stage $\geq pT2$, while we observed more stage $\geq pT2$ (18.0 vs. 11.1%) in men and no differences regarding tumor grade distribution (64.0 vs. 61.1%). However, the comparability of Henning et al.'s and our findings is limited due to the small sample size in our population. Nevertheless, the gender distribution in Henning et al.'s cohort ($n = 168$), with 77.0% male and 23.0% female patients, and in our cohort ($n = 68$), with 73.5% male and 26.5% female patients, was similar [2]. Moreover, the questionnaire developed by Henning et al.

Table 1. Descriptive characteristics of 68 patients with an initial diagnosis of UCB

| | Entire population (n = 68) | Men (n = 50) | Women (n = 18) | p |
|--|-------------------------------|-----------------|-------------------|--------|
| <i>Demographics</i> | | | | |
| Age, years (median; IQR) | 68 (61; 76) | 68 (58; 76) | 69 (63; 74) | 0.583 |
| <i>Smoking habits</i> | | | | |
| Non-smoker | 23 (33.8%) | 18 (36.0%) | 5 (27.8%) | 0.425 |
| Smoker | 16 (23.5%) | 13 (26.0%) | 3 (16.7%) | |
| Ex-smoker | 29 (42.6%) | 19 (38.0%) | 10 (55.6%) | |
| Number of pack-years, smokers (mean ± SD) | 34±19 | 34±20 | 32±14 | 0.893 |
| Number of pack-years, ex-smokers (mean ± SD) | 24±15 | 25±19 | 21±4 | 0.772 |
| <i>Profession</i> | | | | |
| Office work | 22 (32.4%) | 16 (32.0%) | 6 (33.3%) | 0.001 |
| Painter/limer/varnisher | 3 (4.4%) | 1 (2.0%) | 2 (11.1%) | |
| Hairdresser | 0 | 0 | 0 | |
| Dye industry | 1 (1.5%) | 0 | 1 (5.6%) | |
| Motor mechanic | 3 (4.4%) | 3 (6.0%) | 0 | |
| Housewife | 4 (5.9%) | 0 | 4 (22.2%) | |
| Other | 35 (51.5%) | 5 (10.0%) | 5 (27.8%) | |
| <i>Clinical symptoms</i> | | | | |
| Presence of gross hematuria within the last 12 months | | | | |
| Yes | 46 (67.6%) | 35 (70.0%) | 11 (61.1%) | 0.562 |
| No | 22 (32.4%) | 15 (30.0%) | 7 (38.9%) | |
| Time from first episode of gross hematuria to initial diagnosis of UCB, months | 11.0±4.0 | 11.3±4.5 | 10.3±6.7 | 0.351 |
| Presence of dysuria and/or bladder pain | | | | |
| Yes | 46 (67.6%) | 19 (38.0%) | 10 (55.6%) | 0.268 |
| No | 22 (32.4%) | 31 (62.0%) | 8 (44.4%) | |
| Incidence of nocturia within the last 4 weeks | | | | |
| Yes | 40 (58.8%) | 31 (62.0%) | 9 (50.0%) | 0.413 |
| No | 28 (41.2%) | 19 (38.0%) | 9 (50.0%) | |
| Incidence of urgency within the last 4 weeks | | | | |
| Yes | 42 (61.8%) | 31 (62.0%) | 11 (61.1%) | 0.947 |
| No | 26 (38.2%) | 19 (38.0%) | 7 (38.9%) | |
| <i>Consultation and treatment</i> | | | | |
| Frequency of treatment by GP/gynecologist before referral to urologist | | | | |
| Never, initial treatment by urologist | 54 (79.4%) | 42 (84.0%) | 12 (66.7%) | 0.120 |
| Once or twice | 13 (19.1%) | 8 (16.0%) | 5 (27.8%) | |
| Three times or more often | 1 (1.5%) | 0 | 1 (1.5%) | |
| Symptomatic treatment before referral to urologist | | | | |
| Never, initial treatment by urologist | 41 (60.3%) | 31 (62.0%) | 10 (55.6%) | 0.868 |
| Once or twice | 11 (16.2%) | 8 (16.0%) | 3 (16.7%) | |
| Three times or more often | 16 (23.5%) | 11 (22.0%) | 5 (27.8%) | |
| Treatment of UTI within the last 12 months | | | | |
| Never | 47 (69.1%) | 40 (80.0%) | 7 (38.9%) | 0.005 |
| Once or twice | 14 (20.6%) | 7 (14.0%) | 7 (38.9%) | |
| Three times or more often | 7 (10.3%) | 3 (6.0%) | 4 (22.2%) | |
| Cystoscopy at first consultation | | | | |
| Yes | 56 (82.4%) | 44 (88.0%) | 12 (66.7%) | 0.068 |
| No | 12 (17.6%) | 6 (12.0%) | 6 (33.3%) | |
| Detection of bladder tumor at first cystoscopy | | | | |
| Yes | 57 (83.3%) | 48 (96.0%) | 9 (50.0%) | <0.001 |
| No | 11 (16.2%) | 2 (4.0%) | 9 (50.0%) | |

Table 2. Gender-specific associations of pathologic tumor stage and grade in 68 patients with an initial diagnosis of UCB

| | Entire population (n = 68) | Men (n = 50) | Women (n = 18) | p |
|--|-------------------------------|-----------------|-------------------|-------|
| Pathologic tumor stage at initial TUR-BT | | | | |
| CIS only | 13 (19.1%) | 4 (8.0%) | 9 (50.0%) | 0.002 |
| pTa | 35 (51.5%) | 29 (58.0%) | 6 (33.3%) | |
| pT1 | 9 (13.2%) | 8 (16.0%) | 1 (5.6%) | |
| ≥pT2 | 11 (16.2%) | 9 (18.0%) | 2 (11.1%) | |
| Tumor grading at initial TUR-BT | | | | |
| Low grade | 25 (36.8%) | 18 (36.0%) | 7 (38.9%) | 0.827 |
| High grade | 43 (63.2%) | 32 (64.0%) | 11 (61.1%) | |

was implemented in our cohort with a response rate of nearly 100%.

The gender-related delay of initial UCB diagnosis might be due to the misinterpretation of hematuria and voiding complaints. Several studies have shown that hematuria is a strong predictor for genitourinary malignancies, especially bladder cancer [7]. Therefore, further evaluation of hematuria is always warranted, since up to 92% of cancers detected during the work-up of hematuria are still locally staged and thus potentially curable [8]. Furthermore, urgency is often misinterpreted as a symptom for UTI that incites the treating physician to prescribe antibiotics and/or estrogen medication in elderly women [9]. A Swedish study demonstrated that referral to the urologist was delayed in women with urgency and hematuria. Thus, women presented with an advanced stage of UCB at initial diagnosis [10]. Nieder et al. [9] conducted a questionnaire-based survey to analyze practice patterns of the evaluation of hematuria by primary care physicians. They observed that up to 31% of patients presenting with gross hematuria were not referred to a urologist for specialized care. Similar results were reported by Yafi et al. [11], who demonstrated that only 48.6% of the evaluated primary care physicians would refer a postmenopausal woman with two consecutive events of significant microscopic hematuria to a urologist. Johnson et al. [12] showed in their findings with 926 healthcare plan participants that men with initial or recurrent episodes of hematuria are advised to consult the urologist more often than women, which is underlined by our findings. In Johnson et al.'s study, women were more likely to turn to the GP and/or gynecologist than men before referral to the urologist, which is also in line with our observations. When taking the aforementioned studies and our cohort into consideration, higher awareness of hematuria and urgency is required on the part of GPs and gynecolo-

gists to avoid a delayed diagnosis of UCB, which is associated with an adverse outcome [13].

Several hypotheses have been generated to explain the underlying reasons for the gender-related disparities in UCB, including anatomy and hormonal involvement [13]. In non-muscle-invasive bladder cancer, Kluth et al. [14] reported that female gender was associated with a higher risk of disease recurrence. Similar findings were observed by the Club Urológico Español de Tratamiento Oncológico [15], Palou et al. [16] and Keck et al. [17], who demonstrated that female gender was an independent predictor of disease recurrence, progression and impaired overall survival. On the other hand, Sylvester et al. [18] did not find an independent impact of gender within EORTC trials comprising roughly 2,600 patients with Ta or T1 non-muscle-invasive bladder cancer after TUR-BT. In muscle-invasive bladder cancer, Kluth et al. [19], in a large multicenter series with roughly 1,600 female patients, previously showed that female gender was significantly associated with disease recurrence and cancer-specific mortality. Mungan et al. [20] reported impaired cancer-specific survival in women across all stages of bladder cancer within an epidemiological survey comprising all types of therapy performed from 1973 to 1996. Horstmann et al. [21] described a significantly reduced 10-year survival in women undergoing radical cystectomy from 1969 to 1997. In addition, two further multicenter studies also found an impaired cancer-specific survival in women, particularly when lymphovascular invasion was present [22, 23]. Interestingly, higher tumor stages were only seen in our male population. Furthermore, 50.0% of the female patients in our cohort presented with CIS only. A subgroup analysis (data not shown) revealed that in 33.3% of the latter patients, bladder tumor was not detected at initial cystoscopy. Although showing statistical significance, our findings in terms of higher tumor stage distri-

bution between men and women are limited due to the small sample of $\geq pT2$ tumors.

Evaluation of urinary cytology samples at the time of first cytology would have been reasonable to detect CIS earlier [24]. To what extent other tests in addition to urinary cytology might lead to a benefit in the early diagnosis of bladder cancer still remains a matter of debate. Here, several studies have evaluated the efficacy of urinary markers as non-invasive tools. Bassi et al. [25] stated that most of the markers tend to be less specific but more favorable in terms of sensitivity compared to urinary cytology. Another comparative study focusing on NMP22, BTA stat test and cytology ascribed NMP22 a higher sensitivity than cytology [26]. Sagnak et al. [27] recommend NMP22 as a cost-effective method in combination with upper tract ultrasonography instead of urine cytology for low-risk patients with asymptomatic microscopic hematuria. Nevertheless, urinary cytology shows excellent tumor detection of relevant high-grade urothelial carcinoma [28]. Hence, it will most likely continue to be used in the initial evaluation of patients with suspected urological malignancy until new markers are indicated to be optimal, showing favorable sensitivity and specificity [29].

Our study is not devoid of limitations. The data are based on a non-validated questionnaire and are poten-

tially hampered by a recall bias regarding the first onset of clinical symptoms prior to diagnosis. Furthermore, we were not able to provide data on oncological outcome. Finally, our findings are limited by the small sample size. However, our data were assessed in a prospective fashion from two tertiary academic centers from two European countries.

Conclusions

This prospective cohort study revealed differences between referral patterns for men and women. Women presenting with clinical symptoms such as hematuria and voiding disorders are frequently misinterpreted by the treating GP and/or gynecologist; this contributes to a deferred diagnosis of UCB, which can be associated with poor outcome. Primary care physicians should be aware of this scenario and therefore consider early referral to specialized care, particularly in patients presenting with treatment-refractory bladder symptoms.

Disclosure Statement

The authors have nothing to disclose.

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