

Sex-related differences in non-urothelial variant histology, non-muscle invasive bladder cancer

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Introduction Non-urothelial variant histology (VH), non-muscle invasive bladder cancer (NMIBC) has received little attention in contemporary urologic literature. Specifically, the effect of female sex on stage at presentation, as well as on cancer-specific mortality (CSM) have not been previously examined in VH NMIBC. Our aim was to test the effect of female sex on stage at presentation and CSM in VH NMIBC.

Material and methods Within the Surveillance, Epidemiology, and End Results (SEER) database (2004–2016), we identified patients aged ≥ 18 years, with histologically confirmed VH NMIBC. Logistic regression models addressed T1 stage at diagnosis after multivariable adjustments for tumor grade, age and race/ethnicity. Before Kaplan-Meier plots and Cox regression analyses, propensity score matched adjusting for histological variants, T-stage, tumor grade, age and race/ethnicity was performed.

Results Overall, 2,205 VH NMIBC patients were identified. Of those, 28% (n = 607) were female. Females were older (77 vs 74 years, $p < 0.001$) and more frequently harbored T1 stage (55 vs 45%, $p < 0.001$). Female sex independently predicted T1 stage (odds ratio [OR] = 1.66, 95% Confidence Interval [CI] = 1.35–2.03, $p < 0.001$). Female sex also exhibited higher CSM, after matching for all assessable variables, including stage (hazard ratio [HR] = 1.91, 95% CI = 1.45–2.54, $p < 0.001$).

Conclusions In VH NMIBC, female sex is an indicator of higher rate of T1 stage and, fully independently of stage, female sex also results in higher CSM.

Key Words: non-muscle invasive bladder cancer \leftrightarrow adenocarcinoma \leftrightarrow neuroendocrine carcinoma \leftrightarrow variant histology \leftrightarrow squamous cell carcinoma \leftrightarrow Surveillance, Epidemiology, and End Results

INTRODUCTION

Non-urothelial variant histology (VH) accounts for 10 to 25% of bladder cancers (BCas) [1, 2]. Relative to urothelial, non-urothelial variant histology

non-muscle invasive bladder cancer (VH NMIBC) has received relatively little attention in all aspects. Specifically, the association between female sex and stage at presentation of VH NMIBC has not been examined. Similarly, the association between female

sex and cancer-specific mortality (CSM) has also not been addressed. We addressed these voids within the most contemporary Surveillance, Epidemiology, and End Results (SEER) database (2004–2016). We relied on the 2016 World Health Organization (WHO) classification and addressed four different VH NMIBC groups, namely squamous cell carcinoma (SCC), adenocarcinoma (AD), neuroendocrine carcinoma (NE), and other types (Other VH) [3]. We hypothesized that female sex affects stage at presentation and CSM, in patients with VH NMIBC.

MATERIAL AND METHODS

Study population

Within the Surveillance, Epidemiology, and End Results (SEER) database (2004–2016), we identified patients treated with transurethral bladder tumor resection (TURBT), aged ≥ 18 years, with histologically confirmed BCa (International Classification of Disease for Oncology site code C67.0-9) of NMIBC ($\leq T1N0M0$), according to the American Joint Committee on Cancer (AJCC), seventh edition. Mixed histology is not coded in the SEER database. Thus, definition of non-urothelial variant histology reflected the predominant histologic subtype [1]. According to the 2016 World Health Organization (WHO) classi-

fication, four major non-urothelial histologic variants BCa of all grades were included: squamous cell carcinoma (SCC) [4], adenocarcinoma (AD) [5], neuroendocrine carcinoma (NE) [6], and other types (Other VH) [3]. Patients with a diagnosis of urothelial carcinoma of urinary bladder (UCUB), as well as autopsy, death certificate-only cases and patients receiving radiotherapy and/or chemotherapy and/or surgical treatment different from TURBT, according to SEER surgery code, were excluded.

Statistical analyses

First, we examined the association between female sex and T stage at diagnosis. Tabulations were complemented with univariable and multivariable logistic regression models (LRM) predicting T1 stage. The main predictor consisted of female vs male sex. Second, we focused on CSM and relied on Kaplan-Meier plots and Cox regression models. The main predictor consisted of female vs male sex. To adjust for sociodemographic and clinical differences between females and males, propensity score matching (PSM) was applied. One to one PSM was applied and relied on histological variants (SCC, AD, NE and Other), T-stage (Ta, Tis, T1), tumor grade (G1–G2, G3–G4 and unknown), age at diagnosis (one-year interval) and race/ethnicity

Table 1. Descriptive characteristics of 2,205 patients diagnosed with non-urothelial variant histology non-muscle invasive bladder cancer (VH-NMIBC), according to sex (female vs male)

Variable	Overall (n = 2,205)	Male (n = 1,598, 72%)	Female (n = 607, 28%)	p-value
Age at diagnosis (years)	75	74	77	<0.001
Median (IQR)	(65–82)	(65–81)	(68–84)	
Follow-up (months)	40	44	28	<0.001
Median (IQR)	(12–87)	(16–88)	(6–82)	
Race/ethnicity				0.3
Caucasian	1,832 (83.1)	1,334 (83.5)	498 (82.0)	
African–American	143 (6.5)	94 (5.9)	49 (8.1)	
Hispanic–Latinos	128 (5.8)	97 (6.1)	31 (5.1)	
Unknown/other	102 (4.6)	73 (4.6)	29 (4.8)	
Variant histology				<0.001
Squamous cell carcinoma	949 (43.0)	639 (40.0)	310 (51.1)	
Adenocarcinoma	316 (14.3)	245 (15.3)	71 (11.7)	
Neuroendocrine carcinoma	104 (4.7)	83 (5.2)	21 (3.5)	
Other	836 (37.9)	631 (39.5)	205 (33.8)	
T stage				<0.001
Ta	594 (26.9)	458 (28.7)	136 (22.4)	
Tis	588 (26.7)	453 (28.3)	135 (22.2)	
T1	1,023 (46.4)	687 (43.0)	336 (55.4)	
Tumor grade				0.037
Low-grade	662 (30.0)	457 (28.6)	205 (33.8)	
High-grade	700 (31.7)	509 (31.9)	191 (31.5)	
Unknown	843 (38.2)	632 (39.5)	211 (34.8)	

n – number of patients; IQR – interquartile range

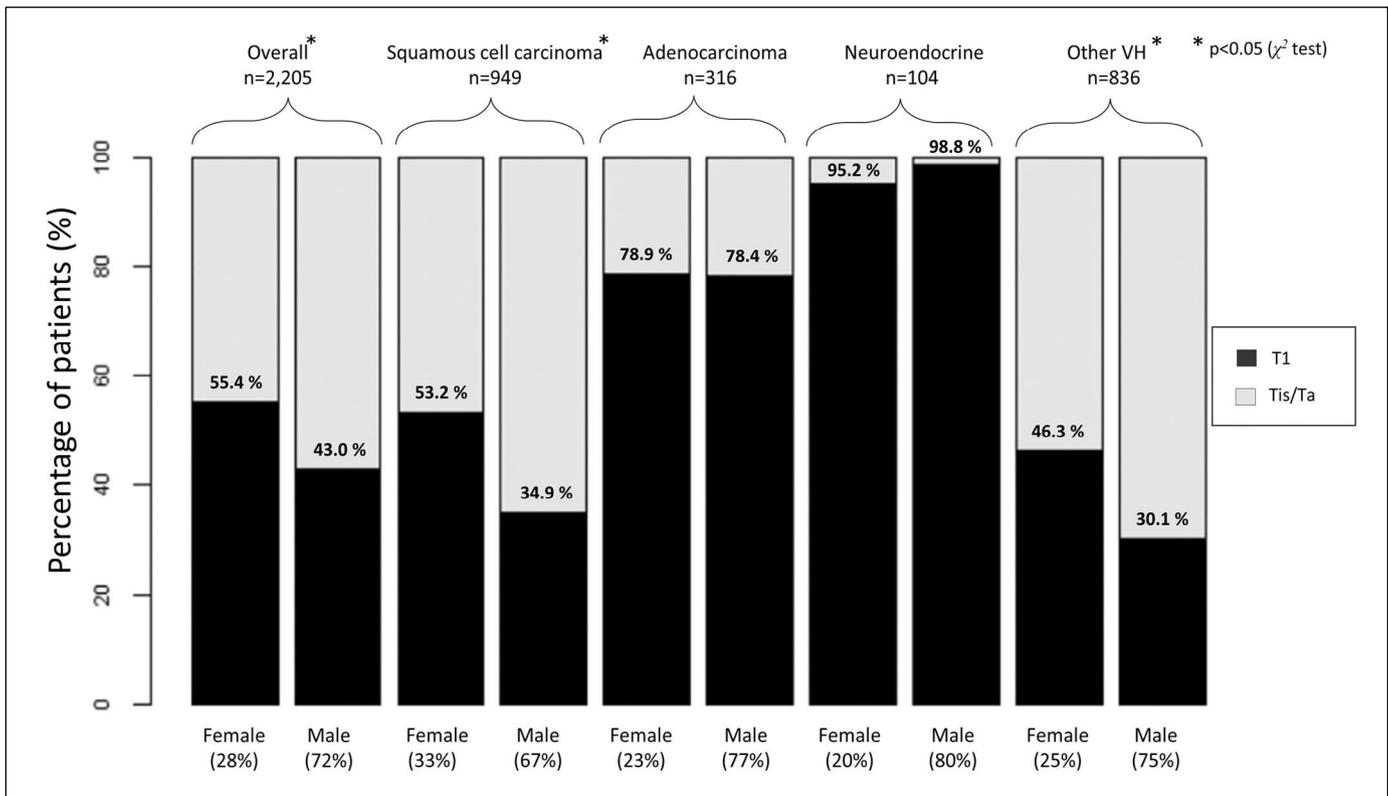


Figure 1. Stacked bar plots depicting stage at presentation (T1 vs Tis-Ta) according to patient sex in the overall cohort and within non-urothelial variant histology non-muscle invasive bladder cancer (VH NMIBC) subgroups.

n – number of patients, VH – variant histology; p – p-value

(Caucasian, African-American, Hispanic-Latinos and Other).

Third, all CSM analyses were repeated within each VH NMIBC subgroup. Prior to CSM analyses, PSM was reapplied in 1:1 fashion in SCC, AD, NE and Other VH. All tests were two-sided with a level of significance set at $p < 0.05$ and R software environment for statistical computing and graphics (version 3.4.3) was used for all analyses [7].

RESULTS

Descriptive characteristics of the non-urothelial variant histology non-muscle invasive bladder cancer

Overall, 2,205 VH NMIBC patients were identified (Table 1). Of those, 28% (n = 607) were female. Female sex was less frequent in all VH NMIBC subgroups, namely SCC (n = 310, 33%), AD (n = 71, 23%), NE (n = 21, 20%) and Other (n = 205, 25%). In the overall cohort of VH NMIBC, females were older (77 vs 74 years, $p < 0.001$) than males. After stratification according to VH NMIBC subgroups, older female age applied to SCC (77 vs 73 years,

$p < 0.001$), AD (80 vs 74 years, $p = 0.013$) and Other (75 vs 72 years, $p = 0.005$), but not to NE (76 vs 80 years, $p = 0.2$).

Effect of female sex on tumor stage

Females were more frequently diagnosed with T1 stage than males (55 vs 45%, $p < 0.001$). This difference applied to the overall VH NMIBC cohort and also specifically applied to SCC and Other ($p < 0.010$, Figure 1), but not to AD and NE (Figure 1).

In the overall VH NMIBC cohort, female sex was an independent predictor of T1 stage, after adjustment for age, tumor grade and race (OR = 1.66, $p < 0.001$, Table 2). Moreover, within VH NMIBC subgroups, female sex was an independent predictor of T1 stage in SCC (OR = 2.21, $p < 0.001$) and Other (OR = 1.77, $p = 0.002$), but not in AD and NE (Table 2).

Effect of female sex on cancer-specific mortality

In the overall VH NMIBC cohort, PSM was applied between 607 females and 1598 males. One to one PSM (VH, T-stage, tumor grade, age and race) resulted in two equally sized groups of 607 females

Table 2. Univariable and multivariable logistic regression analyses predicting T1 in overall cohort of non-urothelial variant histology non-muscle invasive bladder cancer (VH-NMIBC), as well as in squamous cell carcinoma (SCC), adenocarcinoma (AD), neuroendocrine carcinoma (NE) and others types (Other VH). Multivariable adjustments were made for tumor grade, patients age and race. Patient sex (female vs male) represented the main predictor

	Univariable logistic regression		Multivariable logistic regression	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Overall (n = 2205) Female vs male	1.64 (1.36–1.99)	<0.001	1.66 (1.35–2.03)	<0.001
Squamous cell carcinoma (n = 949) Female vs male	2.12 (1.61–2.80)	<0.001	2.21 (1.63–3.00)	<0.001
Adenocarcinoma (n = 316) Female vs male	1.03 (0.55–2.02)	0.9	1.01 (0.53–2.01)	1
Neuroendocrine carcinoma (n = 104) Female vs male	0.24 (0.01–6.35)	0.3	0.23 (0.01–6.80)	0.3
Other VH (n = 836) Female vs male	2.01 (1.45–2.77)	<0.001	1.77 (1.24–2.53)	0.002

n – number of patients; VH – variant histology; OR – odds ratio; CI – confidence interval

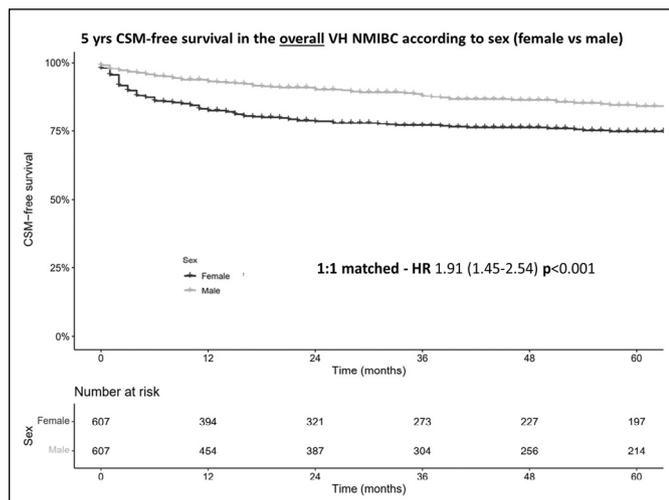


Figure 2. Kaplan-Meier plots illustrating five-years CSM-free survival in females versus males: after 1:1 matching for VH, T stage, grade, age and race in the overall VH NMIBC cohort. CSM – cancer-specific mortality; VH NMIBC – variant histology non-muscle invasive bladder cancer; p – p-value; HR – hazard ratio

vs 607 males, with no residual statistically significant differences in VH, T stage, tumor grade, age and race. In Kaplan-Meier plots (Figure 2), five-year CSM-free survival was 75% (95% CI = 71–79%) for females vs 84% (95% CI = 81–87%) for males (log-rank test, $p < 0.001$), which translated into a hazard ratio (HR) of 1.91 (1.45–2.54, $p < 0.001$) for females vs males. Subsequently, all the above steps including PSM were repeated in each VH NMIBC subgroup. In SCC patients (n = 949, 43%), PSM was applied between 310 females and 639 males. One to one PSM (T stage,

tumor grade, age and race) resulted in two equally sized groups of 310 females vs 310 males, with no residual statistically significant differences in T stage, tumor grade, age and race. In Kaplan-Meier plots (Figure 3A), five-year CSM free-survival was 71% (95% CI = 66–77%) for females vs 88% (95% CI = 84–92%) for males (log-rank test, $p < 0.001$), which translated into a hazard ratio (HR) of 2.42 (1.64–3.56, $p < 0.001$).

In AD patients (n = 316, 14%), PSM was applied between 71 females and 245 males. One to one PSM (T stage, tumor grade, age and race) resulted in two groups of 71 females vs 71 males, with no residual statistically significant differences in T stage, tumor grade, age and race. In Kaplan-Meier plots (Figure 3B), five-year CSM-free survival was 70% (95% CI = 59–84%) for females vs 81% (95% CI = 71–93%) for males (log-rank test, $p = 0.2$), which translated into a hazard ratio (HR) of 1.55 (0.73–3.30, $p = 0.3$).

In NE patients (n = 104, 5%), PSM was applied between 21 females and 83 males. One to one PSM (T stage, tumor grade, age and race) resulted in two groups of 19 females vs 19 males, with no residual statistically significant differences in T stage, tumor grade, age and race. No sex-related differences in CSM were recorded in this subgroup. In Kaplan-Meier plots (Figure 3C), five-year CSM-free survival was 75% (95% CI = 59–99%) for females vs 66% (95% CI = 45–97%) for males (log-rank test, $p = 0.5$), which translated into a hazard ratio (HR) of 0.62 (0.14–2.62, $p = 0.5$).

In Other VH patients (n = 936, 38%), PSM was applied between 205 females and 631 males. One to one PSM (T stage, tumor grade, age and race) re-

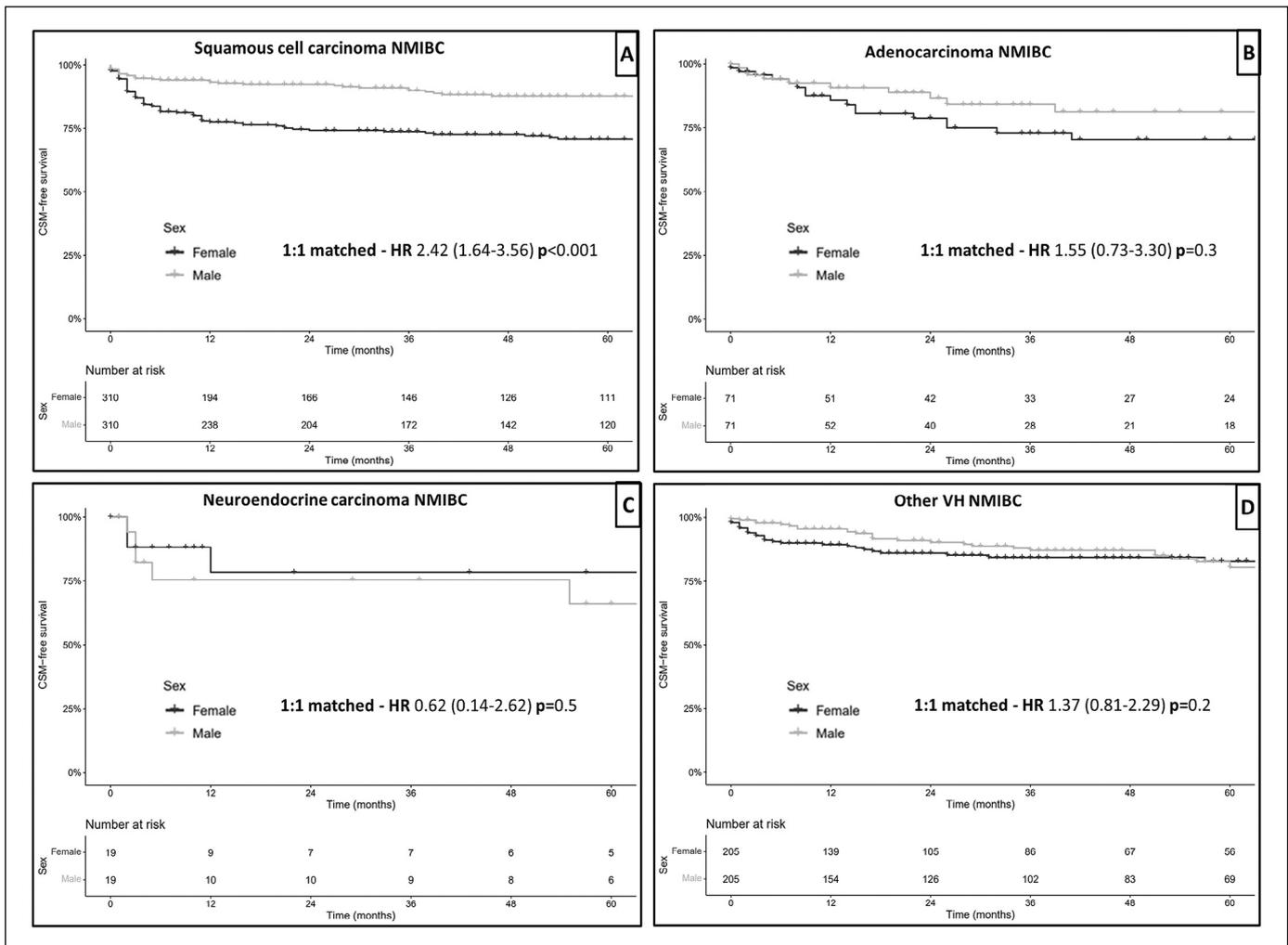


Figure 3. Kaplan-Meier plots illustrating five-years CSM-free survival in females versus males after 1:1 matching for T stage, grade, age and race in SCC subgroup (A); after 1:1 matching for T stage, grade, age and race in AD subgroup (B); after 1:1 matching for T stage, grade, age and race in NE subgroup (C); after 1:1 matching for T stage, grade, age and race in Other VH subgroup (D).

n – number of patients, CSM – cancer-specific mortality; HR – hazard ratio; VH NMIBC – variant histology non-muscle invasive bladder cancer

sulted in two groups of 205 females vs 205 males, with no residual statistically significant differences in T stage, tumor grade, age and race. In Kaplan-Meier plots (Figure 3D), five-year CSM-free survival was 83% (95% CI = 77–89%) for female vs 80% (95% CI = 74–88%) for male (log-rank test, $p = 0.2$), which translated into a hazard ratio (HR) of 1.37 (0.81–2.29, $p = 0.2$).

DISCUSSION

We hypothesized that female sex affects stage at presentation and CSM among patients with VH NMIBC. Moreover, we tested whether stage and CSM sex-related differences also applies to VH NMIBC subgroups, namely SCC, AD, NE and Other VH. We explored

these three hypotheses within the SEER database and observed important differences between females vs males.

First, we observed sex distribution differences and age distribution differences in VH NMIBC. Specifically, female sex was less frequent in the overall cohort, as well as in all VH NMIBC subgroups. Similarly, females were older in the overall VH NMIBC cohort, as well as in SCC, AD and Other VH NMIBC subgroups but not in NE.

Second, we also observed sex-specific stage distribution differences. Specifically, females more frequently harbored T1 stage vs males. This observation applied to the overall VH NMIBC cohort, as well as to SCC and Other VH, but not to AD and NE. Independent predictor status of female sex for T1 stage was

observed in multivariable logistic regression models in the overall VH NMIBC cohort, as well as in SCC and Other VH, but not in AD and NE. In consequence, female sex predisposes to T1 stage in VH NMIBC and specifically, in SCC and Other VH.

Third, female sex exhibited higher CSM, after matching for stage, in the overall VH NMIBC cohort. Moreover, higher CSM in females, after matching, also applied to SCC, but not to AD, NE and Other VH. In consequence, in SCC, female sex should not only be interpreted as a risk factor for higher stage, but also for higher CSM. Lack of association between female sex and CSM in the AD, NE and Other VH, might be related to limited sample size or might reflect true absence of association. Unfortunately, our observations were too scant to distinguish between these two explanations.

Fourth, it is important to emphasize a two-step process, whereby female sex independently predisposes to both more advanced stage and higher CSM, even after adjustment for stage and other variables in CSM models. This two-step adverse relationship between female sex and stage, as well as female sex and CSM, was previously described by Rosiello et al. in UCUB treated with radical cystectomy [8]. Similarly, other studies reported stage disadvantage and higher CSM in females vs males [9–12]. However, to the best of our knowledge, the relation between female sex and T1 stage, as well as female sex and higher CSM have never been specifically examined in a population-based cohort of VH NMIBC treated with TURBT. Consequently, our findings cannot be directly compared to previous reports.

The clinical implications of our findings are two-fold. First, it may be possible that female sex does not represent a biological determinant of more advanced stage in VH NMIBC, as well as in UCUB treated with cystectomy. Under such scenario, as reported by Rosiello et al., stage disadvantage in females may reflect a female-specific delay in BCa diagnosis. Indeed, sex-related differences in referral patterns were reported by Mansson et al. [13], who found that a higher proportion of females with BCa were referred to a department other than urology (26.9 vs 3.7%) for initial hematuria work-up compared to males. Moreover, Cohn et al. reported significantly longer delays from initial hematuria diagnosis to urological assessment in females vs males (85.4 vs 73.6 days, $p < 0.001$) [14]. These findings are not surprising, since in females, most general practitioners associate microscopic or even gross hematuria with urinary tract infections [15]. In consequence, efforts should be made to implement better referral patterns and to avoid, or even to eliminate diagnostic delays [16]. Last but not least, detailed longitudinal studies should

examine whether delays in diagnosis represent a valid explanation for the stage disadvantage observed in females or whether female sex truly represents a biological determinant of more advanced stage. Unfortunately, the nature of our database does not allow us to address this question.

The second clinical implication of our work pertains to increased risk of CSM observed in females, after adjustment for stage. Here, the relation between female sex and higher CSM purely and evidently no longer can be explained by diagnostic delays, since stage adjustment was made. In consequences, it may be postulated with reasonable certainty that female sex represents a biological determinant of higher CSM, in VH NMIBC, to a similar extent that was reported by Rosiello et al. in UCUB treated with radical cystectomy. Unfortunately, other important variables, such as number of recurrences [17], TURBT completeness [18], use of intravesical therapy [19], type of intravesical therapy [20], presence of associated carcinoma in situ (CIS) [21], molecular or mutational characteristics [22], smoking [23, 24] and environmental exposure [25] or estrogen effect [26] are routinely not documented in institutional or population databases, although they may also have contributed to these sex-related differences [27]. For example, it is possible that female patients were even more prone to under-staging, since the higher risk of bladder perforation during TURB would prevent surgeons from performing a more aggressive local surgical treatment [28]. Previous studies, looking at non-urothelial VH NMIBC, have reported local under-staging rates of 27% to 57% in clinical stage T1 [29, 30] and rates of occult metastatic disease as high as 27% to 44% [31]. Hypothetically, a higher percentage of patients staged as T1 among women compared to men, might directly correlate to an increased proportion of under-staging in the former group.

To the best of our knowledge, we are the first to report the association between female sex and T1 stage, as well as female sex and higher CSM in VH NMIBC. Nonetheless, we are expanding upon previous findings of Rosiello et al. Despite the novelty of our findings, our observations are limited in several regards. First, our findings are based on limited sample size. However, the current cohort represents the largest group of VH NMIBC ever reported. Nonetheless, subgroups of our cohort were still too small to allow valid analyses. Second, our analysis is retrospective, with all inherent biases such as absence of centralized analysis of TURB specimen. However, no prospective studies investigating VH NMIBC have been published so far. Third, TURBT related information is unknown (surgeons' experience, TURBT completeness, etc.). Last but

not least, recurrence and progression rates are unknown. In consequence, progression rates to muscle invasive, as well as to radical cystectomy cannot be assessed. Nonetheless, our survival analysis allows assessment of CSM, which represents the ultimate and most valid endpoint. These, as well as all other limitations related to the retrospective, population-based nature of the SEER database, apply to this, as to other similar analyses that were based on the SEER database or on other similar large-scale data repositories, such as the National Cancer Data Base, National Inpatient Sample, or National Surgical Quality Improvement Program.

CONCLUSIONS

In VH NMIBC, female sex is an indicator of higher rate of T1 stage and, fully independently of stage, female sex also results in higher CSM.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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