Urologic Oncology: Seminars and Original Investigations 37 (2019) 853−861

UROLOGIC ONCOLOGY

Clinical-Bladder cancer

Bladder cancer survival: Women only fare worse in the first two years after diagnosis

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Received 5 April 2019; received in revised form 23 July 2019; accepted 4 August 2019

Abstract

Objectives: It has consistently been shown that women who are diagnosed with bladder cancer have lower survival than men, but the exact mechanism remains unknown. Most studies assumed that the sex-specific mortality ratio is constant over time, possibly resulting in inaccurate estimates in various periods of follow-up. This study aimed to investigate the sex-specific excess mortality in bladder cancer patients and its variation over follow-up time.

Methods: Observational cohort study. Using data from the population-based Netherlands Cancer Registry, we studied 24,169 patients diagnosed between 2003 and 2014 with histologically confirmed ≥T1 bladder cancer with follow-up until January 2018. We used flexible parametric relative survival models to estimate excess mortality as a function of time for each sex and to explore the effect of covariates on these functions.

Results: Female patients (24%) had worse clinical tumor, node, and metastasis-stage at diagnosis and more often a nonurothelial tumor histology. The excess mortality ratio of sex was not constant over time; in the first two years after diagnosis excess mortality rates for women were higher than for men, but lower thereafter; this applied to both nonmuscle-invasive and muscle-invasive bladder cancer subgroups. Baseline differences in age, tumor, node, and metastasis-stage and histology accounted for only part of the excess mortality gap.

Conclusions: The assumption of proportional hazards over time leads to underestimation of the excess mortality ratio for women in the first two years and overestimation thereafter, when excess mortality is comparable for women and men. Clinicians should incorporate the initial sex-specific poorer outcome in their considerations regarding prognosis and treatment options for female patients, e.g., more invasive treatment and neo-adjuvant treatment. These findings also point towards a mechanism of micrometastatic disease, warranting assessment of sex-specific efficacy in randomized controlled trials on treatments in this patient population.

Keywords: Bladder cancer; Sex differences; Gender differences; Prognosis; Survival

1. Introduction

It is known that women with bladder cancer have worse survival outcomes than men [1−3], in contrast to other cancer types [4,5]. Various factors may account for (part of) this difference, such as a longer diagnostic delay in women, [6,7] differences in risk factor distributions that affect tumor characteristics, anatomy, carcinogen metabolization, and level of sex steroids, [1] and a higher proportion of women presenting with nonurothelial tumors [8]. However, the survival gap is still not explained [7,8].

Cox regression, the most commonly used model for survival outcomes in medical science yields no insight into how the sex-specific mortality rates change over time since diagnosis. In addition, Cox regression by default assumes that hazard ratios (e.g., the ratio of mortality among females

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https://doi.org/10.1016/j.urolonc.2019.08.001
1078-1439/

compared to males) remain constant over time since diagnosis. Although it is possible to relax the assumption of proportional hazards, i.e., to allow the effect of a determinant to vary during the follow-up time, the vast majority of studies on sex differences in bladder cancer survival inappropriately assume proportional hazards.

Flexible parametric survival models are conceptually similar to Cox models, but facilitate easier estimation of sex-specific hazard functions and time-varying hazard ratios [9]. Through such models, the association of baseline patient and disease characteristics can also be explored more adequately. This approach was recently used to study the survival gap in bladder cancer for the first time, resulting in valuable new insights into sex-specific risk profiles over time, i.e., over and underestimation at different time points, although survival was only adjusted for age and T-stage at diagnosis [10].

The current study aims to corroborate and expand these insights by investigating the differences in sex-specific excess mortality in bladder cancer patients and its variation over follow-up time, and by exploring how much of the differences can be explained by differences in patient and tumor characteristics at diagnosis. This will result in more accurate information regarding a sex-specific excess mortality hazard over time and may aid clinicians in decision-making regarding treatment and follow-up scheme.

2. Methods

2.1. Patient cohort and data collection

The Netherlands Cancer Registry (NCR) is a nationwide population-based registry serving the total Dutch population of 17 million inhabitants. All newly diagnosed malignancies are included, mainly based on notification from the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA). Additional sources are the national registry of hospital discharges, hematology departments, and radiotherapy institutions. Independent and trained data managers of the NCR extract high quality data on each patient's diagnosis, staging, and treatment from the medical records [11].

Topography and histology are coded according to the International Classification of Diseases for Oncology (ICD-O-3) [12]. Tumors are staged according to the tumor, node, and metastasis (TNM) classifications of the International Union Against Cancer (UICC) [13] that were applicable at time of diagnosis.

This study included all patients who were newly diagnosed with histologically-confirmed invasive bladder cancer (i.e., ≥T1, N-any, M-any) between 2003 and 2012 in the Netherlands. Only first diagnoses of bladder cancer were included. cT-stage was based on (re-)TURs and imaging where applicable. cN-stage and cM-stage were based on physical examination and imaging. Vital status was obtained through annual linkage with the Municipal Administrative Database, in which (date of) emigration and (date of) death is recorded for all inhabitants of the Netherlands. Information on vital status was available until January 2018.

According to the Central Committee on Research involving Human Subjects (CCMO), this descriptive type of study does not require approval from an ethics committee in the Netherlands. The study was approved by the Privacy Review Board of the Netherlands Cancer Registry.

2.2. Statistical analysis

Follow-up time was determined by the difference between date of death and date of diagnosis if the patient was deceased, or date of linkage with the Municipal Administrative Database if the patient was still alive at time of linkage, in which case they were censored. All patients still alive after 10 years were censored at 10 years.

Survival was analyzed by flexible parametric survival models with sex as independent variable and age at diagnosis, clinical T-stage, clinical N-stage, clinical M-stage, and histology were included as covariates. Interaction terms were included between time and sex, age, and T-stage to allow for nonproportional effects, as well as interactions between the covariates and sex. The baseline hazard was modeled by means of a natural cubic spline function with 4 degrees of freedom. Relative survival was modeled by incorporating a background mortality hazard rate based on age, sex, and period matched life-table data of the general Dutch population retrieved from Statistics Netherlands. Relative survival models yield measures of excess mortality, which represents the excess mortality attributed to bladder cancer over the expected hazard of mortality due to other causes, irrespective of whether the excess mortality is directly or indirectly associated with the disease [14].

Standardized relative survival functions were estimated by forcing identical covariate distributions on male and female patients using the full model to adjust for imbalances in covariates between men and women [15]. All modeling choices were based on the Akaike Information Criterion.

Sensitivity analysis was carried out to assess the impact of potential bias from estimating relative survival based on a population that may have a different smoking background than the patient population (see Appendix). All analyses were carried out in R3.5.2 (package *rstpm2*). Analysis code is available on Github.com/AnkeRichters.

3. Results

3.1. Cohort

In the period of 2003−2012, 24,542 patients were diagnosed with incident clinical T ≥ 1 bladder cancer and recorded in the NCR. Of those, 24,169 (98.5%) had histologically confirmed disease, forming the cohort for this study. Median time from diagnosis to end of follow-up was 4.4 years (interquartile range: 1.3−7.8 years).

The majority of patients were men (76%) and median age at diagnosis was 72 years (Table 1). Women had less favorable cT-stage distribution, with only 36% cT1 at diagnosis compared to 48% in men. In addition, more women than men had lymph node involvement or distant metastasis at diagnosis and women more often had a nonurothelial histological tumor type.

3.2. Overall and relative survival

Men had higher observed overall survival than women, with 5 and 10-year survival probabilities of 43.3% and 27.9%, vs. 37.4% and 26.5%, respectively (Log-rank $P < 0.001$). Five and 10-year overall survival rates in women were 44.9% and 31.9% in the NMIBC subgroup and 12.3% and 8.7% in the MIBC subgroup. For men, these were 47.6% and 30.8% in the NMIBC subgroup and 16.6% and 10.2% in the MIBC group.

The 10-year relative survival rates (i.e., the ratio of all-cause survival in bladder cancer cohort/expected survival in age, sex, period matched general population) also displayed a survival disadvantage in women (Fig. 1).

3.3. Standardized relative survival and excess mortality ratios

Fig. 2A shows unadjusted relative survival curves for men and women. In addition, it shows the adjusted curve of the predicted relative survival in women if they had the distributions of age at diagnosis, cT, cN, cM, and histology of the male study population. It shows that women have lower 10-year relative survival, even after taking into account differences in distribution of prognostic factors at diagnosis. Fig. 2B shows the accompanying absolute excess mortality rates over time, with the absolute excess mortality being highest over the first years and stabilizing at a relatively low excess mortality after 3 years after diagnosis.

In Fig. 2, the excess mortality ratio is plotted against the time since diagnosis, with hazard ratios above 1 indicating higher mortality risk for female patients and hazard ratios below 1 indicating higher mortality risk for male patients at that time. Fig. 3A displays the excess mortality ratio for female patients relative to male patients over time, before and after adjusting for other covariates. The excess mortality ratios over time of other covariates are displayed in Fig. 3B.

Table 1
Baseline characteristics of a population-based cohort of 24,169 bladder cancer patients

	Sex		
	Men N (%)	Women N (%)	All N (%)
All	18,345 (76%)	5,824 (24%)	24,169 (100%)
Age at diagnosis			
0−50	622 (3%)	356 (6%)	978 (4%)
51−60	2,322 (13%)	800 (14%)	3,122 (13%)
61−70	5,101 (28%)	1,378 (24%)	6,479 (27%)
71−80	6,637 (36%)	1,818 (31%)	8,455 (35%)
80−90	3,418 (19%)	1,317 (23%)	4,735 (20%)
90+	245 (1%)	155 (3%)	400 (2%)
Age at diagnosis (median, IQR)	72 (64−79)	73 (63−81)	72 (64−79)
cT at diagnosis			
T1	8,809 (48%)	2,091 (36%)	10,900 (45%)
T2	7,014 (38%)	2,390 (41%)	9,404 (39%)
T3	1,306 (7%)	664 (11%)	1,970 (8%)
T4	1,216 (7%)	679 (12%)	1,895 (8%)
cN at diagnosis			
N0	10,319 (56%)	3,335 (57%)	13,654 (56%)
NX	6,330 (35%)	1,757 (30%)	8,087 (33%)
N+	1,696 (9%)	732 (13%)	2,428 (10%)
cM at diagnosis			
M0	14,354 (78%)	4,539 (78%)	18,893 (78%)
MX	2,825 (15%)	790 (14%)	3,615 (15%)
M1	1,166 (6%)	495 (9%)	1,661 (7%)
Concomitant carcinoma in situ*			
No	6,761 (43%)	2,334 (52%)	9,095 (45%)
Yes	9,062 (57%)	2,147 (48%)	11,209 (55%)
Histological type			
Urothelial cell carcinoma	17,577 (95.8%)	5,276 (90.6%)	22,853 (94.6%)
Squamous cell carcinoma	249 (1.3%)	310 (5.3%)	559 (2.3%)
Adenocarcinoma	164 (0.9%)	87 (1.5%)	251 (1.0%)
Small cell carcinoma	284 (1.6%)	88 (1.5%)	372 (1.5%)
Other histology	71 (0.4%)	63 (1.1%)	134 (0.6%)

* Presence of concomitant carcinoma in situ is only recorded for patients with cT1 or cT2, and if reported by the pathologist.

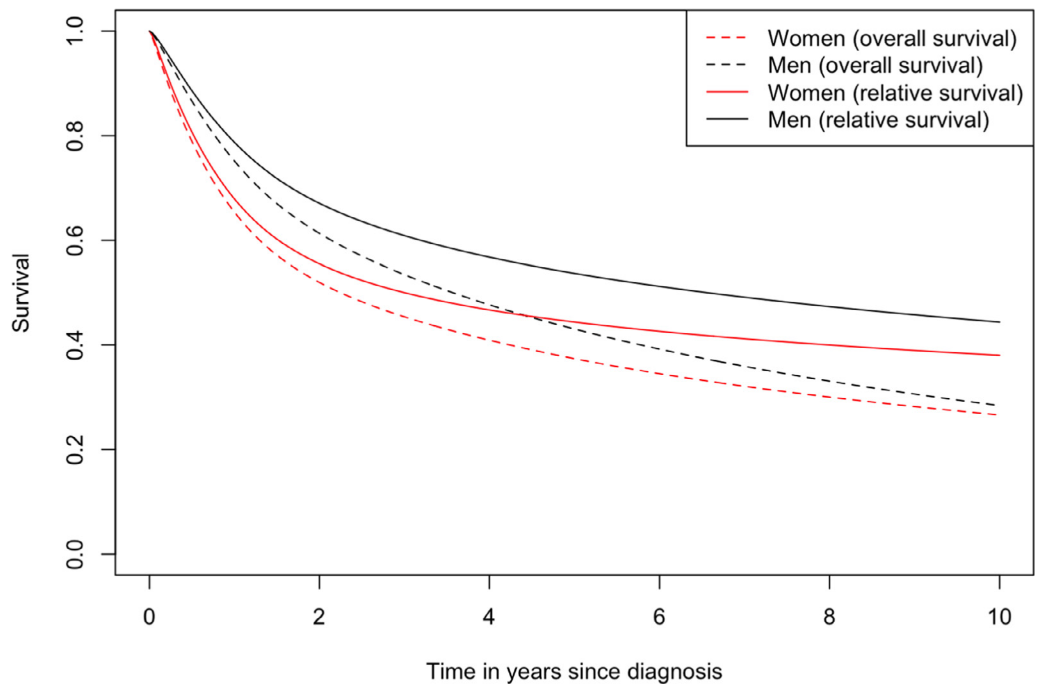

Fig. 1. Modeled overall and relative survival of male and female bladder cancer patients.

In Fig. 4A, the adjusted excess HR for sex is displayed for NMIBC and MIBC separately and for different age groups. The effect of female sex, both the negative effect in the first years as well as the positive effect in later years, is slightly stronger in MIBC patients than in NMIBC patients, although the overall trend is similar. Fig. 4B shows that the excess mortality ratio trend for women is slightly different in the ages above 80 with a consistently higher hazard ratio over almost the entire follow-up period; in this age group the hazard ratio does not fall below 1 at all, leaving women worse off over the entire follow-up period.

Calculated excess mortality ratios for sex in different scenarios of smoking exposure for sensitivity analysis are shown in Appendix 1.

4. Discussion

The current study corroborated lower relative survival in women compared to men after being diagnosed with bladder cancer. Importantly, the ratio of excess mortality in men and women was not constant over time. Within the first 2 years after diagnosis, the excess mortality ratio for sex was considerably higher than during later years. Immediately after diagnosis, excess mortality among women was approximately 1.5 times higher than excess mortality among men, dropping to an equal risk after approximately 2 years. Thereafter, women had a slightly lower excess mortality, but given the strong decrease in absolute hazard after 2 years compared to the first 2 years, this can be considered a negligible disadvantage for men after 2 years.

Women had prognostically worse disease characteristics at diagnosis, including higher disease stage and more often nonurothelial tumors, but adjustment for the distribution of prognostic factors only accounted for part of the difference in excess mortality profiles between men and women. Both NMIBC and MIBC patient subgroups showed a similar hazard ratio trend. The trend was only different for patients over 80 years old. In this subgroup, the mortality risk for women remained higher throughout the 10 years after diagnosis.

Literature consistently reports higher mortality for women than men, but only constant hazard ratios reflecting the complete follow-up periods of 5 or 10 years have been reported [1,3,16,17]. Moreover, the hazard ratios varied considerably among different patient populations, most of which were not population-based. One population-based study showed a hazard ratio for cancer-specific death of 1.39, which was not corrected for TNM-stages at diagnosis, thereby probably overestimating the difference [3]. The sex-specific risk profiles over time from the current study clearly show how single hazard ratios that are supposed to reflect the entire follow-up provide a misleading understanding of the actual mortality risk over time [17]. Forcing the assumption of a constant hazard ratio throughout follow-up time resulted in underestimation of the excess mortality ratio for women in the first period after diagnosis, with reported hazard ratios of 1.17 and 1.25, whereas we demonstrated a hazard ratio of approximately 1.5 right after diagnosis [1]. On the other hand, the constant hazard ratios cause a serious overestimation thereafter, where women actually have lower risk of mortality.

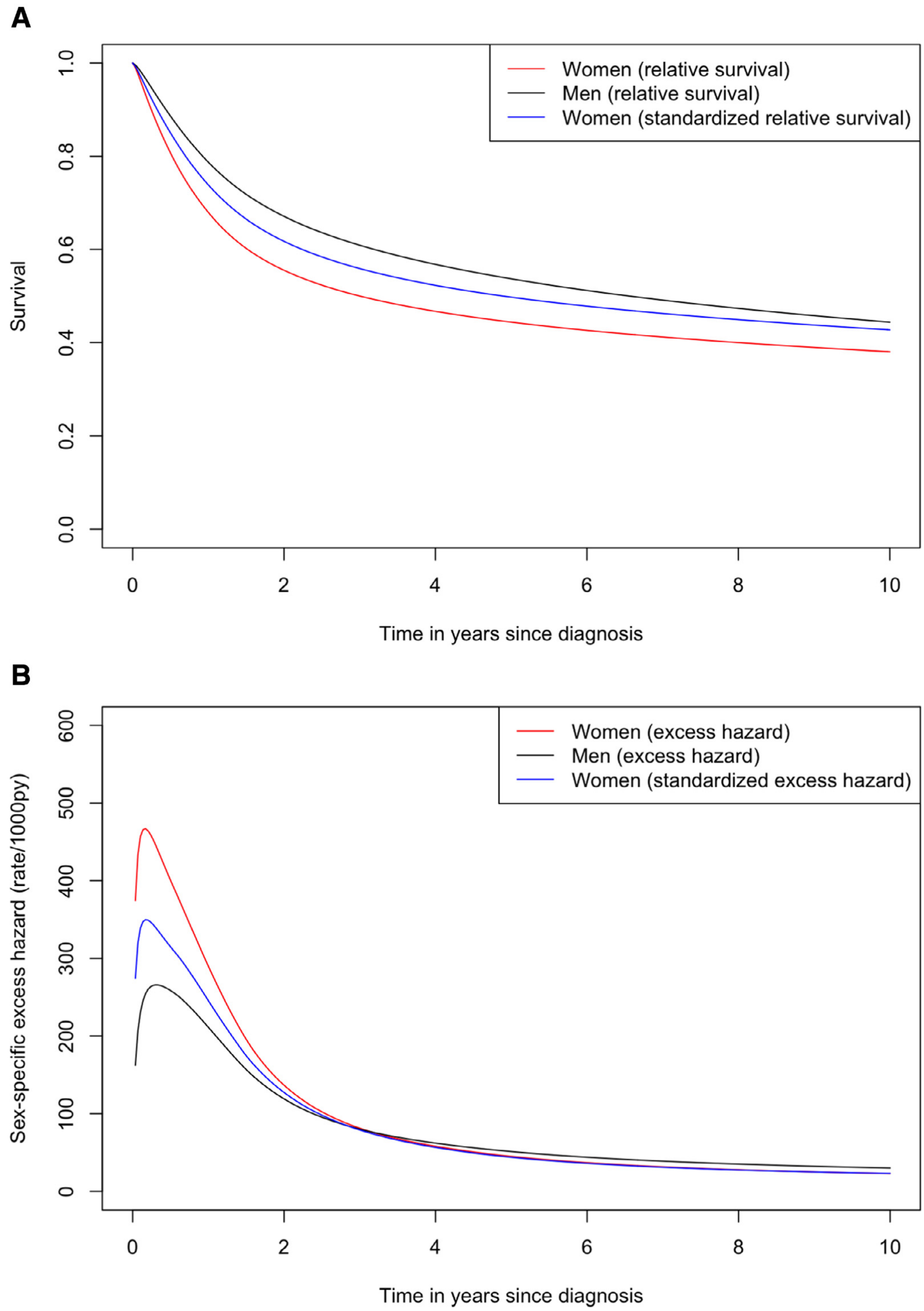

Fig. 2. (A) Unadjusted and adjusted relative survival by sex in bladder cancer patients. (B) Unadjusted and adjusted excess hazard by sex in bladder cancer patients. Red/black line: modeled relative survival of women and men, respectively, only standardized for age at diagnosis. Blue line: modeled relative survival of women, if they would have had similar distributions of age, TNM, and histology at diagnosis. Red/black line: modeled excess hazard of women and men, respectively, only standardized for age at diagnosis. Blue line: modeled excess hazard of women, if they would have had similar distributions of age, TNM, and histology at diagnosis.

A similar analysis recently performed by Andreassen et al. on a population-based cohort of Norwegian bladder cancer patients also yielded sex-specific survival functions over time [10]. Our findings support their conclusions about the hazard ratio not being constant over time and the highest mortality hazard ratio for women in the first couple of years after diagnosis and lower thereafter. In addition, our analysis included complete baseline staging including nodal

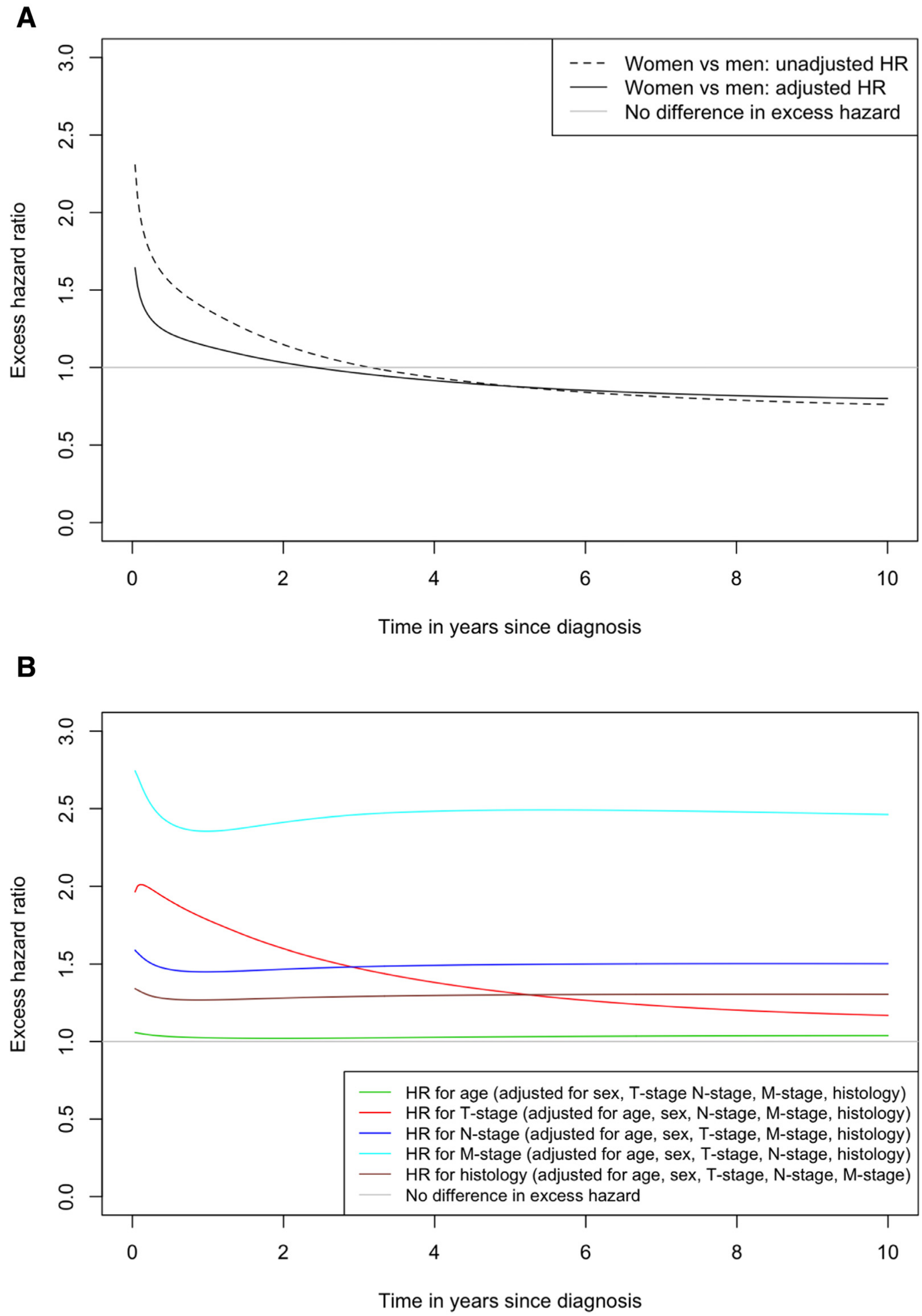

Fig. 3. (A) Unadjusted and adjusted excess hazard ratio for sex. (B) Adjusted excess hazard ratios for age, T-stage, N-stage, M-stage and histology in bladder cancer patients. Dashed line: excess hazard ratio of sex, only taking into account age at diagnosis. Solid line: excess hazard ratio of sex, as if women had similar distribution of age, TNM-stage, and histology at diagnosis as men. Each line represents the excess hazard ratio of that factor, adjusted for all other factors.

status and distant metastasis status, as well as histological subtype, and shows that the survival gap is still not fully explained by sex differences in these characteristics.

New insights that have not been reported before were achieved through employment of statistical methods that yield more valid and clinically more relevant results, i.e., accurate estimates of sex-specific excess mortality at each time point after diagnosis. It should be noted that we have only adjusted for baseline imbalances between men and women, where other factors can also alter survival

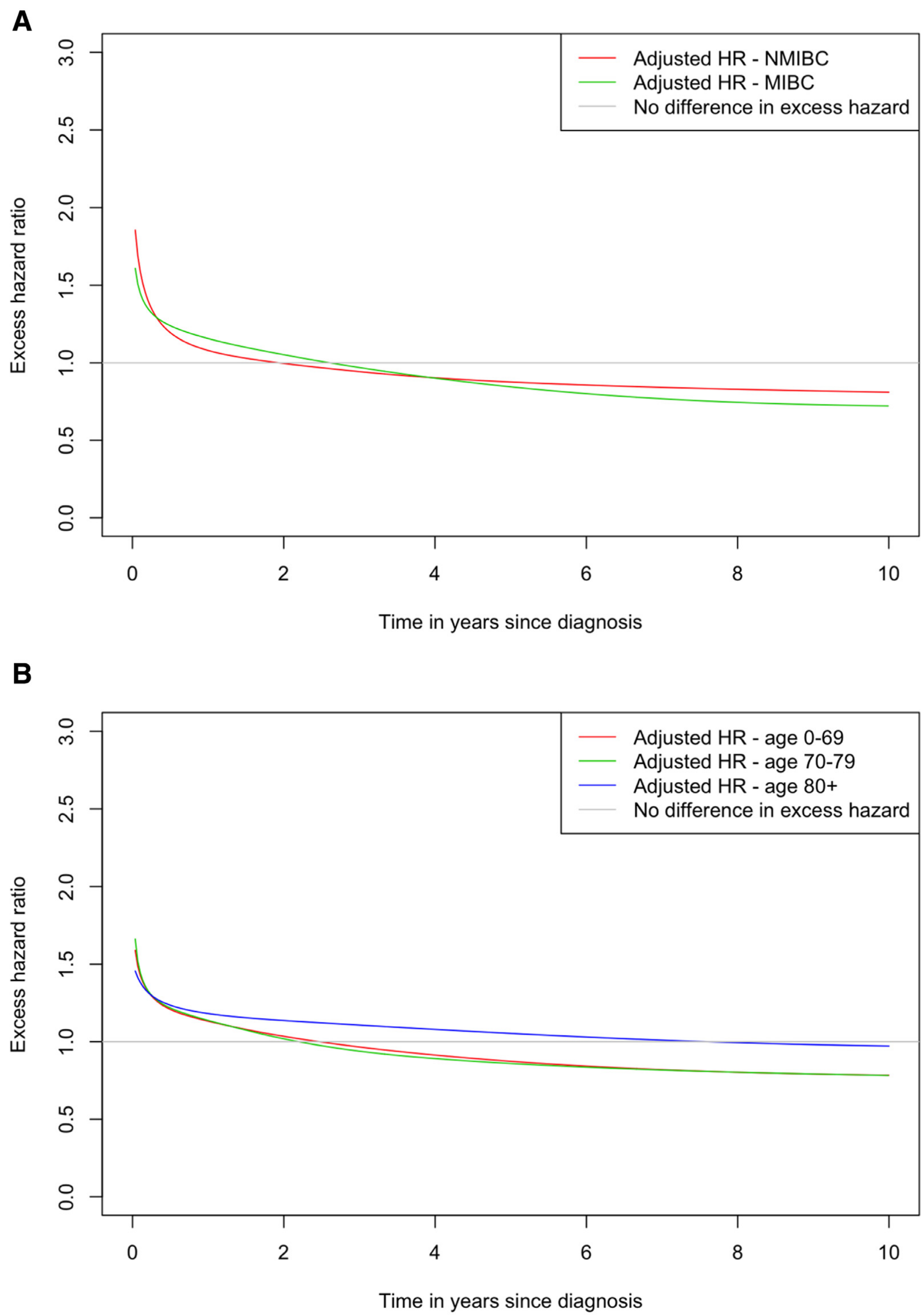

Fig. 4. (A) Adjusted excess hazard ratios for sex in patients with NMIBC and MIBC. (B) Adjusted excess hazard ratios for sex in patients aged up to 69, 70 to 79 and over 80.

probabilities in patients after their diagnosis, including treatment and life-style. In the NMIBC group, both men and women underwent a cystectomy in 6%. In the MIBC group, men and women underwent a cystectomy in 39% and 37%, neoadjuvant chemotherapy in 8% and 9%, and radiotherapy in 29% and 26% and this lack of differential treatment has also been demonstrated before [18,19]. Although treatment is not explored in more detail, this broad exploration does not indicate that this may have distorted results. Second, the results were derived from relative survival models using life-tables for the general Dutch population. A sensitivity analysis (Appendix 1) was performed to see how sensitive the results were to potential bias introduced by inaccurate representation of smoking history of bladder cancer patients in the general population. This analysis showed that the overall hazard ratio trend is robust to different smoking distributions in the general population, in line with earlier analyses on this issue [20]. Finally, a possible longer period between symptom onset and diagnosis in female patients might introduce a lead-time bias. The estimation of the "diagnostic delay" is around 2 months [21,22] in both men and women, making it unlikely that the difference in delay between men and women [22] is large enough to distort our findings.

These findings have several implications. Consideration of patients' prognosis is an inherent aspect of clinical decision-making. These results indicate that independent of other prognostic factors (TNM stage and histological type), women have an initial worse outcome. This finding, combined with the fact that women do present with less optimistic prognostic factors, both result in less favorable survival rates. This would advocate more aggressive treatment in women, for instance considering radical cystectomies in female high-risk NMIBC patients or more frequent application of neo-adjuvant chemotherapy in female MIBC patients. Additionally, the fact that women present with higher stage disease again advocates focus on efforts to increase early diagnosis in women.

The fact that increased excess mortality in women disappears after 2 years also affects hypotheses on the potential mechanism behind the sex difference. Risk factor exposure, diagnostic delay, and sex hormones have been associated with incidence, stage, and histology differences between male and female populations, [1] but are unlikely to explain the remaining difference after correction for prognostic factors. Furthermore, these factors' hypothesized pathological pathways are not consistent with the sex difference in excess mortality risk disappearing after 2 years.

Current findings support the hypothesis that it may be a result of a thinner bladder wall in women [23]. This may be associated with more (micro) metastatic disease at diagnosis than men within strata of T-stage, [24] which would assert a harmful effect especially in the first years after diagnosis. If this mechanism is indeed at play, it would advocate a revised perspective on neoadjuvant treatment to eradicate micrometastases prior to cystectomy. Yet, RCTs on which the EAU guidelines base their recommendations regarding neo-adjuvant treatment on have not assessed the possibility that neo-adjuvant treatment may work differently in male and female patients [25−27]. In fact, women are often underrepresented in these trials. Reanalysis could provide additional insight into this hypothesis.

5. Conclusion

The current study showed how the excess mortality hazard ratio for sex varied over time in bladder cancer patients, where the excess mortality for women was highest in the first 2 years after diagnosis and became lower than the hazard of men after that. Imbalances in prognostic factors at diagnosis accounted for a considerable part, but not all of the survival gap. This result may have consequences for clinical practice, for instance in clinical decision-making regarding treatments where more aggressive treatment in women may be warranted. Furthermore, accurate insight into prognosis, both the less favorable initial risk profile and the mostly equal risk profile thereafter in women, should improve overall available information for both clinician and patient.

Acknowledgements

No funding or other financial support was received for this research. Data are used from the Netherlands Cancer Registry and cannot be made freely available by the authors. Data requests can be done, however, through the NCR.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.08.001.

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