Sex Differences of $\geq$ pT1 Bladder Cancer Survival in Austria: A Descriptive, Long-Term, Nation-Wide Analysis Based on 27,773 Patients

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Key Words

Bladder cancer · Gender · Population based · Survival · Tumour stage

Abstract

Introduction: In recent days, the relationship between gender, tumour stage and survival of bladder cancer has attracted interest. **Materials and Methods:** The Austrian cancer registry was linked to the national death statistics. All patients with urothelial cancer of the urinary bladder with stages pT1, pT2, pT3 and pT4 diagnosed between 1983 until 2012 were followed for up to 15 years. Overall and cancer-specific mortality were estimated by cumulative incidence. **Results:** A total of 27,773 patients were analysed. The male:female ratio declined from 3:1 for stage pT1-tumours (n = 16,416) to 2.6:1 for pT2 (n = 6,548), 2.1:1 for pT3 (n = 3,111) and 1.9:1 for pT4 (n = 1,698). The 5 years cumulative overall death rate for pT1 tumours was slightly lower for women (0.31 vs. 0.32; p = 0.016). The opposite was observed for more advanced tumour stages: pT2: women 0.66, men: 0.60 (p = 0.0001); pT3: women 0.76, men 0.72 (p = 0.0004) and for pT4: women 0.90, men 0.85 (p = 0.0001). Cancer-specific survival was identical for pT1-tumours in both sexes, while women had a worse cancer-specific survival in both age cohorts (<70 years and $\geq$ 70 years) with higher tumour stages. **Conclusions:** This population-based study demon-

strates that (1) a rise of advanced bladder cancer stages in women and (2) that women with tumour stages $>$ pT1 have a shorter cancer-specific and overall survival.

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Introduction

Urothelial carcinoma of the bladder (UCB) is a tumour entity characterised for its sex-dependent disparities [1]. On one side, the higher incidence of UCB in men has long been observed and was linked to several possible explanations such as increased exposure to carcinogens or the involvement of androgens in bladder carcinogenesis [1]. On the other hand, women generally present with more advanced tumour stages and face a less favourable prognosis according to some studies [2–7]. The complex relationship between gender, tumour stage and survival has recently been subject to thought-provoking research. Apparently, disparities in stage distribution do not account for all the excess mortality in females as differences seem to persist even after adjustment for tumour stage [4–7].

Since decades, Austria (total population: 8.4 million) has an equal access health care system with compulsory state insurance and a national cancer registry. For the current analysis we linked the national cancer registry data to the national death statistics data base. We aimed

at analysing the relation between gender, UCB tumour stage and cumulative overall and cancer-specific mortality in a long-term, population-based setting.

Materials and Methods

Patients with UCB in Austria were identified using data from the Austrian National Cancer Registry for the period between 1983 and 2010. The collected information included the following variables: date of birth, date of diagnosis, stage, site and histotype of the tumour according to the Standard International Classification of Diseases for Oncology (ICD-O-3). Statistics related to the causes of death (Statistics Austria) was used for passive follow up and information related to the date of death (up to 2012) and cause of death (coded as ICD-9- before 2002) was obtained. The complete data was re-coded into the ICD-10 and included incidence as well as survival data of code C67 ('Malignant neoplasm of bladder', exclusive of C67.7, 'location unspecified'). To account for the higher overall mortality of older people, we divided the data set into two age groups, <70 and ≥70.

The overall mortality was estimated by the Kaplan-Meier method. Bladder cancer-specific mortality was estimated by cumulative incidence using the %CIF macro provided by SAS (SAS Institute Inc., Cary, N.C., USA) with mortality due to other causes as competing risk. The SAS macro allows estimating cumulative incidence functions with competing risks and provides comparison of cumulative incidence functions by the Gray test [8]. The respective 95% confidence incidences are indicated in square brackets. Corresponding p values are explorative in the sense that no pre-specified hypotheses were set up in advance of the study. No adjustments for multiple tests were applied. The length of follow-up was set to 15 years for the analysis. All calculations were done in SAS 9.4.

Results

Patients and Stage Distribution

In the time period 1983–2012, a total of 27,773 patients (27% women) with the initial diagnosis of UCB with stage ≥pT1 were identified and included in the study. In the Austrian Cancer Registry pTa and Carcinoma, in situ cases are grouped and cannot be separated. Therefore, we decided to omit this cohort because the biological behaviour of the two entities is not comparable.

The mean age was 70.6 years (±11.4 SD) for the entire cohort, 69.8 ± 11.3 years for men (n = 20,285) and 72.8 ± 11.6 years for women (n = 7,488). The mean age for male patients with pT1-tumors was 69.2 ± 11.4 years, 70.8 ± 10.9 years with pT2-tumours, 70.4 ± 11.2 years with pT3 tumours and 70.7 ± 11.1 years with pT4 tumours; the figures for the female cohort were 71.6 ± 11.9 years, 74.8 ± 10.9 years, 73.9 ± 11.2 years and 73.5 ± 11.4 years, respectively.

Table 1. Sex-specific stage distribution (n = 27,395)

Stage	Total	Female	Male	M/F ratio
pT1	16,416	4,086	12,330	3:1
pT2	6,548	1,821	4,727	2.6:1
pT3	3,111	999	2,112	2.1:1
pT4	1,698	582	1,116	1.9:1
Total	27,773	7,488	20,285	2.7:1

The stage distribution was as follows: pT1 (n = 16,416, 59.1%), pT2 (n = 6,548, 23.6%), pT3 (n = 3,111, 11.2%) and pT4 (n = 1,698, 6.1%). The male:female ratio declined stage-dependent from 3:1 for stage pT1 to 2.6:1 for pT2, 2.1:1 for pT3 and 1.9:1 for pT4 tumours (table 1).

Overall Survival

Figure 1 describes the cumulative overall death rate in both sexes dependent on the tumour stage. The 5 years cumulative overall death rate in the female cohort for pT1 tumours was 0.31 [0.29–0.32], for pT2 tumours 0.66 [0.64–0.68], for pT3 tumours 0.76 [0.73–0.79] and for pT4 tumours 0.90 [0.87–0.92] (fig. 1). The corresponding figures for the male cohort were 0.32 [0.31–0.33], 0.60 [0.58–0.61], 0.72 [0.70–0.74] and 0.85 [0.83–0.87] (fig. 1). At 10 years, men with pT1-tumours still faced a worse prognosis regarding the cumulative overall survival, while it was just the opposite in the case for patients with >pT1-tumours (fig. 1). The gender differences in cumulative incidence functions were highly significant for all stages: pT1: p = 0.0016; pT2: p = 0.0001; pT3: p = 0.0004; pT4: p = 0.0001.

Figure 2 describes the cumulative overall death rate in the two age groups (<70 vs. ≥70 years) again stratified according to sex and the tumour stage. In general, sex differences regarding stage-specific overall survival were more prominent in the younger age cohort (fig. 2a). For pT1-patients, the 5 years cumulative overall death rate was higher for men (0.17) [0.16–0.18] than for women (0.13) [0.11–0.14] (p = 0.0001) (fig. 2a). The 5 years overall cumulative death rate for more advanced cases, however, was consistently higher for women in both age cohorts (fig. 2). In the <70 years age cohort, the cumulative overall death rate of pT2-tumours was 0.43 [0.41–0.45] for men versus 0.46 [0.42–0.51] for women; the corresponding figures for pT3-tumours were 0.60 [0.57–0.63] vs. 0.62 [0.56–0.67] and for pT4-tumours 0.79 [0.75–0.83] vs. 0.87 [0.81–0.91]. For pT2 and pT3-tumours sur-

Fig. 1. Cumulative overall sex- and tumour stage-specific death rate in the total study cohort.

vival differences beyond 5 years of follow-up declined, while they remained substantial for pT4-tumours up to 15 years of follow-up (fig. 2a). A similar trend was observed when grouping patients into localised disease (5 years cumulative death rate: pT1/pT2/N0 male: 0.21 [0.19–0.22], female: 0.18 [0.16–0.21] and locally advanced disease (pT3/pT4/N0 male: 0.53 [0.48–0.57], female: 0.58 [0.50–0.66]). For pN+ patients, the 5 years overall survival was almost identical (male: 0.77 [0.73–0.80], female: 0.76 [0.70–0.81]). In the older cohort (fig. 2b), a similar trend was observed (higher cumulative overall death rate of men with pT1-tumours, while for more advanced tumour stages women had a higher cumulative death rate). The respective differences were most dominant within the first 5 years after the initial diagnosis (fig. 2b). When grouping patients as indicated above in localised, locally advanced and pN+ patients men had a higher death rate for localised disease (0.50 [0.49–0.52] vs. 0.48 [0.46–0.51]), whereas in the remaining two groups, women had a higher 5 years cumulative death rate: locally advanced disease (0.78 [0.72–0.83] vs. 0.75 [0.70–0.79]; pN+ patients 0.90 [0.86–0.93] vs. 0.86 [0.83–0.89]).

Cancer Specific Survival

The cumulative incidence of cancer-specific mortality in the two age cohorts largely confirms the data on overall mortality (fig. 3a, b). The 5 years cumulative cancer-specific death rate in the younger cohort (≤ 70 years) for pT1-tumours was almost identical for both sexes: 0.06 [0.05–0.06] for men and 0.05 [0.04–0.07] for women ($p > 0.05$); the respective figures for pT2-tumours were 0.27 [0.25–0.28] vs. 0.31 [0.27–0.35] ($p = 0.05$), for pT3-tumours 0.45 [0.41–0.48] vs. 0.45 [0.39–0.50] ($p > 0.05$) and for pT4-tumours 0.60 [0.55–0.64] vs. 0.70 [0.63–0.76] ($p = 0.005$; fig. 3a). The 5 years cumulative cancer-specific mortality was identical in both sexes for localised disease (pT1/pT2/pN0: 0.09), while it was higher for women with locally advanced (0.42 [0.34–0.50] vs. 0.37 [0.32–0.41]) and pN+ patients (0.58 [0.51–0.64] vs. 0.55 [0.51–0.59]). In the older age-cohort, the 5 years cumulative cancer-specific mortality was numerically slightly higher for women with pT1-stage (0.15 [0.14–0.17] vs. 0.13 [0.12–0.14]; $p > 0.05$) (fig. 3b). Again, in the more advanced stages, women faced a worse prognosis: pT2: 0.47 [0.45–0.50] vs. 0.41 [0.39–0.43] ($p = 0.0001$); pT3: 0.56 [0.52–0.59] vs. 0.51 [0.48–0.54] ($p = 0.05$) and pT4: 0.69 [0.64–

Fig. 2. Cumulative overall sex- and tumour stage-specific death rate in the two age cohorts. **a** <70 years; **b** ≥70 years.

Fig. 3. Cumulative cancer specific sex- and tumour-stage specific death rate in the two age cohorts. **a** <70 years; **b** ≥70 years.

0.74] vs. 0.63 [0.59–0.67] ($p = 0.001$) (fig. 3b). The same holds true when grouping patients into localised (0.21 [0.19–0.23] vs. 0.18 [0.16–0.19]), locally-advanced (0.52 [0.45–0.58] vs. 0.43 [0.38–0.48]) and pN+-disease (0.59 [0.54–0.64] vs. 0.57 [0.53–0.61]).

Discussion

This large-scale, long-term and population-based analysis has two major findings: (1) women present with more advanced tumour stages and (2) women have a worse prognosis with invasive bladder cancer in stages >pT1.

Before we start discussing our findings, some advantages and limitations of the current study design need to be mentioned. Strengths are (1) the population-based approach, (2) the large cohort, (3) the fact that since decades Austria has an equal access health care system, and (4) that there is an almost complete follow-up (unless the patient left Austria). The major limitation is the lack of any clinical information, such as the type of primary/secondary oncological treatments and comorbidities. A further limitation is the staging inaccuracy particularly for the more advanced stages (>pT1). While accurate pathological staging is feasible following radical cystectomy, this is not the case for patients who underwent bladder sparing approaches. As we have no information on primary/secondary treatment, this might lead to a bias in the results.

A few studies have demonstrated that women present with more advanced bladder tumour stages at initial diagnosis. In an analysis of the Surveillance Epidemiology and End Results (SEER) database, women were more likely to be diagnosed with muscle-invasive disease compared to men (22 vs. 25% in Caucasian patients and 30 vs. 43% in Afro-American patients, $p < 0.001$) [2]. Another survey of over 20,000 patients from the Netherlands Cancer Registry reported of a higher share of early stages of bladder cancer in males compared to females (71% in males vs. 63% in females for pTa, CIS and pT1) [3]. This difference changed to the opposite with advanced tumour stages (7% in males vs. 9% in females for pT4, N+ and M+) [3]. In the current population-based study, the men-to-female ratio declined constantly from 3:1 for pT1 tumours to 1.9:1 in those with pT4 tumours, thus underlining this shift towards advanced stages in women.

This unequal stage distribution of bladder cancer has been linked to sex differences, such as the different pelvic anatomy and vascular and lymphatic drainage or the involvement of androgens in carcinogenesis and progression [9, 10]. Alternatively or additionally, this phenome-

non may be due to a delay in diagnosis due to differing clinical symptoms, evaluations prior diagnosis and referral patterns. Henning et al. have shown that referral patterns of patients with the first diagnosis of bladder cancer did indeed differ substantially between both sexes [11]. Less than half of the women compared to 81% of the men directly consulted an urologist for haematuria [11]. Women were more often treated for urinary tract infection and were given symptomatic treatment without further clinical evaluation more frequently than men before being referred to an urologist [11]. Similar data have recently been reported by Aziz et al. using the same questionnaire developed by Henning et al. [11, 12]. These data suggest that an unequal referral pattern might indeed be – at least partly – responsible for the higher tumour stages in women at initial diagnosis [10].

This large-scale population-based study supports the hypothesis that women with advanced UCB have a worse cancer-specific and overall survival even if controlled for tumour stage (see fig. 1–3). Kluth et al. assessed the impact of gender on the outcome of pT1-patients in a retrospective, multi-centre trial of 916 patients [13]. In this cohort, treatment was very heterogeneous where only approximately 25% received the recommended intravesical BCG-therapy [13]. In this series, women had a higher recurrence rate but identical rates of disease progression, cancer-specific and overall survival thus being largely in line with our series [13]. Suer et al. have shown that the risk of a residual tumour in a repeat TURP after initial pT1 bladder cancer was not correlated to the tumour stage [14].

In our population-based analysis, men with pT1-tumours had a worse overall survival as compared to women (with the opposite in more advanced stages). We believe that this is most likely due to the fact that non-cancer death rates override cancer-specific survival in pT1-cases; CSS was identical of pT1-tumours in both sexes (fig. 3). Mungan et al. analysed the SEER-data base for gender-differences of bladder cancer outcome [3, 4]. The male vs. female 5 years survival among stage groups I, II, III, and IV was 96.5 vs. 93.7%, 65.5 vs. 59.6%, 58.8 vs. 49.6%, and 27.1 vs. 15.2%, respectively. This study suggests that the survival difference increases with advancing tumour stage. A similar observation was made in our analysis (see fig. 1–3).

Otto et al. analysed the impact of gender on the outcome of a large retrospective cystectomy multicentre data base ($n = 2,483$) [15]. In this series, the 5 years CSS was significantly lower for women (60 vs. 66%, $p = 0.005$) [15]. Among other factors, female gender was an independent predictive factor for CSS in a multivariate analysis [15]. Mitra et al. performed matched-pair comparison based on demographics,

tumour and treatment characteristics of patients undergoing radical cystectomy [16]. In this tumour-stage-matched series, no differences in cancer-specific and overall survival between both sexes were seen [16]. However, when compared with an independent unmatched male control cohort, females had significantly poorer outcomes [16]. The authors concluded that females have similar UCB outcomes to males when matched for demographic, clinic-pathologic, and management characteristics [16]. However, they present with more advanced tumours, thus explaining the observation of poor outcomes in an unmatched cohort. Keck et al. analysed the impact of gender on the outcome of invasive bladder cancer managed by a multimodal bladder sparing approach in 105 female and 386 male patients [17]. In this series, the median overall survival was 5.1 years for men versus only 2.3 years for women ($p = 0.045$) [17]. The estimated median cancer-specific survival was 7.1 years for female versus 12.7 years for male patients [17].

Taken together, the data suggest that – if managed by radical cystectomy – women with invasive bladder cancer have a similar survival as men if matched according to the tumour stage [18]. In non-stage-matched cohorts, the poorer survival of women is most likely driven by the more advanced stages in women. This might also apply

for the bladder-sparing series mentioned earlier where no exact tumour staging is feasible [17]. The differences in survival seen in our stage-matched population-based series is therefore most likely due to (1) staging inaccuracy as not all patients with invasive bladder cancer were managed by radical cystectomy, thus providing accurate staging; (2) delayed or inappropriate therapy for women with invasive bladder cancer, and (3) a potentially true biological gender-related difference.

Conclusions

The increasing incidence of bladder cancer in women, the delayed referral for specialised care, a higher rate of advanced disease and a poorer survival even if corrected for tumour stage at least in a population-based setting underlines the clinical importance of this topic for both general practitioners and urologists.

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