

ORIGINAL ARTICLE



Beta-blocker use and urothelial bladder cancer survival: a Swedish register-based cohort study

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ABSTRACT

Background: Recent observational studies linked β -adrenergic receptor blocker use with improved survival in patients with several cancer types, but there is no information on the potential effects of β -blockers in patients with bladder cancer. Literature from pre-clinical studies is also limited, but urothelial cancer can exhibit significant overexpression of β -adrenergic receptors relative to normal urothelial tissue, suggesting that urothelial cancer may benefit from β -blockade therapy. We thus aimed to explore the possible association between β -blocker use and bladder cancer-specific mortality (BCSM) among patients with urothelial bladder cancer.

Material and methods: Patients diagnosed during 2006–2014 and identified from the Swedish Cancer Register ($n = 16,669$) were followed until 31 December 2015. Cox regression was used to evaluate the association of β -blockers dispensed within 90 days prior to cancer diagnosis with BCSM (primary outcome) and all-cause mortality, while controlling for socio-demographic factors, tumor characteristics, comorbidity, other medications and surgical procedures. Hazard ratios (HR) with 95% confidence intervals (CI) were reported.

Results: Overall, β -blocker use was associated with lower BCSM [HR 0.88 (95%CI 0.81–0.96)]. Especially use of nonselective β -blockers showed a clear inverse association in comparison with both nonuse [0.66 (0.50–0.86)] and use of other antihypertensive medications [0.72 (0.54–0.95)]. The inverse association was most pronounced among patients with locally advanced/metastatic disease: [0.35 (0.18–0.68)]. A lower-magnitude inverse association was observed for selective β -blocker use [0.91 (0.83–0.99)]. Largely similar inverse associations were observed for hydrophilic [0.82 (0.70–0.95)] and lipophilic [0.91 (0.83–1.00)] β -blocker use.

Conclusion: β -blocker use, particularly of the nonselective type, was associated with lower BCSM, especially in patients with locally advanced/metastatic urothelial bladder cancer.

ARTICLE HISTORY

Received 22 September 2021
Accepted 12 July 2022

KEYWORDS

Adrenergic signaling; beta-blocker; urothelial bladder cancer; survival; cohort study

Introduction

Urinary bladder cancer, one of the most common cancers of the genitourinary tract, is the tenth most common cancer worldwide [1]. Histologically, most bladder tumors are urothelial (90%), and about 70%–75% are non-muscle-invasive (NMIBC) at diagnosis [2,3]. Most NMIBC have a low probability (10%–20%) of progression and a high 5-year overall survival rate (about 90%) [2,3]. Muscle-invasive (MIBC) disease is associated with poor prognosis, and metastatic disease has a 5-year survival probability of less than 10% [3]. The survival rates are largely unchanged since the 1990s [2], highlighting potential gaps in diagnosis, monitoring and treatment of these patients.

Age [4–6], sex [4–6], marital status [5], diabetes [7], stage [4–6], grade [4,6,8], histology [4–6], surgical treatment [6], and molecular subtypes [9] have previously been linked with bladder cancer survival. Other factors, including obesity and blood pressure, have been investigated but the associations are less clear [7,10]. Although the results from individual studies are somewhat inconsistent, meta-analyses suggest that smoking is associated with higher overall and cancer specific mortality [11,12].

A growing body of evidence suggests a role of β -adrenergic signaling in tumor biology, and links pharmacological inhibition of the β -adrenergic receptors with reduced cancer progression [13], *via* inhibition of various cancer-related

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 Supplemental data for this article is available online at <https://doi.org/10.1080/0284186X.2022.2101902>.

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cellular and molecular processes involved in sympathetic nervous system activation [14–17]. Observational studies suggest that β -blockers may improve survival across several cancer types [18–20]. However, the combined evidence is inconsistent, and in some studies β -blocker use was associated with poorer survival [21], or no association was found [22]. Associations with mortality may vary not only by tumor site [23], but also by tumor subtype [24,25] and disease stage [20].

The urinary tract is highly innervated by autonomic nerves, and the related neural signals may be dysregulated in the presence of genitourinary diseases, both benign and malignant [16]. Urothelial cancer has shown significant overexpression of β -adrenergic receptors relative to the normal non-diseased tissue counterparts, suggesting that urothelial tumors may respond to β -blockade [26]. However, data from pre-clinical studies are limited and to the best of our knowledge, no previous clinical study has evaluated the association between β -blocker use and bladder cancer survival.

Recognizing a potential promise of β -blockers as adjunct to standard anti-cancer therapy, we tested the hypothesis that β -blocker use at cancer diagnosis may reduce bladder cancer mortality in a large population-based cohort of patients with primary urothelial bladder cancer (UBC).

Material and methods

Study population and data sources

This retrospectively defined cohort study is based on prospectively collected data from the Swedish Cancer Register [27], which has been linked to several other nationwide registers using the unique personal identification number assigned to all Swedish residents.

From the Swedish Cancer Register, we identified all patients aged 18 years or older diagnosed with primary urothelial carcinoma of the bladder between 1 January 2006 and 31 December 2014 [topographical code C67 (except C67.7) and morphological codes 8120 and 8130 according to the International Classification of Diseases for Oncology, third revision (ICD-O-3)]. Patients with previous malignancies other than non-melanoma were excluded. The Swedish Cancer Register also provided information on major established prognostic factors such as stage, grade, year of diagnosis, and age at diagnosis.

From the Prescribed Drug Register [28], we identified β -blocker use as well as use of other relevant medications dispensed during the 90-day period before cancer diagnosis using the Anatomic Therapeutic Chemical (ATC) classification system (Supplementary Table 1). The number of distinct medication classes (medications with the same initial five characters of ATC classification) was used to derive a medication-based comorbidity score measure to account for overall disease burden [18,20]. Information on chemotherapy was not available, but therapy was presumably cisplatin-based (for fit patients), according to the guidelines used during the study period [29].

The National Patient Register [30] provided data on comorbid conditions to define the Charlson comorbidity

index, as well as surgical procedures [transurethral resection of a bladder tumor (TURBT), radical cystectomy and lymphadenectomy] (Supplementary Table 2). Other population-based registers provided information on level of attained education, marital status and region of residence (the Longitudinal Database of Education, Income and Occupation [31]); migration (the Total Population Register); as well as the underlying cause and date of death (the Cause of Death Register [32]).

β -Blocker exposure assessment

Patients were classified as exposed at the time of bladder cancer diagnosis if they had collected at least one prescription of β -blockers from the pharmacy during the 90 days preceding their cancer diagnosis, since prescriptions normally cover a period of 30–90 days in Sweden. β -blocker exposure was further defined by receptor selectivity [cardio-selective (ATC codes: C07AB, C07FB02), and nonselective (C07AA, C07AG)], and by solubility (lipophilic, hydrophilic). Patients using both selective and nonselective types were placed in the nonselective subgroup, while users of both lipophilic and hydrophilic types were included in the lipophilic subgroup. Where possible, associations with individual β -blockers were examined.

In a sensitivity analysis, patients were classified as exposed if they collected β -blockers from the pharmacy during a period of 3–6 months before cancer diagnosis. In another sensitivity analysis performed in patients diagnosed on or after 1 October 2006, β -blocker users were classified as incident or prevalent users, wherein users were defined as incident if they collected their β -blockers from the pharmacy within 90 days before cancer diagnosis date, but had no recorded collection in the previous year.

Primary outcome assessment

Bladder cancer-specific mortality (BCSM) was identified from the Cause of Death register using ICD-10 code C67. Survival time was computed from the date of cancer diagnosis until date of BCSM and was censored at the date of emigration, competing cause of death, or end of follow up (31 December 2015), whichever occurred first.

Statistical analysis

The distribution of baseline characteristics was tabulated by β -blocker use and compared using the Pearson χ^2 , ANOVA or median tests as appropriate.

The observed 5-year overall survival proportions were estimated using the actuarial method. Cox proportional hazards models with time since diagnosis in years as the underlying time scale were fitted to estimate hazard ratios (HR) and 95% confidence intervals (CI) for BCSM and all-cause mortality associated with β -blocker use. Linearity of relationships between continuous variables and the log-hazard of mortality was assessed by the 'mvs' routine implemented in Stata [33]. Test and plots of Schoenfeld residuals were used to

evaluate the assumption of proportional hazards, which was satisfied for the β -blocker exposure variable. The adjusted Cox model included age at cancer diagnosis modeled using spline functions with four degrees of freedom; medication-based comorbidity score and year of diagnosis modeled as linear measures; sex; tumor stage [NMIBC (Tis/Ta/T1, N0/X, M0/X), MIBC (T2-4a, N0, M0), at least MIBC (T2-4a, NOMX, NXM0), locally advanced/metastatic (T4b/N+/M1) and unspecified (TX, NX, MX)]; tumor grade [grade I (well differentiated), grade II (moderately differentiated), grade III (poorly differentiated) and unspecified]; education [compulsory (up to 9 years), secondary (10–12 years), and postsecondary (more than 12 years)]; marital status (unmarried, married/cohabiting, divorced/separated, or widowed); region of residence; and Charlson comorbidity index (divided into four categories: 0, 1, 2, >2). A further adjusted model (referred to as fully adjusted) included TURBT, cystectomy, and lymphadenectomy modeled as time-varying covariates using time-dependent Cox regression. A multiplicative interaction term was added to the adjusted model to test whether the β -blocker-BCSM association differed for men and women as well as for patients <75 years of age and older. The analyses were performed in the entire study cohort as well as stratified by disease stage.

To further address potential sources of confounding, we performed a sensitivity analysis where β -blocker users were compared with a more comparable reference population of nonusers who were prescribed other antihypertensive medications. Analyses were also performed among patients with smoking related diagnoses and/or medications (Supplementary Tables 1 and 2).

We also estimated covariate-adjusted bladder cancer survival functions by β -blocker use [34,35]. This analysis was run after flexible parametric survival analysis [36], wherein the baseline hazard function was fitted using restricted cubic splines with four degrees of freedom.

All analyses were performed with STATA software version 14SE.

Ethical approval

The study was approved by an ethical review board in Uppsala (DNR: 2012-361). Informed consent from individual patients was waived in view of using register-based anonymised data.

Results

Patients and tumor characteristics

In total, 16,669 patients (76% male, 24% female) with primary UBC were included in the analysis (Supplementary Figure 1). Median age at diagnosis was 72 years [range: 28–101 years, interquartile range: 65–80 years]. Cancer diagnosis was mainly based on histopathology (97.7%) and for only a few patients on cytology (2.3%). About 73% of patients were diagnosed with NMIBC, and 26% with muscle

invasive disease. Locally advanced/metastatic disease was identified in about 5% of the patients.

Overall survival estimates

A median follow-up based on the reverse Kaplan–Meier estimator [37] was 5 years. Over a total observation period of 64,795 person-years, 6,330 (38.0%) patients died, and another 38 (0.2%) emigrated. The underlying causes of death included bladder cancer ($n = 3,180$), other tumors ($n = 873$), cardiovascular disease ($n = 1,284$), and other causes ($n = 994$). The estimated 5-year overall survival proportions ranged from 8% (metastatic) to 74% (NMIBC).

β -Blocker use and patient, tumor, and treatment characteristics

Overall, 4,449 (27%) patients used β -blockers at the time of UBC diagnosis: $n = 4,118$ (92.6%) selective and $n = 345$ (7.8%) nonselective (Supplementary Table 3). β -blockers with partial agonist activity were uncommon. Only a few users of nonselective ($n = 10$) and selective ($n = 186$) types met the incident user definition for a sensitivity analysis.

β -blocker use was more common in male patients, and users tended to be older, and had higher comorbidity scores (Table 1). Other antihypertensive medications were also more common among β -blocker users. Disease stage and tumor grade at diagnosis were similarly distributed between users and nonusers (Table 1).

β -Blocker use and bladder cancer specific mortality

Nonselective β -blocker users had lower [43.3 (95% CI 33.3–56.3)], while users of selective types had higher [57.9 (95% CI 54.1–62.0)] BCSM rates (per 1000 person-years) than nonusers [46.6 (95% CI 44.7–48.6)], with corresponding crude HRs of 0.90 (0.69–1.18) and 1.17 (1.08–1.27). In multivariable adjusted analyses, nonselective β -blocker use was associated with 34% lower BCSM, while a lower-magnitude inverse association was observed for selective β -blocker use (Table 2). Analyses differentiating β -blockers by solubility suggested 18% lower BCSM for hydrophilic and 9% lower BCSM for lipophilic β -blocker use (Table 2). The β -blocker-BCSM association was largely similar for men and women, and for patients less than 75 years of age as well as 75 years and above, particularly for nonselective β -blockers (Supplementary Table 4).

Analysis exploring associations with selected individual β -blockers was in agreement with the analysis defining β -blockers by receptor selectivity and by solubility in aggregate (Supplementary Table 5).

Inverse and largely similar associations were suggested in our sensitivity analysis for both incident (n of events = 3) and prevalent (n of events = 45) use of nonselective β -blockers [HRs 0.72 (0.23–2.25) and 0.74 (0.55–1.00), respectively].

Sensitivity analysis comparing β -blocker users with a more comparable reference population of nonusers who dispensed other antihypertensive medications, produced largely similar

Table 1. Baseline characteristics of patients diagnosed with primary urothelial bladder cancer in Sweden in 2006 to 2014 by β -blocker use at cancer diagnosis.

	Nonselective β -blocker (N = 345)		Selective β -blocker (N = 4,104)		No β -blocker (N = 12,220)		<i>p</i> ^a
	N	Col %	N	Col %	N	Col %	
Age at diagnosis, years (mean, SD)	74.6	9.6	75.0	9.1	70.7	11.3	<0.001 ^b
Male	267	77.4	3216	78.4	9140	74.8	<0.001
Attained education							<0.001
Compulsory	151	43.8	1994	48.6	4944	40.5	
Secondary	123	35.7	1507	36.7	4698	38.4	
Post-secondary	71	20.6	603	14.7	2578	21.1	
Marital status at diagnosis							<0.001
Unmarried	29	8.4	356	8.7	1390	11.4	
Married/cohabiting	191	55.4	2309	56.3	6926	56.7	
Divorced/separated	51	14.8	656	16.0	2024	16.6	
Widowed	74	21.4	783	19.1	1880	15.4	
Grade							0.174
Grade 1	98	28.4	1014	24.7	3159	25.9	
Grade 2	89	25.8	1095	26.7	3352	27.4	
Grade 3	108	31.3	1489	36.3	4219	34.5	
Unspecified	50	14.5	506	12.3	1490	12.2	
Disease stage ^d							0.210
NMIBC (Tis/Ta/T1, N0/X, M0/X)	257	74.5	2977	72.5	8890	72.7	
MIBC (T2-4a, N0, M0)	23	6.7	311	7.6	1052	8.6	
At least MIBC (T2-4a, N0MX, NXM0)	44	12.8	589	14.4	606	5.0	
Advanced (T4b/N+/M1)	18	5.2	195	4.8	1572	12.9	
Unspecified (TX, NX, MX)	3	0.9	32	0.8	100	0.8	
Medication-based comorbidity score (median, IQR) ^e	7	5–10	7	5–9	3	1–6	<0.001 ^c
Charlson comorbidity index							<0.001
0	133	38.6	1284	31.3	7436	60.9	
1	101	29.3	1212	29.5	2721	22.3	
2	48	13.9	764	18.6	1148	9.4	
>2	63	18.3	844	20.6	915	7.5	
Other antihypertensive medications within 90 days before diagnosis ^f							
ACEi	89	25.8	1361	33.2	1508	12.3	<0.001
ARB	72	20.9	784	19.1	1073	8.8	<0.001
CCB	83	24.1	1129	27.5	1412	11.6	<0.001
Thiazide diuretics	20	5.8	287	7.0	435	3.6	<0.001

Notes: Patients were considered exposed to β -blocker use at cancer diagnosis if they collected at least one prescription during the 90-day period before cancer diagnosis, and unexposed otherwise. Patients using both selective and nonselective β -blockers ($n = 14$) are in the nonselective subgroup. Grade1 includes Papilloma (SNOMED 3: 81201) and PUNLMP (SNOMED 3: 81301).

Abbreviations: IQR: interquartile range; MIBC: muscle invasive bladder cancer; NMIBC: non-muscle invasive bladder cancer; PUNLMP: papillary neoplasm of low malignant potential; SD: standard deviation.

^a*p* Values are from a χ^2 test.

^bRobust one-way ANOVA.

^cMedian test.

^dEvaluations of N and M stages have not been performed for most patients with Ta and Tis tumors and many patients with T1 tumors, as well as for many older patients with T2–T4 tumors. Where possible, morphological codes have also been used to identify T stage (Tis: 81202; Ta: 81302; PUNLMP: 81301; muscle invasive: 81203, 81303).

^eNumber of distinct medication classes (medications with the same initial five characters of ATC classification) within 90 days before cancer diagnosis were used to derive a medication-based comorbidity score.

^fMedications (yes/no variables) are dispensed within 90 days before cancer diagnosis and are not mutually exclusive.

results [nonselective β -blockers: HR 0.72 (0.54–0.95); selective β -blockers: 0.99 (0.89–1.10)]. Analyses restricted to patients with smoking ($n = 1,861$) related diagnoses and/or medications also suggested lower BCSM in relation to nonselective β -blocker use [HR 0.31 (0.10–0.99)] but not in relation to selective β -blocker use [HR 1.12 (0.88–1.44)].

Stage-stratified analysis suggested that nonselective β -blockers had a more pronounced mortality rate reduction among patients with a locally advanced/metastatic disease at diagnosis, but not among patients with NMIBC (Table 3, Figure 1). Sensitivity analysis using a different time window (3–6 months before diagnosis) for exposure measurement produced comparable results (Supplementary Table 6).

Similar associations were observed for β -blocker use in relation to all-cause mortality (Table 4).

Discussion

In this large population-based cohort of patients with first primary UBC, nonselective β -blocker users had lower disease-specific mortality rate than nonusers, especially among patients with inoperable, locally advanced/metastatic disease (T4b and/or N+ and/or M1). Lower-magnitude inverse association was suggested for nonselective β -blocker use among patients with MIBC, and no clear association was observed

Table 2. Cox proportional hazards regression analyses for the association between β -blocker use and bladder cancer-specific mortality in patients diagnosed with primary urothelial bladder cancer ($N = 16,669$) in Sweden in 2006 to 2014.

β -blockers ^a	No. of events	HR ^b (95% CI)	p	HR ^c (95% CI)	p	HR ^d (95% CI)	p
Any β -blocker	894	0.99 [0.91,1.07]	0.743	0.88 [0.81,0.96]	0.004	0.88 [0.81,0.96]	0.005
Nonselective ^e	56	0.77 [0.59,1.00]	0.052	0.66 [0.50,0.86]	0.002	0.66 [0.50,0.86]	0.002
β 1-receptor selective ^f	838	1.01 [0.93,1.09]	0.880	0.90 [0.83,0.99]	0.024	0.91 [0.83,0.99]	0.026
Lipophilic ^g	702	1.00 [0.92,1.09]	0.956	0.91 [0.83,1.00]	0.039	0.91 [0.83,1.00]	0.043
Hydrophilic ^h	192	0.95 [0.82,1.10]	0.500	0.81 [0.70,0.95]	0.007	0.82 [0.70,0.95]	0.008

Abbreviations: CI: confidence interval; HR: hazard ratio.

^aExposed if collected at least one prescription during the 90-day period before bladder cancer diagnosis, unexposed otherwise. Patients using both selective and nonselective β -blockers ($n = 14$) are in the nonselective subgroup, and patients using both lipophilic and hydrophilic β -blockers ($n = 18$) are in the lipophilic subgroup.

^b β -blocker use compared with nonuse, adjusting for age at diagnosis.

^c β -blocker use compared with nonuse, adjusting for age at diagnosis, sex, disease stage, tumor grade, diagnosis year, healthcare/residence region, attained education, marital status, medication-based comorbidity score, Charlson comorbidity index.

^dFurther adjusted for transurethral resection of a bladder tumor (TURBT), radical cystectomy and lymphadenectomy modeled as time-varying covariates.

^eIncludes: pindolol, propranolol, timolol, sotalol, labetalol, carvedilol.

^fIncludes: metoprolol, atenolol, bisoprolol, metoprolol + felodipine.

^gIncludes: bisoprolol, carvedilol, labetalol, metoprolol, pindolol, propranolol, timolol, metoprolol + felodipine.

^hIncludes: sotalol, atenolol.

Table 3. β -blocker use at bladder cancer diagnosis compared with nonuse in relation to bladder cancer-specific mortality by tumor stage in patients diagnosed with primary urothelial bladder cancer ($N = 16,669$) in Sweden in 2006–2014.

Disease stage	Total N	Nonselective β -blockers			β 1-receptor selective β -blockers		
		No. of events ^a	HR ^b (95% CI)	p	No. of events ^a	HR ^b (95% CI)	p
NMIBC (Tis/Ta/T1, N0/X, M0/X)	12,124	25	1.06 [0.71,1.60]	0.762	274	0.94 [0.80,1.09]	0.396
Low/intermediate risk (TaG1-2)	6,734	9	1.12 [0.56,2.24]	0.751	68	1.00 [0.73,1.36]	0.991
High risk (TaG3/Tis/T1)	4,812	15	1.04 [0.62,1.75]	0.884	199	0.94 [0.78,1.12]	0.476
MIBC (T2-4a, N0, M0)	1,386	9	0.66 [0.34,1.30]	0.234	141	0.90 [0.73,1.11]	0.339
At least MIBC (T2-4a, NOMX, NXM0)	2,205	13	0.68 [0.39,1.19]	0.173	274	0.86 [0.74,1.00]	0.053
Advanced (T4b/ N+/ M1)	819	9	0.35 [0.18,0.68]	0.002	148	0.97 [0.78,1.20]	0.757

Abbreviations: CI: confidence interval; HR: hazard ratio; MIBC: muscle invasive bladder cancer; NMIBC: non-muscle invasive bladder cancer; advanced: locally advanced/metastatic.

^aNumber of events among β -blocker users.

^bCox regression models were adjusted for age at diagnosis, sex, disease stage, tumor grade, diagnosis year, healthcare/residence region, attained education, marital status, medication-based comorbidity score, and Charlson comorbidity index modeled as time-invariant covariates as well as transurethral resection of a bladder tumor (TURBT), radical cystectomy and lymphadenectomy modeled as time-varying covariates.

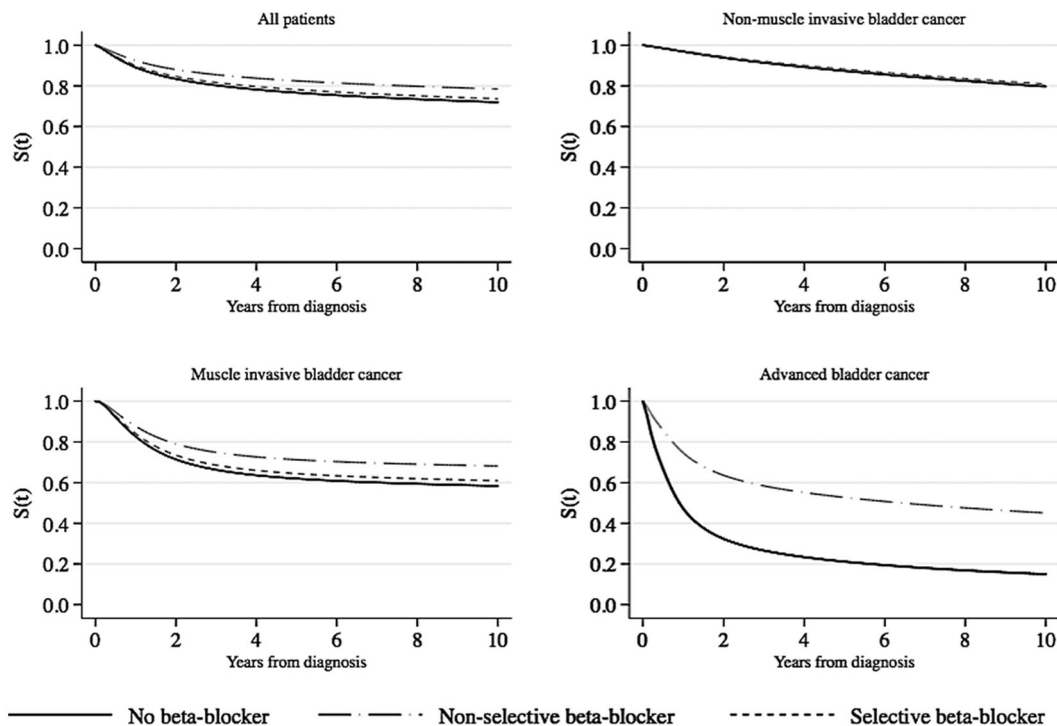
**Figure 1.** Bladder cancer-specific survival for nonusers and β -blocker users standardized to the observed covariate distribution in the sample at diagnosis (age, sex, year, grade, stage, marital status, education, health care region, medication-based comorbidity score, Charlson comorbidity index).

Table 4. β -blocker use at bladder cancer diagnosis compared with nonuse in relation to all-cause mortality by tumor stage in patients diagnosed with primary urothelial bladder cancer ($N = 16,669$) in Sweden in 2006–2014.

Disease stage	Total N	Nonselective β -blockers			β 1-receptor selective β -blockers		
		No. of events ^a	HR ^b (95% CI)	p	No. of events ^a	HR ^b (95% CI)	p
NMIBC (Tis/Ta/T1, N0/X, M0/X)	12,124	111	1.14 [0.94,1.39]	0.185	1,016	0.90 [0.83,0.98]	0.013
Low/intermediate risk (TaG1-2)	6,734	56	1.11 [0.84,1.46]	0.472	460	0.90 [0.80,1.02]	0.089
High risk (TaG3/Tis/T1)	4,812	48	1.21 [0.90,1.63]	0.198	510	0.91 [0.81,1.01]	0.089
MIBC (T2-4a, N0, M0)	1,386	16	0.85 [0.51,1.42]	0.532	200	0.90 [0.76,1.08]	0.255
At least MIBC (T2-4a, N0MX, NXM0)	2,205	31	0.93 [0.64,1.34]	0.701	433	0.84 [0.75,0.96]	0.007
Advanced (T4b/ N+/ M1)	819	14	0.45 [0.26,0.78]	0.004	179	0.94 [0.77,1.15]	0.567

Abbreviations: CI: confidence interval; HR: hazard ratio; MIBC: muscle invasive bladder cancer; NMIBC: non-muscle invasive bladder cancer, advanced: locally advanced/metastatic.

^aNumber of events among β -blocker users.

^bCox regression models were adjusted for age at diagnosis, sex, disease stage, tumor grade, diagnosis year, healthcare/residence region, attained education, marital status, medication-based comorbidity score, and Charlson comorbidity index modeled as time-invariant covariates as well as transurethral resection of a bladder tumor (TURBT), radical cystectomy and lymphadenectomy modeled as time-varying covariates.

among patients with NMIBC. Selective β -blocker use was associated with a slightly better bladder cancer survival rate in the overall, but not in the stage-stratified analyses.

Although some studies have suggested a survival disadvantage for women with UBC [38], β -blocker – BCSM associations were similar for men and women in the present study. Advanced age may be associated with worse outcome, and cancer patients over the age of 74 years may not receive the same care as younger patients [39,40]. However, the observed associations were largely similar for younger (<75) and older patients, particularly for nonselective β -blockers.

Previous studies have suggested a role of β -adrenergic signaling in the pathobiology and survival of various tumor types [14,18–20,41], but the evidence is inconsistent and associations with mortality may vary by tumor site [23], subtype [24,25], disease stage [20], and β -blocker type.

The literature on β -adrenergic receptor distribution in different tumor subtypes or disease stages is limited, but urothelial cancer has been found to exhibit significant overexpression of β -adrenergic receptors relative to normal urothelial tissue, suggesting that urothelial cancer may benefit from β -blockade therapy [26]. However, to our knowledge, pre-clinical and clinical studies have not yet explored this hypothesis, and this is the first cohort study evaluating the association between β -blocker use and survival among patients with bladder cancer. Nevertheless, a trial among high risk NMIBC patients has been initiated to assess propranolol as an adjuvant treatment in combination with BCG for disease recurrence, progression and survival as outcomes (<https://clinicaltrials.gov/ct2/show/NCT04493489>).

Clinically, bladder cancer can be divided into non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC) and advanced bladder cancer (locally advanced and/or with distant metastatic lesions), which differ in prognosis, management, and therapeutic aims [42]. Although the tumor microenvironment may be most sensitive to this type of therapy in early-stage disease when the metastatic capacity is physiologically modifiable [13,20,23], a potential for some benefit has been suggested even for late-stage disease due to treatment-sensitizing effects of β -blockers [43]. In our study, β -blocker use was associated with a survival benefit among patients with advanced-stage disease. Other studies have also linked β -blockers with survival

improvement among patients with advanced disease, such as metastatic triple negative breast cancer [44]. Advanced urothelial cancer is generally considered an incurable disease, and cisplatin- or carboplatin-based chemotherapy is a standard first-line treatment [29]. The finding of our study may indicate a synergistic interaction of β -blockers with chemotherapy. Indeed, the results from several studies support a role of β -blockers as promising candidates for chemotherapy adjuvants. For example, a role of β -blockers in mitigating the cardiotoxic effects of chemotherapy has been demonstrated in randomized controlled trials [45,46]. Moreover, β -blockers have been shown to increase the response to chemotherapy via direct antitumor and anti-angiogenic mechanisms in neuroblastoma [47]. Angiogenesis is regulated by numerous angiogenic molecules including vascular endothelial growth factor (VEGF) [17,48], and the VEGF pathway could be a potential therapeutic target for metastatic bladder cancer [49]. β -adrenergic antagonists can modulate VEGF expression in cancer [15], and nonselective propranolol has been shown to completely abolish VEGF production in cancer cells [50]. β -blockers may also block stress response induced by chemotherapy [51].

Although β 1- and β 2-receptors are in general very similar, and the majority of β -blockers used in clinical practice show little selectivity for the β 1- over the β 2-adrenoreceptor [52], it has been suggested that the β 2-adrenoreceptor is the adrenoreceptor most involved in cancer related processes [53]. The role of β -blocker selectivity may vary across tumor types, and β -adrenergic receptor status of tumor cells could serve as a biomarker for selecting the best β -blocker for adjuvant therapy [54]. For example, selective β -blockers were associated with improved survival in patients with pancreatic adenocarcinoma [20], but not in patients with epithelial ovarian cancer, in whom improved survival has been observed for nonselective β -blocker users [41]. Likewise, in a population-based study by Barron *et al.*, breast-cancer specific survival benefit was observed among patients who were on propranolol, but not among patients on atenolol [18].

Strengths of this study include use of high-quality prospectively collected data from national registers in the setting of a tax-supported universal health care system, which reduces the risk of selection bias and thus increases the generalizability of findings. The use of such data also reduces

the likelihood of the findings being confounded by socioeconomic characteristics, and limits the losses to follow-up to only those who emigrated before study end date.

Exposure to medications was defined through dispensed prescriptions from the Prescribed Drug Register, which is virtually complete for the entire population. This prevents problems such as recall bias or failure to fill prescribed medication (a key component of non-adherence). Although medication exposure misclassification is still possible, the degree of misclassification is likely to be similar among those experiencing the outcome and those not experiencing it, and our definition of exposure eliminates the possibility of immortal time bias. Since the medication data are only available since the start of the register in July 2005, we could not evaluate the role of duration of β -blocker use, the significance of which is largely unknown [55]. Besides studying β -blockers in aggregate, we studied some individual β -blockers with varying β -receptor ligand selectivity and lipophilicity/hydrophilicity. However, this analysis is limited by low numbers of individual nonselective β -blocker users. Comparison of prevalent users with nonusers could be subject to selection bias [56]. To address this, we compared incident β -blocker use with nonuse. This analysis, although limited by a small number of incident users, did not reveal any clear differences between estimates for incident and prevalent use.

To assess the potential impact of confounding by indication and of possible adherence bias [57], we performed a sensitivity analysis restricted to β -blocker users and nonusers who were dispensed other antihypertensive medications, which produced similar results, particularly for nonselective β -blockers. However, due to the observational nature of the study, the possibility of residual confounding cannot be excluded, which potentially limits causal inference.

Meta-analyses have reported positive associations between smoking and mortality in patients with bladder cancer [11,12]. However, in order to explain the observed inverse association between β -blocker use and mortality, smoking would also need to be strongly associated with avoidance of β -blocker use [58,59]. As this seems unlikely [60,61], confounding by smoking would not be expected to explain an inverse association between β -blocker use and bladder cancer mortality.

Smoking has been associated with a reduced efficacy of β -blockers possibly because β -blockers must compete with nicotine derived nitrosamine for β -adrenergic binding sites in smokers [62]. Nevertheless, our sensitivity analysis among patients with smoking related diagnoses and/or medications, suggested an inverse association for nonselective β -blocker use. Future studies with more detailed information on smoking could directly investigate the potential effect modifying effect of smoking in the β -blocker-mortality association.

To conclude, in this exploratory analysis, patients with advanced UBC receiving nonselective β -adrenergic receptor blockers had significantly better survival compared with non-exposed patients. With promises of a potentially low cost additional therapy, these results support investigating blockade of β -adrenergic receptors as a potential strategy to treat

advanced UBC, which has dismal prognosis and where chemotherapy and recently introduced immunotherapy remain the only treatment options.

Ethical approval

The study was approved by an ethical review board in Uppsala (DNR: 2012-361).

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This study was funded by a grant from the Swedish Cancer Society (CAN 2013/650 to Dr Katja Fall).

Data availability statement

The data come from national population and health registers, and are not publicly available due to ethical restrictions.

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