Original Article

Treatment and prognosis of patients with urinary bladder cancer with other primary cancers: a nationwide population-based study in the Bladder Cancer Data Base Sweden (BladderBaSe)

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Objective

To study how patients with urinary bladder cancer (UBC) with previous or concomitant other primary cancers (OPCs) were treated, and to investigate their prognosis.

Patients And Methods

Using nationwide population-based data in the Bladder Cancer Data Base Sweden (BladderBaSe), we analysed the probability of treatment with curative intent, and UBC-specific and overall survival (OS) in patients with UBC diagnosed in the period 1997–2014 with or without OPC. The analyses considered the patient's characteristics, UBC tumour stage at diagnosis, and site of OPC.

Results

There were 38 689 patients, of which 9804 (25%) had OPCs. Those with synchronous OPCs more often had T2 and T3 tumours and clinically distant disease at diagnosis than those with UBC only. Patients with synchronous prostate cancer, female genital cancer and lower gastro-intestinal cancer were more often treated with curative intent than patients with UBC only. When models of survival were adjusted for age at diagnosis, marital status, education, year of diagnosis, Charlson Comorbidity Index and T-stage, UBC-specific survival was similar to patients with UBC only, but OS was lower for patients with synchronous OPC, explained mainly by deaths in OPC primaries with a bad prognosis.

Conclusions

OPC is common in patients with UBC. Treatment for UBC, after or in conjunction with an OPC, should not be neglected and carries just as high a probability of success as treatment in patients with UBC only. The needs of patients with UBC and OPC, and optimisation of their treatment considering their complicated disease trajectory are important areas of research.

Keywords

bladder cancer, other primary cancer, cohort study, management, outcome, #uroonc, #BladderCancer, #blcsm, #utuc

Introduction

The occurrence of urinary bladder cancer (UBC) after or in combination with another primary cancer (OPC) is a common clinical problem, which is becoming more frequent as survival after/in many cancers improves. In Northern Europe, UBC is the fourth most common secondary primary malignancy after a previous cancer diagnosis, constituting 10% of all secondary malignancies [1]. Consistent with these data, Surveillance, Epidemiology and End Results (SEER) data show that UBC as a new primary is common after cancers associated with smoking [2,3]. Epidemiological studies indicate that some cancer therapies, such as cyclophosphamide and pelvic radiotherapy (RT), may induce UBC as a secondary primary [4,5].

While there is literature reporting on the occurrence of UBC after cancer at other sites [1,4], there has to our knowledge been no study to inform about treatment and prognosis for patients with UBC and a synchronous or metachronous OPC. An earlier or concomitant cancer may influence and limit treatment possibilities, as previous treatments can have delivered maximum doses of RT or selected chemotherapeutic drugs or may have caused side-effects resulting in contraindications to treatment. Furthermore, having two or more malignancies may signal a reduced host resistance to cancer, which can lead to worse prognosis than in patients with UBC only. Thus, a previous cancer diagnosis may for several reasons influence clinical decision-making, so that management diverges from clinical guidelines. Our present study hypothesis was that patients with UBC and a synchronous or metachronous OPC had a worse prognosis than patients with UBC only, and we thus studied the stage of disease at diagnosis, the given treatment, the prognosis and causes of death in 9804 patients with UBC and OPC as compared to 28 885 patients with UBC as the first primary.

Patients And Methods

The study cohort consisted of all patients with UBC reported in the Bladder Cancer Data Base Sweden (BladderBaSe) from 1 January 1997 to 31 December 2014. The BladderBaSe was initiated in 2015 with the linkage of the Swedish National Registry for Urinary Bladder Cancer (SNRUBC) to a number of healthcare and demographic registers in Sweden [6]. The project was approved by the Research Ethics Board at Uppsala University, Sweden (EPN Reference number; 2015/277). Data on UBC included patient and tumour characteristics and primary treatment. Clinical TNM stage was based on CT and/or MRI examinations and pathological examination of the transurethral resection of bladder specimen from the bladder tumour. Data on OPC included primary tumour site and date of diagnosis. The diagnosis of OPC was based on the morphological codes according to the WHO International Classification of Diseases for Oncology,

using ICD-7 and ICD-10 classifications. The codes were retrieved from the National Cancer Registry to which both pathological and clinical departments in Sweden have been bound by law to continuously report on all cases of newly diagnosed cancer since 1958.

The Charlson Comorbidity Index (CCI) was calculated from the codes in the Swedish Patient Register based on a list of diseases with a specific weight assigned to each disease category. The separate weights are collated to an overall score, categorised into: 0 for no comorbidity, 1 for mild comorbidity, 2 for intermediate, and ≥ 3 for severe comorbidity [6]. Marital status was categorised as married or non-married, with the latter category including never married, widowed and divorced patients. Educational level was categorised as low (≤ 9 years of primary school level), intermediate (10–12 years secondary school level), and high (≥ 13 years university level), corresponding to mandatory school, high school, and college or university. Date and cause of death were obtained from the Cause of Death Register and death from UBC was defined as ICD-7 code 1810 or 1816 and ICD-10 code C67 as underlying death cause. Curative treatment was considered to be radical cystectomy (RC) or RT with curative intent.

Definitions

OPC was defined as another cancer detected before or concomitantly with the diagnosis of UBC. The OPC group was further subdivided into metachronous and synchronous cancers. We used the International Association of Cancer Registries and International Agency for Research on Cancer (IACR/IARC), which suggests an interval of 6 months to distinguish between synchronous and metachronous cancers if they arise at different sites [7,8]. Thus, synchronous OPC was defined as another cancer detected within 6 months before or after the diagnosis of UBC. Metachronous OPC was defined as another primary cancer detected more than 6 months before the diagnosis of UBC. OPCs according ICD-7 and ICD-10 codes are shown in Table S1. Stratification of OPC was performed as follows: respiratory tract cancer (including larynx and lung), gastro-intestinal (GI) tract cancer (sub-stratified in in upper and lower GI tumours), male genital cancer (including prostate cancer, testicular cancer, and penile cancer), female genital cancer (including uterine cervix cancer, uterus cancer, and ovarian cancer), urinary tract cancer (including renal, renal pelvis, ureter, and urethra), skin cancer (including melanoma and non-melanoma skin cancer) and haematological cancer (including lymphoma and leukaemia) for further analyses.

Statistics

Differences in the distribution of covariates and in the probability of receiving treatment with curative intent

between groups were statistically tested using the chi-squared test. *P* values <0.05 were considered to be statistically significant. Uni- and multivariate Cox regression survival analyses adjusted for age at diagnosis, marital status, education, year of diagnosis, CCI and T-stage were used to compare UBC-specific survival and overall survival (OS) between groups. In the survival analyses, the starting date was the date of UBC diagnosis, and last date of the study was either the date of death, emigration, or the administrative date of the end of follow-up (31 December 2014), whichever happened first.

Results

Of 38 689 participants in the BladderBaSe cohort, 2503 (6.5%) had a synchronous OPC and 7301 (19%) individuals had a metachronous OPC. The median (interquartile range) follow-up was 2.3 (0.9–5.8) years.

Patient Characteristics For Patients With OPC Vs Those With UBC Only

Compared to UBC-only patients, patients with synchronous OPC were more often male, older, had a higher CCI score, and had a higher proportion of T2 tumours, but a similar distribution of clinical node and distant metastases status (Table 1). Patients with metachronous OPC were more often female, older, and had a higher CCI score, but a similar stage distribution as patients with UBC only. Patients with synchronous OPC were more often unmarried, but otherwise the socio-economic status was similar for the groups. For both patients with synchronous and metachronous OPC the distribution over diagnosis periods was skewed towards later time periods: the proportion of all patients with UBC with synchronous or metachronous OPC increased from 5.5% and 16% to 7% and 22% respectively from 1997–2001 to 2011–2014.

Curative Treatment Offered

Treatment of UBC with curative intent (RC or RT) was given more often to patients with synchronous OPC as compared to patients with UBC only (Tables 2 and 3). Table 2 shows that this pattern was especially marked for men, younger individuals and patients with more favourable stages, and also for 861/5164 (17%) patients with non-muscle-invasive disease received such treatment. For patients with metachronous OPC, the probability of being offered treatment with curative intent was lower for those with T2–4 compared to those with UBC only: 33% vs 42% were offered such treatment.

Looking at organ system of OPC as a determinant of being offered treatment with curative intent, it was mainly men with synchronous prostate cancer that were offered such

treatment. Also, patients with synchronous female genital cancer and lower GI cancer were more often treated with curative intent than patients with UBC only (Table 3).

Survival and Causes of Death

When UBC-specific survival for all patients with synchronous OPC was compared with that for patients with UBC only in a Cox regression model adjusted for gender, age at diagnosis, education, marital status, year of diagnosis, CCI category and T-stage, survival was 22% better in relative terms for those with synchronous OPC (Table 4); however, OS was similar (Tables 4 and 5). The distribution of patient characteristics and differences in treatment patterns motivated further survival analyses that were stratified by gender and called for one analysis where men with synchronous prostate cancer were excluded. The estimates from those models show that it was mainly the men with synchronous prostate cancer that drove the trend for patients with synchronous OPC to do better in UBC-specific survival (Table 4). The prognosis for men with synchronous prostate cancer also influenced the estimates of OS; when women and men (excluding those with synchronous prostate cancer) were looked at separately, patients with synchronous OPC had a worse OS (relative hazards [95% CI] of 1.27 [1.06–1.54] and 1.46 [1.31–1.63] respectively; Table 4). Patients with metachronous OPC had estimates of relative hazards for UBC-specific and OS close to unity, with small CIs when compared to patients with UBC only. A further study of the vital status and causes of death in the patients with OPC showed that it was the cancers with known worse prognosis that conferred the greater overall risk of death (Table 5).

Discussion

In all, 25% of all patients diagnosed with UBC had a metachronous or synchronous OPC. Patients with OPC were older and had more comorbidities. A larger proportion of the patients with synchronous OPC were men, while the opposite was true for patients with metachronous OPC compared to patients with UBC only. Those individuals with synchronous OPC more often had stage T2 and T3 tumours at diagnosis than those with UBC only. Patients with synchronous OPC in the prostate, female genital tract and lower GI tract were more often treated with curative intent than patients with UBC only. When models of survival were adjusted for age at diagnosis, marital status, education, year of diagnosis, CCI and clinical T-stage, UBC-specific survival was similar to patients with UBC only, but OS was lower for patients with synchronous OPC, explained mainly by deaths in those OPCs that have a bad prognosis.

Metachronous and synchronous OPC in patients with UBC is a common clinical situation, e.g. in Germany and Sweden

Table 1 Patients with OPCs in the cohort of population-based UBC in Sweden 1997–2014.

Variable, n (%)	OPC + UBC		UBC only, n = 28 885	Total, N = 38 689	P
	Synchronous, n = 2503	Metachronous, n = 7301			
Gender					
Male	2210 (88)	4753 (65)	21 880 (76)	28 843 (75)	<0.001
Female	293 (12)	2548 (35)	7005 (24)	9846 (25)	
Age group, years					
≤60	258 (10)	498 (7)	4892 (17)	5648 (15)	<0.001
61–70	717 (29)	1527 (21)	7817 (27)	10 061 (26)	
71–80	1073 (43)	2816 (38)	9696 (34)	13 585 (35)	
>80	544 (18)	2457 (34)	6461 (22)	9373 (24)	
Social status					
Unmarried	881 (35)	2970 (41)	11 438 (40)	15 289 (40)	<0.001
Married	1622 (65)	4331 (59)	17 447 (60)	23 400 (60)	
Education					
Low	1158 (46)	3381 (46)	12 984 (45)	17 523 (45)	0.242
Intermediate	863 (35)	2478 (34)	10 111 (35)	13 452 (35)	
High	405 (16)	1206 (17)	4763 (16)	6374 (16)	
Missing	77 (3)	236 (3)	1027 (4)	1340 (4)	
CCI					
0	1255 (50)	2156 (30)	19 207 (67)	22 618 (59)	<0.001
1	320 (13)	717 (10)	5508 (19)	6545 (17)	
2	552 (22)	2420 (33)	2214 (8)	5186 (13)	
≥3	376 (15)	2008 (27)	1956 (7)	4340 (11)	
Healthcare region					
Stockholm	454 (18)	1358 (18)	5125 (18)	6937 (18)	<0.001
Uppsala/Örebro	511 (20)	1411 (19)	6245 (22)	8167 (21)	
South-East	257 (10)	846 (12)	3397 (12)	4500 (12)	
South	555 (22)	1635 (22)	5958 (21)	8148 (21)	
West	494 (20)	1435 (20)	5407 (19)	7336 (19)	
North	232 (9)	616 (8)	2753 (9)	3601 (9)	
Diagnosis periods					
1997–2001	536 (21)	1500 (21)	7587 (26)	9623 (25)	<0.001
2002–2005	511 (20)	1411 (19)	6259 (22)	8181 (21)	
2006–2010	758 (30)	2216 (30)	8070 (28)	11 044 (29)	
2011–2014	698 (28)	2174 (30)	6969 (24)	9841 (25)	
cT-stage					
TX	67 (3)	195 (3)	665 (2)	927 (2)	<0.001
Ta, T1,Tis	1462 (58)	5177 (71)	21 302 (74)	27 941 (72)	
T2–T4	974 (40)	1879 (26)	6918 (24)	9821 (25)	
cN-stage					
N0	964 (39)	1922 (26)	7955 (28)	10 841 (28)	<0.001
N+	129 (5)	232 (3)	1006 (4)	1367 (4)	
Nx	1410 (56)	5147 (71)	19 924 (69)	26 481 (68)	
cM-stage					
M0	1047 (42)	1924 (26)	7837 (27)	10 808 (28)	<0.001
M1	80 (3)	282 (4)	907 (3)	1269 (3)	
Mx	1376 (55)	5095 (70)	20 141 (70)	26 612 (69)	
Curative treatment					
No	1650 (66)	6532 (90)	25 343 (88)	33 525 (87)	<0.001
Yes	853 (34)	769 (10)	3542 (12)	5164 (13)	
Specific death					
Alive	1060 (42)	3071 (42)	14 832 (51)	18 963 (49)	<0.001
UBC	533 (22)	1548 (21)	6284 (22)	8365 (22)	
OPC	536 (21)	1257 (17)	1919 (7)	3712 (10)	
Other cause	374 (15)	1425 (20)	5850 (20)	7649 (20)	

Figures represent number of patients (% of the column).

UBC is the fourth most common second primary malignancy after another primary cancer [1]. Estimates from French cancer registries imply a similar situation with e.g. a 10.5% and 11.3% cumulative incidence of UBC in men at 10 years after a first diagnosis of lung and prostate cancer, respectively [9]. UBC as a secondary primary malignancy is especially

common after cancers of the lung and bronchus, head and neck and stomach cancer, with which there is a shared strong association with tobacco smoking [1–3]. There is also a biological rationale to explain the association seen with a previous treatment for some cancers such as breast, prostate, rectal, and gynaecological cancers where treatments with

Table 2 Probability in different strata of patient and tumour characteristics of receiving radical treatment with curative intent (RC/RT) for 5164 patients with UBC with synchronous or metachronous OPC, compared to patients with UBC only.

Variable, n (%)	OPC + UBC, n = 9804 (25%)		UBC only, n = 28 885 (75%)	Total, N = 38 689
	Synchronous, n = 2503 (25%)	Metachronous, n = 7301 (75%)		
Gender				
Male	802 (36)	462 (10)	2622 (12)	3886 (13)
Female	51 (17)	307 (12)	920 (13)	1278 (13)
Age group, years				
≤60	127 (49)	80 (16)	417 (9)	921 (16)
61–70	306 (43)	231 (15)	1247 (16)	1784 (18)
71–80	373 (35)	355 (13)	1302 (13)	2030 (15)
>80	47 (10)	103 (4)	277 (4)	427 (5)
Social status				
Unmarried	278 (32)	329 (11)	1383 (12)	1990 (13)
Married	575 (35)	440 (10)	2159 (12)	3174 (14)
Education				
Low	361 (31)	344 (10)	1538 (12)	2243 (13)
Intermediate	331 (38)	270 (11)	1354 (13)	1955 (15)
High	149 (37)	147 (12)	594 (12)	890 (14)
Missing	12 (16)	8 (3)	56 (5)	
CCI				
0	583 (46)	271 (13)	2663 (14)	3517 (16)
1	133 (42)	78 (11)	554 (10)	765 (12)
2	95 (17)	270 (11)	192 (9)	557 (11)
≥3	18 (9)	150 (7)	133 (7)	325 (7)
Diagnosis period				
1997–2001	126 (24)	149 (10)	864 (11)	1139 (12)
2002–2005	183 (36)	129 (9)	742 (12)	1054 (13)
2006–2010	280 (37)	223 (10)	1077 (13)	1580 (14)
2011–2014	264 (38)	268 (12)	859 (12)	1391 (14)
cT-stage				
Tis, Ta, T1	169 (12)	132 (3)	560 (3)	861 (3)
T2–4	676 (69)	628 (33)	2913 (42)	4217 (43)
Tx	8 (12)	9 (5)	69 (10)	86 (9)
cN-stage				
N0	529 (55)	440 (23)	2102 (26)	3071 (28)
N+	74 (57)	64 (28)	362 (36)	500 (37)
Nx	250 (18)	265 (5)	1078 (5)	1593 (6)
cM-stage				
M0	600 (57)	509 (26)	2458 (31)	3567 (33)
M1	17 (21)	26 (9)	90 (10)	133 (10)
Mx	236 (17)	234 (5)	994 (5)	1464 (6)

cyclophosphamide and pelvic RT have been implicated as risk factors [10–12]. The situation is likely to be similar across countries where smoking is still a major risk factor for UBC and where guidelines for e.g. breast, gynaecological, prostate and colorectal cancers have implied adjuvant systemic treatments and/or RT to the pelvic region. As expected from that, a certain time at risk is needed to develop a second cancer, patients with OPC were older, and they also had a higher CCI because of older age and possibly previous sequelae from cancer treatment.

The different gender distribution between patients with synchronous and metachronous OPC and those with UBC only is explained for men by the common joint diagnoses of UBC and prostate cancer, with incident prostate cancer frequently detected during clinical examination and evaluation of the UBC diagnosis prior to RC or in the cystoprostatectomy specimen. Other studies have found similar, strong associations between UBC and prostate cancer

[13,14] and there may also be common biological pathways to the inception of these cancers [15,16]. In women, the increased risk for a metachronous cancer with a gynaecological cancer or with breast cancer plays a role. Previous treatments with cyclophosphamide for rheumatic diseases, breast cancer and other malignancies or RT for cervical or endometrial cancer have been implicated as risk factors for UBC [4,5,10,17–20]. In breast cancer, the wide indications for systemic adjuvant treatment also in early breast cancer with good prognosis give the opportunity for long induction times to have an effect after a previous, possibly carcinogenic exposure during a treatment episode. Previous cancer treatment may also limit the therapeutic arsenal for the UBC, e.g. by having reached maximum exposure to RT in the pelvic area.

The higher risk for patients with a clinically locally advanced UBC (clinical stage T2 and T3) to have a synchronous OPC might partly be explained by the use of more detailed staging

Table 3 Groups of UBC with OPC (synchronous/metachronous) in relation to treatment modality.

	Total	Treatment		P
		Non-curative	Curative	
Respiratory tract				
Synchronous	128 (24)	114 (24)	14 (24)	1.000
Metachronous	415 (76)	370 (76)	45 (76)	
Upper GI tract				
Synchronous	82 (32)	77 (33)	5 (19)	0.133
Metachronous	177 (68)	155 (67)	22 (819)	
Lower GI tract				
Synchronous	198 (15)	156 (14)	42 (29)	<0.001
Metachronous	1087 (85)	984 (86)	103 (71)	
Breast				
Synchronous	42 (6)	35 (6)	7 (7)	0.646
Metachronous	631 (94)	542 (94)	89 (93)	
Female genital				
Synchronous	42 (4)	30 (3)	12 (7)	0.009
Metachronous	1164 (96)	1014 (97)	150 (93)	
Male genital*				
Synchronous	1466 (40)	735 (28)	731 (74)	<0.001
Metachronous	2195 (60)	1935 (72)	260 (26)	
Urinary tract				
Synchronous	332 (35)	293 (34)	39 (44)	0.059
Metachronous	625 (65)	576 (66)	49 (56)	
Skin/melanoma				
Synchronous	137 (9)	126 (9)	11 (7)	0.548
Metachronous	1399 (91)	1259 (91)	140 (93)	
Haematological				
Synchronous	68 (14)	58 (13)	10 (17)	0.420
Metachronous	423 (86)	375 (87)	48 (83)	
Endocrine/neuro				
Synchronous	15 (5)	13 (4)	2 (6)	0.667
Metachronous	313 (95)	280 (96)	33 (94)	
Other				
Synchronous	47 (26)	40 (24)	7 (26)	0.810
Metachronous	149 (76)	129 (76)	20 (74)	
UBC only	28 885	25 343 (88)	3542 (12)	<0.001

Figures represent number of patients (% of the column). *Prostate cancer represents 97% of the patients.

investigations such as fluorodeoxyglucose positron-emission tomography/CT to support clinical decision-making for patients with two malignancies; however, information about radiological investigations applied were not available in BladderBaSe. A concomitant diagnosis of an OPC related to simultaneous treatment of adjacent organs, such as prostate cancer in males treated with cystoprostatectomy [21] and

female genital cancer when hysterosalpingo-oophorectomy, as well as excision of the anterior vaginal wall as an integral part of RC in females, also contribute in patients with locally advanced UBC.

Our present investigation was partly driven by a concern that patients with metachronous or synchronous OPC would have been less actively treated and thus would have missed out on treatment opportunities. We noted a propensity to treat patients with metachronous T2–T4 or cN positive tumours less aggressively, but patients with earlier stages were treated very similarly in the three groups. Patients with a synchronous OPC in the pelvic region were even more often offered treatment with curative intent than patients with UBC only, indicating that the patients' UBC was actively treated despite two malignant diagnoses [21,22]. We do not hold data on the treatment of the OPC; case studies to review the quality of care for both tumours could provide information on important aspects of the management of these patients

Despite the difference in treatment in the T2–T4 and cN strata, the multivariate models imply that stage by stage, the UBC-specific survival was similar between patients with synchronous OPC and those with UBC only. The survival analyses indicate that the policy to offer treatment with curative intent in a similar degree to patients with metachronous or synchronous OPC and to patients with UBC only was successful; the risk of dying from the UBC was similar in the three groups.

However, the OS was lower among those with synchronous OPC, mainly influenced by deaths from OPC with a bad prognosis, e.g. lung cancer. Thus, many patients with UBC and OPC with a known serious prognosis are very likely to experience recurrence from the OPC during follow-up of the UBC and will have a complicated disease trajectory. The high morbidity and resource-demanding management of the UBC together with management of recurrence of the OPC will require advanced multidisciplinary care. In this scenario, suboptimal treatment of the UBC is a disservice to patients.

Table 4 Relative hazards (RHs) for UBC-specific death for patients with synchronous or metachronous OPC as compared to patients with UBC only.

	RH (95% CI) synchronous OPC	RH (95% CI) synchronous OPC (excluding men with synchronous prostate cancer)	RH (95% CI) metachronous OPC
All patients, UBC death	0.78 (0.71–0.87)	NA	0.92 (0.85–0.99)
All patients, overall	1.01 (0.95–1.07)	NA	1.01 (0.97–1.06)
Women, UBC death	0.89 (0.65–1.21)	NA	0.89 (0.79–1.00)
Women, overall	1.27 (1.06–1.54)	NA	1.01 (0.93–1.08)
Men, UBC death	0.78 (0.70–0.87)	1.07 (0.87–1.31)	0.95 (0.86–1.05)
Men, overall	0.99 (0.93–1.06)	1.46 (1.31–1.63)	1.01 (0.96–1.07)

Models are adjusted for age at diagnosis, education, marital status, year of diagnosis, CCI category and T-stage. Models for all patients are additionally adjusted for gender.

Table 5 Vital status and causes of death in groups of OPC.

	Living	Death UBC	Death OPC	Death other causes	All
Respiratory tract	149 (27)	111 (20)	175 (32)	108 (20)	543 (5.5)
Upper GI	64 (25)	37 (14)	104 (40)	54 (21)	259 (2.6)
Lower GI	507 (40)	259 (20)	245 (19)	274 (21)	1285 (13)
Breast	296 (44)	168 (25)	95 (14)	114 (17)	673 (6.9)
Female genital	544 (45)	304 (25)	147 (12)	211 (18)	1206 (12)
Male genital*	1606 (48)	727 (20)	738 (20)	590 (16)	3661 (37)
Urinary tract	459 (48)	117 (12)	231 (24)	150 (16)	957 (10)
Skin/melanoma	619 (40)	389 (25)	173 (11)	355 (23)	1536 (16)
Haematological	160 (33)	103 (21)	138 (28)	90 (18)	491 (5.0)
Endocrine/neuro	169 (52)	65 (20)	36 (11)	58 (18)	328 (3.3)
Other	63 (32)	48 (25)	49 (25)	36 (18)	196 (2.0)
UBC only	14 832 (51)	6284 (22)	1919 (7)	5850 (20)	28 885
Median %	43	21	18		

Figures represent number of patients (% of the row). *Prostate cancer represented 97% of the patients.

Strengths And Limitations

The BladderBaSe has a high coverage, a complete follow-up through use of national registration numbers, and a detailed characterisation of patients due to extensive linkage [6]. The BladderBaSe is defined with the UBC as a starting point and currently there is no detailed information about stage of disease or treatment of the OPC. Thus, we could not study e.g. specifically the prognosis for patients where a previous cancer treatment may have induced the UBC, or the prognosis for patients with distant spread of the OPC at the time of UBC diagnosis. Likewise, we lacked information about smoking status, which might affect both UBC survival and risk of smoking-associated OPCs. There may be some misclassification for men with synchronous prostate cancer, where some who were initially reported as having prostate cancer may have had an extensive UBC and vice versa. However, our analyses without men with synchronous prostate cancer did not change the overall pattern.

Conclusion

An OPC is a common clinical problem in patients with UBC. Our present findings indicate that treatment for UBC after or in conjunction with an OPC carries just as high a probability of success as treatment in patients with UBC only. There are indications that treatment for UBC should be intensified in general, and the present study raises the hypothesis that treatment for patients with metachronous or synchronous OPC also should be intensified, and similar improvements in prognosis can result. Research into these patients' needs and optimising their treatment considering their complicated disease trajectory is an important area of research in supportive care.

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Conflicts Of Interest

None declared.

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Abbreviations: BladderBaSe, Bladder Cancer Data Base Sweden; CCI, Charlson Comorbidity Index; GI, gastrointestinal; ICD, International Classification of Diseases; OPC, other primary cancers; OS, overall survival; RC, radical cystectomy; RT, radiotherapy; UBC, urinary bladder cancer.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. ICD-7 and ICD-10 codes of OPC.