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

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## Abstract

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

**Methods:** Using nationwide population-based data in the Bladder Cancer Data Base Sweden (BladderBaSe), we analysed the probability of treatment with curative intent, and bladder cancer specific and overall survival 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 38689 patients, of which 9804 (25%) had OPC. Those with synchronous OPC 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, CCI and T-stage, UBC-specific survival was similar to patients with UBC only, but overall survival 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 probability of success as treatment in patients with UBC only. The needs of patients with UBC and OPC and optimisation of their treatment in light of their complicated disease trajectory are important areas of research.

## 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, urinary bladder cancer (UBC) is the fourth most common secondary primary malignancy after a previous cancer diagnosis, constituting 10% of all secondary malignancies [1]. In line with these data, 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, 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 radiotherapy 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 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 9 804 patients with UBC and OPC as compared to 28 885 patients with UBC as the first primary.

## Material and Methods

The study cohort consisted of all patients with UBC reported in the Bladder Cancer Data Base Sweden (BladderBaSe) from January 1, 1997 to December 31, 2014. The BladderBaSe was initiated in 2015 with the linkage of the Swedish National Registry for Urinary Bladder Cancer (SNRUBC) to a number of health care 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 computed tomography and/or magnetic resonance imaging examinations and pathological examination of the TURB 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 World Health Organization´s 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 or more

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 bladder cancer 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 radiotherapy with curative intent (RT).

**Definitions**

OPC was defined as other primary 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 six 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 six months before or after the diagnosis of UBC. Metachronous primary cancer (MPC) was defined as another primary cancer detected more than six months before the diagnosis of UBC. OPCs according ICD-7 and ICD-10 codes are shown in Supplementary Table 1. Stratification of OPC was performed as follows: respiratory tract cancer (including larynx and lung), gastrointestinal tract cancer (substratified in in upper and lower GI tumors), 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 leukemia) for further analyses.

**Statistics**

Differences in the distribution of co-variates 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 multi-variate Cox regression survival analyses adjusted for age at diagnosis, marital status, education, year of diagnosis, CCI and T-stage were used to compare bladder cancer-specific survival (CSS) 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 (December, 31, 2014), whichever happened first.

## Results

Out of 38689 participants in the BladderBaSe cohort, 2503 (6.5%) had a synchronous (OPC) and 7301 (19%) individuals had a metachronous OPC. The median follow-up time was 2.3 (IQR 0.9-5.8) years.

**Patient characteristics for patients with OPC versus those with UBC only (table 1)**

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. 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 UBC patients 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 (table 2 and 3)**

Treatment of UBC with curative intent (cystectomy or radiotherapy) was given more often to patients with synchronous OPC as compared to patients with UBC only. Table 2 shows that this pattern was especially marked for men, for younger individuals and for patients with more favourable stages, and that also 861/5164 (17%) 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 gastro-intestinal (GI) cancer were more often treated with curative intent than patients with UBC only (table 3).

**Survival and causes of death (table 4 and 5)**

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, overall survival was similar. 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 is mainly the men with synchronous prostate cancer that drive 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 influences the estimates of overall survival; when women and men (excluding those with synchronous prostate cancer) are looked at separately, patients with synchronous OPC have a worse overall survival (relative hazards with 95% confidence interval 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 overall survival close to unity, with small confidence intervals when compared to patients with UBC only. A further study of the vital status and causes of death in the patients with OPC shows that it is the cancers with known worse prognosis that confer the greater overall risk of death (table 5).

## Discussion

Twenty-five percent of all patients diagnosed with UBC had a metachronous or synchronous other primary cancer (OPC). Patients with OPC were older and had more co-morbidities. 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 gastro-intestinal 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 overall survival was lower for patients with synchronous OPC, explained mainly by deaths in those OPC primaries which have a bad prognosis.

Meta- and synchronous OPC in patients with UBC is a common clinical situation, e.g. in Germany and Sweden 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 ten 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 cyclophosphamide and pelvic radiotherapy 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 colo-rectal cancers have implied adjuvant systemic treatments and/or radiotherapy 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 a higher age and possibly previous sequelae from cancer treatment.

The different gender distribution between patients with synchronous, 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 workup of the bladder cancer diagnosis prior to cystectomy 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 radiation for cervical or endometrial cancer may 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 radiation 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 investigations such as FDG-PET-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 radical cystectomy in females is performed also contribute in patients with locally advanced UBC.

Our 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 overall survival 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.

**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**

OPC is common clinical problem in patients with UBC. Our findings indicate that treatment for UBC after or in conjunction with an OPC carries just as high probability of success as treatment in patients with UBC only. There are indications that treatment for UBC should be intensified in general, and this 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 in light of their complicated disease trajectory is an important area of research in supportive care.

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**References**

[1] Chen T, Fallah M, Jansen L, et al. Distribution and risk of the second discordant primary cancers combined after a specific first primary cancer in German and Swedish cancer registries. Cancer letters. 2015 Dec 1: **369**:152-66

[2] Anderson JK, Alanee S, Lindgren B, Slaton J. The risk of bladder cancer in patients diagnosed with other primary neoplasms: analysis of the SEER database. Urol Oncol. 2013 Aug: **31**:862-5

[3] Curtis RE FD, Ron E, Ries LAG, Hacker DG, Edwards BK, Tucker MA, Fraumeni JF Jr. (eds). . New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000; 2006

[4] Berrington de Gonzalez A, Curtis RE, Kry SF, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. The Lancet Oncology. 2011 Apr: **12**:353-60

[5] Pathak AB, Advani SH, Gopal R, Nadkarni KS, Saikia TK. Urinary bladder cancer following cyclophosphamide therapy for Hodgkin's disease. Leukemia & lymphoma. 1992 Dec: **8**:503-4

[6] Haggstrom C, Liedberg F, Hagberg O, et al. Cohort profile: The Swedish National Register of Urinary Bladder Cancer (SNRUBC) and the Bladder Cancer Data Base Sweden (BladderBaSe). BMJ Open. 2017 Sep 27: **7**:e016606

[7] Muir CS. The International Association of Cancer Registries. The benefits of a worldwide network of tumor registries. Connecticut medicine. 1985 Nov: **49**:713-7

[8] Vogt A, Schmid S, Heinimann K, et al. Multiple primary tumours: challenges and approaches, a review. ESMO open. 2017: **2**:e000172

[9] Moitry M, Velten M, Tretarre B, et al. Development of a model to predict the 10-year cumulative risk of second primary cancer among cancer survivors. Cancer epidemiology. 2017 Apr: **47**:35-41

[10] Travis LB, Curtis RE, Glimelius B, et al. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. Journal of the National Cancer Institute. 1995 Apr 5: **87**:524-30
[11] Travis LB. The epidemiology of second primary cancers. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2006 Nov: **15**:2020-6
[12] Jin T, Song T, Deng S, Wang K. Radiation-induced secondary malignancy in prostate cancer: a systematic review and meta-analysis. Urologia internationalis. 2014: **93**:279-88
[13] Kellen E, Zeegers MP, Dirx M, et al. Occurrence of both bladder and prostate cancer in five cancer registries in Belgium, The Netherlands and the United Kingdom. European journal of cancer (Oxford, England : 1990). 2007 Jul: **43**:1694-700
[14] Singh A, Kinoshita Y, Rovito PM, Jr., et al. Higher than expected association of clinical prostate and bladder cancers. The Journal of urology. 2008 May: **179**:S2-5
[15] Singh A, Jones RF, Friedman H, et al. Expression of p53 and pRb in bladder and prostate cancers of patients having both cancers. Anticancer research. 1999 Nov-Dec: **19**:5415-7
[16] Wang CY, Jones RF, Debiec-Rychter M, Soos G, Haas GP. Correlation of the genotypes for N-acetyltransferases 1 and 2 with double bladder and prostate cancers in a case-comparison study. Anticancer research. 2002 Nov-Dec: **22**:3529-35
[17] Dores GM, Metayer C, Curtis RE, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002 Aug 15: **20**:3484-94
[18] Brennan P, Scelo G, Hemminki K, et al. Second primary cancers among 109 000 cases of non-Hodgkin's lymphoma. British journal of cancer. 2005 Jul 11: **93**:159-66
[19] Landgren O, Pfeiffer RM, Stewart L, et al. Risk of second malignant neoplasms among lymphoma patients with a family history of cancer. International journal of cancer. 2007 Mar 1: **120**:1099-102
[20] Chaturvedi AK, Engels EA, Gilbert ES, et al. Second cancers among 104,760 survivors of cervical cancer: evaluation of long-term risk. Journal of the National Cancer Institute. 2007 Nov 7: **99**:1634-43
[21] Fernandez-Conejo G, de la Pena E, Hernandez V, Castro A, Perez-Fernandez E, Llorente C. Incidence and prognosis of clinically significant incidental prostate cancer after radical cystectomy for bladder cancer. Archivos espanoles de urologia. 2019 Nov: **72**:915-20
[22] Abdelhady M, Abusamra A, Pautler SE, Chin JL, Izawa JI. Clinically significant prostate cancer found incidentally in radical cystoprostatectomy specimens. BJU international. 2007 Feb: **99**:326-9

**Table 1. Patients with other primary cancers (OPC), in the cohort of population-based bladder cancer from Sweden 1997 to 2014. Figures represent number of patients (% of the column).**

| | OPC+UBC | | UBC only (n=28885) | Total (N= 38689) | P |
|---|---|---|---|---|---|
| | Synchronous (n=2503) | Metachronous (n=7301) | | | |
| **Gender** | | | | | |
| Male | 2210 (88) | 4753 (65) | 21880 (76) | 28843 (75) | |
| Female | 293 (12) | 2548 (35) | 7005 (24) | 9846 (25) | < 0.001 |
| **Age group** | | | | | |
| ≤60 | 258 (10) | 498 (7) | 4892 (17) | 5648 (15) | |
| 61-70 | 717 (29) | 1527 (21) | 7817 (27) | 10061 (26) | |
| 71-80 | 1073 (43) | 2816 (38) | 9696 (34) | 13585 (35) | |
| >80 | 544 (18) | 2457 (34) | 6461 (22) | 9373 (24) | < 0.001 |
| **Social status** | | | | | |
| Unmarried | 881 (35) | 2970 (41) | 11438 (40) | 15289 (40) | |
| Married | 1622 (65) | 4331 (59) | 17447 (60) | 23400 (60) | < 0.001 |
| **Education** | | | | | |
| Low | 1158 (46) | 3381 (46) | 12984 (45) | 17523 (45) | |
| Intermediate | 863 (35) | 2478 (34) | 10111 (35) | 13452 (35) | |
| High | 405 (16) | 1206 (17) | 4763 (16) | 6374 (16) | |
| Missing | 77 (3) | 236 (3) | 1027 (4) | 1340 (4) | 0.242 |
| **CCI** | | | | | |
| 0 | 1255 (50) | 2156 (30) | 19207 (67) | 22618 (59) | |
| 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) | < 0.001 |
| **Healthcare region** | | | | | |
| Stockholm | 454 (18) | 1358 (18) | 5125 (18) | 6937 (18) | |
| 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) | < 0.001 |
| **Diagnosis periods** | | | | | |
| 1997-2001 | 536 (21) | 1500 (21) | 7587 (26) | 9623 (25) | |
| 2002-2005 | 511 (20) | 1411 (19) | 6259 (22) | 8181 (21) | |
| 2006-2010 | 758 (30) | 2216 (30) | 8070 (28) | 11044 (29) | |
| 2011-2014 | 698 (28) | 2174 (30) | 6969 (24) | 9841 (25) | < 0.001 |
| **cT-stage** | | | | | |
| TX | 67 (3) | 195 (3) | 665 (2) | 927 (2) | |
| Ta, T1,Tis | 1462 (58) | 5177 (71) | 21302 (74) | 27941 (72) | |
| T2-T4 | 974 (40) | 1879 (26) | 6918 (24) | 9821 (25) | <0.001 |
| **cN-stage** | | | | | |
| N0 | 964 (39) | 1922 (26) | 7955 (28) | 10841 (28) | |
| N+ | 129 (5) | 232 (3) | 1006 (4) | 1367 (4) | |
| Nx | 1410 (56) | 5147 (71) | 19924 (69) | 26481 (68) | < 0.001 |
| **cM-stage** | | | | | |
| M0 | 1047 (42) | 1924 (26) | 7837 (27) | 10808 (28) | |
| M1 | 80 (3) | 282 (4) | 907 (3) | 1269 (3) | |
| Mx | 1376 (55) | 5095 (70) | 20141 (70) | 26612 (69) | < 0.001 |
| **Curative treatment** | | | | | |
| No | 1650 (66) | 6532 (90) | 25343 (88) | 33525 (87) | |
| Yes | 853 (34) | 769 (10) | 3542 (12) | 5164 (13) | < 0.001 |
| **Specific death** | | | | | |
| Alive | 1060 (42) | 3071 (42) | 14832 (51) | 18963 (49) | |
| 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) | < 0.001 |

**Table 2. Probability in different strata of patient- and tumour characteristics of receiving radical treatment with curative intent (cystectomy/radiotherapy) for 5164 patients with urinary bladder cancer (UBC) with synchronous or metachronous other primary cancer (OPC), compared to patients with UBC only**

| | OPC+UBC n=9804 (25%) | | UBC only n=28885 (75 %) | Total (N= 38689) |
|---|---|---|---|---|
| | Synchronous n=2503 (25%) | Metachronous n=7301 (75%) | | |
| | N (% of total) | N (% of total) | N (% of total) | N (% of total) |
| **Gender** | | | | |
| Male | 802 (36) | 462 (10) | 2622 (12) | 3886 (13) |
| Female | 51 (17) | 307 (12) | 920 (13) | 1278 (13) |
| **Age group** | | | | |
| ≤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 periods** | | | | |
| 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) |

**Table 3. Groups of UBC with OPC and (Synchronous/Metachronous) in relation to treatment modality. Figures represent number of patients (% of the column). GI=gastro intestinal tract.**

| | Total | Treatment | | P |
|---|---|---|---|---|
| | | Non-curative | Curative | |
| **Respiratory tract** | | | | |
| Synchronous | 128 (24) | 114 (24) | 14 (24) | |
| Metachronous | 415 (76) | 370 (76) | 45 (76) | 1.000 |
| **Upper GI** | | | | |
| Synchronous | 82 (32) | 77 (33) | 5 (19) | |
| Metachronous | 177 (68) | 155 (67) | 22 (819 | 0.133 |
| **Lower GI** | | | | |
| Synchronous | 198 (15) | 156 (14) | 42 (29) | |
| Metachronous | 1087 (85) | 984 (86) | 103 (71) | <0.001 |
| **Breast** | | | | |
| Synchronous | 42 (6) | 35 (6) | 7 (7) | |
| Metachronous | 631 (94) | 542 (94) | 89 (93) | 0.646 |
| **Female genital** | | | | |
| Synchronous | 42 (4) | 30 (3) | 12 (7) | |
| Metachronous | 1164 (96) | 1014 (97) | 150 (93) | 0.009 |
| **Male genital*** | | | | |
| Synchronous | 1466 (40) | 735 (28) | 731 (74) | |
| Metachronous | 2195 (60) | 1935 (72) | 260 (26) | <0.001 |
| **Urinary tract** | | | | |
| Synchronous | 332 (35) | 293 (34) | 39 (44) | |
| Metachronous | 625 (65) | 576 (66) | 49 (56) | 0.059 |
| **Skin/melanoma** | | | | |
| Synchronous | 137 (9) | 126 (9) | 11 (7) | |
| Metachronous | 1399 (91) | 1259 (91) | 140 (93) | 0.548 |
| **Hematological** | | | | |
| Synchronous | 68 (14) | 58 (13) | 10 (17) | |
| Metachronous | 423 (86) | 375 (87) | 48 (83) | 0.420 |
| **Endocrine/neuro** | | | | |
| Synchronous | 15 (5) | 13 (4) | 2 (6) | |
| Metachronous | 313 (95) | 280 (96) | 33 (94) | 0.667 |
| **Other** | | | | |
| Synchronous | 47 (26) | 40 (24) | 7 (26) | |
| Metachronous | 149 (76) | 129 (76) | 20 (74) | 0.810 |
| **UBC only** | 28885 | 25343 (88) | 3542 (12) | <0.001 |

*prostate cancer represent 97% of the patients

**Table 4. Relative hazards for UBC-specific death for patients with synchronous or metachronous other primary cancer as compared to patients with UBC only. 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.**

| | RH (95% CI) Synchronous OPC | RH (95% CI) Synchronous OPC (excluding men with synchronous PC) | 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) |

**Table 5. Vital status and causes of death in groups of other primary cancer. Figures represent number of patients (% of the row). GI= gastro intestinal cancer**

| | Living | Death BC | Death OC | 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) |
| **Hematological** | 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) |
| **BC only** | 14832 (51) | 6284 (22) | 1919 (7) | 5850 (20) | 28885 |
| **Median percent** | **43** | **21** | **18** | **18** | |

*prostate cancer represent 97% of the patients