

Trends in Bladder Cancer Survival in Switzerland

Christine Bouchardy, Matthias Lorez, Kerri Clough-Gorr and the NICER Working Group^s

Keywords: Bladder Cancer, Observed Survival, Relative Survival, Survival, Switzerland

Introduction

In Switzerland, bladder cancer is the fifth most frequently diagnosed cancer in men but is much less frequent in women (age standardized incidence rate for 2005-2009: 18.7 per 100,000 men and 4.5 per 100,000 in women) [1]. The gender difference in incidence has been partly explained by differences in smoking habits and professional exposures between the sexes [2]. Other countries have also shown that men and women have differences in bladder cancer survival, with men having better survival than women for reasons that are still unknown. International comparisons of bladder cancer statistics are difficult to interpret due to changes in classifications and differences in coding practices over time and between countries. Bladder cancer is a heterogeneous disease [3 - 8] and prognosis, like other cancers, depends on the grade and stage of the tumour. However, the classification of bladder cancers may be unclear in particular when the diagnosis is based solely on cystoscopy and cytology. Registration of bladder cancer diagnoses includes benign bladder lesions known as papillomas, non-muscle malignant tumours, non-muscle in situ carcinomas, and muscle malignant tumours. Incidence and survival trends can be challenging to compare if the inclusion or exclusion of the types of bladder cancer diagnoses differ. To date there is a lack of information about bladder cancer survival in Switzerland. The aim of this study is to analyse national trends in bladder cancer survival using available data from Swiss population-based cancer registries.

Table1: Contribution of Bladder cancer cases to the national pooled dataset by thirteen Swiss cantons.

Patients and methods

The present study is based on the National Core Dataset (NCD) managed by the Foundation National Institute for Cancer Epidemiology and Registration (NICER) for the purpose of national cancer monitoring in Switzerland. Sixteen of twenty-six Swiss cantons currently transmit cancer data annually for the NCD. Cancer cases from thirteen cantons were pooled for this report: Basel City and Basel Land (BS/BL), Fribourg (FR), Geneva (GE), Grison and Glarus (GR/GL), Lucerne (LU), St. Gallen, Appenzell Outer-Rhodes and Appenzell Inner-Rhodes (SG/AR/AI), Ticino (TI), Valais (VS) and Zurich (ZH). Neuchâtel, Jura and Vaud could not be included because they do not provide survival information to the NCD.

Cancer registries recorded all incident cancer cases diagnosed in their resident population and assessed cases' survival by active or passive follow-up as of 31.12.2010. The incidence date refers to the date of confirmation of diagnosis or the date of hospitalization if it preceded the diagnosis and was related to their cancer. We included only malignant bladder cancer based on the International Classification of Disease for Oncology (ICD-O, 3rd edition; [9]): topography codes C67.0-C67.9, all morphology codes except lymphoma/leukaemia codes 9590-9989, malignancy code 3. We excluded all in situ and non-invasive papillary carcinomas. Cases diagnosed between 20 and 99 years of age (excluded only 9 cases) and between 1980 and 2010 were selected. For BS/BL the latest available year of diagnosis was 2008. Bladder cancer cases that were preceded by a primary cancer of a different topography were included [10]. In persons with >1 malignant bladder cancer diagnoses, the first occurring was selected. We excluded all cases diagnosed at death or with a death certificate as only source of information (N=332). Recent active follow-up was lacking for N=112 (7%) cases

Cantons	Diagnosis period	Number of cases			Person-years	% of pooled person-years
		Men	Women	Both		
GE	1980-2010	1357	437	1794	9014.1	22.6
SG/AR/AI	1980-2010	1229	446	1675	6961.0	17.4
BS/BL	1981-2008	1134	436	1570	6632.0	16.6
ZH	1997-2010	1426	485	1911	5932.3	14.9
VS	1989-2010	669	200	869	4298.5	10.8
TI	1996-2010	733	232	965	3477.6	8.7
GR/GL	1989-2010	573	171	744	3204.0	8.0
FR	2006-2010	114	30	144	312.1	0.8
LU	2010	37	12	49	68.1	0.2
Total		7272	2449	9721	39899.7	100.0

in BS/BL, N=60 (8%) in GR/GL, N=161 (19%) in VS and N=542 (24%) for ZH. The vital status of these cases was set lost to follow-up using the date of last contact. Of the pooled cases N=351 (3.5%) were excluded because only the date of diagnosis was given. A total of 9,721 cases were included in the survival analysis (93% of those eligible). Completeness of case ascertainment for bladder cancer could be assessed in GE, GR/GL, SG/AR/AI, TI and VS and was found to be higher than the international standard of at least 90% within two years after the date of diagnosis [11]. Observed (OS) and relative survival (RS) probabilities were derived for consecutive years after diagnosis during

which the hazards were assumed to remain constant. RS was calculated as the ratio of the observed probability of survival of cancer cases and the expected survival of persons in the general population matching in age, sex, calendar year of death and cantonal pool (i.e. estimation of mortality due to bladder cancer by accounting for competing risks of death) [12]. Expected cancer survival proportions were estimated using the Ederer II method applied to combined all-cause mortality tables for the cantons included supplied by the Swiss Federal Statistical Office. All-cause death probabilities, transformed from age-, sex- and calendar year-specific death rates, were interpolated

		Calendar period for analysis: 1991 - 2000											
Age in years	Years since diagnosis	Observed survival %			Relative survival ¹ %								
		Men	Women	Both	Men	95% CI		Women	95% CI		Both	95% CI	
						LL	UL		LL	UL		LL	UL
20 - 59	1	85.2	80.7	84.3	85.7	81.6	89.1	80.9	71.3	87.6	84.7	81.0	87.8
60 - 69		84.0	72.2	81.5	85.5	82.4	88.1	72.8	65.6	78.8	82.8	79.9	85.3
70 - 79		74.9	66.3	72.8	78.2	74.9	81.1	67.8	61.7	73.3	75.6	72.7	78.2
80+		54.9	44.6	51.0	62.6	57.5	67.5	49.4	43.1	55.5	57.5	53.5	61.3
20 - 59	5	61.5	61.2	61.4	63.6	58.0	68.6	62.3	51.4	71.5	63.3	58.4	67.8
60 - 69		57.1	47.2	55.0	63.1	58.8	67.2	49.5	41.7	56.9	60.1	56.4	63.8
70 - 79		43.2	37.4	41.8	55.4	51.0	59.8	43.1	36.4	49.8	52.3	48.6	56.0
80+		18.8	20.2	19.3	38.0	31.2	45.3	34.5	27.0	42.6	36.8	31.6	42.2
standardized ²	1	77.3	68.7	75.2	80.0	78.2	81.7	70.1	66.5	73.5	77.4	75.8	79.0
	5	48.5	44.2	47.6	57.2	54.7	59.7	49.0	44.7	53.1	55.3	53.1	57.4
		Calendar period for analysis: 2001 - 2010											
20 - 59	1	89.1	77.2	86.4	89.5	86.4	92.0	77.4	69.7	83.3	86.7	83.9	89.2
60 - 69		85.1	79.7	84.1	86.2	83.8	88.4	80.3	74.1	85.2	85.1	82.9	87.2
70 - 79		78.6	68.1	76.2	81.3	78.8	83.5	69.4	64.2	74.0	78.5	76.3	80.6
80+		59.9	46.3	55.2	67.0	63.3	70.5	50.7	45.7	55.6	61.3	58.3	64.2
20 - 59	5	63.1	55.8	61.4	64.9	59.8	69.5	56.6	47.3	64.9	63.0	58.6	67.1
60 - 69		55.2	54.2	55.0	59.5	55.5	63.3	56.4	48.1	63.9	58.9	55.3	62.3
70 - 79		42.0	38.5	41.2	51.4	47.6	55.2	43.4	37.2	49.6	49.6	46.3	52.8
80+		19.8	18.0	19.1	36.4	31.1	42.1	29.6	23.2	36.7	34.0	29.8	38.4
standardized ²	1	80.6	70.6	78.1	82.8	81.5	84.1	71.9	68.8	74.7	80.1	78.9	81.3
	5	48.3	44.7	47.4	55.2	53.0	57.4	48.7	44.7	52.5	53.6	51.7	55.5

¹ Survival analysis using the complete approach

² Age-standardized using ICSS weights

Note: 95% confidence interval, 95%CI; lower limit, LL; upper limit, UL

Table 2: Observed and relative survival estimates after malignant bladder cancer diagnosis with 95% confidence intervals by calendar period, age at diagnosis and sex. Data pooled from thirteen Swiss cantons.

and smoothed using the Elandt-Johnson formula [13]. RS ratios were estimated using the strsr command (version 1.3.7) [14] written for the Stata Statistical Software [15]. Complete survival analysis was used for the comparison of diagnosis periods 1991 to 2000 and 2001 to 2010. Period survival analysis was used for the analysis of time trends [16]. In brief, complete analysis describes the survival experience of cases defined by dates of diagnosis, whereas period analysis defines cases by follow-up dates. The latter is achieved by left truncation of person-times at risk at the beginning of the specified follow-up period in addition to right censoring at its end. RS estimates were age-standardized using weights specific for bladder cancer from the International Cancer Survival Standards (ICSS) [17]. Standard weights for age-groups were: 0.28 (20-59 years), 0.28 (60-69 years), 0.29 (70-79 years) and 0.15

(80-99 years). Ninety five percent confidence intervals (95% CI) were estimated using Greenwood's method [18] in complete analysis and in period analysis by applying the delta method to a transformation of the cumulative hazard. For age-standardized RS, 95% CI were estimated as described in [17].

To test for linear time trends of one- and five-year RS in age strata, piecewise Poisson regression models for the logarithm of excess number of deaths were fitted as linear functions of the logarithm of person-time (offset) and calendar period of follow-up as numeric covariate. The p-value for inclusion of calendar period as explanatory variable, based on the Wald test, indicated the significance of a linear trend. The significance of a linear trend independent of age was tested by additionally adjusting the Poisson model for age. Average annual percentage change (AAPC) = $100 \left(\frac{RS_{lastyear} - RS_{firstyear}}{RS_{firstyear}} \right) \Delta t^{-1}$.

		Calendar period of death or censoring					AAPC ²	Linear trend p-value ³
		1986/1990	1991/1995	1996/2000	2001/2005	2006/2010		
Age in years	Years since diagnosis	Relative survival ¹ %	Relative survival ¹ %	Relative survival ¹ %	Relative survival ¹ %	Relative survival ¹ %		
Men								
20-69	1	84.8	86.9	85.4	86.6	87.0	0.1	0.421
70+		63.0	74.4	71.6	75.3	74.7	0.7	0.002
20-69	5	56.0	62.8	62.7	62.3	61.5	0.4	0.052
70+		35.5	46.8	48.1	48.3	44.4	1.0	0.901
standardized ⁴	1	75.5	81.3	79.7	81.4	82.6	0.4	0.001
	5	47.4	55.4	56.3	56.3	54.9	0.6	0.194
Women								
20-69	1	77.9	74.7	75.2	81.9	78.2	0.0	0.433
70+		53.1	60.7	57.3	55.9	59.2	0.5	0.611
20-69	5	49.0	55.0	53.7	54.6	58.6	0.8	0.914
70+		31.2	34.2	38.0	34.3	37.4	0.8	0.658
standardized ⁴	1	67.1	71.2	70.0	71.5	72.4	0.3	0.414
	5	41.2	47.9	48.8	46.9	51.1	1.0	0.721

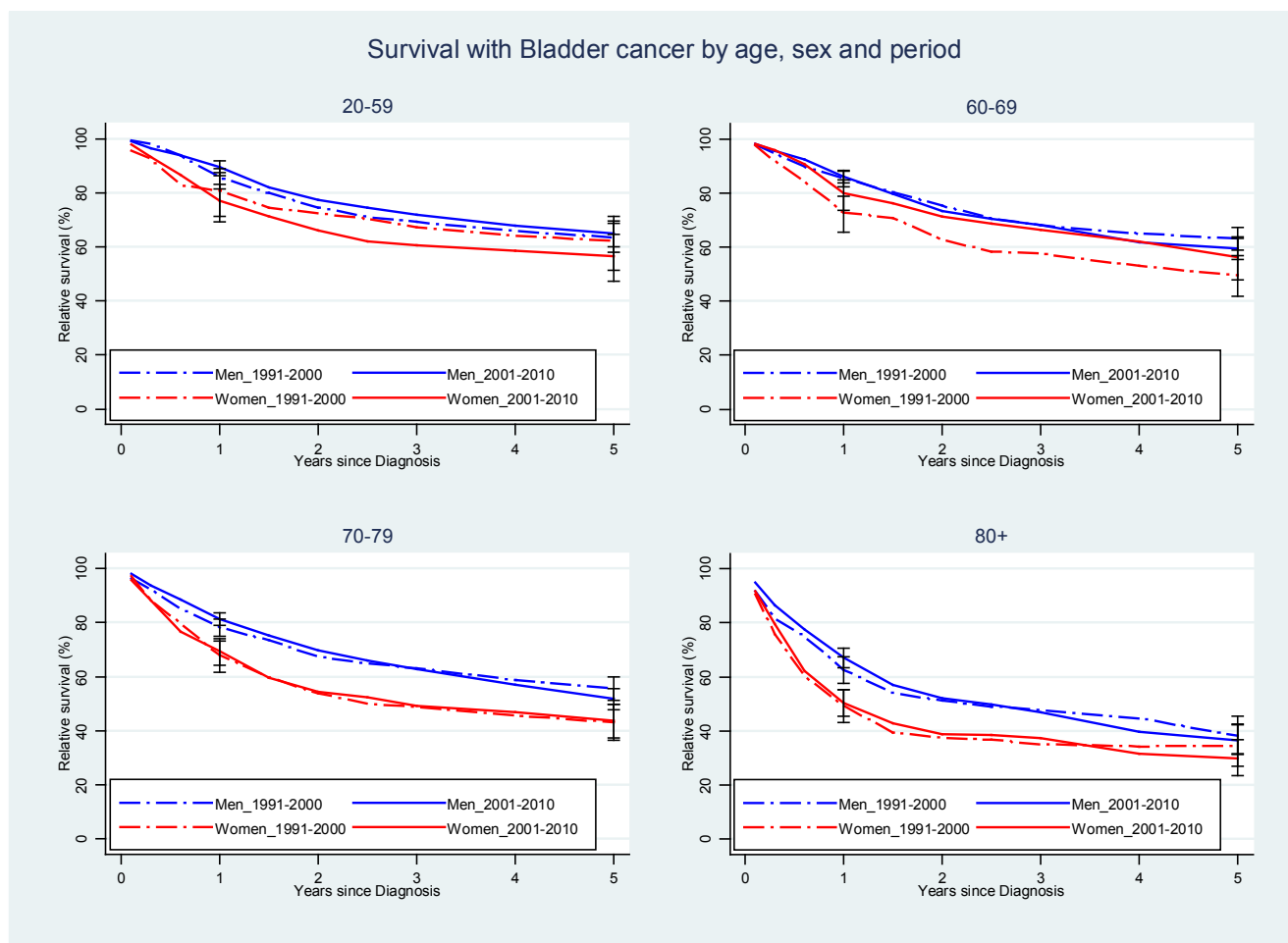
¹ Survival analysis using the period approach

² Average annual percentage change

³ p-Value of Wald test for calendar period in a Poisson regression model of excess mortality.

⁴ Age standardized using ICSS weights

Table 3: Trends in relative survival of bladder cancer cases pooled from thirteen Swiss cantons for successive five-year calendar periods of follow-up between 1986 and 2010.



Results

Table 1 shows the distribution of patients with malignant bladder cancer by canton, diagnosis period, sex as well as the distribution of person-years per canton in the pooled dataset. The pooled data represents about one-half of the total at-risk population in Switzerland (in 2010) and included approximately 10,000 bladder cancers representing almost 40,000 person-years. The median follow-up duration was 2.2 years for the whole cohort.

Table 2 lists one- and five-year age-specific OS and RS for two ten-year calendar periods by sex. The RS estimates by age group and period are also shown in Figure 1. In contrast to most cancer types, men had a consistent survival advantage over women. For the diagnosis period 2001-2010, the age-standardized RS for the first year after diagnosis was 82.8% in men versus 71.9% in women and for the fifth year after diagnosis it was 55.2% in men versus 48.7% in women. Both OS and RS at one and five years decreased with increasing age at diagnosis regardless of sex and the period considered. For men and women combined, the five year RS was 63% (95%CI 59%-67%) for

Figure 1: Age-, sex- and diagnosis date-specific one- and five-year relative survival curves with 95% confidence intervals for two calendar periods (1991-2000 and 2001-2010) of cancer diagnosis. Bladder cancer cases were pooled from thirteen Swiss cantons.

persons <60 years and decreased to 34% (95%CI 30%-38%) for those aged 80 years or older.

Table 3 shows trends in one- and five-year age-specific as well as age-standardized RS after a bladder cancer diagnosis in five successive five-year calendar periods of follow-up. In general, trends in RS were flat in both men and women. Survival improved slightly between the first two periods 1986-1990 and 1991-1995 but remained mostly unchanged over follow up for both sexes. For men, we observed a slight statistically significant improvement of one year RS during the study period (linear trend $p=0.001$) and for the subgroup of men aged 70 years or older. This improvement in survival appeared to be confined to the difference observed between the first two periods. All other time trends were not statistically significant.

Discussion

This study describes survival after a primary malignant bladder cancer diagnosis in Switzerland based on the Swiss national dataset. We found that men have better overall survival than women and older persons have worse survival than younger persons. Generally there has been little improvement in bladder cancer survival in Switzerland over the last decade. The estimate of RS after a primary malignant bladder cancer diagnosis in Switzerland is similar to that observed in other developed countries publishing data on malignant bladder cancer. For example, the United Kingdom, Ireland, Australia, United States, and France [19-23]. With regards to international comparisons of survival, the EUROCARE-4 study found that the mean five-year RS for all European countries was 72.8% for males and 69.3% for females for the period 1995-1999 [24]. For Switzerland, the five-year RS in both sexes was lower (55.3%) than the European mean. However, the EUROCARE-4 study included not only malignant bladder cancer but also non-infiltrating tumours whenever collected by cancer registries. For Switzerland, only malignant cancers were included which may explain the lower survival rates observed [24].

While men have a more than five-fold higher bladder cancer incidence rate than women, survival among men is also better than among females. This gender difference is also observed in numerous statistical reports in particular the EUROCARE-4 study and has been the subject of several investigations [24, 26, 27]. This gender difference is not explained by age differences at diagnosis because it exists across age groups in our study as well as in reports from other countries [24]. It has been hypothesized that physicians might be more aware and reactive to symptoms such as haematuria or urinary infections in male patients than in female patients. However, studies have shown that gender differences persist in analyses stratified by stage at diagnosis [27]. Some authors have suggested that differences in urinary tract anatomy between the sexes could modify blood and lymph node drainage leading to differences in the processes of metastasis occurrence [27].

The results of our study show lower RS among older persons diagnosed with a malignant bladder cancer. This has been observed internationally for numerous cancers including bladder [24]. The poorer prognosis of older persons may be explained by a later stage at diagnosis and lower provision of aggressive/curative treatment such as cystectomy, because of more co-morbidities and lower life expectancy in older persons [28]. Unfortunately, we were unable to examine survival by stage and treatment in this study. Consistent with numerous other studies, we observed a negligible increase in five-year bladder cancer RS according to period of diagnosis [19-23]. In contrast, the EUROCARE studies reported a slight increase in cancer

survival [24]. However, inclusion criteria for cancer types have changed over time. In general, the lack of progress in bladder cancer survival may be linked to a shortage of effective treatments (such as radiotherapy or chemotherapy) but also to changes in tumour classifications and coding practices which can hinder interpretation of time trend analysis [24, 29].

In conclusion, bladder cancer survival data are difficult to interpret because of differences in pathology inclusion/exclusion criteria and changes in classification and registration practices over time and between countries. Nevertheless, this study indicates that bladder cancer prognosis is still rather poor in Switzerland with important sex and age differences and minimal progress in survival. Additional studies including stage and treatment information are warranted.

References*

1. NICER · Foundation National Institute for Cancer Epidemiology and Registration <http://www.nicer.org/> accessed Apr. 2013
2. Negri E, La Vecchia C: Epidemiology and prevention of bladder cancer. *Eur J Cancer Prev* 10 (1): p. 7-14, 2001
3. Lee R, Droller MJ: The natural history of bladder cancer. Implications for therapy. *Urol Clin North Am* 27 (1): p. 1-13, vii, 2000
4. Zhang Y, Zhu C, Curado MP, Zheng T, Boyle P: Changing patterns of bladder cancer in the USA: evidence of heterogeneous disease. *BJU Int* 109 (1): p. 52-56, 2012
5. Miyamoto H, Miller JS, Fajardo DA, Lee TK, Netto GJ, Epstein JI: Non-invasive papillary urothelial neoplasms: the 2004 WHO/ISUP classification system. *Patol Int* 60 (1): p. 1-8, 2010
6. Hodges KB, Lopez-Beltran A, Davidson DD, Montironi R, Cheng L: Urothelial dysplasia and other flat lesions of the urinary bladder: clinicopathologic and molecular features. *Hum Pathol* 41 (2): p. 155-162, 2010
7. Pellucchi F, Freschi M, Ibrahim B, Rocchini L, Maccagnano C, Briganti A, Rigatti P, Montorsi F, Colombo R: Clinical reliability of the 2004 WHO histological classification system compared with the 1973 WHO system for Ta primary bladder tumours. *J Urol* 186 (6): p. 2194-2199, 2011
8. Mostofi FK, Sobin LH, Torloni H: World Health Organization (WHO) (eds): Histological typing of urinary bladder tumours. Springer, Washington, D.C., USA, 1999, p. 1-104
9. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S (eds): ICD-O International classification of diseases for oncology. World Health Organization (WHO), Geneva, 2000
10. Lorez M, et al. and NICER Working Group: Completeness of case ascertainment in Swiss cancer registration. 2013. (in preparation)
11. Ederer F, Axtell LM, Cutler SJ: The relative survival rate: a statistical methodology. *Natl Cancer Inst Monogr* 6 p. 101-121, 1961
12. Ederer F, Heise H: Instructions to IBM 650 Programmers in Processing Survival Computations. Methodological note no 10, End Results Evaluation Section. 1959. Bethesda MD, National Cancer Institute.
13. Elandt-Johnson RC, Johnson NL: Survival Models and Data Analysis. New York: John Wiley&Sons. 1980
14. Dickman PW, Coviello E, Hills M: Estimating and modelling relative survival. *The Stata Journal* (in press)
15. StataCorp LP: Data Analysis and Stata Statistical Software. Release 12: 2011. College Station, TX (USA), StataCorp.

16. Brenner H, Gefeller O: An alternative approach to monitoring cancer patient survival. *Cancer* 78 (9): p. 2004-2010, 1996
17. Corazziari I, Quinn M, Capocaccia R: Standard cancer patient population for age standardising survival ratios. *Eur J Cancer* 40 (15): p. 2307-2316, 2004
18. Cox DR, Oakes D: Analysis of survival data. New York (USA), Chapman and Hall/CRC. 1984
19. Cancer Research UK Cancer Research UK : Bladder cancer key facts <http://www.cancerresearchuk.org/cancer-help/type/bladder-cancer/> accessed Apr. 2013
20. Gavin A, Donnelly DW: Survival of cancer patients in Northern Ireland: 1993–2004. Northern Ireland Cancer Registry, Queen's University, Belfast, 2007, p. 1-174
21. Cancer Australia Bladder cancer statistics in Australia <http://cancer-australia.gov.au/affected-cancer/cancer-types/bladder-cancer> accessed Apr. 2013
22. Abdollah F, Gandaglia G, Thuret R, Schmitges J, Tian Z, Jeldres C, Passoni NM, Briganti A, Shariat SF, Perrotte P, Montorsi F, Karakiewicz PI, Sun M: Incidence, survival and mortality rates of stage-specific bladder cancer in United States: A trend analysis. *Cancer Epidemiol* 37 (3): p. 219-225, 2013
23. Grosclaude P, Estève J, Bossard N, Remontet L, Belot A, Faivre J, Bouvier A, Launoy G, Velten M, Maynadié M, Arveux P: Étude des registres du réseau FRANCIM (eds): Survie des patients atteints de cancer en France. Springer, 2007, p. 1-406
24. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R: EURO-CARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. *Eur J Cancer* 45 (6): p. 931-991, 2009
25. May M, Stief C, Brookman-May S, Otto W, Gilfrich C, Roigas J, Zacharias M, Wieland WF, Fritsche HM, Hofstadter F, Burger M: Gender-dependent cancer-specific survival following radical cystectomy. *World J Urol* 30 (5): p. 707-713, 2012
26. Otto W, May M, Fritsche HM, Dragun D, Aziz A, Gierth M, Trojan L, Herrmann E, Moritz R, Ellinger J, Tilki D, Buchner A, Hofner T, Brookman-May S, Nuhn P, Gilfrich C, Roigas J, Zacharias M, Denzinger S, Hohenfellner M: Analysis of sex differences in cancer-specific survival and perioperative mortality following radical cystectomy: results of a large German multicenter study of nearly 2500 patients with urothelial carcinoma of the bladder. *Genit Med* 9 (6): p. 481-489, 2012
27. Mungan NA, Aben KK, Schoenberg MP, Visser O, Coebergh JW, Witjes JA, Kiemeny LA: Gender differences in stage-adjusted bladder cancer survival. *Urology* 55 (6): p. 876-880, 2000
28. Bouchardy C, Rapiti E, Fioretta G, Laissue P, Neyroud-Caspar I, Schafer P, Kurtz J, Sappino AP, Vlastos G: Undertreatment strongly decreases prognosis of breast cancer in elderly women. *J Clin Oncol* 21 (19): p. 3580-3587, 2003
29. Patriarca S, Gafa L, Ferretti S, Vitarelli S, Cesaraccio R, Crocetti E, Ferrante MC, Rollo P, Tagliabue G: Coding criteria of bladder cancer: effects on estimating survival. *Epidemiol Prev* 25 3(Suppl): p. 42-47, 2001

*For additional information on cancer in Switzerland please see NICER website <http://nicer.org/default.aspx?NavigationID=42>

§Members of the NICER Working Group for these analyses included:

Basel	G. Jundt
Fribourg	B. Camey
Geneva	C. Bouchardy
Grison/Glarus	H. Frick (S. Ess)
Lucerne	J. Diebold
St. Gallen/Appenzell	S. Ess
Ticino	A. Bordoni
Valais	I. Konzelmann
Zurich	S. Dehler

Correspondence:

Matthias Lorez
 Foundation National Institute for Cancer
 Epidemiology and Registration (NICER)
 c/o University of Zürich
 Seilergraben 49, CH-8001 Zürich
 ml@nicer.org