Effects of age and stage on prostate cancer survival in Switzerland

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Introduction

Prostate cancer is the most common incident cancer in men in Switzerland with an incidence rate of 112.5/100,000 person-years (py) in 2012/2013 (EU-standard population). Although still high, a stabilisation and more recently even a decrease in incidence rates since about 2005 can be seen in Switzerland (Swiss Cancer Report 2015) as well as in other industrialized countries (Wong et al. 2016). With regards to mortality, rates are decreasing in Switzerland by about 2.2% per year between 2004 and 2014. In numerous European countries and in North America, mortality also decreases since about the early 2000's (Wong et al. 2016; Bouchardy et al. 2008). We have previously shown that 5-year relative survival has increased from 81.4% in 1995-1999 to 88.9% in 2005-2009 (Dehler et al. 2013). This change is due to several factors such improvements in treatment, but another reason for this improvement in survival is an earlier diagnosis, i.e., at an earlier stage, due to more intense use of early detection methods such as measuring prostate-specific antigen (PSA) concentration. An analysis of the Swiss Health Surveys, representative cross-sectional studies on health topics conducted every 5 years, showed that ever use of prostate cancer screening (opportunistic digital rectal examination and/or PSA-testing) increased from 55.3% to 70.0% between 1992 and 2012 (Guessous et al. 2016). This improving survival was mostly observed in younger patients and to a lesser extent in men aged 70 years and more (Gondos et al. 2008). In Switzerland, even a pejoration of survival among elderly was observed (Gondos et al. 2008) probably linked to lack of PSA screening and to under-treatment. Therefore, this study aims to assess the effect of age and stage in prostate cancer survival in Switzerland.

Methods

This study is based on the National Core Dataset (NCD) managed by the National Institute for Cancer Epidemiology and Registration (NICER) for the purpose of national cancer monitoring in Switzerland (Heusser et al. 2011). Data from six Swiss population-based cancer registries (CR) were pooled to represent the Swiss population: Basel-Stadt and Basel-Landschaft (BS/BL), Fribourg (FR), Geneva (GE), Ticino (TI), Valais (VS), and Zurich (ZH). Other Swiss population-based CRs were not included because they did not provide survival information (VD), or tumour extent before 2009 (GR/GL, SG/AR/AI, NE/JU), or if cancer registration started after 2008 (LU/UR/OW/NW, ZG, TG, AG, BE).

Selected cases were all incident invasive primary prostate cancers diagnosed between 2000 and 2013 (N=31'160). The CRs BS/BL (2000-2011) and FR (2006-2013) covered this time period only partially. Age at diagnosis was restricted to 35-100 (excluding N=11 or 0.03% of cases). Patients with multiple primary tumours were included (N=6'531 or 21%). The vital status was actively and/or passively followed-up until the end of the year 2013. We excluded all cases diagnosed at death or with a death certificate as the only source of information (N=426 or 1.4%). Excluded were cases without active follow-up (N=338 or 1.1%). Recent active follow-up was lacking for 7'032 or 23% of cases (i.e. last date of follow-up < 2013 with vital status alive). We did not assume survival up to 2013 in the absence of reported death, because in some CRs there was incomplete linkage of the official vital statistics to registered cases as well as incomplete active vital-status follow-up for some incidence years. Completeness of case ascertainment for prostate cancer was estimated with the Flow method and resulted in 82% to 93% at three years after diagnosis, depending on CR (Lorez et al. 2017).

The stage of prostate cancer was derived from UICC Tumour, Node, Metastasis categories, based on pathological, and when absent, on clinical information (Sobin et al. 2009). When no information was available on distant metastasis, we assumed that none existed, i.e. M0 (Wittekind et al. 2012). Stage groups were formed according to the SEER classification as local (T1/2 N0 M0), regional (T3/4 N0 M0 or any T N+ M0), distant (any T any N M1), and unknown (Young et al. 2001). In addition, the UICC stage grouping was used: Stage I (T1/T2a N0 M0), II (T2b/T2c N0 M0), III (T3 N0 M0), IV (T4 N0 M0 or any T N1 M0 or any T any N M1), and unknown (Sobin et al. 2009).

Incidence rates are expressed as events per 100,000 person years (py) of mid-year risk population. Rates were age-adjusted with the direct method using the European standard population (Doll and Cook 1976).

For survival analysis, the period approach was used, based on 26'240 patients who had a follow-up event between 2008 and 2013 (Brenner and Gefeller 1996). The relative survival (RS) was derived for consecutive time intervals of increasing length after diagnosis during which the mortality hazard ratios were assumed to remain constant (Dickman and Coviello 2015). RS was calculated as the ratio of the observed survival of cancer cases and the expected survival of persons in the general population after matching for age, sex, calendar year of death, and canton (Ederer et al. 1961). Expected cancer survival was estimated using the Ederer II method applied to all-cause mortality tables specific for canton (Ederer et al. 1959). All-cause death probabilities, transformed from age-, sex-, canton-, and calendar year-specific death rates, were interpolated and smoothed using the Elandt-Johnson formula (Elandt-Johnson and Johnson 1981). RS ratios were estimated using the «strs» command (version 1.4.2) written for the Stata Statistical Software (Dickman and Coviello 2015). RS estimates were age-standardised using the International Cancer Survival Standards (ICSS) weights for prostate cancer (Corazziari et al. 2004). Confidence intervals at 95% (95% CI) were estimated by applying the delta method to a transformation of the cumulative hazard. For age-standardised RS, 95% CI were estimated as described (Corazziari et al. 2004).

Results

Our study included 31,148 prostate cancer cases from six Swiss cancer registries. Zurich as the largest registry contributed almost half of the cases (Table 1). DCO rates in all registries are well below 5% and the proportion of

Tab. 1. Comparison of cancer registries: distribution of prostate cancer cases diagnosed 2000-2013 by age at diagnosis and tumour stage group

	Registries combined	Cancer registry					
		FR*	TI	VS	GE	ZH	BA**
Number of cases	31148	1690	3022	3418	4204	14256	4558
DCO (%)	1.4	0.4	1.4	0.8	0.8	2.0	1.7#
MV (%)	94.1	98.3	91.1	92.3	94.0	93.3	98.4
Age, years (%)							
35-49	1.0	1.1	0.7	1.0	1.6	1.0	0.9
50-59	12.8	14.0	11.0	12.7	15.0	12.8	11.6
60-69	38.1	39.6	35.9	39.3	37.8	38.2	38.5
70-79	32.2	33.0	35.6	31.2	29.4	31.5	34.8
80-99	15.9	12.3	16.8	15.9	16.1	16.5	14.2
Age, years (median)	69.5	69.1	70.5	69.4	69.0	69.5	69.7
Tumour stage, SEER (%)							
Local	61.2	61.3	50.5	66.0	55.4	63.9	61.3
Regional	17.4	20.4	21.2	20.7	24.1	14.0	16.1
Distant	6.5	4.7	11.3	7.8	9.9	5.1	4.1
Unknown	14.9	13.7	17.0	5.5	10.6	17.0	18.5
Tumour stage, UICC (%)							
I	38.4	35.1	24.8	37.5	27.7	42.6	46.4
II	22.7	26.2	25.6	28.5	27.7	21.3	15.0
III	13.1	16.2	15.8	15.8	19.2	10.2	11.7
IV	10.8	8.9	16.7	12.7	14.7	8.9	8.4
Unknown	14.9	13.7	17.0	5.5	10.6	17.0	18.5

* 2006-2013; ** 2000-2011; # 2002-2007 DCO: Death certificate only MV: Microscopically verified diagnosis

microscopically confirmed cases exceeds 90%. Mean age at diagnosis was 69.5 years, which was very similar in all registries. About 70% of the cases were diagnosed between 60 and 79 years of age. Most cases (38.4%) were diagnosed at stage I. This proportion ranged between 24.8% in Ticino and 46.4% in Basel. The opposite is true for stage IV cases, i.e. their proportion was highest in Ticino (16.7%) and lowest in Basel (8.4%). Overall, tumour stage was unknown for 14.9% of cases, ranging from 5.5% in Valais to 18.5% in Basel.

Stage distribution differed by age (Table 2) with the highest proportion of cases with localised disease in men younger than 60 years old; regional disease was observed for 10-20% of patients with the lowest percentage in men ≥ 80 years old. Distant disease was diagnosed in only 3-6% of men who were younger than 80 years and in 17% of men ≥ 80 years old. The percentage of unstaged tumours increased with age representing 7%, 18%, and 35% of tumours in men aged < 70, 70-79, and ≥ 80 years, respectively.

Over time, we observed an increase in the age-standardised incidence rates of localised tumours (2000/2001: 63.5/100,000 py to 2012/2013: 77.2/100,000 py), whereas the rates of regional (2000/2001: 24.6/100,000 py; 2012/2013: 21.8/100,000 py) and distant tumours (8.8/100,000 in both incidence periods) remained approximately constant (Tab. 3). We also observed a strong decrease in the percentage of unstaged cancer (28.9/100,000 py to 4.6/100,000 py). Overall, incidence of prostate cancer (all stages combined) reached its peak in 2002/2003 (137,2/100,000 py) and then steadily declined during the subsequent decade (112,5/100,000 py in 2012/2013).

At 1 and 5 years, survival was similar for localised and regional disease in all age groups except elderly. In men aged ≥ 80 years, regional disease had statistically significantly worse survival than localised disease.

At 10 years, the relative survival decreased with advancing stage: 11.0% for distant, 75.4% for regional and 87.1% for localised disease (Fig. 1; Table 4). This observation is true for any age group (Fig. 2; Table 4). Similar patterns are seen when cancers are shown by UICC stages I-IV (Fig. 3 and 4).

We observed a strong effect of age on relative prostate cancer survival. For example, the prognosis of localised disease at 10 year was around 90% for men younger than 80 years and only about 50% for men aged ≥ 80 years. This was also true for regional disease. Also, the decrease of survival over time was more pronounced among elderly.

Discussion

Our analyses support the observation of other studies that men with prostate cancer diagnosed at an early stage have high survival rates. Only men diagnosed with distant disease have markedly decreased relative survival.

Only few studies so far examined survival of prostate cancer patients by stage. In a comparative study using US Surveillance Epidemiology and End Results (SEER) data and data of the German Cancer Registries (GEKID), 5-year relative survival of men with localised disease was 102.3% in Germany and 103.5% in the US; respective numbers for regional disease were 96.5% and 97.5% and for distant disease 27.5% and 30.1% (Winter et al. 2016). In our set of patients, 5-year relative survival for localised (96.1%) and regional disease (88.9%) was lower than in the German and US datasets, but numbers for distant disease were similar (30.4% in our analysis). The reason is partly methodological because Swiss survival statistics is based on active follow-up information without applying the often used assumption of continued survival up to the latest analysis date in the absence of reported death (see Methods). The proportion of such cases, where active follow-up information has not been updated to the latest analysis date, was higher in localised (28%) or regional (20%), as compared with distant disease (3%).

Using data of the cancer registry in the Rostock area (Germany), Leuchter et al. (2015) observed 5-year relative survival rates for UICC stages I-III of about 100%, which is slightly higher than in our analysis with 5-year

Age, years (%)	Tumour stage				Total (N)
	Local	Regional	Distant	Unknown	
35-49	72.0	17.1	5.3	5.6	321
50-59	71.5	18.6	3.3	6.6	3988
60-69	68.9	20.5	3.2	7.4	11882
70-79	59.4	16.5	6.6	17.5	10020
80-99	37.0	11.1	16.7	35.3	4937

Tab. 2. Distribution of prostate cancer cases by age at diagnosis and tumour stage group (SEER)

Tumour stage	Diagnosis interval						
	2000-2001	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013
Local	63.5	69.3	82.1	85.6	87.4	89.7	77.2
Regional	24.6	21.1	21.8	23.0	23.9	23.8	21.8
Distant	8.8	8.1	8.9	7.9	7.3	8.5	8.8
Unknown	28.9	38.7	21.4	14.5	12.7	6.0	4.6
All stages	125.7	137.2	134.1	131.0	131.3	127.9	112.5

Age-adjusted incidence rates
(cases per 100'000 person-years; EU-standard population)

Tab. 3. Prostate cancer incidence trends by tumour stage group (SEER)

relative survival rates of about 95%. For stage IV tumours, Leuchter et al. observed 5-year relative survival rates of less than 60%. In our own dataset, age-adjusted 5-year relative survival for stage IV tumours is very similar (54.1%); rates for stage I, II, and III tumours are slightly lower than those observed in the Rostock area (95.2%, 95.8%, and 92.9%, respectively). 5-year relative survival in an analysis of Cancer Research UK using data of the Former Anglia Cancer Network, 2002-2006, were 112% for stage I, 99.4% for stage II, 93.3% for stage III, and 30.4% for stage IV cases (Cancer Research UK 2016). These results show that relative survival of prostate cancer patients is high when diagnosed at an early stage. Some countries even observed relative survival above 100%, which means that survival is better compared with the general population. This is likely an effect of selection bias such that men who use PSA screening, but also other types of early cancer detection, are generally healthier and are more health conscious than the general population (Mathers et al 2011; Zeliadt et al. 2007). An analysis of the Geneva Cancer Registry showed that cancers of men of lower socioeconomic status were less often detected

Tab. 4. Relative survival of prostate cancer patients, by age at diagnosis and tumour stage group (SEER)

Age, years	Survival period, years	All patients			Tumour stage											
					Local			Regional			Distant			Missing		
		Rel	Lo	Hi	Rel	Lo	Hi	Rel	Lo	Hi	Rel	Lo	Hi	Rel	Lo	Hi
50-59	1	**99.6**	99.0	100.0	**100.2**	99.7	100.4	**99.5**	97.6	100.2	**88.6**	77.1	94.6	**98.5**	87.2	100.2
	5	**94.7**	93.3	96.0	**97.8**	96.4	99.0	**94.8**	90.9	97.5	**29.2**	17.8	41.7	**93.8**	83.6	98.8
	10	**87.2**	84.5	89.7	**94.7**	91.8	97.1	**75.9**	68.6	82.2	**11.7**	4.0	24.1	**84.2**	71.7	92.8
60-69	1	**99.7**	99.4	100.0	**100.2**	99.8	100.5	**99.9**	99.1	100.4	**90.2**	84.1	94.2	**97.5**	94.2	99.3
	5	**96.4**	95.5	97.3	**99.6**	98.7	100.5	**97.1**	95.0	98.8	**29.7**	22.3	37.6	**88.5**	83.1	92.8
	10	**89.7**	87.8	91.5	**94.6**	92.4	96.7	**88.8**	84.7	92.6	**14.9**	8.7	22.8	**77.2**	70.0	83.7
70-79	1	**98.6**	98.0	99.2	**100.2**	99.6	100.8	**100.6**	99.3	101.4	**81.7**	76.3	86.1	**96.2**	93.2	98.3
	5	**89.6**	88.0	91.1	**97.8**	96.0	99.5	**90.2**	86.1	93.8	**33.6**	27.2	40.2	**76.6**	71.6	81.3
	10	**76.1**	73.2	79.0	**90.5**	86.5	94.4	**76.6**	69.8	83.2	**10.3**	5.7	16.7	**54.5**	48.5	60.6
80-99	1	**88.1**	86.0	90.0	**99.8**	97.5	101.8	**91.2**	85.0	96.0	**65.1**	59.4	70.3	**84.1**	79.5	88.2
	5	**62.0**	58.2	65.8	**85.3**	78.8	91.6	**66.0**	54.5	77.4	**21.1**	15.4	27.7	**54.8**	48.2	61.5
	10	**35.6**	29.4	42.6	**51.2**	38.7	65.5	**41.6**	24.7	63.6	**2.7**	0.4	10.5	**33.0**	23.9	44.0
Age-adjusted	1	**97.5**	97.1	97.9	**100.2**	99.4	100.5	**98.6**	97.2	99.3	**82.7**	79.0	85.9	**95.7**	94.3	96.8
	5	**88.3**	87.4	89.2	**96.1**	94.6	97.2	**88.9**	86.3	91.1	**30.4**	25.9	35.1	**81.5**	78.5	84.2
	10	**76.2**	74.5	77.8	**87.1**	83.7	89.8	**75.4**	70.7	79.5	**11.0**	7.1	15.9	**65.2**	60.4	69.6

Rel: cumulative relative survival (%). Lo, Hi: 95% confidence-limits of Rel

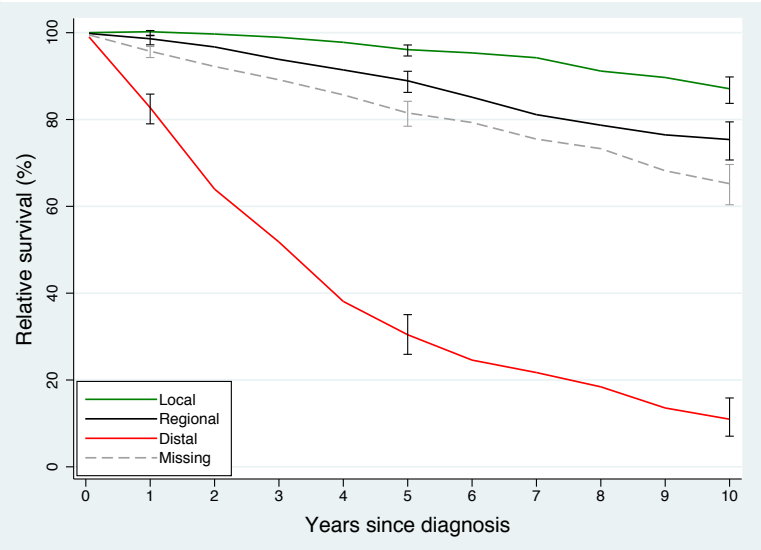


Fig. 1. Age-adjusted relative survival of prostate cancer patients by SEER tumour stage group

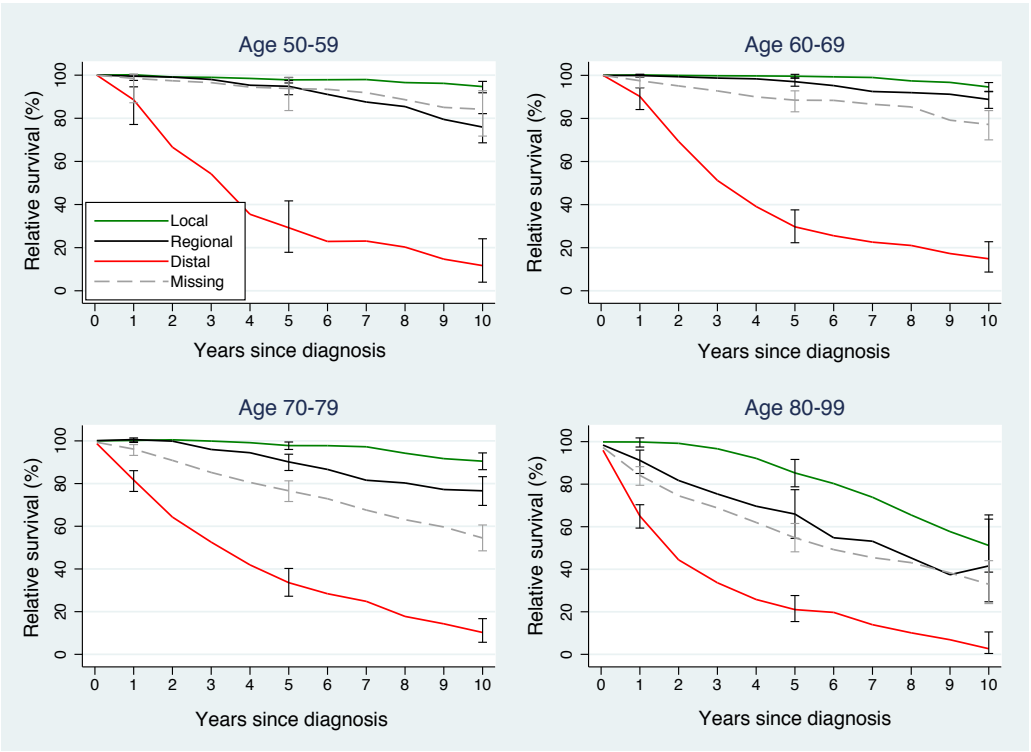


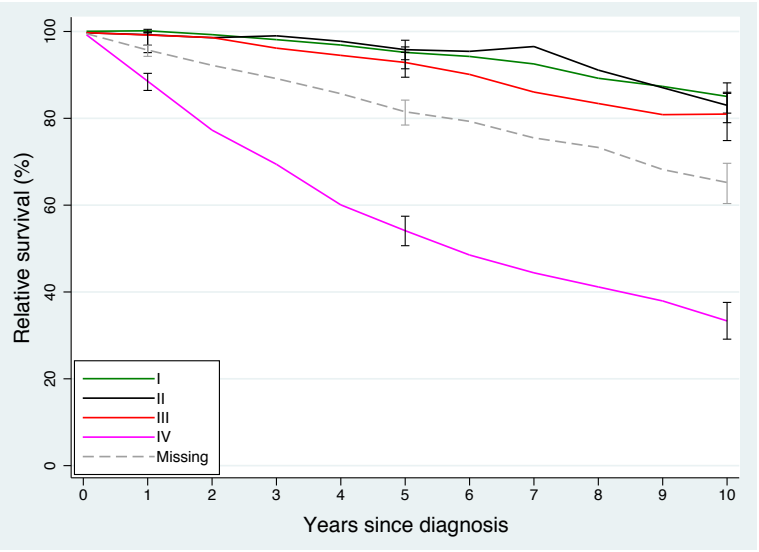
Fig. 2. Relative survival of prostate cancer patients by age at diagnosis and SEER tumour stage group

by screening compared to men of higher socioeconomic status (Rapiti et al. 2009). In addition to the fact that health conscious men participate in screening measures more frequently, they might also be willing to change their lifestyle after a prostate cancer diagnosis, which in turn affects survival (Pleisch et al. 2016). On the other hand, relative survival is low when patients are diagnosed with advanced disease, in particular among patients with distant metastases. Swiss survival rates of patients with distant metastases or stage IV tumours are largely comparable with results from other registries. The only exception appears to be England, where lower 5-year relative survival for men with stage IV tumour is considerably lower compared with Switzerland or Germany. Although results are adjusted for age, it might be that the spectrum of co-morbidities differs between patients of different countries, but more importantly, treatment might differ between countries, leading to differences in survival (Holmberg et al. 2012).

An effect of age on relative survival was hardly visible until the age of 80. Only in men 80+ years old, relative survival decreased over follow-up period even for men with localised disease. One might speculate that these men, even if they «only» have localised tumours might have other or more co-morbidities and do not tolerate side effects of treatment as well as younger patients. Older men might more likely to be treated with androgen-deprivation therapy (ADT) even if without metastatic disease, and a recent publication from the UK has shown that men who experienced two or more cardiovascular events before ADT therapy had a particularly high risk of a new CVD event due to that therapy (O'Farrell et al. 2015).

An interesting observation with respect to age is the rather strong decrease in relative survival in men younger than 60 years of age with regional disease, which was not seen in men 60-69 years old. One explanation might be that rather young men decide not have radical prostatectomy because of potential side effects such incontinence and impotence. However, an analysis of the Zurich Cancer Registry has shown that younger men are more likely to have radical prostatectomy compared with older age groups (Matthes et al. 2017). Secondly, men with prostate cancer diagnosed at younger age might have more aggressive disease than cases diagnosed at an older age. A German analysis showed that relative survival for men with localised/regional disease was worse if the tumour was poorly

Fig. 3. Age-adjusted relative survival of prostate cancer patients by UICC tumour stage group



differentiated or undifferentiated (Brenner & Arndt 2005; Kinnear et al. 2016). Patients with unstaged tumours have relative survival rates that appear to represent the mean of all staging groups.

Two issues need to be taken into account when interpreting these results. Firstly, both SEER and TNM classification used to evaluate the prognosis of prostate cancer may not be optimal for assessing or classifying the prognosis for early stage prostate cancer (Rajab et al 2011). Secondly, survival is poor among elderly due to less screening activity, but also due to under-treatment or sub optimal treatment such that they are less often treated with radical prostatectomy or radiotherapy despite life expectancy of more than 10 years (Lunardi et al. 2016; Bratt et al. 2105).

In summary, our data show that men whose tumour is diagnosed at an early stage do not have worse survival than the general population with the exception of men who were 80 years or older at diagnosis. However, survival of men diagnosed with distant metastases quickly decreased independent of age. This highlights the needs for early diagnosis. The drawback, however, is the problem of lead time bias and overtreatment. Hence, future studies should take into account, for example, the mode of cancer detection but also treatment for a clearer picture of prostate cancer survival. In addition, despite good long-term survival, prostate cancer patients face many other problems such as incontinence and impotence due to surgical procedures, osteoporosis and cardiovascular diseases due to hormone treatment and others, which also need to be addressed in the future (Khan et al. 2011).

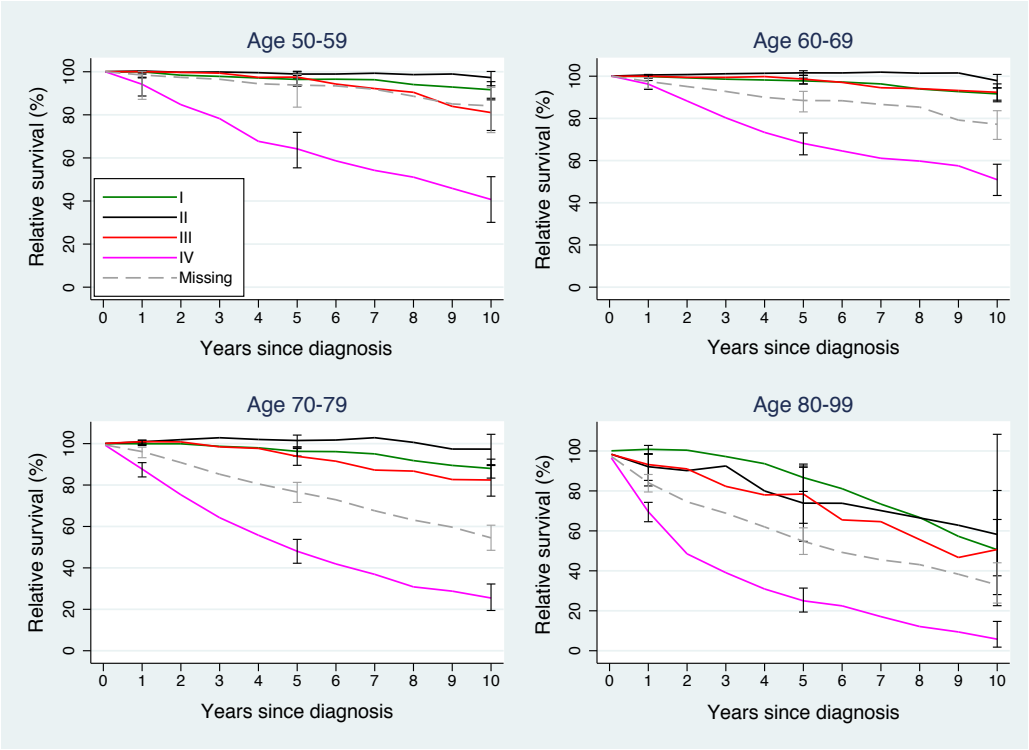


Fig. 4. Relative survival of prostate cancer patients by age at diagnosis and UICC tumour stage group

References will be available in the online version

*For additional information on cancer in Switzerland, please see the NICER website at *http://nicer.org/*

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