Trends in Hepatic Cancer Survival in Switzerland

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Keywords: hepatic cancer, observed survival, relative survival, survival, Switzerland

Introduction

Swiss incidence as well as mortality rates for liver cancer have increased only slightly over the last 20 years [1]. The ratio of the two is close to unity, indicating that cure from liver cancer is rare.

Malignant liver cancers represent primarily hepatocellular carcinomas (90%) followed by cholangiocarcinomas (10%). Other forms of malignant liver cancer, such as angiosarcoma, are extremely rare. Hepatocellular carcinomas and intrahepatic cholangiocarcinomas deserve our attention for several reasons. Firstly, their incidence is rising, and in some countries distinctly, as has been documented by a number of epidemiological studies in the last 20 years [2, 3, 4]. Rising chronic hepatitis C infections and the surge in obesity and diabetes mellitus have been proposed as explanations for the increase in hepatocellular carcinoma [5, 6, 7, 8]. A second reason is the decidedly poor prognosis of hepatocellular carcinoma and cholangiocarcinoma [9]. These tumours can grow extensively before the appearance of symptoms. When symptoms ultimately lead to diagnosis, the therapeutic options are limited and mainly palliative. Thirdly, both tumour types are often associated with underlying liver diseases [5, 3]. Eighty percent of the patients with hepatocellular carcinoma have a cirrhosis and cholangiocarcinoma is associated with cholestatic liver diseases, particularly primary sclerosing cholangitis. Reduced hepatic functions further limit treatment options.
Thus, treatment of primary liver cancer is challenging and there is a large need for progress in the short-term and long-term outcomes in these patients. In the present manuscript, epidemiological information from tumour registries of several Swiss cantons has been combined to examine the survival pattern of patients diagnosed with primary liver cancer during the last 30 years.

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. Sixteen of 26 Swiss cantons currently transmit cancer data annually to the NCD. Cancer cases from thirteen cantons were pooled for this report: Basel-Stadt and Basel-Landschaft (BS/BL), Fribourg (FR), Geneva (GE), Graubünden and Glarus (GR/GL), Lucerne (LU), St. Gallen, Appenzell Ausserrhoden and Appenzell Innerrhoden (SG/AR/AI), Ticino (TI), Valais (VS) and Zurich (ZH). The cantons of Neuchâtel, Jura and Vaud could not be included, because they do not provide information on survival to the NCD.

Cancer registries recorded all incident cancer cases diagnosed in their resident population and assessed cases' survival by active and/or passive follow-up. Cases were followed-up to 31 December 2010. We extracted 7,490 malignant cancer diagnoses for liver and intrahepatic bile ducts (ICD-10 C22.0-C22.9) from 1980 to 2010. For the cantons BS and BL the latest available year of diagnosis was 2008. We excluded all cases diagnosed at death (N=850; 11.3%) or with a death certificate as the only source of information (N=285; 3.8%). Patients with multiple primary tumours were included [10]. Excluded were N=96 or 1.3% of cases, because no active follow-up has been performed. A total of 6,256 cases remained for analysis, with 90% of observations uncensored (i.e. patients who have died). Recent active follow-up was lacking for

Table 1: Number of malignant hepatic cancer cases used for survival analysis in the Swiss national dataset, stratified by Swiss cantons.

Cantons	Diagnosis period	Number of cases			Person-years	% of pooled person-years
		Men	Women	Both		
ZH	1980-2010	1304	556	1860	1738	23.9
SG/AR/AI	1980-2010	533	201	734	744	10.2
GE	1980-2010	902	263	1165	1682	23.1
BS/BL	1981-2008	434	130	564	619	8.5
TI	1996-2010	602	164	766	1197	16.4
VS	1989-2010	608	119	727	869	11.9
GR/GL	1989-2010	231	93	324	324	4.4
FR	2006-2010	71	18	89	90	1.2
LU	2010	17	10	27	21	0.3
Total		4702	1554	6256	7282	100.0

N=151 (2.4%) cases. The vital status of these cases was set lost to follow-up using the date of last contact. Because we did not assume survival up to 31 December 2010 in the absence of reported death, our survival estimates will be conservative.

Completeness of case ascertainment for hepatic cancer could be assessed in the cantons GE, GR/GL, SG/AR/AI, TI and VS and was found to be slightly higher than the international standard of at least 90% within 1.5 years after the date of diagnosis for diagnosis years 2005-2010 [11]. Case finding via death certificates was substantial: between 7% and 38%, depending on cancer registry and diagnosis year. Two registries did not utilize death certificates for case finding during all diagnosis years: ZH (1980-1996) and BS/BL (1981-2001, 2008). If ZH and BS/BL were removed from the pooled dataset for the years indicated, the maximal deviation in survival proportion found in any of the analysis endpoints was 3.0% (for age-group 55-64 during period 1990-1999).

Observed survival (OS) and relative survival (RS) were derived for consecutive time intervals of increasing length after diagnosis during which the hazards were assumed to remain constant.Time intervals were: 0-0.1, 0.1- 0.3, 0.3-0.6, 0.6-1.0, 1.0-1.5, 1.5-2.0, 2.0-2.5, 2.5-3.0, 3-4, 4-5 and 5-6 years. RS was calculated as the ratio of the observed 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 [12]. Expected cancer survival was estimated using the Ederer II method applied to all-cause mortality tables for the cantons combined [13]. All-cause death probabilities, transformed from age-, sex- and calendar year-specific death rates, were interpolated and smoothed using the Elandt-Johnson formula [14]. RS ratios were estimated using the strs command (version 1.3.7) [15] written for the Stata Statistical Software [16]. Partially complete survival analysis was used for the comparison in Table 2. Period survival analysis [17] was used for the analysis of time trends in Table 3. In brief, partially complete analysis describes the survival of cases defined by dates of diagnosis, and period analysis defines cases by follow-up dates. RS estimates were age-standardized using weights specific for hepatic cancer from the International Cancer Survival Standards (ICSS) [18]. Standard weights for age groups were: 0.19 (0-54 years), 0.23 (55-64), 0.29 (65-74) and 0.29 (75-99). Ninety-five percent confidence intervals (95% CI) were estimated using Greenwood's method [19] in partially 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 [18].

To test for linear time trends of RS, the annual percentage change (APC) was estimated with the Joinpoint Regression Program v4.0.4 [20].

Years since diagnosis	Age in years	Observed survival %			Relative survival[1] %								
		Calendar period of diagnosis 1990 - 1999[4]											
		Men	Women	Both	Men	95% CI[3] LL	UL	Women	95% CI[3] LL	UL	Both	95% CI[3] LL	UL
1	00 - 54	36.8	52.6	40.4	36.9	30.0	43.9	52.7	38.8	64.9	40.5	34.3	46.7
	55 - 64	29.1	34.2	30.0	29.4	24.7	34.2	34.4	24.0	45.1	30.2	25.9	34.6
	65 - 74	26.5	26.9	26.6	27.2	23.2	31.4	27.2	19.9	35.0	27.1	23.6	30.7
	75 - 99	19.7	12.6	17.4	21.5	17.2	26.3	13.6	8.8	19.4	18.8	15.4	22.4
	00 - 99	26.8	25.7	26.5	27.7	25.3	30.2	26.4	22.3	30.7	27.3	25.2	29.4
3	00 - 54	23.7	25.8	24.2	24.0	18.0	30.6	25.9	14.7	38.6	24.4	19.0	30.2
	55 - 64	13.3	13.3	13.3	13.8	10.2	17.9	13.5	6.6	23.0	13.7	10.4	17.4
	65 - 74	9.4	7.9	9.2	10.3	7.5	13.7	8.2	3.8	14.8	9.8	7.4	12.6
	75 - 99	2.7	3.1	2.8	3.6	1.6	7.1	3.9	1.3	9.2	3.6	1.9	6.3
	00 - 99	10.8	9.3	10.5	11.9	10.0	13.9	9.9	7.1	13.5	11.3	9.7	13.0
1	stand.[2]	27.1	29.3	27.3	27.9	25.5	30.4	29.8	25.4	34.2	27.9	25.8	30.1
3		11.1	11.1	11.1	11.8	10.0	13.8	11.6	8.3	15.4	11.7	10.1	13.4
		Calendar period of diagnosis: 2000 - 2009[4]											
1	00 - 54	50.1	55.3	51.2	50.2	44.5	55.7	55.4	44.5	65.0	51.4	46.3	56.2
	55 - 64	44.4	49.6	45.3	44.8	40.6	48.9	49.9	40.5	58.5	45.6	41.8	49.3
	65 - 74	41.1	41.2	41.1	42.0	38.4	45.5	41.6	35.0	48.1	41.8	38.7	44.9
	75 - 99	26.4	27.1	26.6	28.1	24.4	31.9	28.3	23.1	33.8	28.1	25.1	31.2
	00 - 99	39.3	38.6	39.1	40.2	38.1	42.3	39.4	35.7	43.0	39.9	38.1	41.7
3	00 - 54	27.8	28.5	28.0	28.1	22.9	33.5	28.7	19.0	39.1	28.2	23.6	33.0
	55 - 64	22.3	20.8	22.0	22.9	19.3	26.7	21.1	14.0	29.2	22.5	19.2	25.9
	65 - 74	18.4	20.5	18.9	19.6	16.7	22.7	21.3	15.9	27.2	19.8	17.3	22.5
	75 - 99	10.2	8.7	9.7	12.4	9.5	15.7	9.9	6.5	14.3	11.4	9.1	13.9
	00 - 99	18.5	16.8	18.0	19.7	18.0	21.6	17.8	14.9	20.9	19.1	17.6	20.7
1	stand.[2]	39.3	41.7	39.8	40.2	38.1	42.2	42.3	38.5	46.0	40.5	38.7	42.3
3		18.7	18.7	18.7	19.9	18.1	21.7	19.4	16.2	22.7	19.6	18.0	21.2

[1] Survival analysis using the partially complete approach

[2] Age-standardized using ICSS weights

[3] CI (confidence interval); LL (lower limit); UL (upper limit)

[4] Diagnoses 1990-1999 were followed-up to 31.12.2000. Diagnoses 2000-2009 were followed-up to 31.12.2010.

Table 2: Observed and relative survival estimates after malignant hepatic cancer diagnosis, with 95% confidence intervals, by 10-year calendar period, age at diagnosis, years since diagnosis and sex. Data pooled from 12 Swiss cantons (ZH, SG/AR/AI, GE, BS/BL, TI, VS, GR/GL, and FR).

Results

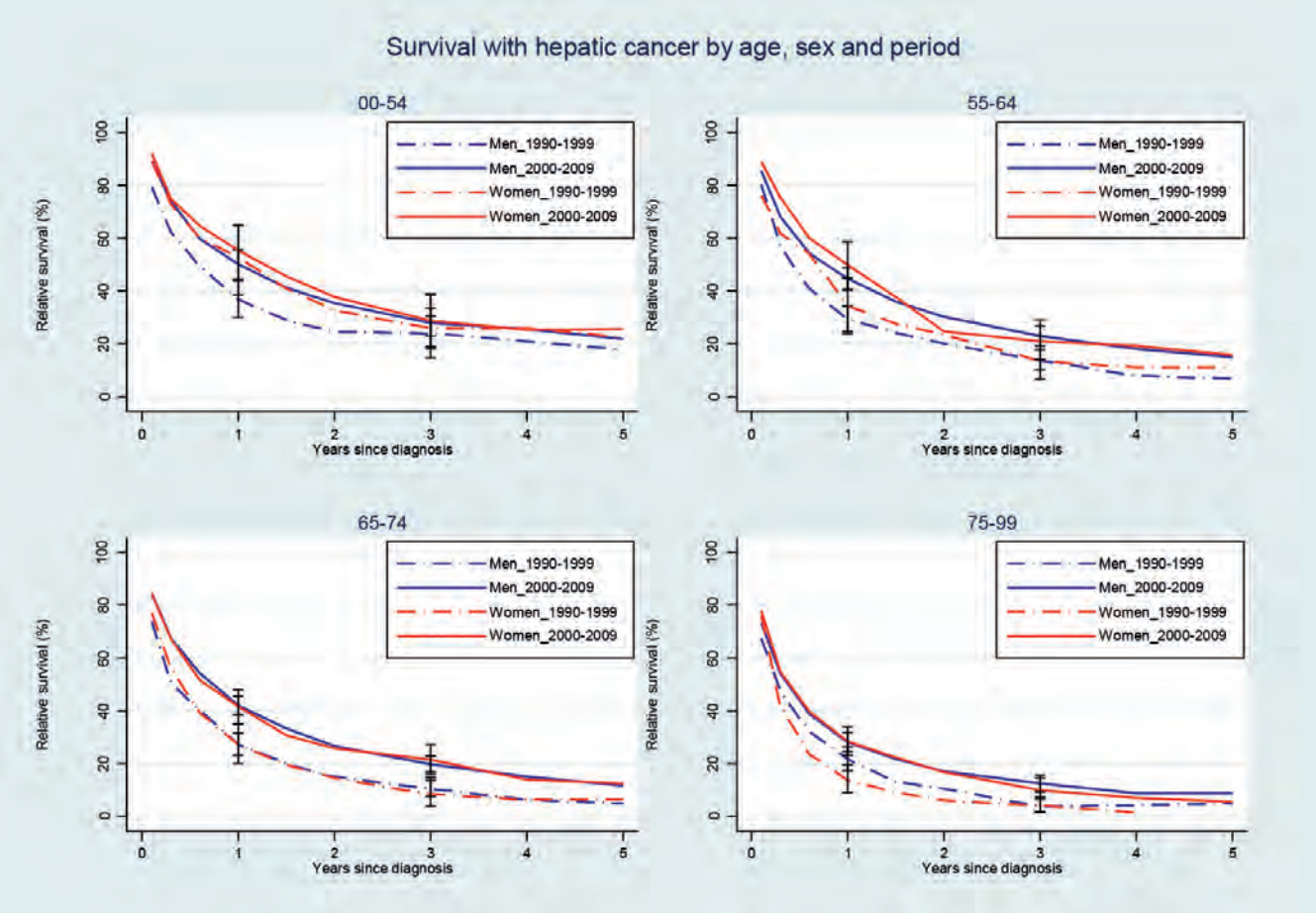
The survival experiences of more than 6,200 persons diagnosed with malignant cancer of the liver or the intrahepatic bile ducts contributed to this study (Tab. 1). The data pool contains increasing numbers of cancer registries over time. Until 1995, the cantons ZH, SG/AR/AI, GE and BS/BL contributed to the pool, whereas canton TI joined in 1996, canton FR in 2006 and canton LU in 2010. The cantons ZH and GE alone contributed almost 50% of the total cases.

Men were about three times more often affected compared to Women. The median age at diagnosis was 68 years (interquartile range IQR 60-75) for Men and 72 years (IQR 63-79) for Women. Just five percent of patients were diagnosed below age 47. The age distribution of the patients remained stable over time. The most common primary malignancy was hepatocellular carcinoma, ranging from 50% - 90% depending on cancer registry. Validity of this estimate was limited by considerable differences in the frequency of unspecified neoplasms (ranging from 1% up to 40%, depending on cancer registry).

The survival experience of Men and Women was remarkably similar, for every age-group and diagnosis period analysed. This is shown in Tab. 2 for survival proportions at one and three years after diagnosis, and by the survival curves in Fig. 1. Estimations for survival proportions five years after diagnosis are not shown in Tab. 2 because they could not be reliably estimated in Women due to the smaller number of cases.

Men and Women shared equally in the prolongation of survival duration over calendar time. The age-standardized relative survival (RS) proportions in Men, diagnosed between 1990 and 1999, were 27.9% and 11.8% for one and three years after diagnosis, respectively, and in Women, diagnosed in the same period, RS was 29.8% and 11.6%, respectively. A decade later (2000-2009), the RS had improved considerably to 40.2% and 19.9% in Men and 42.3% and 19.4% in Women.

Figure 1: Age- and sex-specific relative survival curves for two calendar periods of diagnosis (1990-1999 and 2000-2009). 95% confidence intervals are shown for survival proportions at one and three years after diagnosis. Hepatic cancer cases were pooled from 12 Swiss cantons (ZH, SG/AR/AI, GE, BS/BL, TI, VS, GR/GL, and FR).



Years since diagnosis	Age in years	Calendar period of death or censoring: 1990/1992 RS[1] % [95% CI]	1993/1995 RS[1] % [95% CI]	1996/1998 RS[1] % [95% CI]	1999/2001 RS[1] % [95% CI]	2002/2004 RS[1] % [95% CI]	2005/2007 RS[1] % [95% CI]	2008/2010 RS[1] % [95% CI]	APC[2] [95% CI]
Both sexes									
1	00-74	22.5 [17.8;26.6]	19.1 [15.3; 23.1]	28.1 [24.2; 32.1]	35.1 [31.0; 39.3]	39.8 [35.7; 43.7]	45.6 [41.7; 49.5]	44.2 [40.5; 47.9]	4.0 [2.0; 6.0]
	75-99	11.1 [6.9;16.6]	10.4 [6.4; 15.5]	12.5 [8.6; 17.1]	17.4 [12.8; 22.5]	18.8 [14.6; 23.4]	24.9 [20.1; 30.0]	25.8 [21.1; 30.8]	5.1 [3.5; 6.7]
5	00-74	5.0 [2.5; 8.6]	5.0 [3.1; 7.6]	7.2 [4.7; 10.4]	9.6 [7.0; 12.7]	13.2 [10.3; 16.4]	14.0 [11.3; 17.1]	15.1 [12.5; 18.0]	5.9 [3.5; 8.3]
	75-99	0.3 [0.0; 4.4]	1.0 [2.2; 4.0]	1.0 [0.2; 3.7]	4.9 [1.6; 11.6]	4.7 [2.2; 8.7]	6.2 [3.5; 10.0]	6.2 [3.6; 9.9]	9.7 [1.8; 18.2]
1	stand.[3]	19.4 [16.0; 23.1]	18.5 [15.3; 22.1]	24.2 [21.1; 27.4]	30.4 [27.1; 33.7]	34.6 [31.4; 37.7]	39.9 [36.7; 43.0]	39.1 [36.1; 42.2]	3.9 [2.3; 5.6]
5		4.1 [2.3; 6.7]	4.8 [3.1; 7.1]	6.1 [4.2; 8.6]	8.2 [5.9; 11.1]	12.5 [10.1; 15.1]	11.9 [9.7; 14.4]	13.1 [10.9; 15.4]	5.6 [2.7; 8.7]

[1] RS (relative survival) analysed with period approach. CI: Confidence interval.

[2] Annual percentage change

[3] Age standardized using ICSS weights

Table 3: Trends in relative survival of hepatic cancer cases pooled from 13 Swiss cantons (ZH, SG/AR/AI, GE, BS/BL, TI, VS, GR/GL, FR, and LU) for successive three-year calendar periods of follow-up.

Temporal survival trends were analysed at higher resolution using seven consecutive time periods of three year duration, starting in 1990 and ending in 2010 (Tab. 3). Men and Women were analysed together and the age groups reduced to two. The enlarged number of observations per stratum allowed estimation of five-year survival proportions. The annual percentage changes (APC) were significantly larger than zero for short term RS (one year after diagnosis) as well as for long term survival (five years after diagnosis) and ranged from 3.9% to almost 10%. Persons above 75 years of age at diagnosis seemed to have gained equally or even slightly more than younger persons (APC 9.7% vs 5.9% for RS after five years, difference not significant). The APC in age-standardized RS proportions were 3.9% [CI 2.3-5.6%] and 5.6% [CI 2.7-8.7%] for one and five year survival, respectively. The overall shape of the trend was not linear but seemed to have been steepest during the time period 1997-2003.

Discussion

Our results confirm that the prognosis of primary liver cancer is still poor. This emphasizes the role of primary prevention. It is important to treat patients with liver diseases before they develop a cirrhosis, which places them at higher carcinogenic risk. Well-tolerated, efficacious treatments against chronic hepatitis B and chronic hepatitis C infections are now available and they have been shown to decrease the rate of hepatocellular carcinoma [21, 22]. Regarding secondary prevention, relevant diagnostic procedures such as ultrasonography, computed tomography and magnetic resonance imaging, have been introduced during the last 20 years to detect hepatocellular carcinoma at an earlier stage. Since the Swiss trend in mortality did not decline relative to the incidence rate, it suggests that earlier diagnosis of liver cancer might have contributed to the observed prolongation of survival, measured as time from diagnosis to death or end of follow-up. Additional efforts could be made through active surveillance of patients at risk and thus offering curative treatments to a larger number of patients as has recently been shown for the Bern HCC cohort [23].

The observed improvements in survival of patients in Switzerland could have several explanations, which are mutually non-exclusive. Novel and effective treatments of hepatocellular carcinoma have been progressively introduced during the last 20 years. Selection of treatments has been facilitated with the introduction of the 'BCLC' algorithm [24] and in particular, the recognition in the late nineties, that patients with a limited tumour burden can be transplanted with a small risk of recurrence [25]. The application of the so-called «Milan criteria» not only cured patients with hepatocellular carcinoma, but also stimulated physicians to

find tumours at an earlier stage, which lead to better screening and clearer radiological definition of the diagnosis [26]. Furthermore, the use of other therapeutic options has been improved, such as transarterial chemoembolization (TACE), either as palliative intervention or as neoadjuvant treatment, the introduction of drug-eluting beads [27], and of a systemic targeted therapy against hepatocellular carcinoma [28]. The contribution of such palliative treatments on long-term survival is limited in comparison with curative approaches such as transplantation [29] or innovative therapeutic combinations [30].

The main strength of our study is the large number of primary hepatic cancer cases that could be combined from thirteen Swiss cantons. The data spans 30 calendar years, thus allowing the analysis of changes over time. There are, however, important limitations to our study. Neither the histological type of the primary tumour nor the progression stage of the disease have been taken into account. It is likely to be hepatocellular carcinoma at a progressed stage in the majority of cases, but we cannot exclude distortion of our results by other forms of hepatic carcinoma or by changes in the case mix over time.

In conclusion, primary liver cancer should attract more attention in the medical community than it does at present. The number of patients could be reduced by vaccination against hepatitis B and by treatment of chronic viral hepatitis, alcoholic liver disease and non-alcoholic steatohepatitis. In addition, increased efforts such as active surveillance of patients at risk could be made in order to diagnose hepatic cancer at an earlier stage.

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

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