Trends in survival from oesophageal cancer in Switzerland

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Introduction

Oesophageal carcinoma is a relatively rare disease with a dismal prognosis. During 2007-2011 about 11 in 100'000 men (or 392 in total) and about 4 in 100'000 women (128 in total) were diagnosed each year with oesophageal cancer, while the yearly death toll due to the disease was 9 in 100'000 men (327 in total) and 3 in 100'000 women (106 in total) [1]. Age-adjusted incidences rates for cancer of the oesophagus have been increasing in Switzerland for both sexes since the beginning of cancer registration in the late Seventies and early Eighties of the 20th Century, with recent signs of levelling off, while mortality rates are steadily declining in men, but remaining stable in women [1]. Disease risk is considerably higher in men and moderately higher in the French- or Italian-speaking part of Switzerland. Both, the sex-specific and the region-specific age-adjusted risk ratios have declined over time from initially 5.0 to 3.8 for men versus women and from 2.0 to 1.4 for French-/Italian- versus German-speaking region, respectively.

In the present descriptive study, epidemiological information from tumour registries of seventeen Swiss cantons have been collapsed to examine the survival patterns of patients diagnosed with malignant primary cancer of the oesophagus 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. Twenty of 26 Swiss cantons have transmitted population-based cancer data to the NCD up to diagnosis date 31.12.2011. Cancer cases from 17 cantons were collapsed for this report: Appenzell Ausserrhoden (AR) and Appenzell Innerrhoden (AI), Basel-Landschaft (BL) and Basel-Stadt (BS), Fribourg (FR), Geneva (GE), Glarus (GL), Graubünden (GR), Lucerne (LU), Nidwalden (NW), Obwalden (OW), St. Gallen (SG), Ticino (TI), Uri (UR), Valais (VS), Zug (ZG) and Zurich (ZH). The cantons of Neuchâtel, Jura and Vaud could not be included, because they do not provide information on patient 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 until 31.12.2011. We extracted 5'519 malignant primary cancer diagnoses for oesophagus (ICD-10 C15) from 1980 to 2011. For the cantons BL and BS the latest available year of diagnosis was 2009. We excluded all cases diagnosed at death (N=86) or with a death certificate as the only source of information (N=107). Case finding via death certificates was infrequent (3%-7%, depending on cancer registry). Patients with multiple primary tumours (22%) were included [2]. Excluded were 78 cases because no active follow-up has been performed. Recent active follow-up was lacking for 133 cases (i.e. follow-up <2011). The vital status of these cases was set lost to follow-up using the date of last contact. A total of 5'248 cases (95%) remained for analysis, with 86% of observations uncensored (i.e. patients who have died).

Because we did not assume survival up to 31.12.2011 in the absence of reported death (i.e. based on passive follow-up alone), our survival estimates will be conservative. Using the assumption of survival in the absence of reported death could overestimate survival because two large registries did not utilize death certificates for several diagnosis years: ZH (1980-1996) and BS/BL (1981-2001, 2008-9).

Completeness of case ascertainment for oesophageal cancer was estimated with the mortality-incidence ratio (MIR). A ratio above unity is suggestive of under-registration of diagnoses. MIRs were determined for consecutive 5-year intervals from 1987 to 2011 for each cancer registry and provided no evidence for systematic under-registration [1]. MIRs ranged usually between 0.7 and 0.9 and were above or close to unity only for ZH and SG in time interval 1987-1996 and for BL/BS in time interval 1992-1996.

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. Temporal divisions were 0.05, 0.1, 0.2, 0.4, 0.6, 1, 2, 3, 4, 5, and 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 [3]. Expected cancer survival was estimated using the Ederer II method applied to all-cause mortality tables for the cantons combined [4]. All-cause death probabilities, transformed from age-, sex- and calendar year-specific death rates, were interpolated and smoothed using the

Elandt-Johnson formula [5]. RS ratios were estimated using the strs command (version 1.3.7) [6] written for the Stata Statistical Software [7]. Partially complete survival analysis was used for the comparison in Table 2. Since diagnoses from 2011 were excluded from this analysis, only 13 of 17 cantons were eligible. Period survival analysis [8] was used for the analysis of time trends in Table 3. Since it included diagnoses from 2011, all 17 cantons contributed to this analysis. 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 cancer of the oesophagus from the International Cancer Survival Standards (ICSS) [9]. Ninety-five percent confidence intervals (95% CI) were estimated using Greenwood's method [10] 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 [9].
To test for linear time trends of RS, the annual percentage change and its 95% CI was estimated with the Joinpoint Regression Program v4.0.4 [11].

Results

This report combines more than 8'500 person-years of survival experience for patients diagnosed with primary malignant cancer of the oesophagus (Tab. 1). The data pool contains increasing numbers of cancer registries over time. Until 1995, only the cantons AR, AI, BL, BS, GE, SG, and ZH contributed to the pool, whereas canton TI joined in 1996, canton FR in 2006, canton LU in 2010, and cantons OW, NW, UR and ZG in 2011. The cantons TI, VS, GR, GL, FR, LU, OW, NW, UR and ZG contributed less than 25% of the total cases.
Age at diagnosis ranged from 29 to 101 years. The median age at diagnosis was 66 years in men (interquartile range IQR 58-74) and 71 years in women (IQR 61-80). Neoplasms are more frequent at deeper anatomic subsites within the oesophagus, and overall, the most common primary malignancy was squamous cell carcinoma (61%), followed by adenocarcinoma (31%), other type (5%), and unspecified type (3%). Adenocarcinoma incidence increased in relative frequency from 29% to 39% if 1991-2000 is compared with 2001-2010, while squamous cell carcinoma incidence decreased from 62% to 53%, and proportions of other or unspecified histologic types remained constant. Information regarding tumour detection was available from the cantons GE, VS and FR and revealed that symptoms were responsible for detection in 88% of the cases.
The survival experience of men and women diagnosed with cancer of the oesophagus is shown in Tab. 2 for survival proportions at one and five years after diagnosis, and by survival curves in Fig. 1. The age-standardized relative survival (RS) proportions in men, diagnosed between 1991 and 2000, were 41.2% and 11.5% for one and five years after diagnosis, respectively. A decade later (2001-2010), the age-standardized RS had improved substantially to 51.1% and 18.5%, respectively. Age-standardized and age-specific relative survival (RS) proportions in women were slightly higher as compared with men, an advantage which declined with time of diagnosis. For diagnoses between 1991 and 2000, age-standardized RS in women were 44.2% and 17.9% for one and five years after diagnosis, respectively. A decade later (2001-2010), the improvement was somewhat less as compared with men, to 51.1% and 21.5%, respectively.
Temporal survival trends were analysed at higher resolution using five consecutive time periods of four year duration, starting in 1992 and ending in 2011 (Tab. 3). The annual percentage changes (APC) were significantly above

Table1: Number of malignant cases for cancer of the oesophagus used for survival analysis in the Swiss national dataset, stratified by Swiss cantons and age group. Seventeen cantons are covered by nine cancer registries.

Cantonal Cancer Registry	Available years of diagnosis	Number of cases							Person-years	% of pooled person-years
		00-59		60-74		75+		all ages		
		Men	Women	Men	Women	Men	Women	Both		
ZH/ZG	1980-2011	324	109	551	183	317	176	1660	2331	27.2
SG/AR/AI	1980-2011	176	21	280	46	151	52	726	1169	13.7
GE	1980-2011	234	52	276	91	145	99	897	1651	19.3
BS/BL	1981-2009	140	45	226	69	113	70	663	1292	15.1
TI	1996-2011	74	15	132	29	87	41	378	669	7.8
VS	1989-2011	111	17	163	41	86	42	460	822	9.6
GR/GL	1989-2011	63	7	112	24	70	27	303	424	5.0
FR	2006-2011	33	7	49	3	20	9	121	174	2.0
LU/UR/OW/NW	2010-2011	6	0	19	4	8	3	40	23	0.3
Total		1161	273	1808	490	997	519	5248	8555	100.0

Years since diagnosis	Age in years	Both			Men			Women		
		Relative survival %	95% CI [1] LL	UL	Relative survival %	95% CI [1] LL	UL	Relative survival %	95% CI [1] LL	UL
		Calendar period of diagnosis 1991 - 2000 [3]								
1	00-59	52.8	48.4	57.0	53.3	48.5	58.0	50.7	40.4	60.0
	60-74	44.4	40.5	48.2	43.6	39.1	47.9	47.8	39.5	55.7
	75 +	27.3	23.0	31.8	27.0	21.6	32.7	28.0	21.1	35.3
	all ages	42.6	40.2	45.1	43.5	40.6	46.3	40.6	35.8	45.4
5	00-59	19.0	15.2	23.1	18.0	13.9	22.7	23.0	14.4	32.8
	60-74	12.4	9.5	15.7	11.0	7.8	14.8	17.8	11.2	25.6
	75 +	4.7	2.3	8.4	1.9	0.3	6.8	7.6	3.4	14.1
	all ages	12.6	10.6	14.7	11.8	9.5	14.3	15.0	11.2	19.4
1	stand.[2]	42.0	39.5	44.4	41.2	38.3	44.0	44.2	38.9	49.3
5	stand.[2]	12.5	10.6	14.7	11.5	9.4	14.0	17.9	13.5	22.9
		Calendar period of diagnosis 2001 - 2010 [3]								
1	00-59	59.0	54.7	63.1	58.8	53.9	63.4	59.7	50.3	67.9
	60-74	54.7	51.6	57.7	55.3	51.8	58.7	53.1	46.3	59.4
	75 +	36.4	32.7	40.2	37.1	32.5	41.7	35.5	29.1	42.1
	all ages	50.3	48.2	52.4	51.3	48.8	53.7	47.7	43.4	51.8
5	00-59	25.5	21.5	29.8	23.0	18.5	27.8	34.2	25.3	43.3
	60-74	19.1	16.3	22.1	19.8	16.6	23.3	17.6	12.2	23.8
	75 +	10.2	7.4	13.5	9.7	6.3	14.1	11.3	6.8	17.1
	all ages	18.1	16.2	20.0	18.0	15.8	20.3	18.8	15.2	22.6
1	stand.[2]	50.92	48.7	53.1	51.1	48.5	53.7	51.1	46.6	55.3
5	stand.[2]	19.1	17.0	21.2	18.5	16.0	21.1	21.5	17.6	25.8

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

[2] Age-standardized using ICSS weights

[3] Follow-up December 2001

[4] Follow-up December 2011

Table 2: Relative survival estimates after diagnosis of malignant cancer of the oesophagus, with 95% confidence intervals, by 10-year calendar period, age at diagnosis, years since diagnosis and sex. Data pooled from 13 Swiss cantons (AR, AI, BL, BS, FR, GE, GL, GR, LU, SG, TI, VS, and ZH).

zero for short term (one year after diagnosis) as well as for long term survival (five years after diagnosis). Persons above 60 years of age at diagnosis seemed to have gained less than younger patients if five-year RS is compared with one-year RS: the gap in RS at five year after diagnosis between age 75+ and <60 has widened from 8% to 22%, and between age 60-74 and <60 from -3 to 11%, while the one-year RS gaps by age remained the same.

Discussion

The main strength of our study is the large number of malignant primary oesophageal cancer cases that could be combined from seventeen Swiss cantons. The data spans 30 calendar years, thus allowing the analysis of changes over time. There are, however, important limitations to our study. We did not stratify survival by histological type of the primary tumour nor by progression stage of the disease due to limited data. In Switzerland we observed the same trend as in the Western world towards more adenocarcinoma compared to the squamous cell carcinoma. Because of slight survival advantages for cases of adenocarcinoma over squamous cell carcinoma [12], different case mix might have contributed to the observed positive trend in survival.

While age-standardized five year RS for men and women combined in Switzerland was close to the European mean for diagnoses during the Nineties of the 20th century, the RS moved to a position clearly above the European mean for diagnoses during the 1st decade of the 21st century. The 4th round of the European cancer registry-based study of cancer patients' survival and care, or EUROCARE-4 [13], estimated age-standardized five year RS for patients diag-

Years since diagnosis	Age in years	Relative survival [1] [%] Calendar period of death or censoring 1992-1995	1996-1999	2000-2003	2004-2007	2008-2011	APC [2]	[95% CI]
1	00-59	49.3	54.0	55.1	60.6	67.4	7.9	[4.9, 10.9]
	60-74	40.3	45.4	48.3	54.7	58.7	9.7	[7.8, 11.7]
	75+	23.5	26.1	31.3	33.4	40.2	14.4	[10.2, 18.7]
5	00-59	11.7	17.2	20.8	24.0	32.8	26.0	[17.5, 35.1]
	60-74	14.6	13.3	12.2	18.3	21.2	13.9	[-3.4, 34.2]
	75+	3.6	5.4	6.2	9.9	10.9	30.0	[14.9, 47.1]
1	stand.[3]	38.4	42.2	45.6	51.3	56.1	10.1	[8.9, 11.3]
5		11.2	12.5	13.0	19.0	22.1	20.6	[10.5, 31.7]

[1] Relative survival analysed with period approach.

[2] Annual percentage change. CI: confidence interval.

[3] Age standardized using ICSS weights

Table 3: Trends in relative survival for cancer of the oesophagus, expressed as the annual percentage change (APC). Cases for men and women were pooled from 17 Swiss cantons (AR, AI, BL, BS, FR, GE, GL, GR, LU, NW, OW, SG, TI, UR, VS, ZG, and ZH) for successive four-year calendar periods of follow-up.

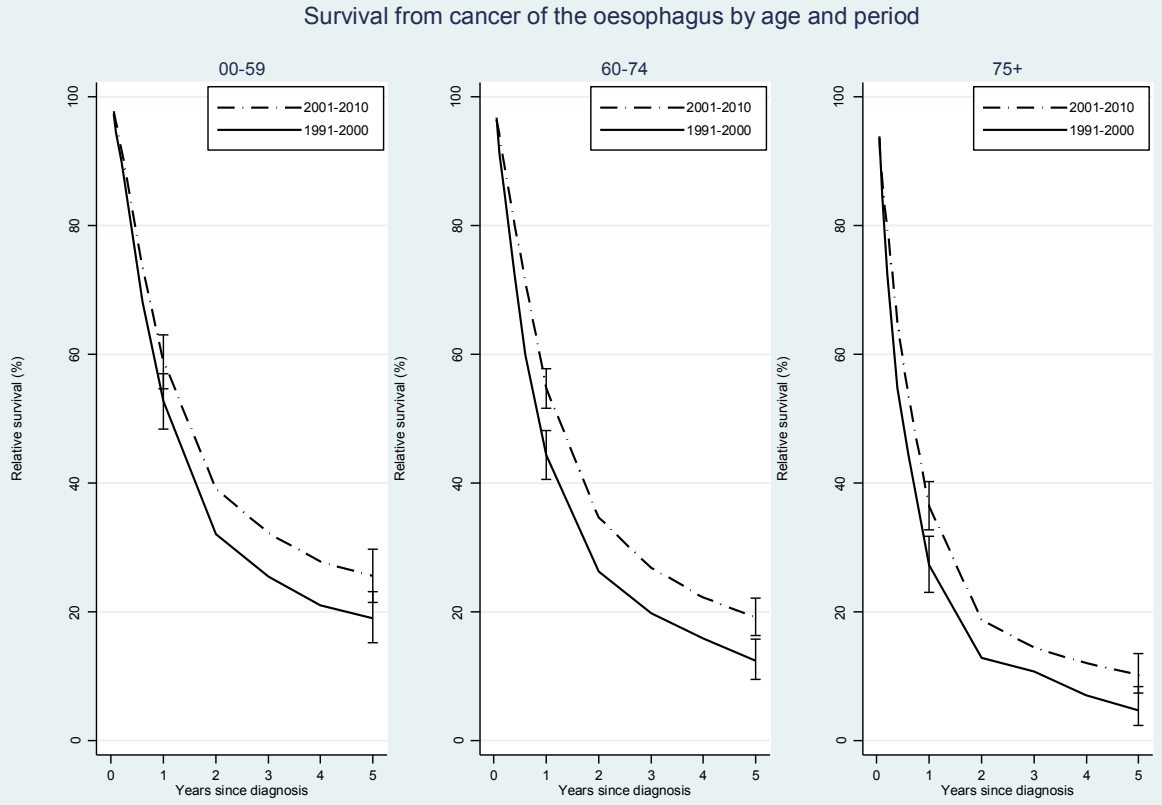

Figure 1: Age-specific relative survival curves for two calendar periods of diagnosis (1991-2000 and 2001-2010). 95% confidence intervals are shown for survival proportions at one and five years after diagnosis. Cases of oesophageal cancer in men and women were pooled from 13 Swiss cantons (AR, AI, BL, BS, FR, GE, GL, GR, LU, SG, TI, VS, and ZH).

nosed with oesophageal cancer in 1995-1999 with 11.1%, which is close to the Swiss estimate of 12.5% for diagnoses in 1991-2000 (Tab. 2) or 1996-1999 (Tab. 3). While the updated EUROCARE-5 estimates of the European mean survival for patients diagnosed 2000-2007 remained low at 12.4% [14], estimates for Switzerland improved to 19.1% for patients diagnosed 2001-2010 (Tab. 2), or 19.0% for 2004-2007 (Tab. 3). There could be several reasons for this observation. Before 2001, patients in Switzerland were treated very heterogeneously. In 2002, the Swiss Group of Clinical Cancer Research (SAKK) started a series of clinical trials in the field of oesophageal carcinoma. Since then almost all clinical centers in Switzerland treating this type of cancer have participated in these SAKK activities. This has certainly led to better standardization of diagnosis and therapy in Switzerland and can explain some increase in quality of care. Other reasons for the increased survival over time are better patient selection and improved perioperative management. Most patients with newly diagnosed oesophageal carcinoma present with locally advanced disease. It remains a challenge to clinically stage these patients. For T-staging endosonography is regarded as the most accurate tool, whereas for N- and M-stage determination the combination of endosonography and PET-CT scan should be used. PET-CT scan detects about 10-20% distant metastasis not seen with conventional staging and is able to prevent this kind of surgery for some patients. In most European countries PET-CT is not registered for oesophageal cancer diagnostics. In Switzerland those diagnostic tools has been widespread and increased the accuracy of staging compared to some other European countries. Similar differences were seen in the peri- and postoperative management keeping in mind that oesophageal surgery is linked with a high perioperative risk for patients and full equipped, highly experienced intensive care unit is key.

In spite of some improvement in survival over time we have to recognize that survival with oesophageal carcinoma is still poor. The main reason is that most of the tumours already have systemic metastases at diagnosis. Progress over the last decade has been modest, and primarily reflects better patient selection and improved perioperative management. To accelerate progress, more research in this field is needed. In addition, public health interventions working towards changes in lifestyle factors associated with increased risk and worse survival, especially tobacco smoking [15, 16], might be beneficial.

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

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