

Trends in Pancreatic Cancer Survival in Switzerland

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

Introduction

In the industrialised world, pancreatic cancer is the fourth leading cause of death from cancer, while ranking only tenth for frequency [1], with increasing incidence for both sexes in Europe [2].

Main risk factors for pancreatic cancer are smoking [3], obesity [4], diabetes [5] and chronic pancreatitis. Efforts to screen for pancreatic cancer have been rather disappointing, but might prove useful for patients at high-risk [6]. Preoperative assessment is usually by CT imaging [7], or alternatively by MRI. Surgical resection is the treatment of choice for localized disease and should be performed in experienced centers [8]. Adjuvant chemotherapy with gemcitabine improves progression-free and overall survival significantly and is considered standard for patients post-surgery in Europe [9, 10].

Patients with unresectable or metastatic disease are treated with chemotherapy, and gemcitabine monotherapy is considered as a standard. Recently, superior results have been shown by adding nab-paclitaxel [11] to gemcitabine, or with folfirinox combination therapy in patients with good performance status [12].

This study analyses pancreatic cancer survival and national outcome trends over three decades and provides a baseline reference for future trials and interventions.

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 13 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 Outer-Rhodes and Appenzell Inner-Rhodes (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 or passive follow-up as of 31 December 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 the cancer. We included malignant pancreatic cancer diagnoses from 1980 to 2010 at ages 20 to 99 years based on the 3rd edition of the International Classification of Diseases for Oncology [13] topography codes C25.0-C25.9 and all morphologies except lymphoma/leukaemia codes 9590-9989. For the cantons BS and BL the latest available year of diagnosis was 2008. We excluded all cases diagnosed at death or with a death certificate as the only source of information (N=1209; 9.8%). Pancreatic cancer cases that were preceded by a primary cancer of a different topography were included [14]. Recent active follow-up was lacking for N=176 (1.6%) cases. The vital status of these cases was set lost to follow-up using the date of last contact. A total of 11,008 cases remained for survival analysis with 96% of observations uncensored. Completeness of case ascertainment for pancreatic cancer could be assessed in the cantons 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 [15].

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: 0.1, 0.3, 0.6, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0 and 6.0 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 [16]. Expected cancer survival was estimated using the Ederer II method applied to all-cause mortality tables for the cantons combined [17]. All-cause death probabilities, transformed from age-, sex- and calendar year-specific death rates, were interpolated and smoothed using the Elandt-Johnson formula [18]. RS ratios were estimated using the `strs` command (version 1.3.7) [19] written for the Stata Statistical Software [20]. Complete survival analysis was used for the comparison in Table 2. Period survival analysis [21] was used for the analysis of time trends in Table 3. In brief, 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 pancreatic cancer from the International Cancer Survival Standards (ICSS) [22]. Standard weights for age groups were: 0.29 (20-59 years), 0.27 (60-69), 0.29 (70-79) and 0.15 (80-99). Ninety-five percent confidence intervals (95% CI) were estimated using Greenwood's method [23] 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 [22].

To test for linear time trends of 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 an 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. Annual percentage change (APC) was estimated as $APC = 100 ((RS_{last} / RS_{first})^{1/\Delta t} - 1)$, with Δt as the difference between last and first calendar year.

Results

This report includes more than 5,300 men and 5,600 women diagnosed with pancreatic cancer from 1980 to 2010 (Tab. 1). The national coverage of the National Core Dataset (NCD) with respect to information on survival increased gradually over time. In 1980, 30% of the Swiss population was covered which increased to 56% in 2010. The median age in the study population was 70 years in

men, 74 years in women, and 72 years for both. The median survival time was less than 5 month: 125 days in men, 129 days in women and 127 days for both. The cantonal cancer registries GE, VS and FR provided information whether persons presented with tumour symptoms or not. The fraction of symptomatic persons amounted to 83% in men, 86% in women and 84% for both.

Table 2 and Fig. 1 compare survival by age, sex and time after diagnosis in two calendar periods of 10 years duration. The age-standardized one-year relative survival in 1991-2000 for men was 20.8% and improved to 29.6% in 2001-2010. For women, the one-year relative survival improved from 22.7% to 33.3%. The 5-year relative survival was only 3.9% in men and 3.2% in women during 1991-2000 and remained at low levels in 2001-2010 with 5.0% and 6.8%, respectively.

As with many cancers, survival with pancreatic cancer decreased with age, even after taking account of the higher background mortality in older people, i.e. relative survival. The proportion surviving at least one year after having been diagnosed at age 80 or older (10.0% for 1991-2000 and 14.7% for 2001-2010) was approximately one-third of the proportion in those diagnosed at below 60 years of age (28.5% for 1991-2000 and 40.3% for 2001-2010) (Tab. 2). This age effect is stronger for 5-year survival.

Table 3 shows temporal trends in relative survival in finer detail for both sexes combined. One- and five-year relative survival was estimated in seven consecutive calendar periods of three-year duration. Clear improvements were seen for one-year survival, independently of whether persons have been diagnosed below or above age 70. The age-standardized one-year survival doubled from 15.4% (95% CI 13.1-17.8) in the first time period to 32.5% (95% CI 30.0-34.9) in the last.

Statistical significance was not reached for five-year survival trends. For persons diagnosed at age 70 or older the trend seemed genuinely flat. For younger ages, the non-significance of the five-year survival trend might be caused by small numbers of persons available for analysis. Age-standardized survival five-years after diagnosis improved slightly from 2.13% (95% CI 1.16-3.61) in the first time period to 5.46% (95% CI 4.18-6.99) in the last time period.

Discussion

Pancreatic cancer incidence is rising in European countries, only partially explained by the obesity epidemic and the ever increasing use of diagnostic imaging[2]. Still, prognosis of pancreatic cancer remains dismal. Even if

Cantons	Diagnosis period	Number of cases			Person-years	% of pooled person-years
		Men	Women	Both		
ZH	1980-2010	1951	2097	4048	3049	34.6
SG/AR/AI	1980-2010	913	984	1897	1405	15.9
GE	1980-2010	764	810	1574	1396	15.8
BS/BL	1981-2008	532	531	1063	1054	12.0
TI	1996-2010	376	416	792	687	7.8
VS	1989-2010	383	379	762	639	7.3
GR/GL	1989-2010	331	340	671	412	4.7
FR	2006-2010	80	79	159	138	1.6
LU	2010	22	20	42	30	0.3
Total		5352	5656	11008	8810	100.0

Table1: Number of malignant pancreatic cancer cases used for survival analysis in the national dataset stratified by Swiss cantons.

treated by curative surgery followed by adjuvant gemcitabine and close monitoring only 21% of all patients live longer than 5 years [10].

In the past, therapeutic nihilism often reigned for patients with advanced disease [24], but also for patients with resectable disease. Surgery has not been offered to 40% of eligible patients [25] with stage I disease and adjuvant chemotherapy has been widely underused [26]. Much debated findings of better outcomes for patients undergoing surgery in high-volume centers [27, 28] have only partially lead to changes in referral patterns.

This is the largest dataset on pancreatic cancer in Switzerland. Over two decades mortality and outcome trends were

analysed and presented herein. The dataset does not allow to attribute any changes in outcome to a specific component in the multimodal management of pancreatic cancer. Advances have been made concerning imaging [7, 29], surgery, pathological assessment of the resected specimen [30], adjuvant therapy [9, 10] and systemic treatment for advanced disease [11, 12], and likely also palliative care [31].

It was among the scope of this analysis to assess if these improvements have resulted in increased survival in the different time periods compared.

This analysis has found important increases in one-year survival rates over the observed periods, irrespective of age and gender, with a doubling of age-standardized one-year survival rates.

Disappointingly, the rates of patients surviving beyond five years remain low, and no outcome improvements have been found in elderly patients over time. In younger patients this analysis showed a non-significant trend for an improvement in five-year survival rates from 2.4% to 7% over time.

Table 2: Observed and relative survival estimates after malignant pancreatic cancer diagnosis, with 95% confidence intervals by calendar period, age at diagnosis, years since diagnosis and sex. Data pooled from 13 Swiss cantons.

		Calendar period of diagnosis 1991 - 2000											
Years since diagnosis	Age in years	Observed survival %			Relative survival ¹ %								
		Men	Women	Both	Men	95% CI ³		Women	95% CI ³		Both	95% CI ³	
						LL	UL		LL	UL		LL	UL
1	20 - 59	27.1	30.4	28.4	27.3	22.8	31.9	30.5	24.8	36.3	28.5	25.0	32.2
	60 - 69	25.0	25.1	25.0	25.4	21.5	29.5	25.3	21.1	29.7	25.4	22.5	28.3
	70 - 79	15.2	18.3	16.8	15.9	12.9	19.2	18.7	15.6	22.2	17.3	15.1	19.7
	80+	8.3	9.4	9.0	9.4	6.3	13.2	10.3	7.9	13.1	10.0	8.1	12.3
5	20 - 59	7.0	4.9	6.1	7.2	4.7	10.3	5.0	2.7	8.3	6.3	4.5	8.5
	60 - 69	4.6	4.0	4.3	5.0	3.2	7.4	4.2	2.5	6.6	4.6	3.3	6.2
	70 - 79	0.9	1.5	1.2	1.2	0.4	2.6	1.7	0.8	3.1	1.4	0.8	2.4
	80+	0.6	0.4	0.4	1.1	0.2	3.7	0.6	0.1	2.1	0.8	0.3	2.0
1	stand. ²	20.3	22.3	21.2	20.8	18.8	22.8	22.7	20.4	25.0	21.7	20.2	23.2
5		3.6	3.0	3.3	3.9	3.0	5.1	3.2	2.2	4.3	3.6	2.9	4.4
		Calendar period of diagnosis: 2001 - 2010											
1	20 - 59	37.9	43.2	40.2	38.1	33.5	42.7	43.3	37.8	48.6	40.3	36.8	43.8
	60 - 69	33.1	37.2	35.0	33.5	29.8	37.3	37.5	33.3	41.7	35.3	32.5	38.1
	70 - 79	24.0	28.8	26.4	24.7	21.6	28.0	29.4	26.1	32.7	27.1	24.8	29.4
	80+	14.1	13.1	13.5	15.5	12.2	19.2	14.1	11.7	16.8	14.7	12.7	16.8
5	20 - 59	6.9	10.0	8.2	7.0	4.6	10.1	10.2	6.8	14.4	8.3	6.2	10.8
	60 - 69	5.6	6.5	6.0	6.0	4.0	8.7	6.8	4.4	9.9	6.3	4.7	8.3
	70 - 79	3.1	5.0	4.1	3.7	2.3	5.7	5.7	3.9	7.9	4.7	3.5	6.2
	80+	1.0	1.6	1.4	1.7	0.5	4.3	2.5	1.3	4.5	2.3	1.3	3.8
1	stand. ²	29.0	32.9	30.8	29.6	27.6	31.6	33.3	31.1	35.5	31.3	29.8	32.8
5		4.6	6.4	5.4	5.0	3.9	6.3	6.8	5.4	8.4	5.8	5.0	6.8

¹ Survival analysis using the complete approach

² Age-standardized using ICSS weights

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

		Calendar period of death or censoring								
		1990/1992	1993/1995	1996/1998	1999/2001	2002/2004	2005/2007	2008/2010		
Years since diagnosis	Age in years	RS ¹ % [95% CI]	RS ¹ % [95% CI]	RS ¹ % [95% CI]	RS ¹ % [95% CI]	RS ¹ % [95% CI]	RS ¹ % [95% CI]	RS ¹ % [95% CI]	APC ²	Linear trend p-value ³
Both sexes										
1	20-69	17.6 [14.3; 21.2]	20.0 [16.5; 23.8]	27.8 [24.0; 31.7]	33.6 [29.7; 37.6]	34.4 [30.5; 38.4]	37.1 [33.3; 40.9]	41.6 [37.8; 45.3]	4.4	<0.001
	70+	10.2 [8.20; 12.4]	7.93 [6.19; 9.93]	11.2 [9.12; 13.4]	12.5 [10.3; 14.8]	14.5 [12.3; 16.9]	20.9 [18.3; 23.5]	18.9 [16.6; 21.3]	3.1	<0.001
5	20-69	2.44 [1.16; 4.55]	4.23 [2.48; 6.69]	5.30 [3.30; 7.99]	6.08 [3.95; 8.85]	6.27 [4.34; 8.69]	7.90 [5.73; 10.5]	6.97 [4.98; 9.39]	5.5	0.690
	70+	1.50 [0.59; 3.27]	0.74 [0.28; 1.67]	0.54 [0.09; 2.06]	1.67 [0.84; 3.03]	0.93 [0.39; 1.96]	3.93 [2.61; 5.67]	2.67 [1.77; 3.87]	3.0	0.931
1	stand. ⁴	15.4 [13.1; 17.8]	15.0 [12.8; 17.4]	21.6 [19.2; 24.1]	24.9 [22.5; 27.4]	27.0 [24.5; 29.6]	31.4 [28.9; 34.0]	32.5 [30.0; 34.9]	3.8	<0.001
		5	2.13 [1.16; 3.61]	2.69 [1.66; 4.12]	3.72 [2.38; 5.52]	4.29 [2.95; 5.98]	4.03 [2.84; 5.54]	6.40 [4.94; 8.10]	5.46 [4.18; 6.99]	4.8

¹ RS (relative survival) analysed with period approach

² Annual percentage change

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

⁴ Age standardized using ICS weights

We can only speculate that pancreatic cancer is a generalized disease and more effective systemic treatments might be needed to improve these long-term outcomes.

Table 3: Trends in relative survival of pancreatic cancer cases pooled from 13 Swiss cantons for successive three-year calendar periods of follow-up.

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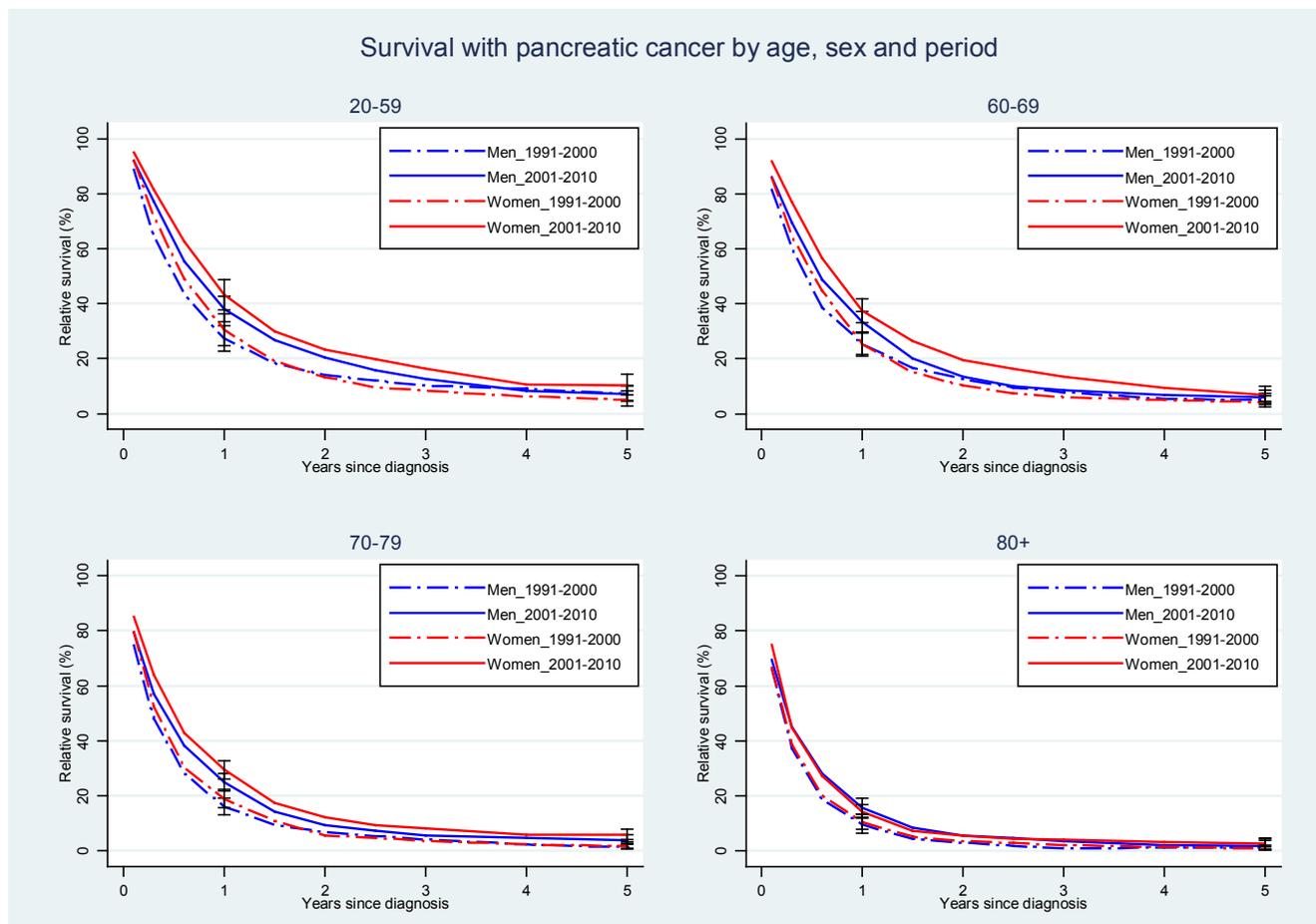


Figure 1: Age- and sex-specific one- and five-year relative survival curves, with 95% confidence intervals for two calendar periods (1991-2000 and 2001-2010) of cancer diagnosis. Pancreatic cancer cases were pooled from 13 Swiss cantons.

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

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