Trends in Survival from Cancer of the Corpus uteri in Switzerland

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Introduction

Swiss incidences as well as mortality rates for cancer of the corpus uteri have decreased slightly over the last 20 years [1]. In the recent past (2006-2010), about 16 in 100'000 women were diagnosed each year with endometrial cancer, while 3 in 100'000 died of their disease. The most common type of cancer is adenocarcinoma of the endometrial lining, which is the most common malignancy of the female genital tract in the Western world.

There are no simple and reliable ways to screen for uterine cancer, but due to symptoms at early stages of the disease, most diagnoses occure early enough that surgery alone may be adequate for cure. Diagnostic symptoms can be postmenopausal bleeding, pyometra or abnormal endometrial cells identified on Pap smear (25%) [2]. It is important to consider the diagnosis of endometrial cancer also in perimenopausal women with abnormal, intermenstrual or increasingly heavy periods [3]. In such patients also a history of anovulation due to obesity or polycystic ovaries should be seen as risk factor. The etiology of abnormal bleeding in endometrial cancer patients can be due to exogenous hormone intake (10-30%), atrophic endometritis/vaginitis (30%), endometrial cancers (15%), cervical/endometrial polyps (10-30%) and endometrial hyperplasia (5%). Less often, it can be due to cervical cancers, uterine sarcomas, urethral caruncles or trauma (10%).

Endometrial cancers are classified into type I (80%) and type II (20%) [4]. The most common type I is estrogen-related, low grade endometrioid, associated with atypical endometrial hyperplasia and is generally expressing estrogen and/or progesterone receptors (ER/PR positive). Risk factors are therefore either endogenous (obesity, anovulatory cycles, estrogen secreting tumors) or exogeneous estrogen exposure (unopposed hormone replacement therapy, Tamoxifen). Other risk factors include diabetes, hypertension, age above 60 years and certain genetic mutations. Type II cancers are completely unrelated to estrogen or endometrial hyperplasia, are ER/PR negative and present as high grade or poor prognostic cell types such as serous, clear cell and mucinous tumors. Patients are often multiparous and have a family history of breast cancer.

Preoperative diagnosis can be best performed via Pipelle de Cornier, which has shown a sensitivity of 99.6% in postmenopausal and 91% in premenopausal patients, with a false negative rate of only 10% [5]. Nevertheless, hysteroscopy and dilatation and curettage remains the gold standard, although the tumor grade is often underestimated. Transvaginal ultrasonography enables the visualization of the endometrial thickness, with endometrial cancers showing an endometrial thickness of 18.2 +/- 6.2 mm [6]. All cancers (100%) and 95% of patients with hyperplasia demonstrated an endometrial thickness of over 5 mm, so that the main rule needs to be: persistent postmenopausal bleeding in the setting of normal sonographic findings requires endometrial sampling [7, 8]. In premenopausal women with polypoid intrauterine lesions it might be helpful to use sonohysterography before hysteroscopic resection. The diagnostic gold standard, however, is still hysteroscopy and fractional curettings. It is important that endocervical curettings (ECC) are always performed first in order to exclude endometrial contamination and to rule out endocervical cancer involvement. However, false positive ECC are found in stage II cancers in 40 to 50%. If the diagnosis is expanded and the ECC are negative, a wedge or cone biopsy might be helpful.

Surgical treatment in endometrial cancer has improved during the past decade due to the development of minimally invasive techniques. Studies have shown that not only is a the total laparoscopic hysterectomy equally effective as the open surgical procedure [9], it is also associated with a significantly decreased risk of major surgical adverse events [10], improved quality of life [11] and cost-effectiveness [12].

In the present descriptive study, epidemiological information from tumour registries of several Swiss cantons have been combined to examine the development in survival pattern of patients diagnosed with primary endometrial 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 have transmitted cancer data to the NCD up to diagnosis date 31.12.2010. Cancer cases from thirteen cantons were pooled for this report: Basel-Stadt and Basel-Land (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

Cantons	Diagnosis period	Number of cases				Person-years	% of pooled person-years
		0-54	55-64	65-74	75 +		
ZH	1980-2010	449	860	1034	954	21192	29.7
SG/AR/AI	1980-2010	265	467	511	452	14053	19.7
GE	1980-2010	208	397	437	420	12008	16.8
BS/BL	1981-2008	195	430	508	453	13564	19.0
TI	1996-2010	96	163	146	173	2988	4.2
VS	1989-2010	130	184	176	163	4029	5.6
GR/GL	1989-2010	84	137	145	132	3204	4.5
FR	2006-2010	19	35	33	36	276	0.4
LU	2010	7	4	12	10	17	0.02
Total		1453	2677	3002	2793	71331	100.0

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

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 until 31.12.2010. We extracted 11'532 malignant cancer diagnoses for corpus uteri and unspecified parts of uterus (ICD-10 C54-C55) from 1980 to 2010. Only 3.5% of tumours had been assigned the unspecified anatomic site code (C55). For the cantons BS and BL the latest available year of diagnosis was 2008. We excluded all cases diagnosed at death (N=98) or with a death certificate as the only source of information (N=107). Case finding via death certificates was infrequent: between 1.1% and 3.8%, depending on cancer registry and diagnosis year. Patients with multiple primary tumours were included [13]. Excluded were N=1'402 or 12.2% of cases, because no active follow-up has been performed. Recent active follow-up was lacking for N=1'498 (13%) 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 31.12.2010 in the absence of reported death, 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). The maximal difference between conservative and possibly overestimated survival proportions in any of the analysis endpoints was +9.1% (5-year survival, age-group 75+, 1990-1999), and for age-standardized survival +5.7% (5-year survival, 1990-1999). A total of 9'925 cases remained for analysis, with 45% of observations uncensored (i.e. patients who have died).

Completeness of case ascertainment for cancer of the corpus uteri could be assessed in the cantons GE, GR/GL, SG/AR/AI, TI and VS and was found to be higher than 95% within one year after the date of diagnosis for diagnosis years 2005-2010 [14].

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 [15]. Expected cancer survival was estimated using the Ederer II method applied to all-cause mortality tables for the cantons combined [16]. All-cause death probabilities, transformed from age-, sex- and calendar year-specific death rates, were interpolated and smoothed using the Elandt-Johnson formula [17]. RS ratios were estimated using the strs command (version 1.3.7) [18] written for the Stata Statistical Software [19]. Partially complete survival analysis was used for the comparison in Table 2. Period survival analysis [20] 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 cancer of the corpus uteri from the International Cancer Survival Standards (ICSS) [21]. Standard weights for age groups were: 0.19 (0-54 years), 0.23 (55-64), 0.29 (65-74) and 0.29 (75+). Ninety-five percent confidence intervals (95% CI) were estimated using Greenwood's method [22] 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 [21].

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 [23].

Results

This report combines more than 71'000 person-years of survival experience for women diagnosed with malignant cancer of the corpus uteri (Tab. 1). The data pool contains increasing numbers of cancer registries over time. Until 1995, only 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, SG/AR/AI, GE and BS/BL contributed more than 85% of the total cases.

Ages at diagnosis ranged from 25 to 100 years. The median age at diagnosis was 67 years (interquartile range 58-76). Just five percent of patients were diagnosed below age 47. The age distribution of the patients remained stable over time. The most common anatomic sub site within the body of the uterus was the endometrium (73.2%), and the most common primary malignancy was adenocarcinoma (77.5%). Poorly specified carcinomas were <3%. Information regarding tumour detection was available from the cantons GE, VS and FR and revealed that symptoms were responsible for detection in 81% of the cases.

The survival experience of women diagnosed with cancer of the corpus uteri 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 women, diagnosed between 1990 and 1999, were 88.1% and 70.5% for one and five years after diagnosis, respectively. A decade later (2000-2009), the age-standardized RS had improved only slightly to 90.3% and 75.2%. The largest survival improvement of 9.4% was seen in the oldest age group (75+; 5 year-RS).

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). The annual percentage changes (APC) were not significantly larger than zero for short term RS (one year after diagnosis) as well as for long term survival (five years after diagnosis). Persons above 75 years of age at diagnosis seemed to have gained slightly (APC 0.7% for RS after five years, statistically not significant). The APC in age-standardized RS proportions were close to zero: 0.1% [CI -0.1 to 0.3%] and 0.2% [CI -0.2 to 0.7%] for one and five year survival, respectively.

Discussion

The main strength of our study is the large number of primary 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 has been taken into account. We cannot exclude distortion of our results by changes in the case mix over time.

There have been major improvements in the treatment of endometrial cancer over the past 30 years. These are

Years since diagnosis	Age in years	Observed survival %	95% CI [1] LL	95% CI [1] UL	Relative survival %	95% CI [1] LL	95% CI [1] UL
		Calendar period of diagnosis 1990 - 1999 [3]					
1	00 - 54	95.3	92.9	97.0	95.5	93.1	97.2
	55 - 64	92.9	90.9	94.5	93.4	91.3	95.0
	65 - 74	87.9	85.7	89.8	89.0	86.8	90.9
	75 +	73.3	70.2	76.1	78.1	74.8	81.1
	all ages	86.0	84.8	87.2	88.0	86.7	89.2
5	00 - 54	83.2	78.9	86.7	84.3	79.9	87.8
	55 - 64	79.6	76.3	82.5	82.1	78.7	85.0
	65 - 74	65.7	62.3	68.9	71.1	67.4	74.5
	75 +	36.2	32.5	39.8	51.9	46.7	57.1
	all ages	63.4	61.5	65.2	71.0	68.8	73.0
1	stand.[2]	86.2	85.0	87.4	88.1	86.8	89.3
5	stand.[2]	63.7	61.9	65.4	70.5	68.4	72.6
		Calendar period of diagnosis: 2000 - 2009 [4]					
1	00 - 54	95.7	93.6	97.0	95.8	93.8	97.2
	55 - 64	94.1	92.5	95.5	94.6	92.9	95.9
	65 - 74	90.9	89.0	92.5	91.9	90.0	93.5
	75 +	77.5	74.9	79.9	81.7	79.0	84.3
	all ages	88.6	87.5	89.6	90.3	89.2	91.3
5	00 - 54	86.2	82.8	89.0	87.1	83.6	89.9
	55 - 64	80.1	77.2	82.7	82.2	79.2	84.9
	65 - 74	71.1	68.0	74.0	76.0	72.7	79.0
	75 +	45.4	42.1	48.6	61.3	56.8	65.6
	all ages	68.2	66.5	69.8	75.3	73.4	77.1
1	stand.[2]	88.7	87.7	89.7	90.3	89.2	91.3
5	stand.[2]	68.6	67.0	70.1	75.2	73.4	77.0

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

[2] Age-standardized using ICSS weights

[3] Diagnoses 1990-1999 were followed-up to 31.12.2000

[4] Diagnoses 2000-2009 were followed-up to 31.12.2010

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

(a) the improvement in minimally invasive surgical techniques which are equivalent in outcome but reduced in morbidity; (b) the subspecialisation of gynaecologists as gynaecological oncologists, being experts for gynaecological cancer treatments; (c) the concentration of cancer treatment in cancer centres with multidisciplinary and multiprofessional care teams; and (d) the increase in knowledge about genetic causes of endometrial cancer which (e) has improved genetic counselling and preventive measures for patients with Lynch Syndrome.

Treatment is performed increasingly with specialist knowledge about disease development, genetic triggers and the need for individual tailoring of treatment as to the particular histological subtype of endometrial cancer. Endometrial cancers have been divided into two types by their genetic origin, epidemiology and behaviour and early stage cancers have been divided even further into three groups by their risk of recurrence, based on tumour grade, histological subtype, lymphvascular stromal and myometrial invasion. Up to date treatment requires fast triaging during surgery depending on the tumour extension into the myometrium and the histological subtype, thus asking for expert surgical and pathological assessment during the procedure. The surgeon needs to be able to add surgical procedures like lymphadenectomies to his routine hysterectomy and bilateral salpingo-oophorectomy (BSO) procedure.

Although these conditions are known to improve patient outcome [24], many gynaecologists still continue to operate on endometrial cancers in a private setting without expert help. Whilst this might be tolerable for a well differentiated endometrioid endometrial cancer which is

		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] [95% CI]
1	00-54	97.3 [92.5; 99.2]	97.8 [92.9; 99.5]	92.0 [85.8; 95.6]	94.0 [88.2; 97.1]	94.6 [90.0; 97.2]	96.6 [92.7; 98.5]	96.3 [92.1; 98.3]	-0.1 [-0.3; 0.2]
	55-64	94.4 [90.5; 96.9]	91.5 [86.6; 94.8]	94.3 [90.5; 96.7]	96.1 [92.6; 98.0]	95.1 [91.8; 97.3]	94.2 [90.9; 96.4]	94.1 [90.4; 96.5]	0.0 [-0.2; 0.2]
	65-74	90.6 [86.2; 93.8]	88.8 [84.2; 92.3]	89.5 [85.3; 92.7]	91.3 [87.3; 94.3]	91.2 [87.4; 94.0]	93.2 [89.7; 95.7]	92.7 [88.8; 95.5]	0.2 [0.1; 0.4]
	75 +	78.4 [71.9; 84.0]	76.9 [70.3; 82.6]	83.2 [77.1; 88.3]	81.6 [75.7; 86.6]	85.1 [79.7; 89.5]	82.8 [78.1; 86.8]	78.3 [72.5; 83.2]	0.2 [-0.4; 0.8]
5	00-54	88.0 [80.3; 93.1]	87.6 [80.1; 91.6]	83.5 [75.5; 89.2]	79.2 [70.7; 85.5]	79.8 [71.9; 85.8]	90.9 [85.4; 94.6]	89.3 [83.5; 93.3]	0.2 [-0.5; 0.9]
	55-64	82.3 [76.1; 87.3]	83.7 [77.4; 88.7]	81.9 [75.8; 86.9]	86.4 [80.7; 90.8]	84.3 [78.9; 88.8]	83.0 [77.9; 87.2]	80.1 [74.5; 84.7]	-0.1 [-0.5; 0.3]
	65-74	77.0 [70.2; 83.0]	73.9 [67.2; 79.8]	77.3 [70.8; 83.0]	71.9 [65.6; 77.5]	75.9 [69.8; 81.2]	83.2 [77.6; 87.9]	75.1 [69.1; 80.3]	0.2 [-0.6; 1.0]
	75 +	58.8 [49.0; 68.6]	50.3 [41.6; 59.2]	57.2 [47.0; 67.4]	64.2 [55.0; 73.1]	63.9 [55.3; 72.3]	66.9 [59.0; 74.5]	60.4 [52.9; 67.7]	0.7 [-0.5; 1.9]
1	stand.[3]	89.2 [86.7; 91.2]	87.7 [85.1; 89.9]	89.2 [86.8; 91.3]	90.1 [87.8; 92.0]	91.0 [88.8; 92.7]	91.0 [89.1; 92.6]	89.5 [87.3; 91.4]	0.1 [-0.1; 0.3]
5		75.0 [71.0; 78.6]	71.9 [68.1; 75.3]	73.7 [69.6; 77.4]	74.4 [70.5; 77.8]	75.1 [71.4; 78.3]	79.9 [76.6; 82.7]	74.7 [71.4; 77.6]	0.2 [-0.2; 0.7]

[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 for cancer of the corpus uteri. Cases were 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.

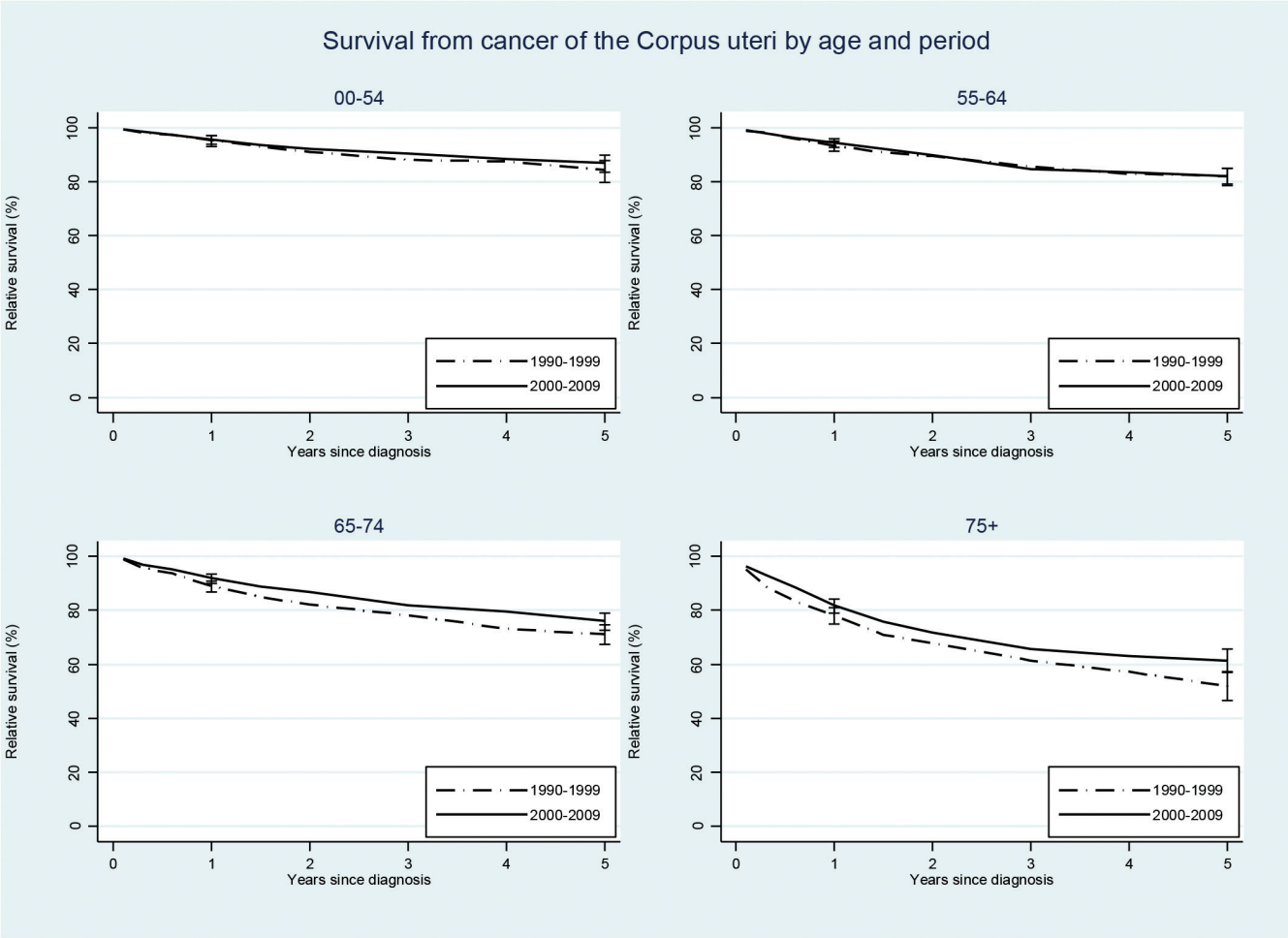

Figure 1: Age-specific relative survival curves for two calendar periods of diagnosis (1990-1999 and 2000-2009). 95% confidence intervals are shown for survival proportions at one and five years after diagnosis. Cases of cancer of the corpus uteri were pooled from 12 Swiss cantons (ZH, SG/AR/AI, GE,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

cured in a FIGO stage IA disease when a standard hysterectomy and BSO is performed, it is inadequate for a more advanced endometrioid cancer and particularly for highly aggressive histotypes like serous or clear cell cancers, which need to be operated like an ovarian cancer and should therefore be performed by trained gynaecological oncologists.

An increasing number of private gynaecologists are sending elderly patients with multiple comorbidities to gynaecological cancer centres for treatment due to the risk of complications. It is possible that this contributed to the observed slight improvement in outcome for elderly patients in the present descriptive study. This high risk group might benefit most from the expertise of a large interdisciplinary group, intensive care units, interprofessional meetings and particularly minimal invasive surgical techniques.

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

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