

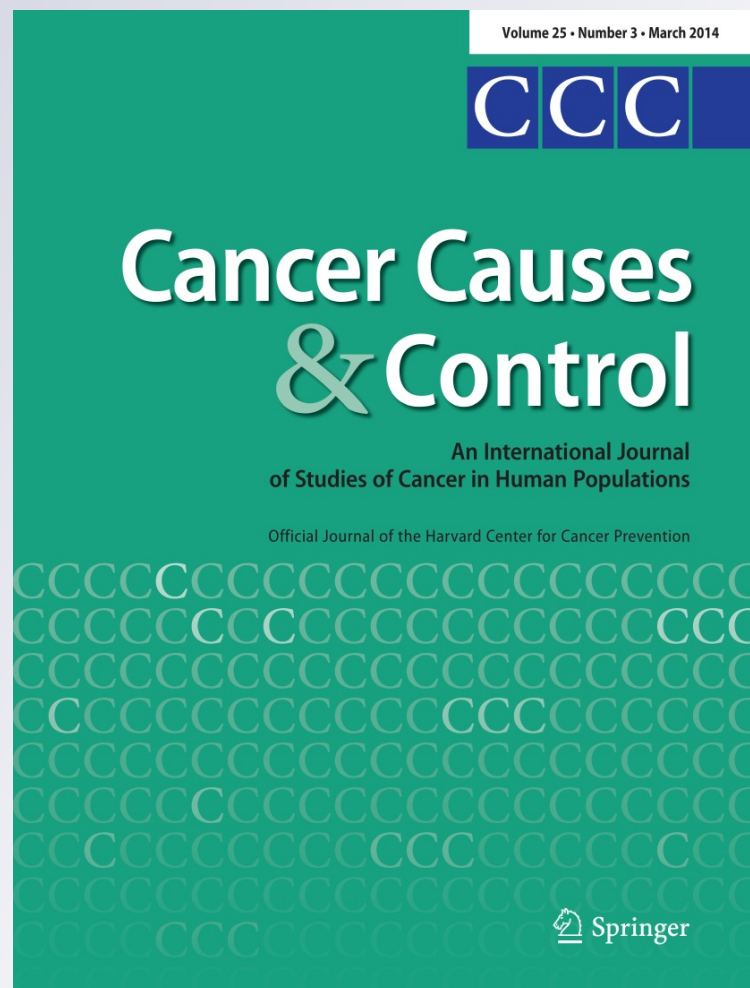
Site-specific proportion cured models applied to cancer registry data

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Site-specific proportion cured models applied to cancer registry data

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Abstract

Purpose Proportion-cured models were applied to evaluate their applicability on data from a relatively small cancer registry and to assess the up-to-date survival level of major cancer types in Tyrol, Austria.

Methods In total, the 25 most common types of cancer were analyzed with mixture cure models using the period approach for estimation of the proportion cured and median survival time of the fatal cases.

Results For several of the cancer types, no estimates could be obtained. The models converged for 14 sites among females and for 15 among males. The highest estimate of the proportion cured was found for cervix cancer (74.0 %; 95 % CI 64.4–83.6) and the lowest for male pancreas cancer (4.6 %; 95 % CI 0.2–9.0). The highest median survival of the uncured was 2.7 years (95 % CI 1.2–6.0) for male larynx cancer and the lowest 0.3 years (95 % CI 0.1–0.6) for male acute myeloblastic leukemia (AML).

Conclusions The estimates seem reliable for stomach, colon, rectum, pancreas, lung, cervix, ovary, central nervous system/brain and AML cancer and among men also for head/neck, esophagus, liver and kidney cancer. Altogether, it is demonstrated that even data from a regional cancer registry covering a rather small region can be utilized to derive up-to-date survival estimates of various cancer types, enabling monitoring of the development and changes in cancer treatment. Moreover, potentially this methodology is advantageously employable in any situation where the number of cancer cases is limited.

Keywords Site-specific cancer survival · Proportion cured · Survival time uncured · Cancer registry · Epidemiology

Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloblastic leukemia
CLL	Chronic lymphoid leukemia
CNS	Central nervous system
NHL	Non-Hodgkin lymphoma
NMSC	Non-melanoma skin cancer

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Introduction

Cancer is one of the main illnesses worldwide with an incidence of more than 11 million in 2004 [1]. The occurrence is rising with the increasing average age of populations, since most cancers affect older adults. With the diagnosis, the question concerning the patients' prospects arises; clinicians have mostly relied on 5-year

survival proportions or other long-term survival rates to indicate the risk of dying of a malignant neoplasm. However, such rates have some limitations when derived from cohort-based survival statistics, pertaining to cohort experiences over a large number of years. Thus, this kind of estimates can quickly become outdated, for example when cancer treatment undergoes changes. A rather novel methodology, based on period approach analysis that is similar to life table techniques, combines recent mortality experiences and incorporates estimates into so-called proportion cured statistical models [2]. Such cancer survival estimation can yield extra information and new insights. The main results from the models are estimates of the chances of getting cured and of the survival duration of those not cured, principally as a population-based statistic.

Although it is difficult to define “cure” when treating an individual cancer patient, there is a statistical alternative that can serve as a proxy. The excess mortality associated with a given disease is reflected in the so-called relative survival. The relative survival rate is calculated as the ratio of the survival of the patients with the specific cancer type and the expected survival of the general population [3]. For many cancer sites the relative survival curve levels off at some point in time after diagnosis. From this time point onwards the group still alive does not experience excess mortality anymore, compared to the general population. Thus, the proportion of patients with the particular cancer diagnosis who live this long is an estimate of the proportion cured and hence represents the chance of an individual from the original group, for the particular cancer diagnosis under consideration, of not dying from this cancer type. The complementary group consists of the so-called uncured patients and for these the median-survival time can be estimated.

Population-based survival studies (and among these typically those based on cancer registries), with which one can determine cancer incidence and prevalence, are indispensable to assess the effectiveness of health care systems [4]. Such studies enable to describe patient survival in a population, where clinical cancer studies usually aim to evaluate effects of interventions [5]. As De Angelis et al. [6] have pointed out cancer registries are most suited for relative survival analyses since patient selection bias is averted. Principally, cancer registries aim to document all cancer cases and thereby incorporate all cancer sites. Also small regional registries can be important sources of information on cancer survival and of particular public health relevance. The objective of this study was to evaluate the applicability of proportion cured models and to assess the level of survival for the major cancer types in Tyrol, a relatively small region with a well-established cancer registry.

Materials and methods

Tyrol-wide incidence and follow-up data were extracted from the population-based Cancer Registry of Tyrol, which was first setup in 1986 [7]. This registry's principle aim is to document all carcinoma cases in the Tyrolean population (with a life expectancy at birth of 84 years for females and 78 years for males) and stresses its obligation to achieve completeness (estimated at 97.5 %), unambiguity, and good quality data [8]. Of the total population of about 360,000 women and 345,000 men in 2009 (11 % foreigners, of which more than three-quarters of European nationality and the largest group being Germans), 1,525 women and 1,736 men had cancer, with a mean age at diagnosis of 65 years (21 % of the female and 13 % of the male patients under 50 years), and 612 women and 804 men died thereof (not including non-melanoma skin cancer [NMSC]). The rate of death certificate only cases was 0.2 % for females and 0.3 % for males. The mortality data are made available to the registry by Statistics Austria, the federal statistics office, and are considered to be complete.

Incidence data on 25 common cancer categories (excluding NMSC) for the diagnostic period of 1988–2009 were obtained, together with follow-up on the matching vital status. Only invasive malignant cancer diagnoses have been considered. Patients with a previous cancer diagnosis were also included (their survival was related to the current site), since such patients are usually diagnosed with tumors with inferior prognoses, so exclusion of these patients would otherwise lead to too high estimates of survival (5 % of the diagnoses were secondary carcinomas). Beginning with a total of 50,632 registered cases of the cancer categories under investigation for the period 1988–2009, 1,985 cases of death certificate only (3.9 %) were excluded. In addition, 16 cases were not included in the analyses because of incomplete data. Therefore, after these eliminations, 48,631 cases were available, of which 20,232 had observation time during the period 2005–2009, with altogether 71,162 person-years of follow-up. For 762 cases the follow-up duration of 0 days was set to 1 day for technical reasons. Close date was December 31, 2010.

Incidence data are presented as age-standardized incidence rates with 95 % confidence intervals (CI). The rates were calculated as the number of incident cases per 100,000 inhabitants, standardized using the SEGI standard population [9].

Relative survival was estimated as the ratio of the observed all-cause survival of the individuals with a certain cancer diagnosis and the expected survival of a sex- and age-matched group from the general population [5]. The observed all-cause survival in the cancer group was modeled as a function of the expected survival and the disease-

related relative survival function, based on the so-called mixture cure proportion model [10]:

$$S_o(t) = S_e(t) \{ \pi + (1 - \pi) S_u(t) \}$$

with: $S_o(t)$ observed survival, $S_e(t)$ expected survival, π proportion cured, $1 - \pi$ proportion uncured, and $S_u(t)$ survival function for the uncured individuals.

In the current study the ‘uncured’ survival function was modeled with a Weibull distribution with two parameters [10]. Although theoretically the cure proportion is only reached asymptotically, it can be estimated as the point in time where the relative survival curve is seen to level off, usually between 5 and 10 years after diagnosis. If the curve does not converge appropriately within the time range of the data, the proportion estimate is extrapolated. The cure model parameters are estimated using maximum likelihood [6], with an extension to model both parameters using the Weibull distribution [11]. The median survival time of cancer patients who die (the uncured, fatal cases) was estimated through the approach suggested by Brenner et al. [2]: all diagnosed cases over the period were used in the modeling, irrespective of the length of their follow-up. The period of diagnosis was categorized into 5-year periods in the statistical models. Model fit was assessed through visual inspection, comparing the survival plots from the cure model and the long-term relative survival.

The proportion-cured patients and the median survival of uncured cases were estimated using the period approach with the 5-year observation window 2005–2009 and a maximum of 10 years of follow-up, to attain sufficient numbers of cases and enough precision. There were no constraints on the time at which a cured proportion would have to be reached.

The statistical analyses were performed with Stata 10. The mixture cure proportion models were fitted with the `strsmix` command (version 1.0.2) [11].

Results

In Tyrol 2005–2009 there were 7,582 female and 8,562 male cancer cases, some 13 % more males (Table 1). The most common sites are breast ($n = 2,063$, 27 % of all cancers among females) and prostate cancer ($n = 2,190$, 26 % of all cancers among males). Other common carcinomas are lung ($n = 598$ [8 %] and $n = 1,147$ [13 %]), melanoma ($n = 637$ [8 %] and $n = 608$ [7 %]), and colon cancer ($n = 569$ [8 %] and $n = 663$ [8 %]). The overall incidence rate is 244 and 317 per 100,000 for women and men, respectively.

The estimated proportion cured and the median survival time of the uncured are listed in Table 2. For several sites no estimates are available because the models failed to

converge, meaning the modeled survival curves did not level off. This was the case for melanoma, breast, corpus uteri, prostate, testis, thyroid gland, low risk non-Hodgkin lymphoma (NHL) and chronic lymphoid leukemia (CLL) cancer, and for females also larynx, kidney and acute lymphoblastic leukemia (ALL) cancer. For most of these sites relative survival is above 80 %. The three most frequent types, for which no estimates were obtained, that is melanoma, breast and prostate cancer, are presented in Fig. 1.

For the sites with obtained estimates, there is a wide range of proportion cured from a mere 10 % for esophagus (males), liver (males), pancreas (see Fig. 2) and acute myeloblastic leukemia (AML) (females) cancer; slightly higher for stomach, liver (females), lung, CNS/brain and AML (males) cancer; intermediate for head/neck, esophagus (females), colon, rectum (see Fig. 2), larynx (males), ovary, bladder and high risk NHL (females) cancer; and up to some 70 % for cervix, kidney (males), high risk NHL (males) and ALL (males) cancer. For the majority of cancer sites the differences in the estimates between men and women are <10 % for the proportion cured. However, for head/neck cancer the difference is 17 %, for liver cancer 14 %, and for bladder cancer 15 %. For esophagus cancer and high risk NHL the difference is much larger, 29 % and 28 % respectively. Overall for all sites combined (but with a differing site mix), there is a lower proportion cured for females with 60.3 % (95 % CI 58.0–62.6), compared to 64.6 % (95 % CI 62.6–66.5) for males.

Concerning the median survival time of the uncured, the worst prospects of <1 year applied to patients with esophagus, stomach, liver, pancreas (see Fig. 2), lung, bladder (females), CNS/brain, ALL (males), and AML cancer. On the other hand, head/neck, colon, rectum (see Fig. 2), larynx (males), cervix, ovary, kidney (males), bladder (males), and high risk NHL cancer came up with longer survival. Apart from colon, rectum and high risk NHL cancer, the difference in survival time between uncured men and women was only minor. In general, males had a slightly lower median survival compared to female fatal cases of a little less than 1 year; the women had an estimate of about 16 months.

Discussion

We analyzed 25 major cancer sites, for males and females separately, and were able to obtain up-to-date estimates for the period of 2005–2009 of the proportion cured and of the median survival time of the uncured for 17 of these sites, even though the data are from a rather small population. The worst outcome in terms of the lowest proportion cured was found for male esophagus, male liver,

female AML, and male and female pancreas cancer. On the other hand, for the diagnoses of cervix, male kidney, male high risk NHL, and male ALL cancer patients have about 70 % chance of becoming cured. The estimated survival time of the fatal cases according to cancer site generally showed congruent results, the median survival being low with about 6 months for esophagus, stomach, pancreas, lung, ALL, and AML cancer and high at 2 years and more for colon, rectum, larynx, ovary, and high risk NHL cancer.

There is only a limited number of studies with comparable results; most frequent are those concerning colon cancer. Such data from Finland, Sweden, and France, based on national or regional population-based cancer registries, gave estimated proportions cured of around 50 % and median survival times of the uncured of a little over 1 year [6, 12–15], slightly lower than our estimates. In an EURO-CARE study involving various cancer sites, the most recent estimates for the period 1997–1999 for colon and rectum cancer together were 49 % and 2.1 years,

Table 1 Number of cancer cases and incidence rates (ASIR) in Tyrol with date of diagnosis between 2005 and 2009 by cancer site, stratified by sex

Cancer site	ICD 10	Females			Males		
		n	ASIR	95 % CI	n	ASIR	95 % CI
Head/neck	C00-14,C30-31	161	5.1	4.3–6.0	360	14.4	12.9–15.9
Esophagus	C15	23	0.7	0.4–1.0	93	3.6	2.8–4.3
Stomach	C16	261	6.3	5.5–7.2	344	11.1	9.9–12.4
Colon	C18-C19	569	14.6	13.3–16.0	663	22.2	20.5–24.0
Rectum	C20-C21	293	8.3	7.2–9.3	356	12.9	11.6–14.3
Liver	C22	78	2.1	1.5–2.6	176	6.1	5.2–7.1
Pancreas	C25	260	6.2	5.4–7.1	242	8.3	7.2–9.3
Larynx	C32	20	0.7	0.4–1.1	135	5.1	4.2–6.0
Lung	C33-C34	598	19.0	17.3–20.6	1,147	41.0	38.5–43.4
Melanoma	C43	637	25.2	23.1–27.3	608	25.8	23.7–28.0
Breast	C50	2,063	69.6	66.4–72.8	13	0.5	0.2–0.8
Cervix	C53	228	8.8	7.6–9.9	–	–	–
Corpus uteri	C54	362	11.0	9.8–12.3	–	–	–
Ovary	C56-C57	313	9.3	8.2–10.4	–	–	–
Prostate	C61	–	–	–	2,190	78.8	75.5–82.2
Testis	C62	–	–	–	181	9.3	7.9–10.7
Kidney	C64-C65	183	5.6	4.7–6.6	285	10.7	9.4–11.9
Bladder	C67	106	2.6	2.0–3.2	322	10.4	9.2–11.5
CNS/brain	C47,C70-C72	104	3.9	3.0–4.7	131	5.5	4.5–6.6
Thyroid gland	C73	291	12.4	10.9–13.9	129	5.6	4.6–6.6
NHL high	^a	105	3.0	2.3–3.7	134	5.0	4.1–5.8
NHL low	^b	116	3.7	2.9–4.4	143	5.4	4.5–6.3
CLL	^c	73	2.1	1.5–2.6	120	4.0	3.3–4.7
ALL	C91.0	19	1.7	0.8–2.6	26	2.3	1.3–3.2
AML	^d	76	2.6	1.9–3.3	77	3.1	2.3–3.8
Other	^e	643	19.4	17.7–21.2	687	26.1	24.1–28.2
Total	^f	7,582	244.0	237.9–250.1	8,562	317.1	310.2–324.1

ALL acute lymphoblastic leukemia, AML acute myeloblastic leukemia, ASIR age-standardized incidence rate (per 100,000 inhabitants, SEGI weights), CI confidence interval, CLL chronic lymphocytic leukemia, CNS central nervous system, n number, NHL non-Hodgkin Lymphoma

^a C82.2, C83.3–C83.5, C83.7, C91.5

^b C82.0, C82.1, C82.7, C82.9, C83.1, C83.2, C84.0–C84.4, C88.0, C91.3, C91.4, C91.7

^c C83.0, C91.1

^d C92.0, C92.2–C92.5, C93.0, C93.2, C94.2

^e All codes in the range C00–C96 and D45–D47 not explicitly contained in one of the sites listed above (excluding non-melanoma skin cancer)

^f All codes in the range C00–C96 and D45–D47 (excluding non-melanoma skin cancer)

Table 2 Estimated proportion cured and median survival time of the uncured in Tyrol during 2005–2009 by cancer site, stratified by sex

Cancer site	Sex	Cured		Uncured	
		Proportion (%)	95 % CI	Median survival (years)	95 % CI
Head/neck	female	55.5	39.4–71.5	1.7	0.8–3.7
	male	38.9	29.4–48.4	1.9	1.4–2.8
Esophagus	female	38.6	1.3–75.8	0.6	0.1–2.9
	male	9.8	1.9–17.6	0.5	0.2–0.9
Stomach	female	27.8	19.1–36.4	0.5	0.3–0.9
	male	22.0	15.6–28.4	0.7	0.5–1.0
Colon	female	61.1	53.4–68.9	1.2	0.8–1.8
	male	51.1	38.4–63.9	2.1	1.1–4.1
Rectum	female	55.4	42.7–68.1	1.1	0.5–2.7
	male	57.6	46.3–68.9	2.2	1.3–3.8
Liver	female	24.6	8.6–40.6	0.7	0.3–1.2
	male	10.9	0.0–22.0	0.9	0.4–1.7
Pancreas	female	10.1	3.8–16.4	0.5	0.3–0.7
	male	4.6	0.2–9.0	0.5	0.3–0.7
Larynx	female	a	a	a	a
	male	61.4	43.7–79.2	2.7	1.2–6.0
Lung	female	14.0	9.7–18.3	0.6	0.5–0.8
	male	14.3	11.1–17.6	0.6	0.5–0.8
Melanoma		a	a	a	a
Breast		a	a	a	a
Cervix	female	74.0	64.4–83.6	1.4	0.7–2.9
Corpus uteri		a	a	a	a
Ovary	female	40.0	31.8–48.3	2.0	1.5–2.7
Prostate		a	a	a	a
Testis		a	a	a	a
Kidney	female	a	a	a	a
	male	71.7	61.0–82.3	1.1	0.5–2.3
Bladder	female	42.4	24.5–60.3	0.8	0.6–1.2
	male	56.9	44.4–69.3	1.2	0.6–2.5
CNS/brain	female	17.1	7.4–26.7	0.6	0.3–1.2
	male	21.7	9.8–33.6	0.9	0.6–1.6
Thyroid gland		a	a	a	a
NHL high	female	44.5	0.0–141.3	3.9	0.0–998.0
	male	72.3	42.2–102.5	2.3	0.2–34.6
NHL low		a	a	a	a
CLL		a	a	a	a
ALL	female	a	a	a	a
	male	67.7	34.4–101.0	0.5	0.3–1.2
AML	female	8.3	0.0–17.6	0.4	0.3–0.8
	male	15.0	1.3–28.7	0.3	0.1–0.6
All sites ^b	female	60.3	58.0–62.6	1.3	1.1–1.5
	male	64.6	62.6–66.5	0.8	0.7–1.0

ALL acute lymphoblastic leukemia, AML acute myeloblastic leukemia, CI confidence interval, CLL chronic lymphocytic leukemia, CNS central nervous system, NHL non-Hodgkin lymphoma

^a Models failed to converge, therefore no estimates available

^b All cancer sites except non-melanoma skin cancer

respectively [16]. Similar estimates of the cured proportion were found in Canada, with 51 % for colon and 49 % for rectum cancer [17]. From the Norwegian Cancer Registry the estimates were very similar to ours, apart from our

somewhat lower estimate concerning rectum cancer among females [18]. A comparable figure was also found in another EUROCORE study, with a period estimate of 10-year age-adjusted relative survival (a surrogate for the proportion cured) for colon and rectum cancer for Europe as a whole in the period 2000–2002, amounting to 53 % [19]. Thus, the results found here for colon and rectum cancer seem consistent with other findings.

Comparing our results for the other cancer sites with those from other multi-site studies with proportion cured [16–18] and a study with 10-year relative survival estimates [19], most figures are rather similar. The 39 % cure proportion we found among female patients with esophagus cancer appears to be quite high, which also applies for our 25 % estimate for female liver cancer. Our estimates are derived from a small number of cases and are therefore rather imprecise; we doubt the validity of these results. Also, the cure estimate of 72 % for men with kidney cancer seems relatively high. On the other hand, our estimates for bladder cancer seem to be somewhat low with 42 % and 57 %, respectively, for females and males, with rather broad confidence intervals indicating imprecision, probably related to changes in the definition of this cancer type as already addressed regarding England [20]. Similar objections

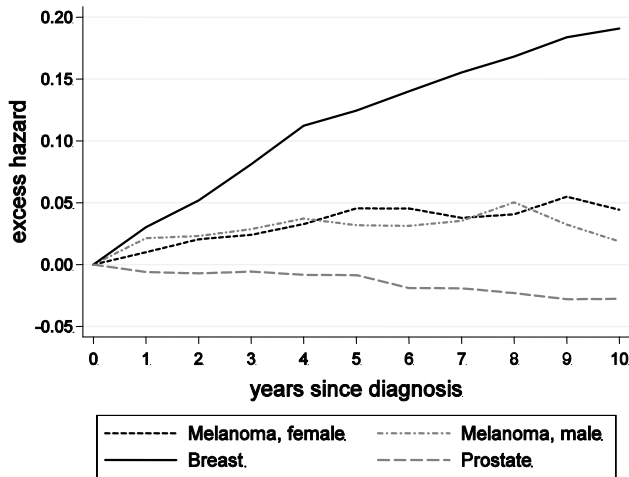


Fig. 1 Excess hazard ^a(1 - relative survival) of female and male melanoma, breast, and prostate cancer according to duration since diagnosis in Tyrol during 2005–2009

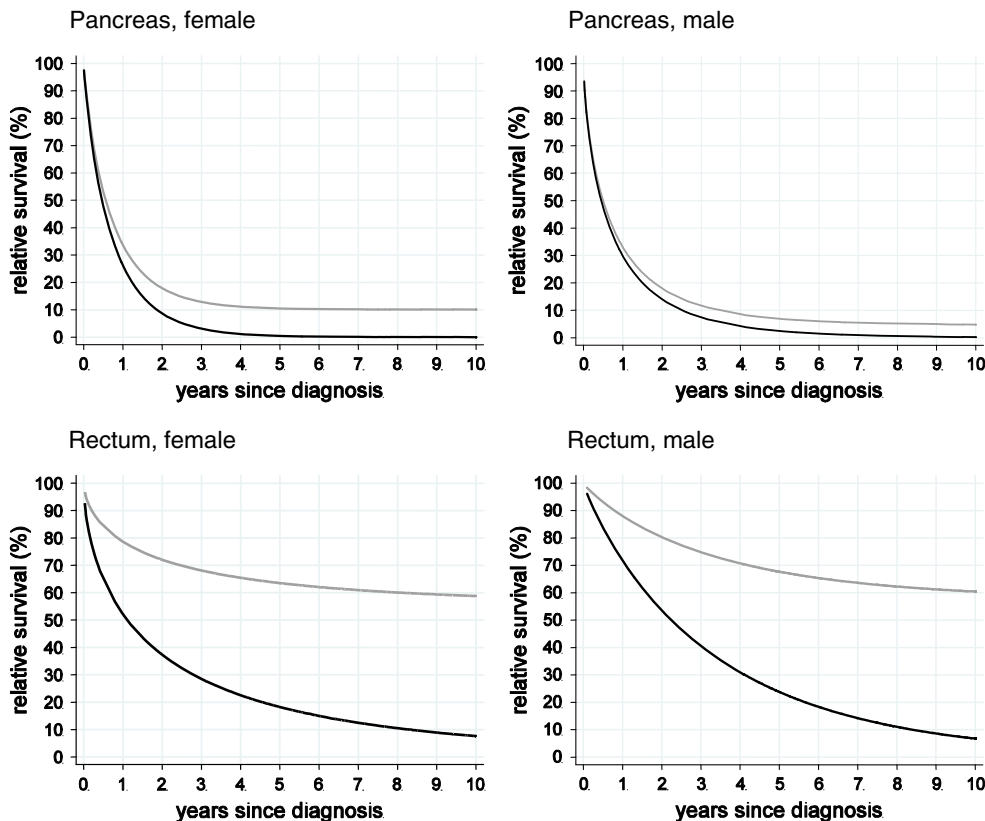
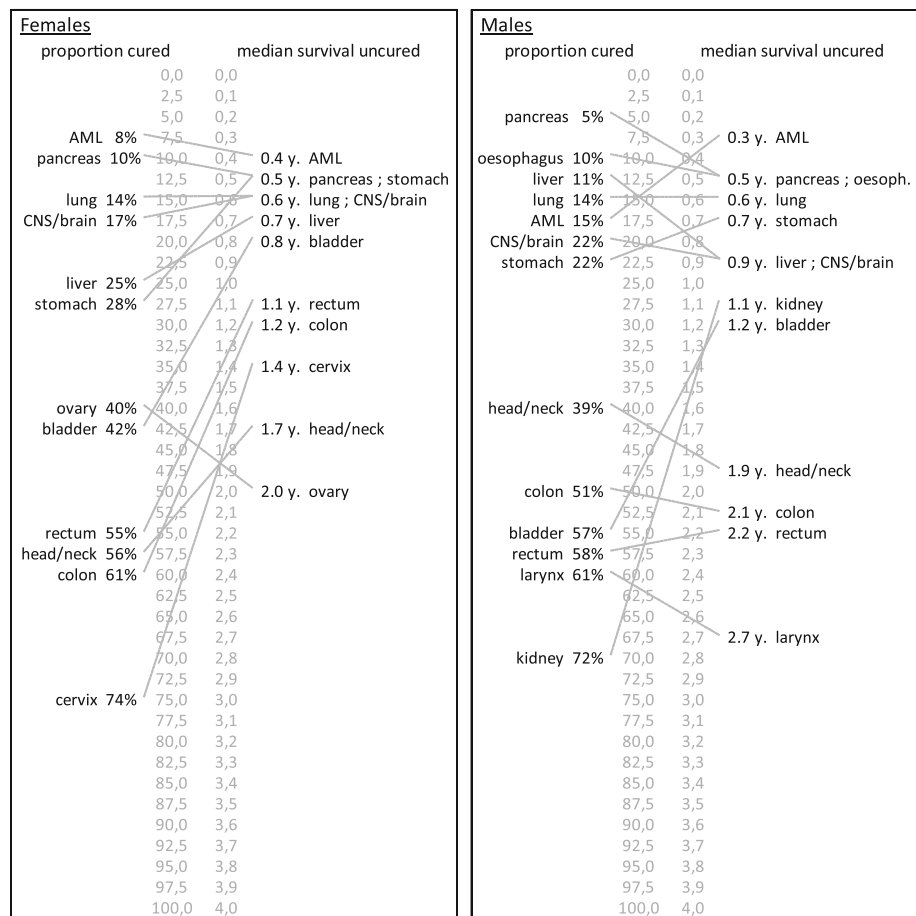


Fig. 2 Estimated relative survival, overall (upper curve, gray) and of the uncured (lower curve, black), for pancreas and rectum cancer according to duration since diagnosis in Tyrol during 2005–2009, stratified by sex

Fig. 3 Estimated levels of the proportion cured (left, in %) compared to levels of the median survival time of the uncured (right, in years) in Tyrol during 2005–2009 by cancer site, stratified by sex
^aacute myeloblastic leukemia, central nervous system
^a(estimates of esophagus cancer (females), high risk non-Hodgkin lymphoma, and acute lymphoblastic leukemia are left out because of wide confidence intervals)



regarding the estimates are also warranted for head/neck cancer among women, for larynx and ALL cancer among men, and for high risk NHL among both sexes. Furthermore, compared to the results presented by Le et al. [21], our male ALL estimate of 68 % seems to be quite high versus the 20 % found there. For AML one study, split up into broad age groups and without sex-differentiation, found estimates compatible with ours [22]. Overall we believe, also in consideration of the precision of our estimates, that the proportion cured estimates for stomach, colon, rectum, pancreas, lung, cervix, ovary, CNS/brain, and AML cancer to be reliable and valid and in addition also those of males with head/neck, esophagus, liver, and kidney cancer.

Little information was found in other studies to compare our estimates for the survival time of the uncured with [16, 18, 21, 22]. Our estimates for kidney, bladder, ALL, and AML cancer seem rather low and among women also those for colon and rectum cancer, possibly in part due to imprecision of the estimates. This uncertainty is also a problem with high risk NHL and, to a lesser extent, female head/neck, female esophagus and male larynx cancer. All in all, our population seems to be slightly worse off concerning the uncured survival time, but slightly better as for

the cure proportion. Possibly, a relatively large proportion of cancer cases are cured, leaving a somewhat small group of uncured cases with a rather bad prognosis.

When comparing the relative levels of the proportion cured with that of the survival time of the uncured (Fig. 3), it would seem that the ranks differ considerably for females for the cancer sites stomach, cervix and ovary, and for males for the sites liver, kidney and AML. The precision of the estimates does not seem to play a role here. More research in this field might bring new insights about our estimates, especially concerning the uncured survival time.

Based on our findings, it does not seem feasible to propose a rule of thumb with a certain number of cases needed to get reliable results (even under the condition that estimates can be calculated). For example, with AML we had rather small numbers but seemingly appropriate estimates, while on the other hand high risk NHL gave unsatisfactory results despite much more cases. One must obviously specifically consider each cancer type and its heterogeneity, especially regarding survival diversity among patients. Also, the level of survival should be taken into account, since when it is high there might not be enough fatal cases for a proper model fit.

A limitation of the applied methodology is that for several cancer sites no estimates could be attained, because the models did not converge. Especially unfortunate is that this also concerns melanoma, prostate and breast cancer, comprising about a third of all cancer diagnoses in Tyrol. However, this phenomenon seems to be inherent for these types of cancer and has been related to the fact that medical cure can sometimes only be established after decades [18], and for example for breast cancer it has been suggested it is to be considered a truly chronic disease that is in some cases never really cured [23]. But also methodological reasons concerning parametric distributions applied and a high cure fraction have been put forward [11]. Of course, with the small registry involved, uncommon sites could not be studied because of insufficient statistical power and some sites with more, but still a limited number of cases, gave imprecise estimates. Also, some cancer types are rather heterogeneous, but further differentiations were not possible due to the lack of extra data and the limited numbers of cases.

This study also has several strengths, especially the high quality and completeness of the data, thereby enabling valid survival estimates. Although for some sites we were not able to obtain estimates, there is a large range of cancer types for which we did have consistent and plausible results. An advantage, in a methodological sense, of the use of the concept of relative survival is that information on death causes is not needed. In addition, the estimates achieved with the models as applied here are up-to-date survival figures.

Thus far, few studies have used proportion cured statistical models, probably due to the novelty of the method, the necessity of good quality population-based registry data, and the uncertainty about its applicability. We have shown that this methodology can be beneficially applied on data from a relatively small cancer registry, having a limited number of cases. This also opens up possibilities for larger registries to investigate smaller cancer groups in more detail, e.g. like with childhood cancer for which Sposto has already shown methodological interest [24], or concerning childhood leukemia [25] and ALL with age under 25 years [26]. Another possibility relates to differentiation according to stage and histology of cancer types. In our registry it will additionally be possible to study time trends and evaluate cancer treatment in Tyrol, also in comparison to other regions.

The general public health relevance of such results as shown here is clear, especially in the field of monitoring the developments of treatment of cancer patients. It concerns an easy and understandable notion from which clinicians working in this field can learn how effective their efforts are and how the improvement of treatment regimes is progressing. But also for patients there is a clear

relevance, although the development of prognostic research still has to be furthered, taking into account competing risks and predictors such as age and tumor stage. At a basic level, the proportion cured of a certain disease is an approximation of the risk of not dying from that disease, therefore it is a partial answer to the question “what are my odds?”.

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Conflict of interest The authors declare that they have no conflict of interest.

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