Cure of cancer for seven cancer sites in the Flemish Region

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Cumulative relative survival curves for many cancers reach a plateau several years after diagnosis, indicating that the cancer survivor group has reached “statistical” cure. Parametric mixture cure model analysis on grouped relative survival curves provide an interesting way to determine the proportion of statistically cured cases and the mean survival time of the fatal cases in particular for population-based cancer registries. Based on the relative survival data from the Belgian Cancer Registry, parametric cure models were applied to seven cancer sites (cervix, colon, corpus uteri, skin melanoma, pancreas, stomach and oesophagus), at the Flemish Regional level for the incidence period 1999–2011. Statistical cure was observed for the examined cancer sites except for oesophageal cancer. The estimated cured proportion ranged from 5.9% [5.7, 6.1] for pancreatic cancer to 80.8% [80.5, 81.2] for skin melanoma. Cure results were further stratified by gender or age group. Stratified cured proportions were higher for females compared to males in colon cancer, stomach cancer, pancreas cancer and skin melanoma, which can mainly be attributed to differences in stage and age distribution between both sexes. This study demonstrates the applicability of cure rate models for the selected cancer sites after 14 years of follow-up and presents the first population-based results on the cure of cancer in Belgium.

Introduction
Cancer survival in population-based research is mostly evaluated on the basis of estimated survival proportions at a given time since diagnosis, often 5 or 10 years. Additional insights into cancer survival can be obtained from the estimation of the proportion of patients that can be considered “statistically” cured. Compared to the general population, a cohort of cancer patients experiences an excess mortality, which will decrease with time when cancer cure is present. The group of cancer survivors can be considered statistically cured when they experience the same mortality as matched individuals from the general population.1 This concept of statistical cure applies at the group level only and is not equal to medical cure at the individual level, which is achieved when no cancerous cells remain in the body.

The remaining cancer patients, the fatal cases, experience an excess death hazard rate with respect to the general reference population. The cure of cancer within a population can therefore be quantified by the proportion cured and the mean or median survival time of the fatal cases.

Cure of cancer can be evaluated with mixture cure models, which assume that the studied population is a mixture of susceptible individuals (fatal population), who may experience the event of interest (death due to cancer) and non-susceptible individuals (cured population) that will never experience it. Early work on mixture cure models was done by Boag2 and Berkson and Gage.3

Cure of cancer can be estimated from the net survival, which is the probability of survival in a hypothetical world where the cancer under study is the only possible cause of death.1 The net survival can be estimated from a cause-specific analysis or by the relative survival.4 In the former case, the specific cause of death needs to be known to identify if the death is due to the cancer or not. In population-based cancer studies relative survival is often used as it provides an estimate of the net survival, without the need for information on cause of death, which may not be available in the Registry or inaccurately reported.5–7 The matching with the general population allows the relative survival to take into account direct (cancer death, treatment) and indirect (suicide, treatment side effects, development of other diseases, etc.) causes of death due to the cancer.1

Relative survival, RS(t), in a group of cancer patients is the ratio of the observed survival, St(t), in the cancer patient...
group and the expected survival, \( S_0(t) \), of a comparable group from the general population: \( R(t) = S(t)/S_0(t) \). This group is matched to the cancer patient group on a set of main factors influencing survival (age, gender, calendar period, etc.). Aggregated relative survival data can be easily derived from cancer registry data and national life tables. If a cured proportion is present for a given cancer, the decrease of the relative survival proportion with survival time will eventually level off and a horizontal plateau is reached, demonstrating that the cancer survivor group attained a similar death hazard as the general population and is considered statistically cured.

Mixture cure models applied to aggregated relative survival curves involve a non-linear parametric fit on the relative survival data. Such models were applied in the EUROCARE study on colon cancer, and the EUROCARE-4 study comparing between-country differences in the cure of cancer. Other methods to evaluate the cure of cancer contain among others the mixture\(^{10,11}\) and non-mixture cure model\(^{11}\) analysis using individual level data on all-cause mortality. Competing risk approaches for cure analysis are also developed.\(^{12}\) The framework of flexible parametric survival models has been applied to cure models, which has recently been extended with competing-risks theory to incorporate non-cancer deaths.\(^{14}\)

The focus of this manuscript is to implement the mixture cure model used in the abovementioned EUROCARE studies\(^{8,9}\) to the Belgian Cancer Registry data. Mixture cure models on seven cancer sites were applied using the relative survival data for the Flemish Region to explore gender and age differences. This work reports the first results on the cure of cancer for Belgium.

**Methods**

**Cancer cases**

Data was obtained from the Belgian Cancer Registry (BCR), which is based on the compulsory registration of cancer cases diagnosed since 2004 at the national level and since 1999 for the Flemish Region. Flemish residents older than 14 years diagnosed with at least one primary malignant tumour in the period 1999–2011 were considered. Missing dates of diagnosis were set to the 15th day of the diagnosis month if month but not day of diagnosis was known and to the 1st of July when only the year of diagnosis was known. Patients without a national social security identification number (INSZ/NISS) were excluded as well as patients who were lost to follow-up or died at the date of incidence. Patients lost to follow-up after the incidence date were censored at the time of the last known contact alive. Follow-up was complete up to the 1st of July 2013. The vital status was derived from linkage with the Belgian Crossroads Bank for Social Security. Since 2006, cancer registration in Belgium is compulsory for the oncological care programs and the laboratories for pathological anatomy, forming the 2 main sources for the Belgian cancer registry. Registration errors in one of these data streams can induce false positive registrations. Therefore registrations received by the cancer registry by only one of these data streams are subjected to additional validation procedures and active trace back to the hospitals to eliminate false positive cases. Furthermore, microscopical confirmation of malignancy is available for 97% of the cancer cases in the Belgian Cancer Registry. The remaining 3% of cases (clinically and technically – but not microscopically – confirmed cancer cases) also undergo an additional verification procedure by contacting the corresponding hospitals to maximally eliminate false positive registrations. If false positive cases are present in the cure model analysis, they do not experience the excess mortality due to the cancer and will therefore artificially increase the estimated cured proportion. The practical impact for our analysis is low due to the small fraction of potential false positive registrations.

Seven cancer sites were considered for the cure model analyses: cervix (ICD-10 C53), colon (ICD-10 C18), corpus uteri (ICD-10 C54), skin melanoma (ICD-10 C43, cases with unknown localization (ICD-O-3 C80.9) were excluded), pancreas (ICD-10 C25, neuroendocrine cases excluded (morphology codes 8150–8159 and 8240–8249), stomach (ICD-10 C16.1–9) and oesophagus (ICD-10 C15.0–9-C16.0). These seven cancer sites were pre-selected from the first publication of cancer survival results in Belgium\(^{15}\) as potential candidates for which a follow-up of 14 years might be sufficient to achieve statistical cure, i.e. a plateau in the relative survival curve appears to be reached. The presence of a cured plateau in the relative survival curve is advised by Yu et al.\(^{16}\) to obtain reliable estimates of cancer cure.

The distribution of age, stage and histological subtype at diagnosis and their evolution with incidence period is given in Table S1 of the supplementary info. If an important change with incidence period is present in these characteristics, the obtained estimated cured proportions and mean
survival times of fatal cases will represent an average over the incidence period.

Relative survival
The expected survival was estimated from the Flemish life tables stratified by age, gender and calendar time. Relative survival was calculated using the Ederer II method aggregated in time intervals of 0.5 year from 0 to 14 years of follow-up. Survival time was calculated from the incidence date to the date of death or until the last known vital status. For each of the selected cancer sites the marginal relative survival was estimated as well as the relative survival by gender or by age strata. Cure models were applied to each of the strata individually.

Cure models
According to the mixture cure model, the overall observed survival function $S(t)$ is a weighted sum of the survival function $S_0(t)$ for the “cured” fraction and the cancer specific survival function $S_1(t)$ for the “uncured” patients:

$$S(t) = \pi S_0(t) + (1-\pi) S_1(t),$$  \hspace{1cm} (1)

with $\pi$ the cured proportion. The cured proportion experiences the same death hazard $h_0(t)$ as the reference population, while the death hazard for the fatal fraction $h_1(t)$ equals the reference hazard $h_0(t)$ with an excess death hazard $h_e(t)$ added to it:

$$h_1(t) = h_0(t) + h_e(t).$$  \hspace{1cm} (2)

The relation between the survival function for the fatal fraction $S_1(t)$ and the hazard $h_1(t)$ is

$$S_1(t) = \exp\left(-\int_0^t h_1(u) du\right) = \exp\left(-\int_0^t h_0(u) du\right) \exp\left(-\int_0^t h_e(u) du\right) = S_0(t) S_e(t).$$  \hspace{1cm} (3)

The survival function for the fatal fraction thus equals the survival function for the reference population multiplied with the survival function $S_e(t)$, corresponding to the excess hazard $h_e(t)$. The overall survival for the cured proportion equals the one for the reference population. The survival (1) then becomes:

$$S(t) = \pi S_0(t) + (1-\pi) S_0(t) S_e(t).$$  \hspace{1cm} (4)

The relative survival, $RS(t)$, is obtained by dividing this last expression by the reference survival $S_0(t)$:

$$RS(t) = \pi + (1-\pi) S_e(t).$$  \hspace{1cm} (5)

The survival function $S_e(t)$ for the excess survival time $T$ can be modeled via standard survival distribution functions. The most popular parametric distributions for failure times are exponential and Weibull distributions. When assuming an exponential distribution for the excess survival times for the fatal cases, the aggregated relative survival function becomes:

$$RS(t) = \pi + (1-\pi) \exp(-\lambda t) = \pi + (1-\pi) \exp(-t/\tau),$$  \hspace{1cm} (6)

with $\lambda$ the hazard and $\tau$ the mean survival time for the fatal cases ($\tau=1/\lambda$).

When assuming a Weibull distribution, the aggregated relative survival function becomes:

$$RS(t) = \pi + (1-\pi) \exp(-\lambda t^\gamma).$$  \hspace{1cm} (7)

and the mean time to death from cancer for the fatal cases is given by: $\tau = \lambda^{-1} \Gamma(1+1/\gamma)$, with $\Gamma$ the Gamma function.

The non-linear fitting of the relative survival functions (6) and (7) to the relative survival curves was performed with the SAS procedure PROC NLIN. The data points were weighted with the inverse of the variance on the relative survival ($w_i = 1/VAR(RS(t_i))$). The 95% confidence interval (CI) on the cured proportion follows directly from the NLIN output, as the cured proportion is one of the estimated model parameters. Similarly, when assuming an exponential distribution for the failure times, the CI on the mean survival time for the fatal cases, $\tau$, follows directly from the NLIN output. However, when assuming a Weibull distribution for the failure times, the mean survival time for the fatal cases is a function of the two estimated Weibull parameters $\hat{\lambda}$ and $\hat{\gamma}$. The distribution on the estimated mean survival time was approximated by resampling 50,000 times $\hat{\lambda}$ and $\hat{\gamma}$ using their joint estimated distribution and calculating the corresponding mean survival time for each random draw. The 2.5th and
97.5th percentiles of the resulting distribution for the mean survival time were taken as borders for the 95% CI.

The Weibull fit was tested against the exponential fit with an $F$-test using the residual weighted sum of squares as reported in Verdecchia et al.\(^8\) Visual inspection of the fit to the relative survival data curves was carried out to assess the goodness-of-fit.

As an illustration of these fitting models, the aggregated relative survival data for colon cancer in the Flemish Region (age of diagnosis $>14$ years, year of diagnosis 1999–2011, follow-up 1st July 2013) is given in Figure 1. The estimated cured proportions and the fatal cases’ mean survival times for both fitted distributions are given in Table 1. Visual inspection shows that the exponential survival function is not as close a fit as the Weibull function, supported by the $F$-test indicating that the Weibull fit is indeed significantly better ($p < 0.001$). The exponential fit overestimates the cured proportion and underestimates the mean survival time of fatal cases compared to the Weibull fit.

Per cancer site considered, the abovementioned parametric fit was applied to the full patient population as well as separately to specific age and gender strata, where applicable. In contrast to this per strata analysis, model (5) can be expanded to incorporate patient and tumour covariates, as

$$RS(t, x) = \pi(x) + (1-\pi(x))S_e(t, x),$$

where $x$ is the covariate vector of a specific cancer patient. This model has been applied to infer the effect of gender on cancer cure adjusted for age and stage (5 levels: I, II, II, IV and X), resulting in 8 estimates per distribution parameter. Together with the estimates for the cured proportion, a total of 24 parameters need to be estimated for the appropriate dummy variables per covariate level. The fit was implemented with the SAS procedure PROC NLIN by adding the 24 parameters to the MODEL statement and providing initial values by trial and error.

### Software
All analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC), the figures were created with SAS version 9.3 or R version 3.1.1.\(^17\)

### Results
#### Patients
The number of patients included in the analysis per cancer site is given in Table 2 together with the number of cases excluded due to unavailable national social security identification numbers, unknown incidence date or no follow-up. The excluded fraction per cancer site was $<1\%$, except for cervix and skin melanoma where it was $1.2\%$ and $1.4\%$ respectively.

#### Cure models
**Per cancer site and age stratified results.** The estimated proportion of cured cases and mean survival time of fatal cases for the seven cancer sites considered (cervix, corpus uteri, colon, skin melanoma, oesophagus, stomach and pancreas) in the Flemish Region (diagnosed from 1999 to 2011, $>14$ year old) are given in Table 3. The relative survival curves and best fits are displayed in Figure 2.
A follow-up of 14 years was used for the relative survival determination, which is enough to observe statistical cure for the cancer sites examined, except for cancer of the oesophagus. The estimated mean survival time of fatal cases for cancer of the cervix is between 2.4 and 2.8 years, depending on the specific age group. The overall estimated cured proportion is

![Table 3. Estimated proportion of cured cases and mean survival time of fatal cases for six cancer sites in the Flemish Region (diagnosed from 1999 to 2011) by gender and by age at diagnosis. The last column specifies if an exponential (E) or a Weibull (W) distribution was used in the fit](#)
Figure 2. Relative survival curves for the cancer sites considered with the cure model fit, overall, by gender or by age group. The vertical lines represent the 95% CI on the relative survival estimates. For the Flemish Region, incidence years 1999–2011, age of diagnosis >14 years and follow-up until 1st July 2013. [Color figure can be viewed at wileyonlinelibrary.com]
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65% but depends strongly on the age group: it is >80% for the youngest age group considered (15–44 years), 64% for the 45- to 64-year-old women and only 35% for the oldest age Group (65+ years).

For colon cancer, the overall mean survival time of fatal cases is almost 3 years with a cured proportion of 54%. Mean survival time of fatal cases is somewhat shorter for females (2.4 years) compared to males (3.3 years), with a higher cured proportion for females (57%) compared to males (51%). Cured proportion decreases with increasing age, from 69% for the youngest (15–49 years), over 59% (50–64 years) down to 51% for the oldest age Group (65+ years).

The estimated mean survival time of fatal cases for cancer of the corpus uteri is about 3 years, which increases to 4 years for the youngest age group. The overall estimated cured proportion is about 74% but depends on the age group: it is almost 84% for the youngest age group considered (15–54 years), 80% for the 55- to 69-year-old women and 65% for the oldest age Group (70+ years).

Skin melanoma has high cured proportions, with an overall cured fraction of 81% and a proportion of 84% for females, which is higher than the 75% for males. The mean survival time of fatal cases for females (4.5 years) is higher compared to males (3.3 years). Again, cured proportion decreases with age from 89% for the youngest (15–34 years), over 82% (35–64 years) down to 74% for the oldest age Group (65+ years), with a mean survival time of fatal cases of about 5 years for the two youngest age groups and only 3 years for the 65+ age group.

Cancer of the pancreas has a low cured proportion (6%) and a short mean survival time of fatal cases (0.8 year), overall as well as for females and males separately. Younger patients (15–59 years) have a twice as high cured proportion (11%) and a somewhat longer mean survival time of fatal cases of 1.2 years. The oldest age group has smaller cured proportion (4%) and shorter mean survival times of fatal cases (0.5 year).

The overall estimated cured proportion for cancer of the stomach is about 25% with a mean survival time of fatal cases around 1.3 years for both males and females, higher cured proportion for females (30%) compared to males (22%) are observed. With increasing age groups, the mean survival time and cured proportion decrease from 1.7 to 1.2 years and 33% to 20%, respectively.

For cancer of the oesophagus very similar relative survival curves are present between the age groups and between males and females. A continuing weak decreasing trend with follow-up time can be observed in these relative survival curves indicating that statistical cure is not yet achieved for cancer of the oesophagus 14 years after diagnosis, in which case no mixture cure model should be applied. Therefore, no cure results for cancer of the oesophagus are given in Table 3.

The cure model results can be represented visually by a scatter plot of the estimated mean survival time of fatal cases versus the estimated proportion of cured cases, see Figure 3. This scatter plot clearly shows the more fatal cancers (stomach and pancreas) versus the cancers with a better prognosis (cervix, colon, corpus uteri and skin melanoma).

**Gender difference.** Estimated cured proportions in the Flemish female patient population are larger than in the Flemish male patient population for cancer of the colon, cancer of the stomach and skin melanoma, while they are somewhat lower for cancer of the pancreas. As the cured fractions for both gender populations are estimated independently, the confidence interval on the difference in the cured proportion is easily constructed using the sum of the individual variances. The 95% confidence intervals on these differences in the cured proportion between males and females do not contain zero, pointing towards significant differences in the cured proportion between the male and female cancer patient population for cancer of the colon, cancer of the stomach, cancer of the pancreas and skin melanoma.

Both age and stage can have a strong impact on cancer patient survival, and should therefore be taken into account when assessing an underlying gender difference in the cured proportion between males and females.

The age and stage distributions between the male and female patient populations for cancer of the colon, cancer of the stomach and skin melanoma are different (all \( p < 0.0001 \), Pearson \( \chi^2 \) test, see Table S2 in the supplementary info). Male patients are more often diagnosed at advanced stages than females for these three cancer sites. There are relatively more females in the oldest age categories for colon and stomach cancer, while there are more males in the oldest age group for skin melanoma. A potential gender effect taking into account age and stage is tested for cancer of the colon, cancer of the stomach and skin melanoma using model (8). Cancer of the pancreas is not further considered, due to the very small and in clinical practice negligible difference of
0.6% in the cured proportion between male and female patient populations.

When adjusting for stage and age, the cured proportion for female colon patients is 0.1% higher compared to male patients, a non-significant difference ($p = 0.60$, 95% CI = $[-0.4, 0.6]$). Fits to the specific age and stage strata are shown in supplementary info Figure S1.

For skin melanoma, a significant difference of 1.2% ($p < 0.0001$, 95% CI $[0.7,1.8]$) remains between female and male cancer patients. As the stratified difference in the cured proportion for skin melanoma was 9% (see Table 3), we attribute the difference in the cured proportion between the male and female patient groups mainly to differences in age and stage distribution at diagnosis.

The model for stomach cancer did not fit appropriately as negative estimated cured proportions were obtained for stage X and the oldest age category.

Discussion

Non-linear parametric mixture cure models using a Weibull or exponential distributions were applied to grouped relative survival curves to evaluate the cure of cancer in the Flemish Region for seven cancer sites (cervix, colon, corpus uteri, malignant melanoma of the skin, pancreas, stomach and oesophagus) diagnosed from 1999 to 2011.

Systematic population-based cure of cancer studies reporting on various cancer sites are rather scarce: the EUROCare-4 study comparing five cancer sites (lung, breast, colorectal, prostate and stomach) among 15 European countries, the cured proportion on 23 cancer sites in Norway and an Italian study on long-term survival, prevalence and cure of cancer for 26 cancer types. Comparing countries between different studies is not straightforward due to differences in cancer site selection and follow-up time. Differences in the incidence period in particular can be very important, as improved cancer care, i.e. higher cured proportion and longer mean survival time, has been observed with the diagnosis period for colon cancer, rectum cancer, stomach, colorectal and lung cancer. The EURCare-4 study allows a limited comparison of the Flemish results with neighbouring countries, in particular France and the Netherlands for cancer of the stomach and colon.

The overall proportion of cured cases and the mean survival time of fatal cases for cancer of the stomach was estimated to be 19% and 0.9 year in the Netherlands and 24% and 1.1 years in France for the incidence period 1988–1999. The Flemish results presented in this work are somewhat higher (25% and 1.3 years). The fact that we are using a more recent incidence period in this work may partly explain these improved results.

For colon and rectum cancer similar cured proportions are reported, while the median survival time of fatal cases for colon cancer is shorter compared to rectum cancer. The Flemish cured proportion of 54% for colon cancer can therefore be compared to the Dutch and French cured proportions for colorectal cancer of 48% and 47% respectively reported in the EUROCare-4 study. The Flemish result is somewhat larger, which might be attributed again to the more recent incidence period considered.

This study observed decreasing estimated cured proportions with increasing age at diagnosis in the Flemish Region for the cancer sites examined (diagnosed from 1999 to 2011). The same age dependence has been observed in many other cure of cancer studies. In this work, the largest absolute difference in the cured proportion between the youngest and oldest age category was observed for cancer of the cervix (about 50%), and the smallest absolute difference for cancer of the oesophagus (about 4%).

We estimated stratified cured proportions for the Flemish female patient population to be higher than the male patient population for cancer of the colon, cancer of the stomach and skin melanoma. This was also observed among Italian cancer patient populations with cancer of the oral cavity, stomach, kidney, bladder, skin melanoma, thyroid cancers and colorectal cancer and among Norwegian cancer patients for 15 cancer sites. The cure models containing gender, age and stage as covariates allowed us to attribute the gender effect totally or mainly to differences in stage and age distribution between male and females patients for cancer of the colon and malignant melanoma. A 5% point (95% CI = [2, 7]) lower standardised cured proportion for males versus females after adjusting for age, stage at diagnosis and anatomical site was also reported for malignant melanoma in Central Sweden.

As is typical for any survival analysis with incomplete follow-up, valid results rely on the assumption of non-informative censoring: patients who are censored are representative of those (with identical covariates) who remain in follow-up. When administrative censoring comes faster for patients diagnosed more recently it introduces a degree of informative censoring as soon as cure rates change with the incidence year. The estimated cure parameters are then a weighted average with lower weights given to contributions from more recent years. In this context it is further assumed that the cured and uncured patients are a priori exchangeable. Appropriate stratification of the national tables then makes the cured and uncured groups comparable in terms of death from other causes than cancer. The Belgian lifetables contain gender, age, calendar year and region but not comorbidity or social-economic status which can both influence survival, cancer diagnosis as well as the cure of cancer. Inclusion of these factors in the lifetables would further increase comparability.

Conclusions

Cure of cancer in the Flemish Region for seven cancer sites (cervix, colon, corpus uteri, malignant melanoma of the skin, pancreas, stomach and oesophagus) diagnosed from 1999 to 2011 was explored using non-linear fits to the grouped relative survival curve. Cure proportions decrease with increasing age groups. Higher cured proportions were observed for the
female patient population compared to the male patient population for cancer of the colon, the stomach and malignant melanoma of the skin, which can totally or mainly be attributed to differences in stage and age distribution for cancer of the colon and skin melanoma. Differences in the cured proportion between age groups or gender were smallest for cancer of the pancreas and oesophagus. This study represents the first cure of cancer results within Belgium. Cure models will be applied more routinely on more cancer sites and at the national level in the coming years when a longer follow-up time becomes available.

Symbols used

\( \gamma \) Survival time distribution parameter

\( h \) hazard

References