Life expectancy as an indicator of outcome in follow-up of population-based cancer registries: the example of childhood leukemia

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Background: Survival analysis is a standard methodology to assess progress in oncology disease treatment. However, survival analysis commonly only measures survival during the treatment period (and the period immediately afterwards), and does not provide an estimate of life expectancy, which is often of more interest to patients and to health policy makers. In this paper we propose a method to estimate childhood acute lymphoblastic leukemia (ALL) life expectancy through the integration of traditional survival analysis and life expectancy tables.

Patients and methods: The study included 305 incident cases registered by the Childhood Cancer Registry of Piedmont in 1979–1991. Vital status on 30 June 2004 was known for 304 cases. Survival analyses were carried out using the Kaplan–Meier method and the Gompertz model, according to the time period of diagnosis and gender.

Results: Cumulative survival at 5 years increased from 58.6% (95% CI 48.9–68.3) for cases diagnosed in March 1979–July 1982 to 79.1% (95% CI 70.8–87.5) in March 1987–February 1991 (P = 0.002). Average life expectancy increased from 46.1 years for boys and 42.6 years for girls diagnosed in March 1979–July 1982 to 58.3 and 69.1, respectively, in March 1987–February 1991.

Conclusions: These analyses show an improvement over the time period of diagnosis of life expectancy for children with ALL.

Key words: acute lymphoblastic leukemia, childhood neoplasm, Gompertz model, life expectancy, survival

Introduction
Cumulative survival [1] and gains in life expectancy [2, 3] are standard indices to assess improvements in cancer survival. In studies of cancer survival, it is common to report the results as cumulative survival percentages at fixed intervals from diagnosis (e.g. 5 years) or as the time when the cumulative survival reaches a given (e.g. 50%, median) value. Although the cumulative survival method has some shortcomings [2], it is the standard presentation of survival data.

An alternative way to address the issue of changes in survival is the estimation of gain in life expectancy [2, 3]. It has been suggested that this measure may be more relevant and useful for health policy makers [2, 4]. Life expectancy is usually computed on the basis of the period under observation, but the resulting information is incomplete when considering diseases with a high proportion of long-term survivors at the end of follow-up. This situation is common in studies of survival after diseases occurring at young ages, unless prognosis is very poor. Although the findings on the increase in mean number of life years observed during the actual follow-up period (i.e. the mean number of person-years contributed by study subjects) are clear, these do not correspond to the information expected by clinicians, patients and the public at large, who focus on life expectancy from birth (or from date of diagnosis) to death rather than on the number of life years gained during an arbitrary period of follow-up. In order to overcome this problem, life expectancy can be estimated using a two-step procedure [5]: first, to estimate the life expectancy in the follow-up period and, secondly, to estimate the life expectancy for the later periods (still not observed) estimated from appropriate external sources. We suggest that this method of presenting the findings may be a useful addition to the standard approach of cumulative survival. General population life tables can be used for estimating the life expectancy for the later periods when there is evidence that after the period of follow-up the same mortality rates of the general population

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apply to the subjects under study (the subjects are ‘cured’). This is the situation with childhood acute lymphoblastic leukemia (ALL) after a follow-up of 10 years with no adverse events [6].

In this paper, we compute population-based life expectancy of children with ALL according to the two-step method and apply it to the evaluation of results by a period of diagnosis (a proxy of corresponding therapy regimen).

The study is based on data provided by the Childhood Cancer Registry of Piedmont (CCRP) [7, 8]. Periods of diagnosis refer to the therapeutic protocols for childhood ALL established by the Italian Association for Pediatric Hematology and Oncology (AIEOP), as considered in a previous paper [9].

materials and methods

Since 1967 the CCRP has provided population-based periodical estimates of cancer incidence and survival in the childhood (age 0–14 years) population of the Piedmont region (north-western Italy). Procedures for data collection, follow-up, classification and data processing, as well as criteria for inclusion in the CCRP database, have been reported elsewhere [7, 8]. The most recent follow-up date was 30 June 2004. The database used for the present analysis included the 305 incident cases of ALL diagnosed in March 1979–February 1991. All cases but one were confirmed through bone marrow examination. No cases were included solely on the basis of the death certificate. At the end of follow-up, 197 cases were alive, 107 were dead and one was lost to follow-up.

Analyses were conducted over three periods of diagnosis (first period: 1 March 1979 to 31 July 1982; second period: 1 August 1982 to 28 February 1987; third period: 1 March 1987 to 28 February 1991), corresponding to the recruitment in the different AIEOP protocols [9]. Since the three periods have different follow-up lengths, the mean survival times cannot be compared directly. We therefore truncated the length of follow-up at 13.2 years from diagnosis to equalize the length of observation for the three subgroups.

Life expectancy for a group of subjects of the same age at time \( t_i \) is [10]:

\[
e^{i} = \frac{\sum_{j=0}^{L_j} h}{s_i} \quad (1)
\]

where \( s_i \) is the number of individuals who are alive at time \( t_i \) and \( L_j \) is the number of person-years (years of life) in the \( j \)th interval starting from time \( t_i \).

For a given time interval \( L_i \) of length \( h \), the number of person-years can be computed as:

\[
hL_i = (h/2) * (s_i + s_{i+h}) \quad (2)
\]

Therefore, substituting (2) in (1) with constant \( h \) we obtain:

\[
e^{i} = \frac{\sum_{j=0}^{L_j} h}{s_i} = \frac{\sum_{j=0}^{\infty} (h/2) * (s_i + s_{i+h})}{s_i} \quad (3)
\]

and

\[
e^{i} = \int_{t_i}^{t_i+h} S(t)dt \quad (4)
\]

Life expectancy was evaluated as a function of years from diagnosis, since the number of years from diagnosis is equivalent to the number of years of ageing.

We employed three different models, based on the Weibull [11], exponential [11] and Gompertz [10, 12] parametric functions [13], to estimate the cumulative survival (S) for each of the three periods of diagnosis. The assessment of fit of the model was carried out for each of them through successive steps. First, a visual examination of the agreement between survival curves as estimated by the model and by the non-parametric Kaplan–Meier method was used [14]. The test proposed by Maller and Zhou [15], which calculates the correlation coefficient \( r \) to test the fit, was then applied for model selection. Statistical significance of the differences in cumulative survival among periods was tested using the log-rank statistic for homogeneity [1].

Measuring the observed life expectancy after a disease requires a long period of observation. In the present case the period of observation spans over a maximum of 25 years and, by design, age at the end of follow-up cannot exceed 39 years (i.e. those cases that were diagnosed at age 14 in 1979 and were alive at the end of follow-up). Therefore lifespan cannot be measured directly for the cases alive at the end of follow-up. In order to estimate life expectancy after the end of follow-up, we added the life expectancy for the general population to the number of person years for the subjects alive at 13.2 years since diagnosis (based on his/her age at the end of follow-up).

Average expected life span (AELS) for a group of subjects was estimated as:

\[
AELS = a + b + c \quad (5)
\]

where \( a \) is mean age at diagnosis, over the number of subjects entering in the study; \( b \) is mean life expectancy during the follow-up period (truncated at 13.2 years) over the number of subjects entering in the study, calculated using (4). In computational terms, \( b \) is the integral under the survival curve as modeled by the selected parametric model; and \( c \) is the mean life expectancy after the follow-up period. For the children alive after 13.2 years of follow-up, the individual contribution to the term is the life expectancy for the Italian general population of the corresponding gender, age and period [16–18], while for deceased subjects the individual contribution is 0. In computational terms, \( c \) is the product of the cumulative survival at 13.2 years in the cohort of cases by the life expectancy for the Italian general population (weighted average according to the frequency distribution of subjects by gender and age at the end of follow-up).

The summed elements \( (a, b, c) \) have the dimension of the average number of person-years, computed for the same number of subjects.

The analyses were conducted with STATA Software (version 7.0). Special attention was paid to the treatment of censored data in the integral function.

results

Table 1 provides descriptive information on the data used in this analysis. Survival at 5 years (estimated by the Kaplan–Meier method) was 69.5% (95% CI 64.3% to 74.7%). It increased in the three time periods from 58.6% (95% CI 48.9% to 68.3%) to 71.3 (95% CI 63.0% to 79.6%) and to 79.1 (95% CI 70.8% to 87.5%) [log rank (LR) test, \( P = 0.002 \)]. Girls showed a small and non-statistically significant advantage over boys in all periods except the first (first period: girls 55.6%, boys 61.1%, LR test \( P = 0.46 \); second period: girls 74.1%, boys 68.4%, LR test \( P = 0.27 \); third period: girls 81.8%, boys 76.6%, LR test \( P = 0.32 \)).

In none of the three periods did exponential (E) and Weibull (W) models fit the data as well as the Gompertz (G) model, as indicated by Maller and Zhou’s test [15]. Correlation coefficients for the models adapted to data of the first (second and third) periods were: \( r_E = 0.938, r_W = 0.969, r_G = 0.996 \) (\( r_E = 0.939, r_W = 0.979, r_G = 0.999; r_E = 0.919, r_W = 0.964, r_G = 0.996 \)). The Gompertz model was therefore chosen for the life expectancy analyses.

Life expectancy estimations for each time period of diagnosis were calculated after stratifying by gender. Table 2 presents the...
mean age at diagnosis (‘a’), mean life expectancy during the follow-up period (‘b’), mean life expectancy after the end of follow-up (‘c’), by period of diagnosis and gender. The cohorts were homogeneous in terms of age at diagnosis (‘a’ similar across periods, slightly higher for boys than for girls). The mean life expectancies during the follow-up period (‘b’) increased across periods for both genders. In the last two cohorts, girls showed higher ‘b’ values than boys, but this was reversed for patients diagnosed in the first period. A similar pattern was observed for the mean life expectancies after the end of follow-up (‘c’), which exhibit a positive temporal trend consistently for both genders, and higher values for girls in the first period.

Figure 1 summarizes the computation of AELS by gender and period, with estimates resulting from adding the terms in Table 2. Compared to boys (and girls in brackets) with ALL diagnosed in the first time period, boys (girls) with cancer diagnosed in the second time period gained 12.2 (26.5) years.

Table 1. Childhood Cancer Registry of Piedmont. Frequency distribution of acute lymphoblastic leukemia cases by period of diagnosis, gender and age at diagnosis

<table>
<thead>
<tr>
<th>Period of diagnosis</th>
<th>Gender</th>
<th>Age at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;1 year</td>
</tr>
<tr>
<td>N (% )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>01.03.1979–31.07.1982</td>
<td>Boys</td>
<td>54 (54.6)</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>45 (45.4)</td>
</tr>
<tr>
<td>01.08.1982–28.02.1987</td>
<td>Boys</td>
<td>57 (49.6)</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>58 (50.4)</td>
</tr>
<tr>
<td>01.03.1987–28.02.1991</td>
<td>Boys</td>
<td>47 (51.7)</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>44 (48.4)</td>
</tr>
<tr>
<td>01.03.1979–28.02.1991</td>
<td>Boys</td>
<td>158 (51.8)</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>147 (48.2)</td>
</tr>
</tbody>
</table>

Table 2. Childhood Cancer Registry of Piedmont. Mean age at diagnosis (‘a’), mean life expectancy during the follow-up period (‘b’), mean life expectancy after the end of follow-up (‘c’) and average expected life span (AELS), by period of diagnosis and gender (follow-up is truncated at 13.2 years)

<table>
<thead>
<tr>
<th>Period of diagnosis</th>
<th>Gender</th>
<th>Period</th>
<th>AELS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>01.03.1979–31.07.1982</td>
<td>Boys</td>
<td>6.3</td>
<td>31.2</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>5.3</td>
<td>29.4</td>
</tr>
<tr>
<td>01.08.1982–28.02.1987</td>
<td>Boys</td>
<td>6.0</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>5.6</td>
<td>10.1</td>
</tr>
<tr>
<td>01.03.1987–28.02.1991</td>
<td>Boys</td>
<td>5.7</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>5.2</td>
<td>10.7</td>
</tr>
</tbody>
</table>

*Using Italian general population life expectancy in 1994, weighted average according to the age at the end of follow-up.

*Using Italian general population life expectancy in 1998, id.

*Using Italian general population life expectancy in 2000, id.

mean age at diagnosis (‘a’), mean life expectancy during the follow-up period (‘b’), mean life expectancy after the end of follow-up (‘c’), by period of diagnosis and gender. The cohorts were homogeneous in terms of age at diagnosis (‘a’ similar across periods, slightly higher for boys than for girls). The mean life expectancies during the follow-up period (‘b’) increased across periods for both genders. In the last two cohorts, girls showed higher ‘b’ values than boys, but this was reversed for patients diagnosed in the first period. A similar pattern was observed for the mean life expectancies after the end of follow-up (‘c’), which exhibit a positive temporal trend consistently for both genders, and higher values for girls in the first period.

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**Discussion**

Life expectancy methodology has been adapted from demography and used in the medical field to produce measures relevant to a wide range of issues relevant to clinicians, to health economists, policy makers and to insurance companies. Changes in life expectancy can be used to evaluate, on one hand, the disease impact on a population (studies for allocation of research funding and health services) [4], and on the other hand, the effectiveness of medical interventions (cost-effectiveness studies of clinical trials and preventive services) [2, 5].

In order to evaluate the effect of different treatment protocols employed in subsequent calendar periods, we have compared...
life expectancy across groups of patients diagnosed in those periods. Contrary to other authors [19], we consider life expectancy to be a suitable population-based indicator even when obtained from observational studies in which some members of the cohort are still alive at the end of follow-up, provided that it is reasonable to assume that the life expectancy of the study participants after the end of follow-up is the same as that of the general population. Messori et al. [5] proposed to extrapolate ‘to infinity’ traditional survival curves in different clinical trials settings. In contrast, we applied to population-based data a method for estimating the total number of years of life expected after the period of follow-up using population-based life tables. The approach is useful in studies of diseases with unchanged survival probabilities after the period of observation, as in the case of childhood ALL in recent years. Of course it is less relevant to diseases that are fatal for almost all patients within the observation period [3, 19], or for which it is not reasonable to assume that life expectancy after the end of follow-up will be the same as for the general population.

We addressed the issue of comparing groups that possibly have different prognosis using a two-step procedure: first, we estimated life expectancy during the period of observation and then we added our best available estimate of future life expectancy for the long-term survivors of the disease.

Regarding the first step, we estimated survival according to the Gompertz [19] model and derived life expectancy from the estimated parameters. In the context of life expectancy evaluation, other authors used parametric models such as exponential [3] or Gompertz [19], in preference to the non-parametric (K–M) approach when achieving good fit to data. The choice of the Gompertz model was the result of testing the adequacy of fit of this model compared with both exponential and Weibull.

With regards to the second step, the selection of the model for the extrapolation after the end of the observed period is critical, as observed by both Wright et al. [2] and Messori et al. [5]. We computed life expectancy using the demographic estimate [16–18] for the general population, i.e. under the assumption that the ‘plateau’ observed in cumulative survival for ALL after 10 years for all the study periods will remain stable [6]. This is the most critical assumption for the present study. We consider it to be a reasonable assumption for the present purpose for several reasons. In previous analyses on the same Registry we observed that changes of the cumulative survival after 10 years since diagnosis were smaller than 2.7% [9, 20]. Consistently, other studies have shown that in children with ALL who survived for 10 years with no adverse events, survival in the following 20 years was 95.3% versus 99.7% for the general US population [6].

In this study we observed a change in life expectancy for subjects enrolled over three subsequent periods of diagnosis, corresponding partly to observed improvements in survival [20], but mainly to the well documented positive secular trend in the general population’s life expectancy [21]. The improvements in survival of our cohorts not only affect the computation of mean life expectancies during the follow-up period, but they also account for increases in mean life expectancies after the end of follow-up (‘c’ terms, which are products of cumulative survivals at 13.2 years and weighted averages of the general population’s life expectancy; Table 2). The changes in the two terms can be summed and have contributed to the increase in the number of person years (total life expectancy) for the more recent periods, consistently for boys and girls (Figure 1). When comparing AELS by gender, it is notable that girls show higher values than boys, for all periods of diagnosis except the first. In fact, it is known that girls with childhood leukemia show better prognosis than boys [9, 22], and also that women on average live longer than men [16–18]. However, the first cohort of diagnosis exhibits an unusual pattern, with higher AELS for boys than for girls. This is mainly due to an advantage in survival for boys: Pastore et al. [9] previously reported a 5% difference in 5-year survival, and we observed a 9% difference in survival at 13.2 years since diagnosis. Neither of the two figures reached statistical significance, but they are still of interest. A possible difference lies in the higher proportion of pre-B immunophenotype cases (at better prognosis, as consistently shown in literature [9, 23]) among boys.

It must be kept in mind that the reported gain in life expectancy is averaged across the target population receiving the treatment (boys and girls recruited over the subsequent periods) and offers no information about the distribution of the gains in life expectancy actually realized by particular patients [2]. When we compare AELS we are considering only point estimates derived from heterogeneous groups of patients, some of whom died shortly after diagnosis and others who were ‘cured’.

The limitations of this approach should also be stressed. First, as noted above, this approach can only be used for diseases and populations for which it is reasonable to assume that patient survival at the end of follow-up is similar to that in the general population. Secondly, Figure 1 shows that the increase in life expectancy across diagnosis periods was largely due to the increases in life expectancy after the end of follow-up, i.e. because of increases in general population life expectancy, and the increases in life expectancy due to improvements in treatment were relatively small. This means that the methods presented here should be regarded as a complement to, rather than a substitute for, standard methods of survival analysis, and that the findings of the analyses presented here should always be presented in their three component parts (as in Figure 1) rather than as a single summary figure.

In conclusion we deem that life expectancy methodology can be applied to the study of survival of many types of childhood cancer, and that the information we derive from it can be useful from a clinical and from a public health perspective.

**appendix**

Gompertz model:

Survival function: $S(t) = \exp(-(\lambda e^{\gamma t})^\gamma)\exp((\gamma t)-1)$

Hazard rate: $h(t) = \lambda e^{\gamma t}$

Cumulative risk: $\Lambda(t) = \lambda e^{\gamma^2 t}$

Non-parametric Kaplan Meier method:

Survival function: $S(t) = \prod_{i=0}^{k} \frac{n_i - m_i}{n_i}$, $t_i \leq t < t_{i+1}$ ($i < k$),

where $n_i$ is individuals at risk and $m_i$ is individuals leaving the interval (dead, censored or lost).
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