Late deaths among five-year survivors of childhood cancer. A population-based study in Piedmont Region, Italy

Elisa Dama
Guido Pastore
Maria Luisa Mosso
Daniela Ferrante
Milena Maria Maule
Corrado Magnani
Franco Merletti

Background and objectives. The aim of this study was to analyze late mortality among 5-year survivors of childhood cancer, in Piedmont (Italy), in terms of risk factors and causes of death.

Design and Methods. From 1967 to 1999, the Childhood Cancer Registry of Piedmont recorded 3164 incident cases. Patients identified only by a death certificate (n=59), lost to follow-up (n=32), alive with a period of observation shorter than 5 years at the end of follow-up (n=65) and records corresponding to a second malignant tumor during childhood (n=9) were excluded from the analyses.

Results. Within 5 years after diagnosis, 1301 children died, and among the 1698 5-year survivors, 144 children subsequently died. Among 5-year survivors, cumulative mortality percentages increased from 5.1% (95% CI 4.0-6.2) at 10 years after diagnosis to 16.0% (12.2-19.8) at 35 years. Period of diagnosis (p=0.006), age at diagnosis (p=0.002), and tumor type (p=0.003) were associated with late mortality. Most deaths were related to cancer recurrence (62.2%) and treatment-related sequelae (22.4%), including second malignant neoplasms, cardiac diseases and other late effects. Compared to the general population, children included in this study had a 9-fold increased risk of overall mortality, and experienced an absolute excess of 4.4 deaths per 1000 person-years.

Interpretation and Conclusions. Among 5-year survivors, patients treated more recently (after 1979) had a statistically significant lower risk of late death than those treated earlier. However, long-term survivors still experienced higher mortality rates than those in the general population, and recurrence or progression of the primary tumor was the first cause of death.

Key words: late deaths, causes of death, childhood neoplasms, population-based studies.

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From the Childhood Cancer Registry of Piedmont. Cancer Epidemiology Unit, CPO Piemonte, CeRMS, S.Giovanni Hospital and University of Torino (ED, GP, MLM, MMM, CM, FM); Division of Pediatrics, Department of Medical Sciences, University of Eastern Piedmont, Novara (GP); Unit of Medical Statistics and Cancer Epidemiology, CPO Piemonte and Department of Medical Sciences, University of Eastern Piedmont, Novara (DF, CM).

Correspondence:
Elisa Dama, Childhood Cancer Registry of Piedmont, V. Santena 7, 10126 Torino, Italy.
E-mail: elisa.dama@cpo.it

With the introduction of more effective treatments, the survival of children (age 0-14 years) affected by cancer increased during the last 4 decades. Nowadays, more than 70% of children may expect to survive at least 5 years after diagnosis, but limited information is available for longer periods of observation.[1-6] Given the increasing number of survivors, attention to long-term outcomes and consequences of therapy has become crucial. Despite the refinement of cancer treatments and supportive therapy, many long-term survivors experience both late effects (such as organ toxicities, growth and endocrine deficits, infertility and second malignant tumors) and higher mortality rates than the general population.[7-20]

The aim of this study was to evaluate long-term mortality in a cohort of children with cancer diagnosed before the age of 15, resident in Piedmont (north-west Italy). Analyses are based on data from the Childhood Cancer Registry of Piedmont (CCRP), a population-based registry specialized in pediatric neoplasms, which has been collecting demographic and clinical data on children with cancer since 1967.[6] We analyzed risk factors for long-term mortality and investigated causes of death in the 1698 children surviving at least 5 years after diagnosis.

Design and Methods

The CCRP has been recording cases of malignant tumors diagnosed in children (0-14 years) resident in Piedmont since 1967. Procedures for data collection, follow-up and tumor classification, and criteria for inclusion in the CCRP database have been reported elsewhere.[6] The CCRP collects both demographic data (gender, town and date of birth, town of residence at diagnosis) and clinical data (date and basis of diagnosis,

cancer site and morphology, tumor type, center where the diagnosis was made and therapy implemented). Cancer site, morphology and behavior are coded according to the International Classification of Diseases for Oncology (ICD-O-2)[21] and tumor types are grouped according to the International Childhood Cancer Classification (ICCC).[22] The CCRP includes intracranial tumors of benign and unspecified histology, while angiomas (even if intracranial) and Langerhans' cell histiocytosis are excluded.

Between 1967 and 1999, 3164 incident cases were recorded in the file of the CCRP. The CCRP personnel periodically (every 2-3 years) updates the vital status of registered cases using information from the Registrar Offices of the town of residence. Vital status was last updated on June 30, 2004. Patients with cancer identified only by a death certificate (n=59), children lost to follow-up (n=32) and children alive with a period of observation shorter than 5 years at the end of follow-up (n=65) were excluded from the analyses. Survival of patients who developed a second malignant tumor in childhood (n=9) was computed starting from the diagnosis of their first tumor and records corresponding to their second tumor were excluded from the database used for the analyses. A total of 2999 patients were included in this study. At the most recent follow-up 1301 (43.4%) patients were reported to have died within 5 years after diagnosis and 1698 (56.6%) survived beyond. Microscopic verification of diagnosis was available for 92.3% of the patients, ranging from 77.8% for patients with tumors of the central nervous system (CNS) to 98.9% for patients with leukemias.

Causes of death

Causes of death among 5-year survivors were obtained from the death certificate provided by the Registrar Office of the town of residence and were coded by CCRP personnel according to the International Classification of Diseases (ICD-9).[23] In addition to the direct cause of death, any useful information, including notes and remarks, recorded on the death certificate was examined by a pediatric oncologist in order to categorize causes of death as (i) recurrence or progression of the first tumor; (ii) treatment-related consequences, including subsequent neoplasm (if mentioned in the death certificate and reported in the relevant medical records), cardiac disease and other sequelae; (iii) non-treatment-related causes of death, including external causes, such as accident or suicide, and other medical conditions.[12] Infectious diseases were classified as treatment-related if the cancer therapy was mentioned in the death certificate. Acute infectious diseases were considered non-treatment-related if they occurred at least 10 years after the cancer diagnosis or if the death certificate stated that the cause of death had no relation to cancer therapies.

Data analyses

The characteristics of children who died more than 5 years after diagnosis were compared to those of children who died within 5 years using χ^2 analysis as a measure of the degree of association between proportions of deaths stratified by period of diagnosis (1967-1978, 1979-1988, 1989-1999), gender, age at diagnosis (0, 1-4, 5-9, 10-14) and tumor type (leukemias, lymphomas and reticuloendothelial neoplasms, CNS tumors and miscellaneous intracranial and intraspinal neoplasms, all other malignant neoplasms). Calendar years of diagnosis were divided into three periods of different lengths to obtain a more uniform case distribution. Time-to-event among 5-year survivors was calculated from 5 years after the date of diagnosis to the last follow-up or to the date of death if this occurred. Cumulative mortality was estimated using the method of Kaplan and Meier[24] and the 95% confidence interval (95% CI) using Greenwood's formula.[25] Statistical significance of differences in cumulative mortality among periods of diagnosis, gender, age at diagnosis and tumor types was tested using the log-rank test for homogeneity.[26,27] p values were considered to be statistically significant when less than 0.05.

Cox regression analysis was used to investigate risk factors for late mortality among 5-year survivors.[28] The proportional hazard assumption was verified first by plotting the logarithm of the cumulative hazard function against the logarithm of survival time and checking for parallelism, and then by using the Schoenfeld residual test. Reference categories were selected *a priori*. Standardized mortality ratios (SMR) were calculated for all children surviving beyond 5 years after diagnosis to quantify the risk of death according to period of diagnosis and gender. SMR were obtained by dividing the number of observed deaths by the number of expected deaths using age-, sex- and calendar period-specific Piedmont population mortality rates. The confidence intervals of SMR were calculated according to the Poisson distribution of observed events.[29] We also calculated the absolute excess risk (AER) of late deaths - or the number of deaths per 1000 patients per year in 5-year survivors - by subtracting the expected number of deaths from the number of observed, dividing by person-year at risk and multiplying by 1000.

Statistical analyses were performed using SAS (Release 8.2, by SAS Institute Inc., Cary, NC, USA), Stata 7.0 (Release 7.0, by Stata Corporation, College Station, Texas, USA) and the Occupational Cohort Mortality Analyses Program OCMAP-PLUS (Release 3.10, by the University of Pittsburgh, Pittsburgh, Pennsylvania, USA).

Results

Descriptive analyses

Table 1 reports the vital status of the 2999 patients included in the study by period of diagnosis, gender, age

Table 1. Childhood Cancer Registry of Piedmont 1967-1999 - Demographic and clinical characteristics of children (0-14 years) included in the study by vital status at the end of follow-up.

	Alive		Dead				Total	
			Within 5 years		After 5 years			
	N.	%	N.	%	N.	%	N.	%
Period of diagnosis								
1967-1978	330	21.2	661	50.8	68	47.2	1059	35.3
1979-1988	552	35.5	391	30.1	53	36.8	996	33.2
1989-1999	672	43.3	249	19.1	23	16.0	944	31.5
Gender								
Male	857	55.1	728	56.0	81	56.2	1666	55.6
Female	697	44.9	573	44.0	63	43.8	1333	44.4
Age at diagnosis								
0139	8.9	104	8.0	2	1.4	245	8.2	
1-4	520	33.5	460	35.4	39	27.1	1019	34.0
5-9	443	28.5	406	31.2	47	32.6	896	29.8
10-14	452	29.1	331	25.4	56	38.9	839	28.0
ICCC Group								
Leukemias	484	31.1	480	36.9	46	32.0	1010	33.7
Lymphomas and reticuloendothelial neoplasms	218	14.0	120	9.2	18	12.5	356	11.8
CNS and miscel. Intracran. and intraspinal Neoplasms	336	21.6	289	22.2	46	31.9	671	22.4
Other malignant neoplasms	516	33.3	412	31.7	34	23.6	962	32.1
Sympathetic nervous system tumors	91	5.9	127	9.8	4	2.8	222	7.4
Retinoblastoma	62	4.0	15	1.2	2	1.4	79	2.6
Renal tumors	95	6.1	43	3.3	5	3.5	143	4.8
Hepatic tumors	7	0.5	20	1.5	1	0.6	28	0.9
Malignant bone tumors	71	4.6	85	6.5	8	5.6	164	5.5
Soft-tissue sarcomas	92	5.9	72	5.5	9	6.3	173	5.8
Germ-cell. trophoblastic and other gonadal neoplasms	39	2.5	27	2.1	1	0.6	67	2.2
Carcinomas and other malignant epithelial neoplasms	50	3.2	17	1.3	2	1.4	69	2.3
Other and unspecified malignant neoplasms	9	0.6	6	0.5	2	1.4	17	0.6
Total	*1554*	*51.8*	*1301*	*43.4*	*144*	*4.8*	*2999*	*100.0*

at diagnosis and tumor type (12 groups according to ICCC). One thousand five hundred and fifty-four (51.8%) children were reported to be alive and 1445 (48.2%) were dead at the end of follow-up. The most frequent diagnoses were leukemias (33.7%), lymphomas and reticuloendothelial neoplasms (11.8%), and CNS and miscellaneous intracranial and intraspinal neoplasms (22.4%). Among the 1445 children who had died, 1301 deaths (90.0%) occurred within 5 years after diagnosis and 144 (10.0%) after 5 years. An excess of deaths within 5 years after diagnosis was observed among younger children (less than 5 years of age, χ^2 test p=0.0003) compared to older ones, and among children diagnosed with leukemias or tumors classified as other malignant neoplasms (χ^2 test p=0.0158).

Survival analyses

Table 2 reports all-cause cumulative mortality for 5-year survivors from 10 to 35 years after diagnosis, and results of the log-rank test according to period of diagnosis, gender, age at diagnosis and tumor type. Cumulative mortality percentages increased from 5.1% (95% CI 4.0-6.2) at 10 years, to 9.3% (7.7-10.9) at 20 years, and from 13.5% (10.9-16.2) at 30 years to 16.0% (12.2-19.8) at 35 years after diagnosis. Differences in mortality among periods of diagnosis (p=0.006), age at diagnosis (p=0.002) and tumor types (p=0.003) were statistically significant (Figure 1).

Table 2 also shows Cox regression results computed including in the model period of diagnosis, age at diagnosis and tumor type as covariates identified by univariate analysis as possible risk factors, and gender as a possible adjusting factor. A statistically significant decreasing trend in relative risk of death over periods of diagnosis was observed (reference category: 1967-1978): HR 0.59 (95% CI: 0.41-0.87) for children diagnosed in the

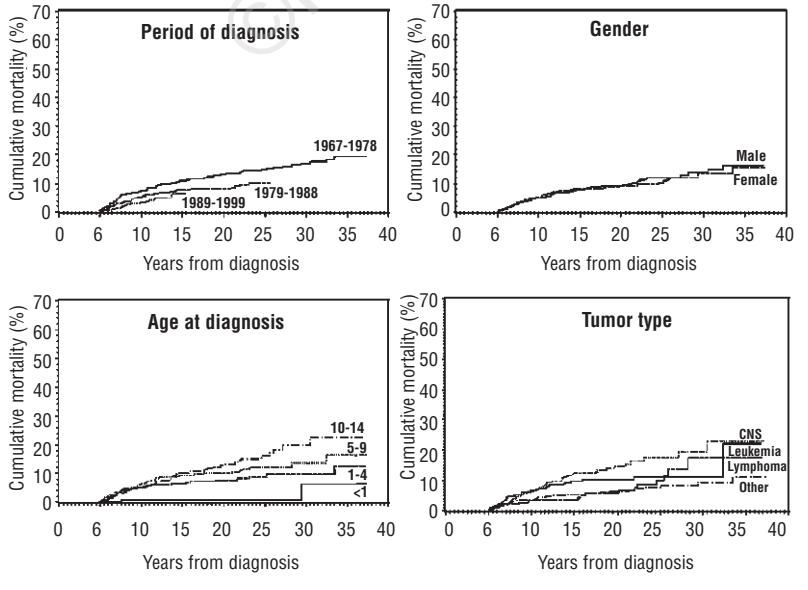

Figure 1. Childhood Cancer Registry of Piedmont 1967-1999 - All-cause cumulative mortality for children (0-14 years) with cancer surviving at least 5 years after diagnosis, by period of diagnosis, gender, age at diagnosis and tumor type.

Table 2. Childhood Cancer Registry of Piedmont 1967-1999 - All-cause cumulative mortality and 95% confidence intervals (95% CI) for children (0-14 years) with cancer surviving at least 5 years after diagnosis, by period of diagnosis, gender, age at diagnosis and tumor type. Multivariate analysis results are shown as hazard ratio (HR) of death and 95% CI - computed according to the Cox model including period of diagnosis, gender, age at diagnosis and tumor type.

	Univariate analysis												Multivariate analysis
	10 years	*(95% CI)*	*15 years*	*(95% CI)*	*20 years*	*(95% CI)*	*25 years*	*(95% CI)*	*30 years*	*(95% CI)*	*35 years*	*(95% CI)*	*log-rank test*	*HR*	*(95% CI)*
Period of diagnosis															
1967-1978	7.3	(4.7-9.8)	11.1	(8.0-14.1)	13.1	(9.8-16.4)	14.8	(11.3-18.3)	17.0	(13.2-20.9)	19.4	(14.8-24.0)		1*	–
1979-1988	5.3	(3.5-7.1)	7.6	(5.5-9.7)	8.2	(6.0-10.4)	10.3	(7.3-13.4)					*p*=0.006	0.59	(0.41-0.87)
1989-1999	3.4	(1.8-5.0)	6.2	(3.0-9.4)										0.43	(0.26-0.72)
Gender															
Male	4.9	(3.5-6.4)	7.9	(5.9-9.8)	9.3	(7.1-11.4)	12.0	(9.2-14.7)	13.6	(10.1-17.1)	16.2	(11.3-21.1)	*p*=0.860	1 *	–
Female	5.3	(3.7-7.0)	8.1	(6.0-10.3)	9.3	(6.9-11.7)	10.2	(7.5-13.0)	13.4	(9.2-17.6)	15.6	(9.7-21.5)		0.94	(0.68-1.31)
Age at diagnosis															
0	0.8	(0.0-2.4)	0.8	(0.0-2.4)	0.8	(0.0-2.4)	0.8	(0.0-2.4)	6.6	(0.0-17.8)	6.6	(0.0-17.8)		0.24	(0.06-1.01)
1-4	5.1	(3.2-7.0)	6.6	(4.4-8.8)	7.7	(5.2-10.2)	8.8	(5.9-11.7)	9.5	(6.3-12.8)	12.6	(6.0-19.2)	*p*=0.002	1 *	–
5-9	6.5	(4.2-8.8)	9.2	(6.4-12.0)	9.9	(7.0-12.8)	12.1	(8.5-15.6)	13.7	(9.0-18.4)	16.2	(9.5-22.9)		1.25	(0.81-1.94)
10-14	4.9	(3.0-6.9)	10.2	(7.2-13.2)	12.7	(9.2-16.3)	16.0	(11.5-20.5)	19.8	(13.8-25.9)	22.4	(14.7-30.1)		1.68	(1.10-2.58)
Tumor type															
Leukemias	6.1	(4.0-8.3)	9.8	(7.0-12.7)	10.2	(7.3-13.1)	10.8	(7.7-14.0)	10.8	(7.7-14.0)	22.0	(1.4-42.6)		1 *	–
Lymphomas and reticuloendothelial neoplasms	3.2	(0.9-5.6)	3.8	(1.2-6.3)	5.8	(2.4-9.2)	10.1	(4.8-15.4)	17.3	(7.7-26.8)	17.3	(7.7-26.8)	*p*=0.003	0.61	(0.35-1.07)
CNS and miscellaneous intracranial and intraspinal neoplasms	6.8	(4.1-9.4)	12.3	(8.5-16.0)	14.7	(10.3-19.1)	17.4	(12.2-22.7)	19.5	(13.0-26.1)	23.2	(13.8-32.6)		1.21	(0.79-1.84)
Other malignant neoplasms	3.7	(2.1-5.4)	5.2	(3.2-7.3)	6.3	(4.0-8.6)	7.7	(4.9-10.5)	9.4	(5.8-13.1)	10.9	(6.3-15.4)		0.63	(0.40-0.99)
Total	*5.1*	*(4.0-6.2)*	*8.0*	*(6.6-9.4)*	*9.3*	*(7.7-10.9)*	*11.2*	*(9.3-13.2)*	*13.5*	*(10.9-16.2)*	*16.0*	*(12.2-19.8)*			

**Reference category.*

period 1979-1988 and HR 0.43 (95% CI 0.26-0.72) for patients diagnosed in the period 1989-1999. Children in the 10-14 age class at diagnosis had the highest risk of death (HR 1.68, 95% CI: 1.10-2.58) and children <1 year at diagnosis had the lowest risk (HR 0.24, 95% CI: 0.06-1.01) (reference category: 1-4 age class). Children with CNS and miscellaneous intracranial and intraspinal neoplasms (HR 1.21, 95% CI: 0.79-1.84) had the highest risk of death, although this was not statistically significant (Table 2).

Causes of death

Among the 1698 5-year survivors, 144 children had died at the end of follow-up. The Registrar Office of the town of residence provided death certificates for all these children, and specified the cause of death for all but one. Most causes of death (89 deaths, 62.2%) were attributed to recurrence or progression of the first childhood cancer. Thirty-two (22.4%) children died of treatment-related consequences, such as subsequent neoplasms (18 patients), cardiac diseases (2 patients) or other sequelae (12 patients). Twenty-two children (15.4%) died of non-treatment-related causes, including external causes (8 patients) and other medical conditions (14 patients) (Table 3). Table 4 shows the distribution of causes of death by tumor type and period of diagnosis. For leukemias, proportions of deaths due to recurrence or progression of the first tumor decreased from 72.7% in 1967-1978 to 57.1% 1989-1999. CNS tumors and miscellaneous intracranial and intraspinal neoplasms caused an increasing proportion of deaths due to recurrence or progression from 55.6% to 70.0%, and the corresponding figures for other malignant neoplasms were 46.1% and 80.0%.

Standardized mortality ratio

Table 5 shows SMR for the 5-year survivors. Overall, the mortality of this cohort was about 9 times higher than that in the general population (SMR 9.3, 95% CI: 7.8-10.9), with statistically significant differences between gender (males 7.1, 5.6-8.8; females 15.7, 12.0-20.1). Differences in SMR over periods of diagnosis were not statistically significant; SMR increased from 6.7 (95% CI: 4.7-9.3) in 1967-1978 to 9.8 (5.3-16.4) in 1989-1998 for males, and decreased from 16.5 (11.2-23.4) to 13.8 (6.3-26.1) for females. Compared to the general population, children included in this study experienced an absolute excess of 4.4 deaths per 1000 person-years. This excess decreased from 5.7 in the first period of diagnosis to 3.1 in the last period.

Table 3. Childhood Cancer Registry of Piedmont 1967-1999 - Causes of death among children (0-14 years) with cancer surviving at least 5 years after diagnosis by tumor type.

Tumor type / *Cause of death*	*Leukemias*	*Lymphomas and reticuloendothelial neoplasms*	*CNS and miscellaneous intracranial and intraspinal neoplasms*	*Other malignant neoplasms*	*Total*
Recurrence (69.6%)	32 (47.1%)	8 (63.0%)	29 (58.8%)	20 (62.2%)	89
Treatment-related consequences	9 (19.5%)	6 (35.3%)	8 (17.4%)	9 (26.5%)	32 (22.4%)
Subsequent neoplasm					
Lip. oral cavity. pharynx. lung	0	0	0	1	1
Digestive organs and peritoneum	0	2	1	0	3
Bone and articular cartilage	1	0	0	2	3
Connective and other soft tissue	0	1	1	1	3
Melanoma and other skin	0	0	0	1	1
Breast	1	0	0	0	1
Genito-urinary organs	0	0	0	3	3
Brain and other parts of nervous system	2	0	0	0	2
Lymphatic and hematopoietic	1	0	0	0	1
Cardiac					
Cardiomyopathy	1	1	0	0	2
Other sequelae					
Infectious disease	1	1	1	0	3
Other sequelae*	2	1	5	1	9
Non treatment-related causes of death	5 (10.9%)	3 (17.6%)	9 (19.6%)	5 (14.7%)	22 (15.4%)
External causes					
Motor vehicle accident	0	0	2	1	3
Other accident	0	1	1	1	3
Suicide	2	0	0	0	2
Medical conditions					
Human immunodeficiency virus	0	1	0	0	1
Other bacterial/ viral infection	1	0	2	1	4
Cerebrovascular disease	0	0	1	0	1
Other medical ° condition	2	1	3	2	8
Total	*46*	*17*	*46*	*34*	*143#*

*#The cause of death was unspecified for one patient. *hypopituitarism (2 cases), graft-versus-host disease (2 cases), increased intracranial pressure in hydrocephalus, intestinal perforation post radiotherapy, aortic rupture in tracheostomy, cerebral softening. cholestatic hepatitis and renal failure after bone marrow transplantation; °systemic lupus erythematosus, intestinal obstruction, chronic renal failure, panniculitis, parathyroidectomy, sickle cell anemia, hemosiderosis, diabetes, asthma, renal amyloidosis, cardiopathy in congenital hydrocephalus, aortic insufficiency, myocardial infarction.*

Discussion

In this population-based study we evaluated late mortality and causes of deaths in children surviving at least 5 years after a diagnosis of cancer. The strength of our study is the availability of periods of diagnosis (until 1999) and follow-up (until June 2004) which are more recent than those used in previously published reports.[9,12-15,17] Among patients diagnosed with cancer during the study period (1967-1999), 56.6% were known to be alive 5 years after diagnosis. These patients cannot be considered cured, since 8.5% of them died thereafter and their overall mortality was 9-fold higher than that expected for the general population. However, the cumulative survival rates of these patients were over 90% at 20 years after diagnosis. These findings compare favorably with those of previously reported studies[9,12-15,17] (Table 6).

Patients treated more recently (after 1979) had a higher short-term survival[6] and a statistically significant lower risk of late deaths than those treated before 1979. This is likely a consequence of higher cure rates due to more effective therapies and better diagnostic techniques.

Older age at diagnosis was associated with a worse long-term survival, while children aged <1 year at diagnosis were at lowest risk of late mortality. In fact, children aged <1 year at diagnosis are at higher risk of early deaths (death occurring within 30 days after diagnosis),[30] but those who survive beyond 30 days have a better prognosis, in particular if diagnosed with Wilms' tumors, neuroblastoma or retinoblastoma. Higher late mortality for older children at diagnosis was also reported in the Scandinavian study by Moller *et al.*[13] In our data, the high risk in the 10-14 year old age class was mainly due to the lower long-term survival of patients with Hodgkin's disease and malignant bone tumors. Exclusion of these diagnoses from the multivariate analysis yielded lower and not statistically significant HR for the 10-14 years old age class (*data not shown*).

Given the lower expected mortality of women than men, SMR were higher for girls than for boys, as already reported in previous studies.[9,12,13] The actuarial risk of late deaths was similar for the two sexes, as was the absolute excess risk. Similar findings have led to the suggestion that the effect of a childhood cancer diagnosis on the risk of death adds to the background risk of death rather than multiplying it.[9]

Modern treatment protocols succeeded in more complete eradication of the primary tumor, resulting in an increased number of patients who survived for more than 5 years after diagnosis. Nevertheless, it is still important to develop new strategies that will further reduce the high percentage of deaths due to recurrent tumors.[31] Monitoring patients to detect cancer relapses promptly is crucial. Although it was recently shown

Table 4. Childhood Cancer Registry of Piedmont 1967-1999 - Causes of death among children (0-14 years) with cancer surviving at least 5 years after diagnosis by tumor type and period of diagnosis. *The cause of death was unspecified for one patient.

Tumor type	Period of diagnosis	Recurrence		Cause of death Treatment-related consequences		Non-treatment related causes of death		Total	
		N.	%	N.	%	N.	%	N.	%
Leukemias	1967-1978	16	72.7	2	9.1	4	18.2	22	47.8
	1979-1988	12	70.6	5	29.4	0	0.0	17	37.0
	1989-1999	4	57.1	2	28.6	1	14.3	7	15.2
Lymphomas and reticuloendothelial neoplasms	1967-1978	7	46.7	5	33.3	3	20.0	15	88.2
	1979-1988	1	100.0	0	0.0	0	0.0	1	5.9
	1989-1999	0	0.0	1	100.0	0	0.0	1	5.9
CNS and miscellaneous intracranial and intraspinal neoplasms	1967-1978	10	55.6	4	22.2	4	22.2	18	39.1
	1979-1988	12	66.7	2	11.1	4	22.2	18	39.1
	1989-1999	7	70.0	2	20.0	1	10.0	10	21.8
Other malignant neoplasms	1967-1978	6	46.1	4	30.8	3	23.1	13	38.2
	1979-1988	10	62.5	5	31.3	1	6.2	16	47.1
	1989-1999	4	80.0	0	0.0	1	20.0	5	14.7
Total	1967-1978	39	57.3	15	22.1	14	20.6	68	47.5
	1979-1988	35	67.3	12	23.1	5	9.6	52	36.4
	1989-1999	15	65.2	5	21.8	3	13.0	23	16.1
	1967-1999	89	62.2	32	22.4	22	15.4	143*	

Table 5. Childhood Cancer Registry of Piedmont. Standardized mortality ratio (SMR) and 95% confidence intervals (95% CI) and absolute excess risk (AER) for children (0-14 years) with cancer surviving at least 5 years after diagnosis, by period of diagnosis and gender.

Period of diagnosis	OBS	EXP	SMR	95% CI	AER*
1967-1978	68	7.4	9.2	7.2-11.7	5.7
Male	37	5.5	6.7	4.7-9.3	5.2
Female	31	1.9	16.5	11.2-23.4	6.3
1979-1988	53	6.0	8.8	6.6-11.5	4.0
Male	30	4.6	6.6	4.4-9.4	4.0
Female	23	1.5	15.5	9.8-23.2	4.1
1989-1999	23	2.1	11.0	7.0-16.5	3.1
Male	14	1.4	9.8	5.3-16.4	3.4
Female	9	0.7	13.8	6.3-26.1	2.7
Total	144	15.5	9.3	7.8-10.9	4.4
Male	81	11.5	7.1	5.6-8.8	4.3
Female	63	4.0	15.7	12.0-20.1	4.6

*OBS: observed; EXP: expected; * per 1, 000 patients per year.*

how excessively frequent follow-up visits are not effective,[32] given the high proportion of late deaths, it is advisable to program a constant, well-spaced in time, long-term follow-up. Recurrence and progression of the childhood cancer were in fact the most common causes of death (ranging from 61.5% to 84.5%) in this and other studies[9,12-15,17] (Table 6). Deaths due to recurrence or progression of the primary cancer did, however, decrease over periods of diagnosis among subjects treated for leukemia. Although more effective treatments have improved long-term survival and decreased the possibility of relapses, patients can still die of treatment-related toxicity;[31] this effect was described by Meadows *et al.* as *the cost of cure*.[33] In CCRP patients, subsequent second neoplasms caused 12.6% of deaths in 5-year survivors, with higher proportions in children diagnosed with cancer classified as *other malignant neoplasms*. This group included retinoblastoma and bone tumors which, because of either genetic susceptibility or high-dose radiation therapy, may predispose to a higher risk of secondary malignant neoplasms.[33]

The limitations of our study include the relatively small number of children and the lack of detailed information about therapies, which precluded both separate analyses for different diagnostic subgroups and investigation of the association between therapies and mortality.

The results of this study on late mortality of children with cancer living in Piedmont are consistent with those reported in other countries. Thanks to advances in anti-cancer therapy, overall survival has greatly improved and long-term survivors have a lower risk of late mortality. However, long-term survivors still experience higher mortality rates than those in the general population and the large majority of late deaths are due to recurrence or progression of the primary tumor. Constant monitoring of long-term survival of childhood cancer patients and careful evaluation of their causes of deaths are crucial to plan interventions aimed at reducing the risk of late effects.

Table 6. Comparison of data for 5-year childhood cancer survivors.

	CCRP	Cardous-Ubbink et al.[9]	Mertens et al.[12]	Moller et al.[13]	Hudson et al.[14]	Green et al.[15]	Robertson et al.[17]
Country	Piedmont - Italy	The Netherlands	United States	Denmark, Finland, Norway, Iceland, Sweden	United States	United States	Britain
Type of study	Population-based	Hospital-based	Hospital-based	Population-based	Hospital-based	Hospital-based	Population-based
Period of diagnosis	1967-1999	1966-1996	1970-1986	1960-1989	1962-1983	1960-1984	1971-1985
Age at diagnosis	0-14 years	0-18 years	0-20 years	0-19 years	0-19 years	0-19 years	0-14 years
Closing date of follow-up	June 30, 2004	at least January 1998	December 31, 1996	December 31, 1995	December 1993	December 31, 1990	December 31, 1990
No. of 5-year survivors	1698	1378	20227	13711	2053	591	9080
Alive	1554 (91.5 %)	1258 (91.3 %)	18197 (90.0 %)	12289 (89.6 %)	1795 (87.4 %)	520 (88.0 %)	8287 (91.3 %)
Dead	144 (8.5 %)	120 (8.7 %)	2030 (10.0 %)	1422 (10.4 %)	258 (12.6 %)	71 (12.0 %)	793 (8.7 %)
Death due to recurrent cancer	89 (62.2 %)	89 (74.2 %)	1246 (67.4 %)	976 (69.6 %)	158 (61.5 %)	60 (84.5 %)	578 (74.0 %)
Death due to second cancer	18 (12.6 %)	19 (15.8 %)	235 (12.7 %)	99 (7.1 %)	52 (20.2 %)	4 (5.6 %)	52 (6.7 %)
Death due to other causes	36 (25.2 %)	12 (10.0 %)	367 (19.9 %)	327 (23.3 %)	47 (18.3 %)	7 (9.9 %)	151 (19.3 %)
Cause of death not traced or unspecified	1		182	20	1		12
Standardized mortality ratio observed/expected (95%CI)	9.3 (7.8-10.9)	17.0 (14.3-20.6)	10.8 (10.3-11.3)	10.8 (10.3-11.5)	1962-1970: 15.0 (12.0-19.0) 1971-1983: 15.0 (13.0-17.0)	patients who did relapse during the first 5 years after diagnosis males: 6.1 (4.2-9.0) females: 12.2 (8.0-19.8)	non-neoplastic causes: 4.0 (3.0-5.0)

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