Population-based analysis of survival after childhood cancer diagnosed during 1970-1998: a report from the Childhood Cancer Registry of Piedmont, Italy

Silvia Viscomi, Guido Pastore, Maria Luisa Mosso, Benedetto Terracini, Enrico Madon, Corrado Magnani, Franco Merletti

Background and Objectives. Survival after childhood cancer has shown a steady improvement from the late 1970s in most developed countries. Since 1967 the Childhood Cancer Registry of Piedmont has been collecting cases of malignant tumor, diagnosed in children aged 0-14 years, living in Piedmont. This work aims to update survival rates to 31.12.2000.

Design and Methods. This study includes 2,678 children diagnosed between 1970-98. Vital status was assessed at the Registry Office of the town of residence. One thousand four-hundred ninety cases were reported to be alive, 1170 dead and for 18 the status was unknown. Thirty-three cases registered with a death certificate only were excluded. Completeness of follow-up was 99.3%. All tumor types were classified according to the Birch-Marsden classification. Histologic verification was available for 94.4% of cases.

Results. Survival at 5 years increased over the period 1970-98 for all tumor types with a statistically significant trend over time ($p<0.0001$). The 5 year survival rate for acute lymphoblastic leukemia (ALL) increased steadily from 24.7% (95%CI 15.0-34.3) to 87.6% (80.9-94.3), for acute non-lymphoblastic leukemia (ANLL) from 0.0% to 38.1% (17.3-58.9), and for non-Hodgkin's lymphomas from 25.2% (0.6-49.8) to 79.7% (61.9-97.5). Five year survival rates of children with centralm nervous system tumors increased from 33.4% in 1970-74 to 78.5% in 1990-94 and decreased in 1995-98 to 70.9%. Age <1 year and >50,000$\times 10^6$ cells/L at diagnosis were negative prognostic factors for ALL. Age <1 year was a favorable prognostic factor for neuroblastoma.

Interpretation and Conclusions. Survival of children with all types of tumors improved in Piedmont. This improved survival is comparable to that reported by other European and North American population-based cancer registries.

Key words: childhood cancer, survival, prognosis, cancer registries, population-based studies.

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From the Childhood Cancer Registry of Piedmont, Cancer Epidemiology Unit of the Center for Cancer Epidemiology and Prevention, CPO Piemonte, S.Giovanni Hospital, Turin (SV, GP, MLM, BT, CM, FM); Unit of Pediatric Oncology S. Andrea Hospital, Vercelli (GP); Pediatric Oncology Department, Hospital for Sick Children 'Regina Margherita' and University of Turin (EM); Unit of Medical Statistics and Epidemiology, Department of Medical Sciences, University of Eastern Piedmont, Novara (CM).

Correspondence: Corrado Magnani, MD, Childhood Cancer Registry of Piedmont, via Santena 7, 10126 Turin, Italy. E-mail: corrado.magnani@tin.it

Survival after a childhood neoplasm has increased as a consequence of the introduction of both improved protocols[1-2] and more efficient diagnostic procedures.[3-4] This increase has been recorded since the early seventies in most developed countries.[5] Positive trends in prognosis have been observed in both population-based studies and clinical trials and for almost all types of tumor.[6] However it would be appropriate to continue survival studies in order to monitor the outcome of new treatments and update results in the cohort of children who first benefited from the new therapies.[7]

The aims of this study, based on population data from the Cancer Childhood Registry of Piedmont (CCRP) in the period 1970-98, were: to update survival rates as of 31.12.2000, and to investigate survival time trends and the role of demographic and clinical prognostic factors. Previous CCRP reports covered children diagnosed up to 1994.[8,9]

Design and Methods

Since 1967 the CCRP has provided periodic population-based estimates of incidence of cancer and survival in the childhood (age 0-14 years) population of Piedmont Region (North Western Italy) (in 1970-75 data were collected only for children resident in the province of Turin, which accounts for about half the population of Piedmont). Procedures for data collection, follow-up, classification and data processing as well as criteria for inclusion in the CCRP database have been reported elsewhere.[9] The population decreased over the period considered in the present report (1970-1998) from approximately 800,000 in 1975-79 to approximately 500,000 in 1995-98 because of the drop in birth rate.

Cancer site, morphology and behavior were coded according to International Classification of Disease for Oncology (ICD-O)[10] and tumor types were grouped according to Birch and Marsden.[11] Intracranial neoplasms of benign and unspecified behavior were included; angiomas (even if intracranial) and histiocytosis X were excluded.

The database used for the present analysis was formed of 2,678 cases diagnosed during the period 01.01.1970-31.12.1998. The CCRP does in fact include 2,721 incident cases for this period, but we excluded 33 cases documented only by a death certificate, 8 second primary tumors, 1 case with missing follow-up data and 1 case of unknown tumor type; all these were excluded from the

Table 1. Childhood Cancer Registry of Piedmont 1970-98– Number of cases (0-14 years) and percentages by period, vital - status and histologic verification.

Diagnostic groups	No. cases	Period of diagnosis 1970-74 %*	1975-79 %	1980-84 %	1985-89 %	1990-94 %	1995-98 %	Life Status Dead %	LFU %	HV %
Acute lymphocytic leukemia (Ia+Ib)	700	11.0	21.6	19.1	16.1	17.1	15.0	38.0	0.3	99.4
Acute non-lymphocytic leukemia (Ic)	138	8.7	23.9	19.6	16.7	15.2	15.9	71.0	0.0	99.3
Hodgkin's disease (IIa)	125	14.4	25.6	17.6	14.4	11.2	16.8	16.0	0.8	99.2
Non-Hodgkin's lymphomas (IIb-IIc-IId)	182	7.1	22.5	19.2	18.7	21.4	11.0	43.4	1.6	98.4
Ependimoma (IIIa)	66	6.1	9.1	24.2	12.1	24.2	24.2	50.0	3.0	98.5
Astrocytoma (IIIb)	222	9.9	18.5	14.4	21.2	19.4	16.7	32.4	0.0	95.9
Medulloblastoma (IIIc)	112	9.8	24.1	21.4	16.1	16.1	12.5	65.2	0.9	98.2
Other gliomas and intracranial/intraspinal neoplasms (IIId+IIIe)	205	11.7	22.0	23.4	19.5	11.7	11.7	47.8	1.0	43.4
Sympathetic system tumors (IVa-IVb)	202	9.4	19.8	20.3	16.8	18.8	14.9	56.4	1.5	93.6
Retinoblastoma (V)	64	10.9	18.8	15.6	7.8	23.4	23.4	20.3	0.0	87.3
Wilms' tumor (VIa+VIc)	118	10.2	26.3	21.2	12.7	15.3	14.4	26.3	0.8	89.8
Osteosarcoma (VIIIa)	86	14.0	17.4	19.8	30.2	15.1	3.5	55.8	0.0	98.8
Ewing's sarcoma (VIIIc)	54	5.6	13.0	25.9	22.2	18.5	14.8	51.9	0.0	98.1
Rhabdomyosarcoma (IXa)	85	4.7	21.2	22.4	22.4	18.8	10.6	41.2	2.4	98.8
Fibrosarcoma (IXb-IXc)	70	20.0	20.0	10.0	20.0	20.0	10.0	47.1	0.0	94.3
Other types	249	21.7	21.3	14.5	15.3	14.9	12.4	51.8	0.4	94.4
All tumor types	2678	11.4	21.1	18.9	17.3	17.0	14.2	43.7	0.7	93.4

*LFU: lost to follow-up; HV: histologic verification.; *1970-74: limited to residents in the Turin province.*

database before survival analyses. Histologic (or cytologic) verification (HV) was available for 93.4% of cases, ranging in the major diagnostic groups from 79.5% for tumors of the central nervous system (CNS) to 99.4% in acute lymphocytic leukemia (ALL) (Table 1).

The life status of each registered case was assessed as of 31.12.2000 at the Registry Offices of the town of residence: 1,490 cases were reported to be alive (55.6%), 1,170 dead (43.7%), while status was unknown for 18 (0.6%). Survival was calculated for all major types of childhood cancer as well as for selected minor categories.[11] Cumulative survival percentages were calculated according to Kaplan and Meier.[12] The statistical significance of the differences in survival among periods were tested using the log-rank statistic for homogeneity[13] and for temporal trends.[14] *p*-values were considered statistically significant when <0.05. Ninety-five percent confidence intervals (95%CI) were computed for proportions and survival rates.[13] A minimum of 50 cases for each category was the admission criterion for analysis. Details are given in the *Appendix*.

A multivariate Cox regression was used to compare periods of diagnosis and to investigate prognostic factors.[15] The latter analyses were limited to selected tumor categories. The assumption of proportionality of risk of death in covariate strata was verified by plotting the cumulative hazard function. Hazard ratios (HR) by period were computed adjusting for gender and age at diagnosis, using male gender, age class 0-4 and period 1970-74 as the reference. The HR can be interpreted as a relative risk. The following prognostic factors were included in the multivariate analysis: gender, age at diagnosis and white blood cell count (WBCC). FAB morphological subgroups were included for acute non-lymphocytic leukemia (ANLL) (134 cases) and immunophenotype was considered for ALL (470 cases), limited to cases diagnosed after 1980.

Statistical analysis was performed using SAS software (Release 6.12, by SAS Institute Inc., Cary, NC, USA, 1996).

Table 2. Childhood Cancer Registry of Piedmont 1970-1998. Cumulative survival by period of diagnosis and tumor type and time trend in children aged 0-14.

Period of diagnosis	*1970-74*					*1975-79*				*1980-84*			*1985-89*			*1990-94*		*1995-98*	
No. of incident cases	306					566				507			464			456		379	*p* value
Years from diagnosis	5	10	15	20	25	5	10	15	20	5	10	15	5	10	15	5	10	5[b]	for trend
Diagnostic groups[a]																			
ALL	24.7	18.2	18.2	18.2	18.2	55.6	51.7	49.0	49.0	60.4	56.7	55.2	77.0	75.2	75.2	79.2	77.9	87.6	<0.0001
ANLL	0.0[c]	0.0[c]	0.0[c]	0.0[c]	0.0[c]	17.6	17.6	14.7	14.7	28.6	25.0	25.0	39.1	39.1	–[d]	38.1	–[d]	63.6	<0.0001
Hodgkin's disease	72.2	66.7	66.7	66.7	55.6	90.6	87.5	87.5	87.5	90.9	90.9	90.9	83.3	83.3	77.8	86.7	86.7	100.0	0.0460
Non-Hodgkin's lymphomas	25.2	25.2	25.2	25.2	25.2	46.3	43.9	43.9	41.5	51.4	51.4	51.4	67.3	67.3	67.3	66.7	–[d]	79.7	0.0001
CNS neoplasms	33.4	31.7	28.4	26.7	25.0	42.0	37.8	35.3	33.6	57.5	53.3	50.8	66.4	61.1	57.8	78.5	75.2	70.9	<0.0001
Ependymoma	33.3	33.3	33.3	33.3	33.3	50.0	16.7	16.7	16.7	43.8	43.8	31.3	50.0	50.0	–[d]	81.3	66.7	56.3	0.1213
Astrocytoma	40.9	36.4	31.8	31.8	31.8	58.5	56.1	53.7	53.7	78.1	71.9	71.9	74.5	68.1	–[d]	84.4	84.4	78.4	<0.0001
Medulloblastoma	0.0[c]	0.0[c]	0.0[c]	0.0[c]	0.0[c]	22.2	14.8	11.1	11.1	45.8	37.5	33.3	77.8	66.7	–[d]	55.6	–[d]	46.9	<0.0001
Other gliomas	41.7	41.7	37.5	33.3	29.2	37.8	37.8	35.6	31.1	54.2	52.1	52.1	55.0	52.5	52.5	83.3	83.3	87.5	<0.0001
Sympathetic system tumors	10.5	10.5	10.5	10.5	10.5	30.0	30.0	30.0	30.0	41.2	38.6	38.6	64.7	55.9	55.9	51.2	51.2	60.8	<0.0001
Retinoblastoma	57.1	57.1	57.1	42.9	42.9	83.3	83.3	83.3	83.3	60.0	60.0	60.0	100.0	100.0	100.0	93.3	93.3	83.0	0.0483
Wilms' tumor	41.7	41.7	41.7	41.7	41.7	64.5	64.5	64.5	64.5	80.0	80.0	80.0	86.7	86.7	86.7	66.7	–[d]	100.0	0.0026
Osteosarcoma	16.7	16.7	16.7	16.7	16.7	20.0	20.0	20.0	20.0	58.8	58.8	47.1	65.4	61.5	57.7	61.5	–[d]	–[d]	0.0004
Ewing's sarcoma	0.0c	0.0c	0.0c	0.0c	0.0c	14.3	14.3	14.3	14.3	50.0	35.7	35.7	50.0	50.0	–	90.0	–[d]	75.0	0.0011
Rhabdomyosarcoma	25.0	25.0	25.0	25.0	25.0	66.7	50.0	50.0	50.0	73.7	68.4	68.4	68.4	63.2	63.2	62.5	–[d]	44.4	0.6547
Fibrosarcoma and other soft tissue sarcoma	35.7	35.7	35.7	35.7	35.7	50.0	50.0	50.0	–[d]	57.1	57.1	42.9	53.3	53.3	–[d]	71.4	–[d]	85.7	0.0359
Other tumor types	31.5	29.6	27.8	24.1	24.1	34.0	32.1	32.1	32.1	30.6	30.6	30.6	68.4	65.8	65.8	70.3	67.6	93.5	<0.0001
All tumor types	29.9	27.3	26.3	25.0	24.0	47.8	44.8	43.4	42.9	56.0	53.0	51.4	68.6	65.5	63.9	72.3	70.0	79.5	<0.0001

ALL: acute lymphocytic leukemia; ANLL: acute non-lymphocytic leukemia; CNS: central nervous system; [a]including tumor types with less than 50 cases; [b]overall, only 80 of the cases of this period had 5-year follow up; [c]all died before; [d]censored data.

Results

Survival description and time trends

For all childhood malignancies, survival at 5 years from diagnosis increased over the study period with a clear temporal trend according to periods of diagnosis (log-rank test for trend: p <0.0001) (Table 2).

For both ALL and ANLL, the increase of survival over periods of diagnosis was highly significant. ALL survival at 5 years improved between 1970-74 and 1975-79 from 24.7% (95% CI: 15.0-34.3) to 55.6% (47.7-63.6) and reached 87.6% (80.9-94.3) in 1995-98 (Table 2, Figure 1A). The probability of death for children diagnosed in 1995-98 was about one tenth of that for children diagnosed in 1970-74 (Table 3). The trend was statistically significant in all age classes (p<0.001), except in the age group of 10-14-year olds in whom the trend was of borderline statistical significance (p=0.088). ANLL survival at 5 years increased from 0.0 % in 1970-74 to 38.1% (95% CI: 17.3-58.9) in 1990-94, reaching 63.6% (43.5-83.7) in 1995-98 (Table 2, Figure 1b).

For Hodgkin's disease (HD), survival at 10 years was already high in 1970-1974 (66.7%; 95% CI: 51.5-92.9) and improved further in 1975-79 (87.5%; 95% CI: 76.0-99.0), stabilizing thereafter (Table 2, Figure 1c). For non-Hodgkin's lymphomas (NHL) survival at 5 years rose steadily from 25.2% (95% CI 0.6-49.8) in 1970-74 to 79.7% (61.9-97.5) in 1995-1998 (Table 2, Figure 1d).

Unlike most other cancer types, CNS tumors did not show the same constant trend. Survival rates at 5 years improved by approximately 10% in each period compared to the previous one until 1994 (from 33.4% during 1970-74 to 78.5% in 1990-94), but decreased to 70.9 % in 1995-98. Nevertheless, the

Table 3. Childhood Cancer Registry of Piedmont 1970-98. Hazard ratios (HR) of death and 95% Confidence Intervals (95% CI) by tumour types and period of diagnosis, adjusted for gender and age at diagnosis (3 classes: 0-4, 5-9, 10-14). Reference period: 1970-74.

Period of diagnosis	*1975-79*		*1980-84*		*1985-89*		*1990-94*		*1995-98*	
Diagnostic groups	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
ALL (Ia+Ib) (a)	0.42	0.30-0.59	0.34	0.24-0.49	0.16	0.10-0.26	0.16	0.10-0.25	0.10	0.05-0.18
ANLL (Ic)	0.58	0.29-1-15	0.33	0.16-0.69	0.29	0.13-0.62	0.31	0.14-0.69	0.15	0.06-0.38
Hodgkin's disease (IIa)(b)	0.44	0.12-1.58	0.33	0.07-1.62	0.97	0.26-3.64	0.36	0.04-3.17	0.00	0.00-.
NHL (IIb+IIc+IId)	0.50	0.23-1.10	0.39	0.17-0.89	0.24	0.10-0.58	0.21	0.09-0.51	0.15	0.05-0.49
CNS neoplasms (IIIa-IIIe)	0.85	0.59-1.22	0.52	0.35-0.77	0.40	0.26-0.61	0.22	0.13-0.36	0.29	0.18-0.48
Ependymoma (IIIa)	1.12	0.21-6.12	0.67	0.14-3.30	0.54	0.09-3.14	0.35	0.06-1.98	0.50	0.09-2.75
Astrocytoma (IIIb)	0.59	0.29-1.19	0.27	0.12-0.64	0.35	0.17-0.72	0.12	0.04-0.33	0.25	0.10-0.61
Medulloblastoma (IIIc)	0.43	0.20-0.93	0.21	0.09-0.47	0.08	0.03-0.29	0.14	0.05-0.35	0.20	0.08-0.52
Other gliomas (IIId-e)	1.04	0.57-1.89	0.67	0.36-1.26	0.63	0.32-1.22	0.21	0.07-0.64	0.14	0.04-0.50
Sympathetic system tumors (IVa-b) (a)	0.52	0.28-0.96	0.40	0.21-0.75	0.24	0.12-0.49	0.26	0.13-0.52	0.26	0.12-0.56
Retinoblastoma (V)	0.19	0.03-1.08	0.66	0.15-2.82	0.00	0.00-.	0.09	0.01-0.81	0.19	0.03-1.08
Wilms' tumor (VIa+VIc)	0.55	0.20-1.47	0.27	0.08-0.88	0.17	0.03-0.87	0.40	0.12-1.37	0.00	0.00-.
Osteosarcoma (VIIIa)	0.71	0.31-1.65	0.17	0.06-0.46	0.18	0.07-0.44	0.16	0.05-0.50	0.12	0.01-0.99
Ewing's sarcoma (VIIIc)	1.35	0.27-6.88	0.47	0.11-2.01	0.43	0.09-1.94	0.12	0.02-0.80	0.25	0.04-1.62
Rhabdomyosarcoma (IXa)	0.37	0.09-1.48	0.20	0.05-0.89	0.25	0.06-1.00	0.29	0.07-1.23	0.46	0.10-2.19
Fibrosarcoma and other soft tissue sarcoma (IXb-c)	0.44	0.14-1.36	0.57	0.17-1.98	0.48	0.16-1.45	0.32	0.10-1.03	0.11	0.01-0.94
All tumor types	0.61	0.52-0.72	0.48	0.40-0.57	0.32	0.26-0.39	0.26	0.21-0.32	0.18	0.14-0.24

ALL: acute lymphocytic leukemia; ANLL: acute non-lymphocytic leukemia; NHL: Non-Hodgkin's lymphomas; CNS: central nervous system; a: the models for acute lymphatic leukemia and sympathetic system tumors include period, gender and age in four classes (0, 1-4, 5-9, 10-14); b: the model for Hodgkin's disease includes period, gender and age in two classes (0-9, 10-14).

test for linear trend computed over the entire study period (1970-98) was statistically significant ($p<0.0001$). The 95% CI were 70.6-86.5 for 1990-94 and 60.6-81.2 for 1995-98; the difference between periods was not statistically significant (Table 2, Figure1e). The trend by period of diagnosis was statistically significant in all age classes ($p<0.01$). Relative to children in age class 1-4 years old, the risk of death for children aged 5-9 and 10-14 years old was 0.75 (0.57-0.99) and 0.65 (0.48-0.87), respectively. The log-rank test for trend was significant ($p<0.0001$) for all types excluding ependymoma. A decrease in survival at 5 years for children with medulloblastoma was observed in periods 1990-94 and 1995-98 compared to the previous period [1985-89: 77.8% (58.6-97.0); 1990-94: 55.6 (95% CI: 32.6-78.5); 1995-98: 46.3% (95% CI: 19.2-74.6)], although the time trend improvement remained statistically significant ($p<0.0001$) (Table 2). Of the 202 cases of sympathetic system tumors (SST), 181 were diagnosed as neuroblastoma. Survival for SST at 5 years increased from 10.5 % (0.0-24.3) in 1970-74 to 60.8% (42.0-79.5) in 1995-98 (Table 2, Figure 1F). The trend was statistically significant in the age class <1 year old ($p<0.01$) and 10-14 years old ($p=0.025$), but not in the 1-4 year olds ($p=0.10$).

A linear trend in improvement was present for retinoblastoma, although fluctuations among periods were observed. The increasing time trend for survival from Wilms' tumors from 1970-74 to 1995-98 was statistically significant ($p=0.003$) and 5-year survival more than doubled. The decrease observed in the period 1990-94 may be explained as a random fluctuation due to the small number of cases.

Survival of children with osteosarcoma increased from 16.7% at 5 years (95% CI: 0.0-37.8) in 1970-74 to 61.5% (35.1-88.0) in 1990-94 (Table 2). The log-rank test for differences according to period of diagnosis was statistically significant ($p=0.0004$). Children aged 10-14 years at diagnosis had a HR of 2.90 (1.31-6.40) relative to those aged 0-9 years at diagnosis. Children with Ewing's sarcoma also showed a significant increasing trend in survival ($p=0.0011$) (Table 3). The survival data of children with soft tissue sarcomas are presented separately for rhabdomyosarcomas and the other types. Survival after rhabdomyosarcoma increased from the period 1970-74 to 1975-79, but no subsequent improvement was observed. In contrast, survival from the non-rhabdomyosarcomas presented a statistically significant linear improvement over period of diagnosis.

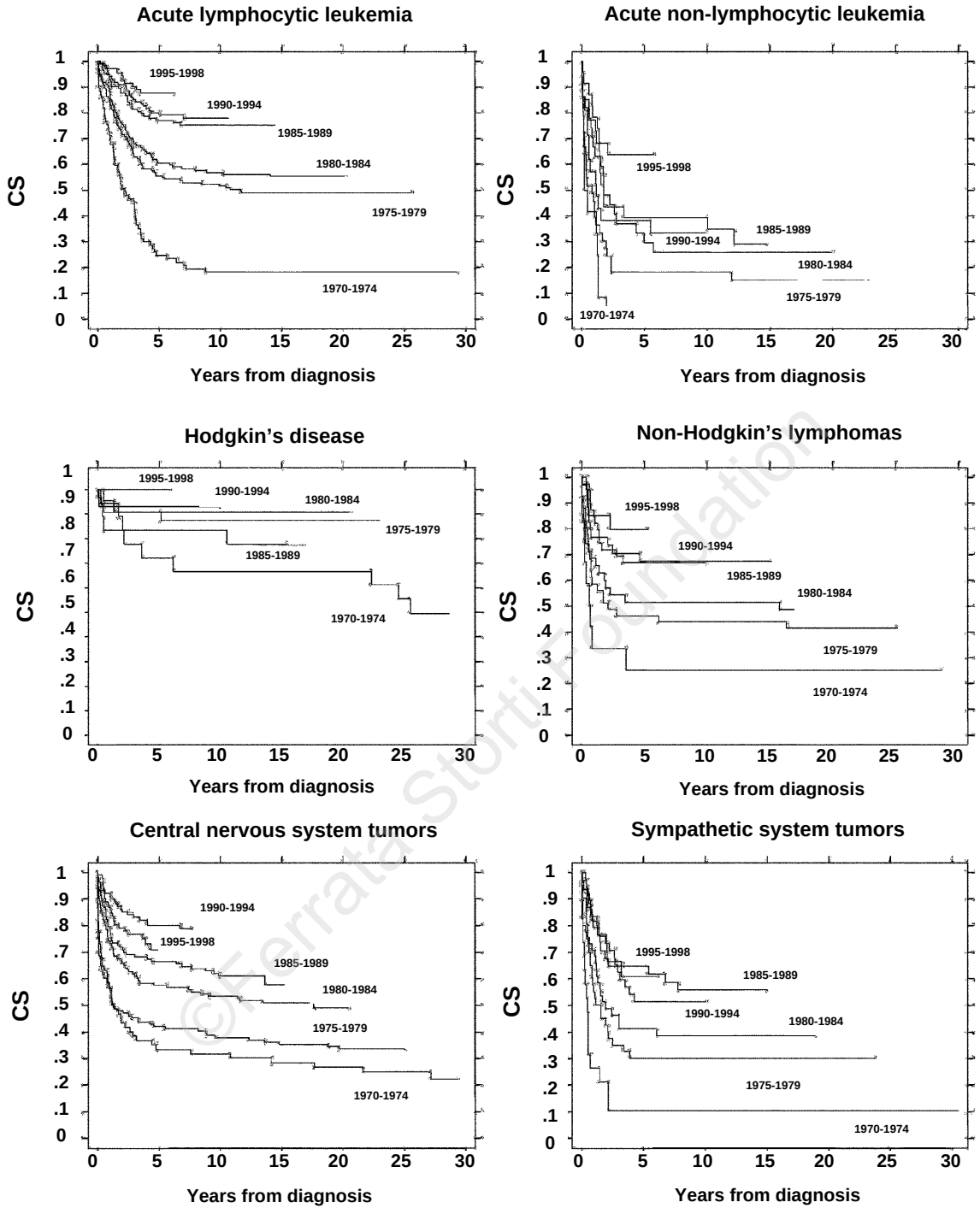

Figure 1. Childhood Cancer Registry of Piedmont, 1970-98. Cumulative survival by selected sites and period of diagnosis.

Prognostic factors

The role of prognostic factors was examined in more detail for ALL, ANLL and SST. Regarding ALL (Table 4), the risk of death (hazard ratios - HR) for children aged < 1 year and for females were, respectively, 2.75 (1.43-5.28) and 0.85 (0.66-1.08) relative, respectively, to the 1-4-year old age class and to males. For children diagnosed during 1980-98, age less than 1 year or over 10 years and WBCC > 50 $\times 10^9$ cells/L at diagnosis were negative prognostic

Table 4. Multivariate survival analyses of ALL cases diagnosed in 1980-98 in Piedmont. The Hazard Ratio (HR) of death and the corresponding 95% confidence interval (95% CI) were computed according to the Cox model including: period of diagnosis, gender, age at diagnosis and white blood cell (WBC) count.

	N. of cases	*HR*	*95% CI*
Period of diagnosis			
1980-84	134	1*	–
1985-89	111	0.43	0.27-0.68
1990-94	120	0.44	0.28-0.70
1995-98	105	0.26	0.14-0.48
Gender			
Male	255	1*	–
Female	215	0.80	0.56-1.15
Age at diagnosis			
<1 year	13	2.41	1.02-5.69
1-4 years	231	1*	–
5-9 years	146	1.40	0.92-2.14
10-14 years	80	1.85	1.16-2.95
WBC count at diagnosis			
$\leq 999 \times 10^6$ cells/L	225	1*	–
10,000-49,999 $\times 10^6$ cells/L	152	1.43	0.93-2.19
$\geq 50{,}000 \times 10^6$ cells/L	89	2.62	1.67-4.09
Missing	4	2.37	0.56-10.14

**Reference category. Subjects with missing value were retained and included as separate levels in the model.*

Table 5. Multivariate survival analyses of 134 ANLL cases diagnosed in 1970-98 in Piedmont. The Hazard Ratio (HR) of death and the corresponding 95% confidence interval (95% CI) were computed according to the Cox model including period of diagnosis, age at diagnosis, white blood cell (WBC) count and cytological type.

	N. of cases	*HR*	*95% CI*
Period of diagnosis			
1970-74	12	1*	–
1975-79	33	0.56	0.26-1.20
1980-84	26	0.25	0.10-0.58
1985-89	21	0.19	0.08-0.49
1990-94	20	0.27	0.11-0.68
1995-98	22	0.10	0.04-0.30
Age at diagnosis			
0-4 years	45	1*	–
5-9 years	45	0.81	0.47-1.43
10-14 years	44	1.20	0.68-2.11
WBC count at diagnosis			
$\leq 9999 \times 10^6$ cells/L	56	1*	–
10000-49999 $\times 10^6$ cells/L	35	1.45	0.82-2.57
$\geq 50000 \times 10^6$ cells/L	23	1.89	1.00-3.61
Missing	20	1.47	0.75-2.87
Cytological type[a]			
Acute non-lymphocytic leukemia M1-M2	58	1*	–
Acute non-lymphocytic leukemia M3	23	1.99	0.97-4.06
Acute non-lymphocytic leukemia M4	16	1.29	0.67-2.48
Acute non-lymphocytic leukemia M5	22	1.97	0.95-4.07
Acute non-lymphocytic leukemia unknown FAB	15	2.11	0.99-4.52

**Reference category. [a]The analysis is limited to ANLL with FAB types M1-M5 or FAB type unknown. Three M6-M7 cases and 1 case of hybrid leukemia were excluded.*

factors with respect to the 1-4-year olds and those with a lower WBCC. Period of diagnosis remained the most important predictor of survival. The immunophenotype did not contribute significantly to the fit of the model and was not included in the final one. Multivariate analysis for factors predicting survival in ANLL included period of diagnosis, age, WBCC and morphologic subtype. The analysis showed a lower HR (corresponding to a better prognosis) for cases diagnosed after 1980 and a higher HR for children with a WBCC > than 50×10^9 cells/L at diagnosis (the reference was the period from 1970-74 and a lower WBCC). Age class and morphologic subtype did not contribute to the model fit. However, children with M3, M4, M5 and *not otherwise specified* ANLL had a higher risk of death (although this was not statistically significant) than children with M1-M2 ANLL (Table 5). The role of gender was opposite for HD and NHL: girls with HD had a 2.88 (1.02-8.16) times higher risk of death than males, whereas if they had NHL, their risk of death was 0.52 (0.29-0.96) that of their male counterparts. Regarding SST, multivariate survival analysis, including period of diagnosis, gender and age group, showed a statistically significant decrease in risk of death for the period of diagnosis (from 0.53 in 1975-79 to 0.26 in 1995-98 compared to 1970-74) and a poor outcome for older children: relative to children aged 1-4 years old, the risk of death was 0.42 (0.24-0.72) for children diagnosed before the first year of age and 2.41 for children aged 5 and older. The trend in decreased risk of death over time was statistically significant ($p<0.001$) in all age classes.

Females affected by osteosarcoma had a lower survival rate and their risk of death relative to that of males was 2.00 (95% CI 1.08-3.70) while for Ewing's sarcoma neither gender nor age at diagnosis resulted to be significant prognostic factors.

Discussion

The analysis of the CCRP survival data confirmed the positive trend for almost all types of tumors, already shown in other developed countries from both hospital and population-based studies.[16-30] The improved survival in Piedmont was particularly evident in the 1970s and continued constantly up to 1998. The largest survival improvements were observed in the categories that previously had a poor prognosis, such as ANLL or Ewing's sarcoma. There was little room for further improvement in some types of cancer (e.g. HD, retinoblastoma) that already had high survival rates. The significant improvement in outcome for children with ALL may be due to bet-

ter diagnostic techniques and more precise risk-tailored therapeutic approaches. Most of the prognostic data are contained in four characteristics at diagnosis: age, gender, WBCC and cytogenetics. The value of these factors has been demonstrated by a variety of clinical studies and are the basis for the current classification of childhood ALL[4,31,32] Among factors known to predict a better outcome, we confirmed the role of a WBCC < 50×10^9 cells/L and age at diagnosis being 1-9 years,[31] while the role of immunophenotype as an independent prognostic factor is unclear.[32] The poorer prognosis for T-cell ALL might be explained by the link with other unfavorable risk factors such as high WBCC and age over 10 years.[33] New therapeutic strategies for such patients with ALL are needed. We also confirmed that survival is higher among females (although our results were not statistically significant). However, a recent large population-based study in Europe showed that gender accounts for only a small difference in survival.[18] The CCRP did not collect information on other prognostic factors such as cytogenetics,[34] leukemia cell burden and response to treatment[4] and socioeconomic status.[35] The outcome of childhood ANLL diagnosed during the early 1970s in developed countries was disappointing: less than 10% survived for at least 5 years, although an increase was recorded from the late 70s. In the 1980s and 1990s the outlook improved and higher 5-year survival rates were observed, presumably due to more effective chemotherapy, better supportive therapies as well as to bone marrow transplantation. Diagnostic techniques also improved in the study period: cytogenetic and monoclonal antibodies became useful tools in recognizing ANLL subtypes as well as hybrid or biphenotypic leukemias. Classification based on these techniques, in addition to morphology, may reveal subgroups of children with good prognosis. However, as yet, few prognostic factors have been consistently identified in ANLL.[19,36] Prognostic factors may also depend on treatment and its intensity and may change as new protocols are introduced. The effect of WBCC on survival is well known and was statistically significant in our data. Age, gender and FAB classification were not related to prognosis of ANLL in this study. The FAB subgroup registered by the CCRP personnel were as reported in the clinical records, but inter-observer variation is well documented.[36] Children with M3 have been reported to have a good long-term survival but their prognosis is poor when they present disseminated intravascular coagulopathy at diagnosis.[19]

In affluent, Western countries HD is an example of childhood cancer which can be cured in over 90% of cases with a reasonable burden of sequelae. Literature data on survival differences according to gender in HD are not consistent.[17,20]

The differential diagnosis between NHL and ALL is not always precise, therefore new treatment programs are obtained as modifications of the protocols for high risk ALL. The survival rates for NHL diagnosed during the period 1995-98 increased with a time trend resembling that observed for ALL. As for ALL, the prognosis of children with NHL has improved in recent periods due to a better understanding of the natural history and heterogeneity of the type of cancer and to refinement of treatment plans. Our database showed that females fared better than males, but this observation is not consistent with literature data.[20]

Survival for children with all CNS tumors except ependymoma showed a highly significant improvement over the periods of diagnosis, but this picture is marred by the decrease in 1995-98. Over the entire 1970-1998 period we observed a statistically significant linear improvement for children with medulloblastoma, but survival for cases diagnosed after 1990 was lower than that for cases diagnosed in 1985-89. Possible causes for this inverse trend include different case-mixes according to prognostic factors or biological features (i.e. age/extent of disease at diagnosis) or changes in clinical approach (i.e. protocol, surgical removal and radiotherapy techniques) with unexpected results. No information on these aspects was available in the data of CCRP and an *ad hoc* study is in progress to investigate their role. Random variation cannot be excluded as survival in Piedmont in the 1980s was much higher than in other countries (*see below*).

The prognosis of SST depends on age, extent of disease at diagnosis, and genetic factors, such as expression of the N-Myc gene, while gender is not related to survival.[23,37-38] SST clinically diagnosed in infants show more favorable characteristics and even spontaneous regression. Age less than 1 year at diagnosis is confirmed to be a good prognostic factor. Moreover, infants with pre-clinical SST detected by abdominal ultrasonography during pregnancy or after birth during detection programs of renal or hip congenital abnormalities, might have better survival due the earlier diagnosis (lead time bias).[39] To date, there are no markers capable of recognizing spontaneously regressing SST. Health systems that provide regular infant examinations would lead to the detection of cases in an early/localized stage: a large number of these good prognosis, incidental cases might artificially increase survival rates.[40] Spix *et al.* demonstrated an association between incidence rates and survival in Europe.[22] Children older than 1 year at diagnosis have a poor prognosis, particularly if they have metastatic disease: so far, aggressive treatment has not improved outcome. Staging procedures, treatment regimens and quality of total care for children with metastatic disease may explain survival differences observed among developed countries.[17,22] The role of screening appears to be limited.[41,42]

The CCRP survival data can be compared with European,[5,18-27,43] USA[7] and Italian survival rates,[27]

although the last largely mirror those of the CCRP. Substantially similar results have been found for all tumors, ALL, ANLL, NHL, osteosarcoma and rhabdomyosarcoma. The survival rates of patients with CNS tumors, SST and Ewing's sarcoma tend to be higher in Piedmont than in other developed countries. The 5-year survival for children with CNS tumors in Piedmont in 1990-94 was high (78 %) in comparison to that in other developed countries in the same period (64% ITACARE, 61 % EUROCARE, 65% USA). The survival rates for HD, medulloblastoma, fibrosarcoma and Wilms' tumors seem to be lower. Survival rates for HD in developed countries exceeded 90% in the last decade of the 20th century, whereas they were 83% and 87% (1990-94 and 1995-98) in Piedmont. The decrease in 5-year survival observed in Piedmont in 1990-98 for medulloblastoma is difficult to compare with international rates, both because of the scarcity of data available for this time period and because the decrease must be put in the context of a highly significant improvement from 1970 to 1990 when CCRP survival rates were higher than those in other countries. Two-thirds of the data analyzed in the EUROCARE Study for Italy were from the CCRP, therefore the two observations were not independent.[21]

Non-biological features associated with better prognosis included: treatment plan directed by a tertiary care unit, size of place of treatment and entry in a large trial,[44-45] while the role of socio-economic status or parental education was limited.[35] Being treated in specialized Centers and according to clinical trials was a well recognized determinant of long-term survival during the decade 1970-1980; thereafter the role of these factors decreased as a result of the use of more standardized treatment in all centers.[33,36] The only exception to this is CNS tumors.[46] The outcome advantage related to being registered in a trial was still increasing, at least for ALL and ANLL and for selected tumor types, in the 1970s and in 1980s.[33,36,45] Since 1970, children resident in our region have mostly been treated in specialized Centers according to well-defined clinical protocols:[46] this fact hampers survival analysis by entry into a protocol. In conclusion, we confirm the positive trend in survival after childhood cancer in recent years and we emphasize the role of childhood cancer registration as an important method to monitor survival rates in the population.

Appendix

Some minor categories were grouped together: acute lymphocytic leukemia (minor category 01A); with other lymphocytic leukemias (01B); non-Hodgkin's lymphomas (02B) with Burkitt's lymphoma (02C); and unspecified lymphomas (02D) other gliomas (03D) with other and unspecified central nervous system tumors (03E); neuroblastoma (04A) with other tumors of the sympathetic system (04B); Wilms' tumors (06A) with unspecified renal tumors (06C); and fibrosarcoma (09B) with other and unspecified sarcomas (09C). Renal carcinoma (06B), chondrosarcoma (08B), gonadal tumors (10B) with gonadal carcinoma (10C), other and unspecified gonadal tumor (10D), other and unspecified tumor were not included in the analyses. The other minor categories not mentioned in the paper were also excluded.

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Pre-publication Report & Outcomes of Peer Review

Contributions

SV: statistical analyses and report writing; GP: conception, design and report writing; MLM: data management; BT: report writing and critical revision; EM: clinical overview; FM: report writing and final approval; CM: report writing, general overview and final approval. Our grateful thanks to Prof. Andrea Pession and to Prof. Fabrizio Bianchi for their comments and to Mrs. Marinella Nonnato for her careful management of the CCRP data and follow-up. Primary responsibility for the publication: GP; primary responsibility for each Table and Figure: SV.

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Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jontly by Professor Cazzola and the Editors. Manuscript received June 5, 2003; accepted July 23, 2003.

In the following paragraphs, Professor Cazzola summarizes the peer-review process and its outcomes.

What is already known on this topic

Survival after childfhood cancer has shown a steady improvement in the last 25 years in most developed countries.

What this study adds

This study confirms the positive trend in survival after childhood cancer in recent years and illustrates the role of childhood cancer registration as an important method to monitor survival rates in the population.