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Survival of children with cancer in Italy, 1989–98. A report from the hospital based registry of the Italian Association of Paediatric Haematology and Oncology (AIEOP)

Andrea Pession[a], Elisa Dama[b], Roberto Rondelli[a], Corrado Magnani[b,c], Marisa De Rosa[d], Franco Locatelli[e], Franca Fagioli[f], Riccardo Haupt[g], Momcilo Jankovic[h], Benedetto Terracini[b], Franco Merletti[b], Guido Pastore[b,i,], on behalf of the Italian Association of Paediatric Haematology and Oncology*

[a]*Paediatric Oncology and Haematology Unit "Lalla Seràgnoli", University of Bologna, Bologna, Italy*
[b]*Childhood Cancer Registry of Piedmont, Cancer Epidemiology Unit – CPO Piemonte, CeRMS, University of Torino, Torino, Italy*
[c]*Unit of Medical Statistics and Epidemiology, Department of Medical Sciences, University of Eastern Piedmont, Novara, Italy*
[d]*Centro Interuniversitario del Nord Est italiano per il Calcolo Automatico, CINECA Casalecchio di Reno, Bologna, Italy*
[e]*Paediatric Haematology/Oncology, University of Pavia, IRCCS Policlinico San Matteo, Pavia, Italy*
[f]*Paediatric Haematology Oncology Unit, Regina Margherita Children Hospital, Torino, Italy*
[g]*Epidemiology and Biostatistics Section, Department of Haematology/Oncology, Gaslini Children's Hospital, Genova, Italy*
[h]*Unit of Paediatrics, University of Milano Bicocca, San Gerardo Hospital, Monza, Italy*
[i]*Division of Paediatrics, Department of Medical Sciences, University of Eastern Piedmont, Novara, Italy*

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ABSTRACT

We describe the survival patterns of 10,791 Italian children (age 0–14) diagnosed with cancer during 1989–1998 and who were included in the hospital-based registry of the Italian Association of Paediatric Haematology and Oncology. Five-year cumulative survival percentages were 76% for lymphoproliferative disorders and 68% for solid tumours. Survival rates in 1994–1998 significantly improved for acute lymphocytic leukaemia (ALL), acute non-lymphocytic leukaemia, Hodgkin's lymphoma and Wilms' tumour. Gender and age were determinants of survival for some specific types of cancer. Girls with ALL and neuroblastoma exhibited a significant advantage (hazard ratio HR 0.72, 0.62–0.83) and disadvantage (HR 0.73, 0.59–0.90) over boys, respectively. Children with a Wilms' tumour diagnosed above age 3 had a worse prognosis than younger children (HR 2.3, 1.4–4.1). The persisting gender-related difference in survival rate for ALL requires understanding as to whether it is attributable to delays in the adoption of more recent therapeutic protocols, while the corresponding findings for Wilms' tumour and neuroblastoma deserve further biological interpretation.

1. Introduction

Approximately 1500 children younger than 15 years of age are diagnosed with cancer each year in Italy.[1,2] The incidence rate increased from 146.9 cases per million children per year in 1988–92 to 176.0 in 1998–2002, as recently reported by the Italian network of Cancer Registries (AIRTUM).[3] Cancer remains the second main cause of death in children aged from 0 to

* *Corresponding author*: Present address: Childhood Cancer Registry of Piedmont, Cancer Epidemiology Unit – CPO Piemonte, CeRMS, University of Torino, Torino, Italy. Tel.: +39 011 6336965; fax: +39 011 6336960.
E-mail address: guido.pastore@cpo.it (G. Pastore).
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14 years after non-intentional injuries, with a mortality rate of 0.41 deaths per ten thousand children.[4]

During the last 3–4 decades, the survival rates of children with cancer greatly increased in high income countries due to refinement of diagnostic tools, therapeutic strategies and development of collaborative groups.[5–8]

Since the 1970s, the habit of collaborative work among Italian paediatric oncologists has been achieved through the Association of Paediatric Haematology and Oncology (AIEOP) which has had a major role in the design and implementation of nationwide controlled clinical trials. Such collaborative work was instrumental in raising the standard for diagnosis and treatment of childhood cancer over the country. Among the tools implemented to monitor the accrual of patients in the clinical trials was a database, set up in 1989 by the AIEOP Operational Office, which collects demographic and clinical information of children aged up to 14 years (0–14) diagnosed, in the AIEOP centres, with tumours. Given that this dataset represents a quasi-national registry of childhood cancer, it was deemed to be suitable to provide an overview of survival rates of childhood cancer in Italy. Survival rates are commonly considered the best indicator of the quality of childhood cancer care on a national basis. This paper reports the survival analysis of cases included in the AIEOP dataset with respect to cancer type, gender and age at diagnosis in the two periods of diagnosis, 1989–93 and 1994–98. It is thought that the Italian model for data centralisation can be of interest to other countries which are not covered by a national childhood cancer registry. Results of specific clinical trials are beyond the aim of the present paper.

2. Patients and methods

2.1. The dataset

Since 1989, clinical and demographic information for each child diagnosed with a cancer before age 15 (0–14 years), at any of the AIEOP centres, have been collected on an *ad hoc* form (*model 1.01*) and filed centrally in a dataset maintained at the AIEOP Operational Office in Bologna, where properly trained clerical staff control the reliability of information.[9] The dataset is kept according to the criteria for Advance Multicentre Research and Security in collaboration with CINECA (Centro Interuniversitario del Nord Est italiano per il Calcolo Automatico), Bologna. As late as 2000, 55 clinical units taking care of the treatment of children with cancer were operating all over the country and are listed in the Appendix. This dataset collects about 75% of all national childhood cancer (80% in Northern and Central regions, 65% in Southern regions), based on estimates of the number of expected cases in Italy.[1,2]

The present analysis includes 10,791 children aged 0–14 (6042 boys and 4749 girls) diagnosed during 1989–98. Children with benign histiocytosis, mesoblastic nephroma, treatment-related acute myeloid leukaemia and second primary neoplasms have been excluded from the present analyses, as well as the cases diagnosed at an older age (15+ years). Cases diagnosed in 1989–93 and 1994–98 were respectively 5202 and 5589. Stage at diagnosis and therapies were reported on the *ad hoc* form by the notifying centre, but were not analysed in the context of the present paper. Table 1 describes the distribution of the cases by cancer types according to the International Classification of Childhood Cancer.[10]

2.2. Ascertainment of vital status

For 7056 subjects, vital status (i.e. whether alive, dead or lost at the closing date of follow up) updated to 2001 was known to the centres and recorded in the dataset. The centres were not in contact with the other 3735 patients and did not have updated vital status information: therefore, during 2003–04 the vital status was obtained from the Vital Statistics Office of the towns of residence using an *ad hoc* request form from the Cancer Epidemiology Unit of the University of Torino. After this process, 7337 (68%) children were found to be alive, 3219 (30%) to have died and 235 (2.2%) to be lost to follow-up. Follow-up and vital status were defined, as of 2001, for all subjects.

2.3. Statistical analyses

In the univariate analysis, survival was estimated for each of the diagnostic categories indicated in Table 1, after stratification by gender, age at diagnosis (three 5-year intervals for all cancer types but leukaemia, neuroblastoma and renal cancer, for which age group 0–4 was broken down into <1 and 1–4) and period of diagnosis. With regard to the latter, the decision of considering two quinquennial periods was based on statistical power and was unrelated to any change in therapeutic protocols. Separate analysis was performed for cancer categories with at least 150 cases. Within each analysis, cumulative survival percentages were estimated using the method of Kaplan–Meier.[11] Standard errors and 95% confidence limits (95% CI) were computed using Greenwood's formula.[12] The statistical significance of the difference in survival among subgroups was estimated with the log-rank test[13,14] and values corresponding to $p < 0.05$ were considered to be significant. Statistical significance was also defined as the 95% confidence interval not including the reference value.

Multivariate analyses were carried out through the Cox semiparametric model[15] including gender, age at diagnosis (three or four classes), and period of diagnosis (two periods). Reference categories were selected *a priori* for gender and period of diagnosis. In order to minimise the standard error for age at diagnosis hazard ratios (HRs), the most frequent age group was selected as reference category. Adequacy of data to the proportional hazard assumptions of the Cox model was verified by plotting the logarithm of the cumulative hazard function against the logarithm of survival time, checking for parallelism. All analyses were carried out using SAS 8.2 statistical software.

3. Results

Cumulative survival is presented in Table 2 and Fig. 1, broken down by main diagnostic categories and periods of diagnosis. Median time of follow-up for living cases was 11 (interquartile range IQR 9–12) and 5 (IQR 4–7) years for those diagnosed in 1989–93 and in 1994–98, respectively. Children lost to follow-up were 235 (2.2%).

Table 1 – AIEOP cancer registry, 1989–98 - Distribution of childhood cancer cases reported to the dataset by histological type, gender and period of diagnosis

	Total	Gender		Period of diagnosis	
		Boys	Girls	1989–93	1994–98
Leukaemias	4279	2362	1917	2103	2176
Acute lymphocytic leukaemia	3541	1953	1588	1732	1809
Acute non-lymphocytic leukaemia	650	369	281	320	330
Lymphomas	1398	950	448	674	724
Hodgkin's lymphoma	542	342	200	251	291
Non-Hodgkin lymphoma	854	606	248	422	432
Tumours of the Central Nervous System	1333	757	576	553	780
Astrocytomas	496	258	238	177	319
Intracranial PNET[a]	418	270	148	184	234
Neuroblastoma and ganglioneuroblastoma	954	535	419	472	482
Other sympathetic nervous system tumour	28	15	13	16	12
Retinoblastoma	187	90	97	83	104
Renal tumours	607	273	334	291	316
Wilms' tumour	555	243	312	273	282
Liver tumours	114	62	52	57	57
Bone tumours	596	295	301	324	272
Osteosarcoma	309	140	169	177	132
Ewing's sarcoma	263	142	121	136	127
Soft tissue sarcomas	725	425	310	372	353
Rhabdomyosarcoma and embryonal sarcoma	401	244	157	206	195
Peripheral PNET[a]	93	51	42	42	51
Germinal and gonadal tumours	304	141	163	134	170
Carcinomas and other epithelial malignant tumours	99	50	49	53	46
Myelodysplasia	91	54	37	41	50
Malignant histiocytosis	46	26	20	19	27
Other and unspecified malignant neoplasms	30	17	13	10	20
All childhood cancers	10791	6042	4749	5202	5589

a Primitive neuroectodermal tumour.

Table 2 – AIEOP cancer registry, 1989–98 - Cumulative survival (CS) of childhood cancer cases reported to the dataset by main diagnostic categories and period of diagnosis

Years since diagnosis	N.	Cumulative survival (95% CI)			
		1	3	5	10
Period 1989–98					
Total	10791	89 (89–90)	77 (76–77)	73 (72–73)	69 (69–70)
Lymphoproliferative disorders (leukaemias, lymphomas and MDS[a])	5768	90 (90–91)	80 (79–81)	76 (75–77)	73 (72–75)
Solid tumours	5023	88 (87–89)	73 (71–74)	68 (67–70)	65 (64–66)
Period 1989–93					
Total	5202	88 (87–89)	74 (73–75)	70 (68–71)	66 (65–68)
Lymphoproliferative disorders (leukaemias, lymphomas and MDS[a])	2818	88 (87–90)	77 (76–79)	73 (71–74)	70 (68–71)
Solid tumours	2384	88 (87–89)	70 (69–72)	66 (64–68)	62 (60–64)
Period 1994–98					
Total	5589	90 (90–91)	79 (78–80)	75 (74–77)	–
Lymphoproliferative disorders (leukaemias, lymphomas and MDS[a])	2950	92 (91–93)	82 (81–84)	80 (78–81)	–
Solid tumours	2639	88 (87–89)	75 (73–76)	71 (69–72)	–

a Myelodysplastic syndromes.

Adjusted hazard ratios (HR) of dying for age at diagnosis, gender and quinquennial period of diagnosis are reported in Tables 3 and 4. Infants with neuroblastoma had better prognosis (HR 0.25, 95% CI 0.18–0.35) than older children. On the contrary, infants with acute lymphocytic leukaemia (ALL) (HR 4.1, 95% CI 3.0–5.7) or an acute non-lymphocytic leukaemia (AnLL) (HR 2.4, 95% CI 1.6–3.5) fared worst. Children with ALL diagnosed in the age class 1–4 years exhibited the best outcome in respect to all the other age classes. Among children with intracranial primitive neuroectodermal tumour (PNET) or Ewing's sarcoma, those aged 0–4 had the highest HR of death, while patients with astrocytoma had the lowest HR. The survival trend for Wilms' tumour suggests a poorer prognosis for older children. In particular, the risk of death for children with Wilms' tumour diagnosed at age 3–14 was twice as high as for children diagnosed earlier (HR 2.3, 95%

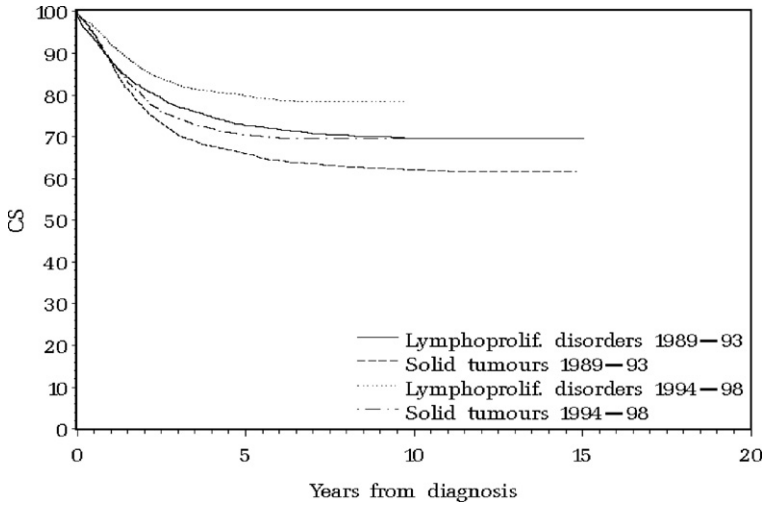

Fig. 1 – AIEOP cancer registry, 1989–98. Cumulative survival of childhood cancer cases reported to the dataset by main diagnostic categories and period of diagnosis.

Table 3 – AIEOP cancer registry, 1989–98 - Multivariate survival analysis for childhood cancer cases reported to the dataset

		Age at diagnosis			
		0	1–4	5–9	10–14
Acute lymphocytic leukaemia	N.	92	1765	1091	593
	HR	4.1 (3.0–5.7)	1[a]	1.6 (1.4–1.9)	2.6 (2.2–3.1)
Acute non-lymphocytic leukaemia	N.	63	207	181	199
	HR	2.4 (1.6–3.5)	1[a]	1.2 (0.88–1.6)	1.2 (0.87–1.6)
Neuroblastoma	N.	322	498	109	25
and ganglioneuroblastoma	HR	0.25 (0.18–0.35)	1[a]	1.1 (0.84–1.5)	0.90 (0.51–1.6)
Retinoblastoma	N.	74	106	6	1
	HR	1.3 (0.46–3.4)	1[a]	Too few cases	
Wilms' tumour	N.	71	325	134	25
	HR	0.77 (0.32–1.8)	1[a]	1.6 (0.95–2.6)	2.2 (0.91–5.1)

		Age at diagnosis		
		0–4	5–9	10–14
Hodgkin's lymphoma	N.	47	169	326
	HR	No events	0.85 (0.36–2.0)	1[a]
Non-Hodgkin lymphoma	N.	213	312	329
	HR	0.77 (0.54–1.1)	0.73 (0.53–1.0)	1[a]
Astrocytoma	N.	180	172	144
	HR	1[a]	1.5 (1.1–2.3)	2.1 (1.4–3.1)
intracranial PNET[b]	N.	164	157	97
	HR	1[a]	0.52 (0.38–0.72)	0.62 (0.43–0.88)
Osteosarcoma	N.	19	67	223
	HR	1.6 (0.74–3.2)	0.95 (0.60–1.5)	1[a]
Ewing's sarcoma	N.	32	85	146
	HR	1.8 (1.1–3.1)	0.95 (0.60–1.5)	1[a]
Rhabdomyosarcoma	N.	197	106	98
and embryonal sarcoma	HR	1[a]	0.50 (0.31–0.80)	1.8 (1.3–2.6)
Other cancer types	N.	713	396	512
	HR	1[a]	1.0 (0.83–1.3)	1.0 (0.84–1.3)
All childhood cancers	N.	5062	3011	2718
	HR	1[a]	1.1 (1.0–1.2)	1.3 (1.2–1.4)

Tumour type-specific hazard ratios (HRs) and 95% confidence intervals (in brackets) for age at diagnosis (adjusted for gender and period of diagnosis). The cancer categories were broken down in three or four age groups according to clinical criteria. The most frequent age group was selected as reference category.

a Reference category.

b Primitive neuroectodermal tumour.

Table 4 – AIEOP cancer registry, 1989–98 - Multivariate survival analysis for childhood cancer cases reported to the dataset

Reference category	HR	
	Gender Boys	Period of diagnosis Cases diagnosed during 1989–1993
Acute lymphocytic leukaemia	0.72 (0.62–0.83)	0.81 (0.70–0.94)
Acute non-lymphocytic leukaemia	0.84 (0.67–1.1)	0.60 (0.48–0.75)
Hodgkin's lymphoma	1.2 (0.53–2.6)	0.31 (0.12–0.78)
Non-Hodgkin lymphoma	0.78 (0.57–1.1)	0.76 (0.56–1.0)
Astrocytoma	1.1 (0.78–1.4)	1.1 (0.81–1.5)
intracranial PNET[a]	0.85 (0.63–1.2)	0.91 (0.68–1.2)
Neuroblastoma and ganglioneuroblastoma	0.73 (0.59–0.90)	0.92 (0.74–1.1)
Retinoblastoma	0.63 (0.23–1.7)	0.48 (0.18–1.3)
Wilms' tumour	1.3 (0.81–2.1)	0.50 (0.30–0.82)
Osteosarcoma	1.2 (0.80–1.7)	0.73 (0.50–1.1)
Ewing's sarcoma	1.2 (0.78–1.7)	1.1 (0.75–1.7)
Rhabdomyosarcoma and embryonal sarcoma	1.2 (0.89–1.7)	0.80 (0.57–1.1)
Other cancer types	0.99 (0.83–1.2)	0.74 (0.62–0.89)
All childhood cancers	0.87 (0.81–0.94)	0.80 (0.74–0.86)

Tumour type-specific hazard ratios (HRs) and 95% confidence interval (in brackets): by gender (adjusted for age at diagnosis and period of diagnosis; reference category: boys) and by period of diagnosis (adjusted for gender and age at diagnosis; reference category: cases diagnosed during 1989–1993).

a Primitive neuroectodermal tumour.

CI 1.4–4.1). Among children with rhabdomyosarcoma and embryonal sarcoma, the best prognosis was observed in the 5–9 year age group (HR 0.50, 95% CI 0.31–0.80).

Gender was a survival predictor for children with ALL (Log-rank test: $p < 0.0001$) and neuroblastoma ($p = 0.02$) (Table 4, Figs. 2 and 3): the statistically significant lower hazard ratios for girls (compared to boys) for these two cancer types (HR 0.72, 95% CI 0.62–0.83 for ALL; 0.73, 0.59–0.90 for neuroblastoma) accounts for the corresponding observation on all cancers considered together.

Survival improved for children diagnosed during the second time period compared to those diagnosed during 1989–93 (Table 4). A statistically significant improvement of prognosis was observed for all childhood cancers (HR 0.80, 95% CI 0.74–0.86) and for some specific categories: ALL (HR 0.81, 95% CI 0.70–0.94), AnLL (HR 0.60, 95% CI 0.48–0.75), Hodgkin's lymphoma (HR 0.31, 95% CI 0.12–0.78) and Wilms' tumour (HR 0.50, 95% CI 0.30–0.82).

An additional analysis of time trend was carried out for ALL cases broken down into four 30-month periods of diagnosis. Survival rates improved clearly for children aged 1–4 and 10–14 at diagnosis, whereas they fluctuated for children aged 5–9 and did not show any improvement for infants (Table 5). Based on four 30-month periods of diagnosis, the survival advantage of girls with ALL tended to be somewhat less evident (and lost statistical significance) with time. Over these four periods the hazard ratios for girls were respectively 0.70 (95% CI 0.53–0.91), 0.73 (0.55–0.97), 0.72 (0.53–0.96), and

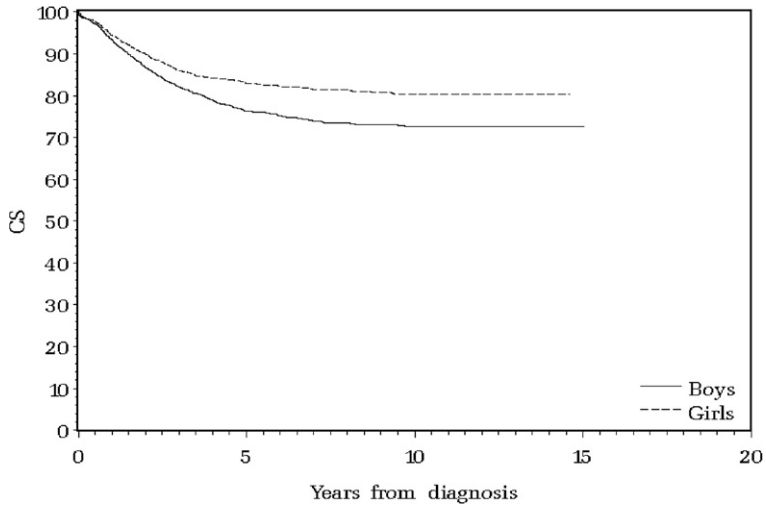

Fig. 2 – AIEOP cancer registry, 1989–98. Cumulative survival for acute lymphocytic leukaemia cases.

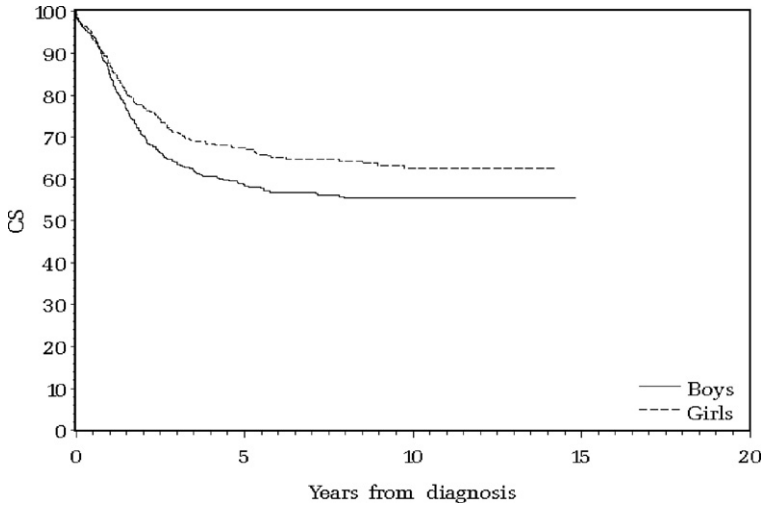

Fig. 3 – AIEOP cancer registry, 1989–98. Cumulative survival for neuroblastoma and ganglioneuroblastoma cases.

Table 5 – AIEOP cancer registry, 1989–98 - Multivariate survival analysis for acute lymphocytic leukaemia cases reported to the dataset

	Age at diagnosis			
	0	1–4	5–9	10–14
Jan 1 1989 to June 30 1991	1[a]	1[a]	1[a]	1[a]
July 1 1991 to Dec 31 1993	1.6 (0.60–4.0)	0.75 (0.55–1.0)	1.2 (0.89–1.7)	0.78 (0.54–1.1)
Jan 1 1994 to June 30 1996	1.5 (0.65–3.4)	0.83 (0.60–1.1)	1.1 (0.78–1.6)	0.85 (0.58–1.2)
July 1 1996 to Dec 31 1998	1.3 (0.55–2.9)	0.50 (0.34–0.73)	0.74 (0.50–1.1)	0.59 (0.40–0.88)

Adjusted hazard ratios by age at diagnosis and period of diagnosis and 95% confidence interval (in brackets). Adjusted hazard ratios were computed according to the Cox model including gender, age at diagnosis and period of diagnosis.
a Reference category.

0.77 (0.54–1.1). The more favourable outcome for females was not observed in infant ALL, for which the hazard ratio for females, based on 92 cases, was 1.6 (95% CI 0.81–3.1).

For neuroblastoma, female gender was a prognostic predictor for children with increasing age, albeit not statistically significant. Hazard ratios of dying for girls aged 0, 1–4, 5–9 and 10–14 were 0.94 (95% CI 0.51–1.7), 0.73 (0.56–0.94), 0.67 (0.39–1.2) and 0.27 (0.05–1.4), respectively.

Girls with Wilms' tumour did not fare statistically better than boys (HR 1.3, 95% CI 0.81–2.1), overall and stratified by age classes. Hazard ratios for girls aged 0, 1–4, 5–9 and 10–14 were 1.3 (95% CI 0.27–6.8), 1.3 (0.66–2.5), 1.0 (0.45–2.4) and 1.9 (0.30–11.9), respectively.

4. Discussion

In terms of natural history of childhood cancers, our data confirm findings from clinical series in the Western world.[5–8] The survival rates for childhood cancer observed from the present hospital-based study compare favourably with recent population-based reports.[6,8,19] However, some observations are worth noticing and deserve comments.

The prognostic importance of age and gender for ALL is well known. The relatively poorer prognosis in boys is due not only to risk of testicular relapses, but also because of the higher frequency in boys of T-cell disease, with high leukocyte count, organomegaly and mediastinal masses at diagnosis.[8,16] Recent protocols have addressed the prevention of testicular relapses using high-dose methotrexate, and consolidation treatment for other negative prognostic factors (i.e. T-Cell ALL) which are more frequent among boys. In Italy, over the decade covered by the present series, there was a moderate, albeit non statistically significant, increase of the hazard ratio for girls (from 0.70 to 0.77). As previously reported,[16] in spite of the availability of refined therapeutic strategies intended to prevent the negative prognostic factors, in the late 1990s, Italian boys with ALL still had increased risk of treatment failure compared to girls. In the United States, a marked difference in 5-year survival around 1980 (57% in boys versus 66% in girls) had largely disappeared 10 years later (respectively 75% and 79%).[8] In a previous analysis of data from European Cancer Registries, among childhood ALL cases diagnosed in 1978–1992, the hazard ratio for girls was 0.76 (95% CI 0.71–0.82).[17] According to a recent study, no gender-related variation in survival of children with ALL was found in a population-based study of cases diagnosed in France since 1990.[18,19] In clinical trials with high 5-year EFS rates (>80%), male gender is no longer an adverse risk factor.[20] However, the extent and the pace at which the new therapeutic strategies have been adopted in different countries is not known.

The risk of death for infants with ALL was significantly higher compared to age 1–4 years. Thus, the present series

(92 cases) confirms the relatively poor outcome for infants affected by ALL[7,16,21,22] and indicates that, until the end of last century, in Italy, there was no improvement in the prognosis of this condition.

Survival for AnLL was poorer than for ALL in all age groups, with infants being at highest risk. On the other hand, in Italy, children with AnLL diagnosed in recent years show better survival rates: this is likely to be due to improved chemotherapy programmes including, in selected cases, haematopoietic stem cell transplantation procedures.[8,23]

Survival was higher for infants with neuroblastoma than for older children. The better outcome of neuroblastoma in girls agrees with the SEER findings.[8] No sound biological explanation of this observation has been given. Indeed, neither common texts of paediatric oncology[24] nor reports of the large series[25–28] mention gender as a determinant of prognosis for children with neuroblastoma. In the present study, the distribution of cases by stage at diagnosis was similar in boys and girls.

Survival of children with PNET improved with increasing age, and was poorest in infants. Clinical and biological characteristics such as histological subtypes and lower rate of complete surgical removal of the tumour in younger children have been associated to differences in survival. A further reason for the low survival rate observed in younger children might be that these cases are usually treated with protocols avoiding or delaying radiotherapy to limit late effects. In addition, delay in diagnosis might also be a further negative determinant of survival in infants and young children, as unspecific symptoms make diagnosis difficult until a tumour reaches large volume.[24]

Our data do not confirm findings of the SEER series[8] suggesting that girls with Wilms' tumour have better survival than boys. In the present study, children diagnosed with this cancer in the age group 0–3 years at diagnosis had a more favourable prognosis than the older groups.[29,30] This observation might be related to histological features such as invasion of the tumour capsule, presence of an inflammatory pseudocapsule, invasion of the renal sinus or intrarenal vessels.[31] These features are significantly less frequent in younger children even if they do not influence the tumour stage.

The present study confirms the importance and usefulness of a clinical registry of childhood cancer based on a national cooperation of clinical centres in spite of the limited individual clinical information which can be systematically validated. The coverage of the present database was not uniformly distributed over the national territory, with a higher underrepresentation of Southern regions. Nevertheless, the coverage was considerably high both in the North-Centre and South of Italy and survival figures obtained trough the analysis of this database can therefore be considered representative for the whole of Italy.

Through internal comparisons - such as those based on gender, age or period of diagnosis - this dataset has the potential to identify some critical aspects of the delivery of cancer care in a country like Italy. No significant difference in survival across macro-areas (North, Centre, South-Isles) of residence was observed in this database. Similar figures were described in a recent report from the Italian network of Cancer Registries (AIRTUM),[3] based on 2142 Italian children with cancer diagnosed during 1998–2002. Further studies may consider the distribution of the clinical variables in children with cancer. A major goal is to estimate the outcome of children with cancer in Italy who are currently treated according to national standard protocols in comparison with children treated according to therapeutic strategies designed locally.

Conflict of interest statement

None declared.

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Appendix A

AIEOP Centres: Madon E. (Torino), Dini G. (Genova), Carnelli V., Fedeli F., Fossati Bellani F. (Milano), Masera G. (Monza-MI), Locatelli F. (Pavia), Cornelli P.E. (Bergamo), Porta F. (Brescia), Dorizzi A., Nespoli L. (Varese), Carli M. (Padova), Marradi P. (Verona), Rodeghiero F., Musi L. (Vicenza), Tamaro P. (Trieste), Mascarin M. (Aviano), Nocerino A. (Udine), Izzi G. (Parma), Paolucci P. (Modena), Pession A., Ambrosioni G., Picci P.(Bologna), Borgna Pignatti C. (Ferrara), Bernini G. (Firenze), Morgese G. (Siena), Favre C. (Pisa), Aversa F. (Perugia), Pierani P. (Ancona), Di Marzio A. (Pescara), Foà R., De Rossi G., Donfrancesco A., Castello M.A. (Roma), Casale F., Poggi V., Auricchio S., Antonelli P. (Napoli), Ladogana S. (S. Giovanni Rotondo-FG), De Mattia D. (Bari), Magro S. (Catanzaro), Nobile F. (Reggio Calabria), Aricò M. (Palermo), Schilirò G. (Catania), Gallisai D. (Sassari), Argiolu F. (Cagliari).

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