EUROPEAN JOURNAL OF CANCER 43 (2007) 2545–2552

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Health-related quality of life of long-term childhood cancer survivors: A population-based study from the Childhood Cancer Registry of Piedmont, Italy

Daniela Alessi[a], *Elisa Dama*[a], *Ronald Barr*[b], *Maria Luisa Mosso*[a], *Milena Maule*[a], *Corrado Magnani*[a,c], *Guido Pastore*[a,d,*], *Franco Merletti*[a]

[a]*Childhood Cancer Registry of Piedmont, Cancer Epidemiology Unit, CeRMS and CPO-Piemonte, University of Turin, Italy*
[b]*Division of Haematology-Oncology, Department of Paediatrics, McMaster University, Hamilton, Ontario, Canada*
[c]*Unit of Medical Statistics and Epidemiology, CPO Piemonte and Department of Medical Sciences, University of Eastern Piedmont, Novara, Italy*
[d]*Division of Paediatrics, Department of Medical Sciences, University of Eastern Piedmont, Novara, Italy*

ARTICLE INFO

Article history:
Received 12 April 2007
Received in revised form 20 July 2007
Accepted 31 July 2007
Available online 14 September 2007

Keywords:
Childhood cancer survivors
Health-related quality of life
Population-based study
Cancer registry

ABSTRACT

Aim of the study: To determine the Health Related Quality of Life (HRQL) in a population-based cohort of long-term survivors of childhood cancer in Piedmont, northwestern Italy.

Patients and methods: During 2003, a 15-item Health Utilities Index questionnaire was mailed to 1005 5-year survivors, identified from the population-based Childhood Cancer Registry of Piedmont, to derive scores for overall HRQL and for eight single attributes of health. Score differences were estimated as adjusted prevalence odds ratios.

Results: A large majority of long-term survivors had moderately high scores for overall HRQL and for each of the single attributes. Males reported better overall HRQL and less morbidity with respect to dexterity, emotion and pain than females. Survivors diagnosed when they were 10–14 years of age had better overall HRQL and less morbidity with respect to emotion, cognition and pain than younger persons. Long-term survivors of central nervous system (CNS) tumours, retinoblastoma and bone tumours had greater impairment of overall HRQL, vision, ambulation, dexterity, cognition and pain than survivors of other forms of cancer.

Conclusion: Many survivors of childhood cancer in Piedmont had fairly good overall HRQL. Greater probability of impaired HRQL was seen for females, survivors of CNS tumours, retinoblastoma and bone tumours, and persons diagnosed before 10 years of age.

1. Introduction

Among children aged 1–14 years in high-income countries, malignant tumours are the most frequent cause of death, after congenital malformations and accidents.[1] The effectiveness of therapy for cancer increased 5-year survival rates from 40% in 1970 to 75% in 1990,[2] so that a large majority of childhood cancer patients are cured and reach a full-blown

* *Corresponding author:* Present address: Childhood Cancer Registry of Piedmont, Via Santena 7, 10126 Torino, Italy. Tel.: +39 11 6336744; fax: +39 11 6334664.
E-mail address: guido.pastore@maggioreosp.novara.it (G. Pastore).
0959-8049/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2007.07.026

adult life. In industrialised societies, one out of every 1000 persons aged 20–29 years is a survivor of malignant disease in childhood or adolescence.[1,3,4]

These survivors often have to cope with long-term effects of their earlier disease and its therapy, which may occur many years after cure. These adverse sequelae include neurocognitive, sensory, endocrinological and growth dysfunctions, impaired fertility and second malignancies.[5,6] The prevalence and severity of sequelae can differ by a number of variables, including gender, original cancer type, age at diagnosis and length of follow-up. Thus, female survivors have a higher incidence of impairment than males, and long-term survivors of brain tumours have the worst health status of all.[7–9]

The concept of 'cure' in oncology has evolved from simple eradication of cancer to a more complex vision of 'restoration of health',[10] in which 'health' is not limited to physical aspects but also includes other features, grouped into the concept of 'quality of life'. Health status is a component of the multi-dimensional concept of quality of life, which includes psychological adjustment and social life goals (educational level, employment and inter-personal relationships).[6,11] Health-related quality of life (HRQL) is a narrower construct, which focuses on the capacity for living afforded by health status.[11] The present study describes the HRQL, measured by the Health Utilities Index Mark III (HUI3), in a large cohort of survivors of cancer in childhood in Piedmont, north-western Italy, where the population-based Childhood Cancer Registry (CCRP) has been active since 1967. In the study design, information was collected from each survivor and from his or her general practitioner within the National Health Service, and the self-assessments were analysed. To the best of our knowledge, this is the first study of this size on this topic carried out in Europe.

2. Patients and methods

2.1. Study population

The CCRP was established 40 years ago; the procedures and criteria for inclusion in the CCRP database and follow-up and coding of cancer types have been reported elsewhere.[12] From the CCRP files, 1119 survivors aged over 15 years at last follow-up in 2000, and who survived for at least 5 years, were identified. We excluded 114 persons who had emigrated ($n = 3$), died (19), were untraceable (43), had no referring general practitioner (21) or had an untraceable general practitioner (28). The HUI questionnaire was mailed to the remaining 1005 persons during 2003. Details on questionnaires dispatch have been reported elsewhere.[13]

2.2. Health Utilities Index questionnaire

The Health Utilities Index is a family of instruments for measuring health status and HRQL: it is a comprehensive, generic, preference-based system that provides validated, reproducible, reliable measures.[14] The usefulness of preference-based measures of HRQL and the superiority of HUI over other instruments of this type have been reported in detail .[15] It consists of two complementary systems, HUI2 and HUI3, which provide utility scores for overall HRQL and numerous single attributes of health. It has been used in several studies of childhood cancer survivors[16–19] as well as in studies of children with other chronic illnesses.[20] HUI questionnaires are available for self or interviewer administration and in self or proxy report formats.

The HUI3 system classifies the health status of each person with respect to eight attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain). The responses to the questionnaires are converted by coding algorithms into attribute levels, which range from 1 (attribute not impaired) to 5 – for speech, emotion and pain – or 6 – for vision, hearing, ambulation, dexterity and cognition – (maximum level of impairment). The attribute levels provide the single-attribute utility scores, estimated on a scale ranging from 0.00 (worst level) to 1.00 (best level or no impairment). The attribute levels are categorical variables, whereas the utility scores are ordinal variables. The multi-attribute utility score for the measure of overall HRQL, ranging from 0.00 (death) to 1.00 (perfect health), is derived from a combination of the eight single-attribute scores by a multiplicative function.[21,22] Negative scores for HRQL have been interpreted as health states worse than death.[14,21] In previous studies, differences of 0.03 in overall HRQL score and 0.05 in single-attribute utility score were considered to be clinically important.[22]

2.3. Statistical analyses

Descriptive analyses were performed of the single-attribute utility scores and the overall HRQL utility score for each person. Values of the 25th centile were used instead of the median because the majority of survivors reported high values for each attribute (the median for almost all attributes was equal to 1.00).

The relevance of score differences was estimated as prevalence odds ratios (PORs) and 95% confidence intervals (CIs) by multivariate logistic regression; i.e. PORs for having an overall HRQL score in the lowest quartile and PORs for having an impairment of any degree (score < 1.00) in each of the eight single-attribute utility scores. Impairment was estimated by considering as a single category persons with any value lower than 1.00, given the high values reported for each attribute.

Both of these PORs were estimated initially by a univariate logistic regression model for gender, age at diagnosis, era of diagnosis, cancer type (as defined by the International Classification of Childhood Cancer[23]), treatment modalities received or not (chemotherapy, surgery, radiotherapy), age at entry into the study and marital status. PORs were then estimated in a multivariate model taking into account only variables that were significantly different in the univariate model: gender, tumours type and age at diagnosis. All the estimated PORs were adjusted for all variables included in the multivariate model. The reference categories were female gender, leukaemia survivors and persons in whom cancer was diagnosed before they were 5 years of age. In order to minimise the standard error for cancer type PORs, the most numerous cancer type group (leukaemia group) was selected as reference category.

As the selection process adopted is specific but has low sensitivity (i.e. a variable might be excluded as not statistically significant because of negative confounding), we also applied stepwise backward selection; the final models did not change. The same model was used to analyse all impairment types.

3. Results

3.1. Responses

Completed questionnaires were returned by 691 of 1005 survivors (68.8%); 47 questionnaires were excluded from the analyses because they were incomplete or had invalid responses ($n = 38$) or were completed by survivors who had additional chronic diseases (five Down syndrome, one Murphy syndrome, one multiple sclerosis, one β-thalassemia, one paraplegia).

Respondents and non-respondents to the questionnaire had similar characteristics with respect to gender, age at diagnosis, era of diagnosis and cancer type; there were differences in age at entry into the study and marital status.[13] The proportions of non-respondents were 33.4% in the age group 15–24, 31.4% in the age group 25–34 and 28.3% for those aged $\geqslant$ 35. Non-response was significantly lower in the 35–44 year age group than in those aged 15–24 years. The non-response rate was significantly higher among married than single persons. The proportion of respondents among survivors of CNS tumours was 64.7%.

3.2. Characteristics of respondents

Table 1 shows the distribution of the cohort by gender, age at diagnosis, age at entry into the study, period of diagnosis and tumours type. As expected, embryonal tumours (neuroblastoma, Wilms' tumours and retinoblastoma) were the predominant tumours among the youngest children, while lymphomas and sarcomas were commonest in the oldest age group. Due to the peculiar age distribution at diagnosis (embryonal tumours are more frequent in the first years of life) and the eligibility criteria (at least 5 years of age at diagnosis and more than 15 years at the last follow-up in 2000), few children with embryonal tumours diagnosed in the period 1987–1996 entered in the present analysis.

3.3. Health-related quality of life

The values of the 25th centile for the utility scores for single attributes and for overall HRQL are reported for each tumour type in Table 2. The single attribute scores range from 0.67 to 1.00 and the overall HRQL scores encompass an even wider range (0.51 to 0.88); in both instances clearly exceeding the criteria for clinical importance. All individual disease groups had mean HRQL scores below the mean score in the North American adult population (0.90).[24] The morbidity burdens were as anticipated, e.g. visual impairment in survivors of retinoblastoma and compromised ambulation in survivors of bone tumours, the lowest overall HRQL being that of long-term survivors of CNS tumours. The results of the multivariate analyses of overall HRQL are shown in Table 3. Males had

Table 1 – Cohort characteristics by cancer type

Characteristic	Leukaemia *n* (%)	NHL *n* (%)	HD *n* (%)	CNS tumours *n* (%)	NB *n* (%)	RB *n* (%)	WT *n* (%)	Bone tumours *n* (%)	STS *n* (%)	Gonadal Tumours *n* (%)	All other tumours *n* (%)
Gender											
Female	86 (46.0)	15 (32.6)	16 (32.6)	64 (48.1)	14 (40.0)	5 (26.3)	19 (45.2)	19 (61.3)	21 (50.0)	14 (70.0)	22 (55.0)
Male	101 (54.0)	31 (67.4)	33 (67.4)	69 (51.9)	21 (60.0)	14 (73.7)	23 (54.8)	12 (38.7)	21 (50.0)	6 (30.0)	18 (45.0)
Age at diagnosis (years)											
0–4	65 (34.8)	5 (10.9)	4 (8.2)	16 (12.0)	28 (80.0)	18 (94.7)	28 (66.7)	2 (6.5)	10 (23.8)	3 (15.0)	6 (15.0)
5–9	68 (36.4)	15 (32.6)	10 (20.4)	53 (39.9)	3 (8.6)	1 (5.3)	12 (28.6)	6 (19.3)	16 (38.1)	6 (30.0)	10 (25.0)
10–14	54 (28.9)	26 (56.5)	35 (71.4)	64 (48.1)	4 (11.4)	0 (0.0)	2 (4.76)	23 (74.2)	16 (38.1)	11 (55.0)	24 (60.0)
Age at entry into study (years)											
15–24	53 (28.3)	8 (17.4)	5 (10.2)	38 (28.6)	12 (34.3)	4 (21.0)	11 (26.2)	11 (35.5)	15 (35.7)	7 (35.0)	2 (5.0)
25–34	107 (57.2)	28 (60.9)	18 (36.7)	66 (49.6)	13 (37.1)	9 (47.4)	20 (47.6)	12 (38.7)	17 (40.5)	8 (40.0)	15 (37.5)
$\geqslant$35	27 (14.4)	10 (21.7)	26 (49.1)	29 (21.8)	10 (28.6)	6 (31.6)	11 (26.2)	8 (25.8)	10 (22.8)	5 (25.0)	23 (57.5)
Era of diagnosis											
1967–1976	23 (12.3)	4 (8.7)	11 (22.5)	15 (11.3)	11 (31.4)	6 (31.6)	16 (38.1)	4 (12.9)	10 (23.8)	5 (25.0)	20 (50.0)
1977–1986	118 (63.1)	26 (56.5)	28 (57.1)	73 (54.9)	23 (65.7)	13 (68.4)	21 (50)	10 (32.3)	15 (35.7)	6 (30.0)	11 (27.5)
1987–1996	46 (24.6)	16 (34.8)	10 (20.4)	45 (33.8)	1 (2.86)	0 (0.0)	5 (11.9)	17 (54.8)	17 (40.5)	9 (45.0)	9 (22.5)

NHL: non-Hodgkin lymphoma; HD: Hodgkin disease; NB: neuroblastoma; RB: retinoblastoma; WT: Wilms tumour; STS: soft tissue sarcoma.

Table 2 – Single-attribute and overall HRQL utility scores by cancer type (25th centile and range)

Cancer type	Sample size	Overall HRQL	Vision	Hearing	Speech	Ambulation	Dexterity	Emotion	Cognition	Pain
Leukaemia	187	0.85 (−0.2–1.0)	0.95 (0.9–1.0)	1.00 (0.0–1.0)	1.00 (0.0–1.0)	1.00 (0.2–1.0)	1.00 (0.4–1.0)	0.91 (0.0–1.0)	1.00 (0.0–1.0)	0.92 (0.5–1.0)
Non-Hodgkin lymphoma	46	0.88 (0.1–1.0)	0.95 (0.9–1.0)	1.00 (0.0–1.0)	1.00 (0.7–1.0)	1.00 (0.8–1.0)	1.00 (0.9–1.0)	0.91 (0. 3–1.0)	1.00 (0.0–1.0)	0.92 (0.0–1.0)
Hodgkin disease	49	0.85 (−0.2–1)	0.95 (0.4–1.0)	1.00 (0.5–1.0)	1.00 (0.0–1.0)	1.00 (0.7–1.0)	1.00 (0.5–1.0)	0.91 (0.3–1.0)	1.00 (0.3–1.0)	0.92 (0.5–1.0)
Central nervous system tumours	133	0.73 (−0.3–1)	0.95 (0.0–1.0)	1.00 (0.0–1.0)	1.00 (0.0–1.0)	1.00 (0.0–1.0)	1.00 (0.0–1.0)	0.91 (0.0–1.0)	0.86 (0.0–1.0)	0.92 (0.0–1.0)
Neuroblastoma	35	0.75 (0.1–1.0)	1.00 (0.6–1.0)	1.00 (1.0–1.0)	1.00 (0.7–1.0)	1.00 (0.0–1.0)	1.00 (1.0–1.0)	0.91 (0.0–1.0)	1.00 (0.7–1.0)	0.92 (0.0–1.0)
Retinoblastoma	19	0.51 (0.1–1.0)	0.95 (0.0–1.0)	1.00 (1.0–1.0)	1.00 (0.7–1.0)	1.00 (1.0–1.0)	1.00 (0.9–1.0)	0.91 (0.7–1.0)	0.92 (0.0–1.0)	0.92 (0.5–1.0)
Wilms tumour	42	0.85 (0.3–1.0)	0.95 (0.9–1.0)	1.00 (1.0–1.0)	1.00 (0.8–1.0)	1.00 (0.8–1.0)	1.00 (0.9–1.0)	0.91 (0.7–1.0)	1.00 (0.3–1.0)	0.92 (0.8–1.0)
Bone tumours	31	0.75 (−0.1–1.0)	0.95 (0.4–1.0)	1.00 (1.0–1.0)	1.00 (0.8–1.0)	0.67 (0. 7–1.0)	1.00 (0.8–1.0)	0.91 (0.3–1.0)	1.00 (0.3–1.0)	0.92 (0.0–1.0)
Soft tissue sarcomas	42	0.85 (−0.3–1.0)	1.00 (0.9–1.0)	1.00 (1.0–1.0)	0.94 (0.0–1.0)	0.97 (0.2–1.0)	1.00 (1.0–1.0)	0.91 (0.0–1.0)	1.00 (0.0–1.0)	0.92 (0.0–1.0)
Gonadal tumours	20	0.83 (0.1–1.0)	0.95 (0.6–1.0)	1.00 (1.0–1.0)	1.00 (0.8–1.0)	1.00 (0.8–1.0)	1.00 (0.9–1.0)	0.91 (0.0–1.0)	1.00 (0.7–1.0)	0.92 (0.0–1.0)
All other tumours	40	0.88 (0.1–1.0)	0.95 (0.9–1.0)	1.00 (1.0–1.0)	1.00 (0.8–1.0)	1.00 (1.0–1.0)	1.00 (0.9–1.0)	0.91 (0.3–1.0)	1.00 (0.3–1.0)	0.92 (0.8–1.0)

the lowest probability of being in the lowest quartile ($p < 0.0005$) and this has been seen also for persons in whom cancer was diagnosed when they were aged 10–14 years ($p < 0.05$). Survivors of CNS tumours, retinoblastoma and bone tumours had significantly higher probabilities than survivors of leukaemia of being in the lowest quartile ($p < 0.0003$, $p < 0.001$ and $p < 0.005$, respectively). Survivors of Hodgkin disease and of non-Hodgkin lymphoma had similar scores for overall HRQL.

In Table 4 are reported gender, age, age at diagnosis, year of diagnosis, therapies received and the list of the impaired single-attribute (score lower than 0.50) for the 11 survivors who obtained an overall HRQL score lower than or equal to 0.00.

The PORs for sensory attributes (vision and speech) are reported in Table 5, those for motor attributes (ambulation and dexterity) in Table 6 and those for emotion, cognition and pain in Table 7. For simplicity, morbidity burden was measured as 'any impairment'. While this may suppress the demonstrable sensitivity of HUI,[14,22] it affords the clarity of clinical face validity as follows. Long-term survivors of both CNS tumours and retinoblastoma had poorer vision than the other groups, and compromised motor function was evident in survivors of CNS tumours (ambulation and dexterity) and survivors of bone tumours (ambulation). Emotional impairment and pain were less prevalent among male than female survivors. Persons in whom cancer had been diagnosed when they were aged 10–14 years had lower probabilities of having speech impairments, emotional or cognitive morbidity or pain than survivors who had received their diagnosis at an earlier age. The comparison of cancer types showed worse cognition and pain in CNS tumours survivors. Pain was also prevalent in survivors of retinoblastoma and bone tumours.

The effect of era of diagnosis in each analysis gave non-statistically significant results (not shown).

4. Discussion

Most of the long-term childhood cancer survivors in this study had high scores for both overall HRQL and each health attribute assessed. This outcome confirms the results of studies of case series in Austria, Israel and the USA of adolescents and young adults who had survived a malignant disease, even when compared with healthy controls.[25] It has been suggested that the experience and the critical pathway for recovery induce former childhood cancer patients to perceive their present life as particularly valuable, so that the potential impairments due to the cancer or its treatment have a lower impact on their perceived HRQL.[26]

Only gender, cancer type and age at diagnosis had statistically significant impacts on HRQL. No effect was seen of era of diagnosis as a proxy for differences in therapeutic strategies. Our finding that male survivors had a higher probability of having a good overall HRQL and less morbidity in dexterity, emotion and pain than females confirms previous findings that women had poorer physical functioning,[6,7] a greater burden of morbidity with respect to emotional and psychological functioning and a greater tendency to express a negative view of their HRQL.[8,9,27] Female gender was reported as a negative

Table 3 – Prevalence odds ratios (PORs) adjusted for all variables in the table and 95% confidence intervals (CIs) for being in the lowest quartile for overall HRQL by survivors' characteristics

Characteristic	Sample size	% in lowest quartile	PORs (95% CIs)
Gender			
Female	295	31.2	1.00
Male	349	19.8	0.51 (0.35–0.74)
Age at diagnosis (years)			
0–4	185	**28.1**	1.00
5–9	200	27.5	0.94 (0.56–1.57)
10–14	259	20.8	0.59 (0.34–1.01)
Cancer type			
Leukaemia	187	20.9	1.00
Non–Hodgkin lymphoma	46	15.2	0.86 (0.35–2.11)
Hodgkin disease	49	14.3	0.86 (0.35–2.13)
Central nervous system tumours	133	36.8	2.48 (1.47–4.18)
Neuroblastoma	35	25.7	1.23 (0.51–2.96)
Retinoblastoma	19	57.9	5.29 (1.89–14.82)
Wilms tumour	42	16.7	0.67 (0.27–1.65)
Bone tumours	31	41.9	3.21 (1.39–7.44)
Soft tissue sarcomas	42	23.8	1.21 (0.54–2.71)
Gonadal tumours	20	20.0	0.94 (0.29–3.04)
All other tumours	40	12.5	0.60 (0.22–1.65)

Table 4 – Characteristics of 11 survivors with overall HRQL score less than 0.00

Pts	Overall HRQL score	Tumour type	Gender	Age (years)	Age at diagnosis (years)	Year of diagnosis	Therapy received	Impaired single attribute
1	−0.22	Leukaemia	F	23	1	1982	CT + RT	speech/ambulation/dexterity/cognition/pain
2	−0.16	HD	F	35	13	1982	CT + RT + S	vision/hearing/dexterity/cognition/pain
3	−0.01	CNS	F	26	5	1983	RT + S	vision/hearing/ambulation
4	−0.26	CNS	M	29	9	1984	S	vision/ambulation/emotion/cognition
5	−0.06	CNS	F	36	12	1980	CT + RT + S	hearing/emotion
6	−0.04	CNS	F	23	6	1987	RT + S	hearing/ambulation/cognition
7	−0.30	CNS	F	24	12	1992	S	vision/speech/ambulation/dexterity/cognition
8	−0.10	Bone	F	44	8	1968	NA	vision/ emotion/cognition/pain
9	−0.27	STS	F	25	14	1993	CT + RT+ S	emotion/cognition/pain
10	−0.18	STS	F	42	7	1969	NA	emotion/pain
11	−0.02	Gonadic	F	33	14	1985	S	emotion/pain

S: surgery, CT: chemotherapy, RT: radiotherapy, NA: not available.

predictor for somatic distress and depression in lymphoma survivors.[28] Some authors consider this difference between male and female subjects to be an effect of the female propensity to discuss problems more than men,[29] as observed in healthy populations.[30]

In the analysis of HRQL of cancer survivors by diagnostic group, the only consistent differences were observed among the survivors of CNS tumours, who had a high probability of impairment in almost all attributes of health and in overall HRQL when compared with leukaemia survivors, the reference category. These results are in line with others, in which CNS tumours survivors had the poorest health status with regard to multiple attributes[9] and a poorer HRQL due to increased risks for neurocognitive, behavioral and social impairment.[31,32]

Overall HRQL was also greatly impaired in survivors of retinoblastoma and bone tumours due to the poor vision and ambulation, respectively. In our study, the overall utility scores of survivors of Hodgkin disease and non-Hodgkin lymphomas were similar, in contrast to a report that the functioning of the former is as poor as that of CNS tumour survivors.[18]

To further confirm the greater impairment of female and CNS tumours survivors it could be observed that these are the most represented category in the group of survivors that reported an overall HRQL score lower than 0.00, that is considered a health status 'worse than death'.[14,21]

A positive effect of older age at diagnosis was observed for both overall HRQL and for almost all HRQL attributes. The well-defined and peculiar age incidence peak (e.g. leukaemia 3 years[2]) and the different age distribution for selected tumours types could be a confounder for this association. Nevertheless, the positive effect of older age at diagnosis seen on overall HRQL and speech, emotion, cognition and pain attributes, in comparison with persons diagnosed at early age, is better explained with the dramatic effect of anti-neoplastic therapy, especially irradiation, on younger children.

A limitation of our study is the possibility of response-related selection bias on HRQL, although the results of the

Table 5 – Prevalence odds ratios (PORs) adjusted for all variables in the table and 95% confidence intervals (CIs) for reporting an impairment in vision or speech of any degree (score < 1.00) by survivors' characteristics

Characteristic	Sample size	Vision		Speech	
		% reporting impairment	PORs (95% CIs)	% reporting impairment	PORs (95% CIs)
Gender					
Female	295	38.3	1.00	8.1	1.00
Male	349	30.9	0.74 (0.53–1.04)	8.3	1.01 (0.56–1.79)
Age at diagnosis (years)					
0–4	185	**25.4**	1.00	**11.3**	1.00
5–9	200	35.5	1.61 (0.98–2.63)	8.0	0.55 (0.26–1.16)
10–14	259	39.8	1.96 (1.19–3.22)	6.2	0.41 (0.19–0.90)
Cancer type					
Leukaemia	187	32.1	1.00	8.0	1.00
Non-Hodgkin lymphoma	46	30.4	0.80 (0.39–1.63)	6.5	1.02 (0.27–3.78)
Hodgkin disease	49	30.6	0.77 (0.38–1.57)	4.0	0.66 (0.14–3.10)
Central nervoussystem tumours	133	46.6	1.57 (0.98–2.52)	12.0	1.95 (0.90–4.23)
Neuroblastoma	35	17.1	0.56 (0.21–1.45)	8.6	0.79 (0.21–3.00)
Retinoblastoma	19	47.4	2.83 (1.04–7.70)	15.8	1.45 (0.36–5.79)
Wilms tumour	42	28.6	1.01 (0.47–2.16)	2.4	0.22 (0.03–1.72)
Bone tumours	31	45.2	1.32 (0.59–2.92)	6.4	1.10 (0.23–5.27)
Soft tissue sarcomas	42	21.4	0.52 (0.23–1.16)	9.5	1.33 (0.41–4.29)
Gonadal tumours	20	35.0	0.89 (0.33–2.40)	5.0	0.74 (0.09–6.01)
All other tumours	40	30.0	0.74 (0.35–1.58)	7.5	1.16 (0.31–4.30)

Table 6 – Prevalence odds ratios (PORs) adjusted for all variables in the table and 95% confidence intervals (CIs) for reporting an impairment in ambulation or dexterity of any degree (score < 1.00) by survivors' characteristics

Characteristic	Sample size	Ambulation		Dexterity	
		% reporting impairment	PORs (95% CIs)	% reporting impairment	PORs (95% CIs)
Gender					
Female	295	8.5	1.00	7.1	1.00
Male	349	5.4	0.72 (0.37–1.39)	2.8	0.37 (0.17–0.82)
Age at diagnosis (years)					
0–4	185	5.4	1.00	4.3	1.00
5–9	200	5.5	0.70 (0.26–1.89)	7.0	1.14 (0.43–3.05)
10–14	259	8.9	0.86 (0.33–2.21)	3.5	0.45 (0.15–1.36)
Cancer type					
Leukaemia	187	3.7	1.00	3.7	1.00
Non-Hodgkin lymphoma	46	2.2	0.62 (0.07–5.25)	2.2	0.82 (0.09–7.01)
Hodgkin disease	49	6.1	1.77 (0.42–7.46)	4.0	1.88 (0.35–9.99)
Central nervous system tumours	133	9.8	2.89 (1.09–7.68)	9.8	3.18 (1.19–8.49)
Neuroblastoma	35	8.6	2.18 (0.51–9.38)	0.0	–
Retinoblastoma	19	0.0	–	5.3	1.55 (0.17–14.55)
Wilms tumour	42	2.4	0.59 (0.07–5.04)	4.8	1.11 (0.22–5.69)
Bone tumours	31	41.9	18.17 (6.03–54.73)	6.4	2.23 (0.41–12.10)
Soft tissue sarcomas	42	4.8	1.29 (0.26–6.50)	0.0	–
Gonadal tumours	20	5.0	1.28 (0.15–11.24)	10.0	3.04 (0.56–16.50)
All other tumours	40	0.0	–	2.5	0.81 (0.09–6.94)

analyses of non-response in our study[13] do not show any significant association for tumour type, sex or age at diagnosis. This aspect will be addressed in more detail in an extension of the study to general practitioners. Previous studies on the quality of life of survivors of childhood cancer omitted to report their evaluation of non-response.[6,7,9] Another limitation of the present study is the lack of external controls (population norms); however, we consider that the internal comparisons presented in this paper provide an original insight into the HRQL of former childhood cancer patients in Europe.

In conclusion, long-term survivors of cancer in childhood in this large Italian cohort appear to have a good overall HRQL, although females, CNS tumour survivors and persons in whom cancer was diagnosed when they were under 10 years of age are at greater risk of impairment in health status and HRQL. This work should be useful in identifying survivors who need more substantial care in long-term follow-up.

Table 7 – Prevalence odds ratios (PORs) adjusted for all variables in the table and 95% confidence intervals (CIs) for reporting an impairment of any degree (score < 1.00) for the emotion, cognition and pain attributes by survivors' characteristics

Characteristic	Sample size	Emotion		Cognition		Pain	
		% reporting impairment	PORs (95% CIs)	% reporting impairment	PORs (95% CIs)	% reporting impairment	PORs (95% CIs)
Gender							
Female	295	52.9	1.00	22.7	1.00	48.1	1.00
Male	349	42.7	0.59 (0.42–0.81)	19.5	0.79 (0.53–1.16)	35.8	0.51 (0.35–0.74)
Age at diagnosis (years)							
0–4	185	54.0	1.00	**24.9**	1.00	42.1	1.00
5–9	200	54.0	1.05 (0.67–1.63)	23.0	0.78 (0.46–1.31)	42.0	0.94 (0.56–1.57)
10–14	259	37.4	0.52 (0.33–0.82)	16.6	0.55 (0.32–0.96)	40.5	0.59 (0.34–1.01)
Cancer type							
Leukaemia	187	47.1	1.00	21.4	1.00	43.3	1.00
Non–Hodgkin lymphoma	46	37.0	0.84 (0.42–1.67)	17.4	0.93 (0.40–2.20)	36.7	0.86 (0.35–2.11)
Hodgkin disease	49	49.0	1.55 (0.80–3.02)	12.2	0.66 (0.25–1.69)	38.8	0.86 (0.35–2.13)
Central nervous system tumours	133	51.1	1.33 (0.83–2.12)	31.6	1.92 (1.14–3.25)	35.3	2.48 (1.47–4.18)
Neuroblastoma	35	60.0	1.60 (0.74–3.46)	20.0	0.78 (0.31–1.98)	45.7	1.23 (0.51–2.96)
Retinoblastoma	19	63.1	1.82 (0.66–5.02)	26.3	1.09 (0.36–3.33)	57.9	5.29 (1.89–14.82)
Wilms tumour	42	47.7	0.88 (0.44–1.76)	19.0	0.74 (0.31–1.76)	45.2	0.67 (0.27–1.65)
Bone tumours	31	32.3	0.66 (0.28–1.52)	9.7	0.48 (0.13–1.68)	38.7	3.21 (1.39–7.44)
Soft tissue sarcomas	42	59.5	1.76 (0.88–3.54)	21.4	1.05 (0.46–2.39)	45.2	1.21 (0.54–2.71)
Gonadal tumours	20	35.0	0.63 (0.24–1.68)	10.0	0.45 (0.10–2.02)	45.0	0.94 (0.29–3.04)
All other tumours	40	32.5	0.63 (0.30–1.31)	12.5	0.60 (0.22–1.65)	42.5	0.60 (0.22–1.65)

Conflict of interest statement

None declared.

Acknowledgement

The CCRP is supported by the Piedmont Region. This project was supported by the Oncology Special Project, Compagnia di San Paolo FIRMS. The study was carried out within the framework of projects partially supported by the Italian Association for Cancer Research (AIRC).

We especially thank Benedetto Terracini and Giulia Cavrini for reading the manuscript and for useful insights and Micaela Ghisleni for advice. Special thanks also to: Doctor Giorgio Dini, Head of the Haematology-Oncology Department, G. Gaslini Hospital, Genoa; Professor Franca Fossati-Bellani Head of the Paediatric Oncology Department, IRCCS Foundation, National Institute for Tumours Study and Cure, Milan; Professor Enrico Madon, Head of the Department of Paediatric and Adolescence Sciences, University of Turin and Regina Margherita Hospital, Turin; and Professor Giuseppe Masera, Head of the Paediatric Clinic, San Gerardo Hospital, University of Milano Bicocca, Milan for caring patients included in this study. We also thank Ms Accornero-Sperandri.

REFERENCES

1. Gatta G, Corazziari I, Magnani C, Peris-Bonet R, Riazzi P, Stiller CAthe EUROCARE Working Group. Childhood cancer survival in Europe. *Ann Oncol* 2003;**14**:119–27.
2. Šteliarová -Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. *Lancet* 2004;**364**:2097–105.
3. Meadows A. Paediatric cancer survivors: Past history and future challenges. *Curr Probl Cancer* 2003;**27**:112–26.
4. Zuccolo L, Dama E, Maule MM, Pastore G, Merletti F, Magnani C. Updating long-term childhood cancer survival trend with period and mixed analyses: good news from population-based estimates in Italy. *Eur J Cancer* 2006;**42**:1135–42.
5. Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer – Review. *Supp Care Cancer* 2002;**10**:579–600.
6. Shankar S, Robison L, Jenney MEM, et al. Health-related quality of life in young survivors of childhood cancer using the Minneapolis-Manchester Quality of Life-Youth Form. *Paediatrics* 2005;**115**:435–42.
7. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA* 2003;**290**:1583–92.
8. Meadows AT. Paediatric cancer survivorship: research and clinical care. *Review. J Clin Oncol* 2006;**24**:5160–5.
9. Pogany L, Barr RD, Shaw A, Speechley KN, Barrera M, Maunsell E. Health status in survivors of cancer in childhood and adolescence. *Qual Life Res* 2006;**15**:143–57.
10. Schwartz CL. Health status of childhood cancer survivors. Cure is more than eradication of cancer. *JAMA* 2003;**290**:1641–3.
11. Feeny D, Furlong W, Mulhern RK, et al. A framework for assessing health-related quality of life among children with cancer. *Int J Cancer* 1999(Suppl12):2–9.
12. Dama E, Pastore G, Mosso ML, et al. Time trends and prognostic factors for survival from childhood cancer: A report from the Childhood Cancer Registry of Piedmont (Italy). *Eur J Pediatr* 2006;**165**:240–9.
13. Alessi D, Pastore G, Zuccolo L, et al. Analyses of non-response in the assessment of health-related quality of life of childhood cancer survivors. *Eur J Cancer Prev* [in press].

14. Furlong W, Feeny DH, Torrance GW, Barr RD. The Health Utilities Index (HUI) system for assessing health-related quality of life in clinical studies. *Ann Med* 2001;**33**:375–84.
15. Furlong W, Barr RD, Feeny D, Yandow S. Patient-focused measures of functional health status and health-related quality of life in paediatric orthopedics: A case study in measurement selection. *Health Qual Life Outcomes* 2005;**3**:3.
16. Barr RD, Simpson T, Whitton A, Rush B, Furlong W, Feeny DH. Health-related quality of life in survivors of tumours of the central nervous system in childhood – a preference-based approach to measurement in a cross-sectional study. *Eur J Cancer* 1999;**35**:248–55.
17. Cardarelli C, Cereda C, Masiero L, et al. Evaluation of health status and health-related quality of life in a cohort of Italian children following treatment for a primary brain tumours. *Pediatr Blood Cancer* 2006;**46**:637–44.
18. Glaser AW, Furlong W, Walker DA, et al. Applicability of the Health Utilities Index to a population of childhood survivors of central nervous system tumours in the UK. *Eur J Cancer* 1999;**35**:256–61.
19. Van Schaik CS, Barr RD, Depauw S, Furlong W, Feeny D. Assessment of health status and health-related quality of life in survivors of Hodgkin's disease in childhood. *Int J Cancer* 1999:32–8.
20. Eiser C, Morse R. A review of measures of quality of life for children with chronic illness. *Arch Dis Child* 2001;**84**:201–11.
21. Feeny D, Furlong W, Torrance GW, et al. Multiattribute and single-attribute utility functions for the Health Utilities Index Mark 3 system. *Med Care* 2002;**40**:113–28.
22. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI®): concepts, measurement properties and applications. *Health Qual Life Outcomes* 2003;**16**:1–54.
23. Šteliarová-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, 3rd ed. *Cancer* 2005, **103**:1457–1467.
24. Grootendorst P, Feeny D, Furlong W. Health Utilities Index Mark 3: evidence of construct validity for stroke and arthritis in a population survey. *Med Care* 2000;**38**:290–9.
25. Dolgin MJ, Somer E, Buchvald E, et al. Quality of life in adult survivors of childhood cancer. *Soc Work Health Care* 1999;**28**:31–43.
26. Maggiolini A, Grassi R, Adamoli L, et al. Self-image of adolescent survivors of long-term childhood leukaemia. *J Pediatr Hematol Oncol* 2000;**22**:417–42.
27. Barr RD, Sala A. Quality-adjusted survival: A rigorous assessment of cure after cancer during childhood and adolescence. *Pediatr Blood Cancer* 2005;**44**:201–4.
28. Zebrack BJ, Zeltzer LK, Whitton J, et al. Psychological outcomes in long-term survivors of childhood leukaemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study. *Paediatrics* 2002;**110**:42–52.
29. Langeveld NE, Grootenhuis MA, Voute PA, de Haan RJ, van den Bos C. Quality of life, self-esteem and worries in young adult survivors of childhood cancer. *Psychooncology* 2004;**13**:867–88.
30. Maunsell E, Pogany L, Barrera M, Shaw AK, Speechley KN. Quality of life among long-term adolescent and adult survivors of childhood cancer. *J Clin Oncol* 2006;**24**:2527–35.
31. Carpentieri SC, Meyer EA, Delaney BL, et al. Psychosocial and behavioral functioning among paediatric brain tumours survivors. *J Neurooncol* 2003;**63**:279–87.
32. Moore 3rd BD. Neurocognitive outcomes in survivors of childhood cancer. *J Pediatr Psychol* 2005;**30**:51–63.