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## Health-related quality of life and adverse late effects in adult (very) long-term childhood cancer survivors

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### ABSTRACT

#### Purpose:

1. To assess health-related quality of life (HRQoL) of adult long term (up to 20 years) and very long term (>20 years) childhood cancer survivors, compared to the HRQoL of an age matched Dutch population sample.
2. To evaluate the impact of cancer-related adverse late effects on the functional, psychological and social health of childhood cancer survivors.

**Method:** The RAND-36 was used to assess HRQoL in all adult ( $\geq 18$  years) survivors who had attended the long-term follow-up clinic since 1995. The survivors were divided into two groups based on the length of follow-up: Group LF (long term follow-up, follow-up  $\leq 20$  years,  $n = 129$ ) and Group VLF (very long-term follow-up, follow-up  $>20$  years,  $n = 184$ ). Data on diagnosis, treatment and complications were obtained from medical records. Late effects were graded using the CTCAEv3.

**Results:** The RAND-36 was completed by 313 (86.2%) out of 363 eligible patients. Except for higher scores on the subscale Bodily pain, LF patients did not differ significantly on the RAND-36 subscales from the population sample; VLF patients had significant lower scores on the subscales Physical functioning ( $P = 0.003$ ), Social functioning, Vitality and General health perception ( $P < 0.001$ ). Significantly more VLF patients ( $P < 0.001$ ) had severe (grade 3 and 4) late effects (47.8%) compared to LF patients (27.9%). Female gender and especially psycho-social late effects were inversely related to HRQoL.

**Conclusion:** Childhood cancer survivors who were diagnosed more than 20 years ago have lower scores on the RAND 36, and have significantly more severe late effects than those diagnosed more recently. Patients with longer follow-up are more likely to become lost to follow-up. Time has come to establish new models of care for adult childhood cancer survivors, which are more flexible and appropriate to the needs of adult childhood cancer survivors.

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## 1. Introduction

Advances in paediatric cancer therapy have led to long-term survival of more than 70% of patients treated.<sup>1,2</sup> Consequently, there have been a growing number of childhood cancer survivors in the last few decades. Along with the impressive gains in survival, negative long-term consequences related to the disease or its treatment, i.e. adverse late effects, have been acknowledged in the recent literature as well. These late effects can seriously impair the survivors' overall health. It is estimated that physical and/or psychosocial complications will develop in as many as two thirds of these young adults.<sup>3–6</sup> Although not all adult childhood cancer survivors appear to suffer from the late sequelae of their disease and/or treatment, many survivors do seem to experience problems, and often their tolerance of disability appears to decline with time. With the increasing number of long-term childhood cancer survivors, the need to improve their overall well-being or health-related quality of life (HRQoL) is becoming even more important and meaningful. 'Health-related quality of life' is seen as a multidimensional psychological construct, which includes at least four domains: physical, cognitive, social and emotional functioning.<sup>7</sup> In some recent studies of young adult survivors of childhood cancer, only small differences, or no differences at all were found between the HRQoL of survivors and healthy controls or norm data.<sup>8–10</sup> In all of these studies, survivors of childhood cancer are still young and the mean time since diagnosis is less than 20 years. But less is known about the HRQoL of survivors diagnosed more than 20 years ago.

Patients' perception of their quality of life may change over time. For example, many cancer patients report benefits from their illness, ranging from an increased ability to appreciate each day, to greater feelings of personal strength, such as more satisfaction with their global quality of life than healthy comparison groups.<sup>11–14</sup> This paradox is considered to reflect a psychological adaptation that occurs in cancer patients as well as in patients with other chronic diseases.<sup>15</sup> It is possible that this mechanism will decline as time since diagnosis increases and adverse late effects appear. With advancing age there is more chance of additional major life events, developing a functional limitation or experiencing chronic disease, which may influence the quality of life. We expected that survivors diagnosed more than 20 years ago might have more serious late effects and subsequently experience their HRQoL as worse compared to survivors diagnosed more recently.

The main purpose of this study was to assess HRQoL of adult long term (up to 20 years) and very long term (>20 years) survivors of childhood cancer, compared to the HRQoL of a comparable group of the Dutch population. The second purpose was to grade treatment- and cancer-related late effects and their impact on the functional, psychological and social health of the childhood cancer survivors.

## 2. Patients and methods

The present study was performed at the Division of Pediatric Oncology of the University Medical Center in Groningen (UMCG), The Netherlands. Three hundred sixty three survivors were included in this study. The study population was

composed of 227 childhood cancer survivors and patients with Langerhans cell histiocytosis (LHC),  $\geq 18$  years, treated with chemo and/or radiotherapy, who had attended the long-term follow-up (LTFU) clinic since 1995. In addition an at-random sample of 136 survivors out of 336 eligible survivors who had been treated in the Department of Pediatric Oncology in the past, but were not yet involved in any kind of follow-up, were recalled to the LTFU clinic and included in this study.

Furthermore, eight bone tumour survivors (osteosarcoma or Ewing's sarcoma) who were older than 18 years at the time of diagnosis and whose chemotherapy at that time had been delivered by the paediatric oncologist were included as well. Brain tumour survivors were not included because they are followed at a separate clinic. All patients were seen by a doctor with special interest in late effects. According to their diagnosis and treatment in the past, the patients underwent risk-based evaluations such as hormonal assessments, echocardiography, bone mineral density tests or pulmonary function tests.

All late effects diagnosed by means of history, physical examination or testing were recorded in a database. Medical data on diagnosis, treatment and health problems were obtained from this registry of the local LTFU clinic. To determine the need for medical and psychosocial care, late effects were graded in terms of severity and the survivors' QoL was measured with the RAND-36. In order to compare the HRQoL between survivors with different lengths of follow-up, we divided the study population into a LF group (LTFU  $\leq 20$  years  $n = 129$ ) and a VLF group (very LTFU, follow up  $> 20$  years  $n = 184$ ).

The cut-off point of 20 years was based on the fact that to our knowledge in the literature no HRQoL studies have been performed that included a significant number of survivors diagnosed more than 20 years ago.

### 2.1. Health-related quality of life (HRQoL)

We used the RAND-36<sup>16</sup> to assess HRQoL. The RAND-36 is an internationally used valid and reliable generic self-report questionnaire to assess HRQoL. It contains eight different subscales: physical functioning (PF), social functioning (SF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), mental health (MH), vitality (VT), bodily pain (BP) and general health perception (GH). For each subscale, scores were coded, summed up and transformed to a scale from 0 (worst health) to 100 (best health). The questionnaire takes about 10 min to complete. The instrument has been translated in Dutch<sup>17</sup> and has been validated for the Dutch population.<sup>18</sup> For the LF patients we used the mean scores of the available Dutch norm group, aged 18–34 years ( $n = 356$ ), and for the VLF patients the mean scores of the available Dutch norm group, aged 25–44 years ( $n = 416$ ).

### 2.2. Grading of late effects

Late effects were graded using the Common Terminology Criteria for Adverse Events, Version 3 (CTCAEv3), developed by the National Cancer Institute (NCI). The NCI common toxicity criteria (CTCv1.0) was created in 1983 to aid in the recognition and grading adverse effects of chemotherapy. It was updated

and expanded in 1998 (CTCv2.0) but remained focused on acute effects.<sup>19</sup> The third version of the CTC has been renamed as common terminology criteria for adverse events v 3.0. The CTCAEv3 represents the first comprehensive, multimodality grading system to include both acute and late effects.<sup>20</sup>

The CTCAEv3 grades adverse effects from 0 to 4. Grade 1 effects are minimal and usually asymptomatic. Grade 2 effects are moderate, are usually symptomatic but do not impair activities of daily living. Grade 3 effects are considered severe requiring more serious interventions. Grade 4 effects are potentially life threatening. Low-grade events (Grades 1 and 2) are considered tolerable and manageable and should be distinguished from severe or very undesirable high-grade events (Grades 3 and 4).

### 2.3. Analysis

The statistical package for social sciences (SPSS) Windows version 11.0 was used for the statistical analyses. Descriptive statistics were calculated for all of the variables. Differences between the mean scores of the RAND-36 in the survivors groups and the Dutch standard population were tested with the One-Sample T-test. Differences in mean scores of the RAND-36 between LF- and VLF patients were analysed with the Student's t-test. Categorical variables were analysed using the Pearson Chi-Square test. Univariate relationships between demographic, medical and treatment on the one hand, and RAND-36 scores on the other hand were assessed by Pearson's correlation coefficients. To investigate which variables predict the survivors QoL, all significant characteristics identified from univariate analysis were studied with multiple linear regression analysis. A significance level of  $P < 0.05$  was applied in all the analyses.

## 3. Results

The RAND-36 was sent to 363 survivors, who fulfilled the inclusion criteria and returned, by 313 patients (response rate 86.2%). The characteristics of patients who returned the questionnaire were compared with the characteristics of those who did not. The respondents were older (median age 29, range 19–60) than the non-respondents (median age 25, range 20–39) and the time since diagnosis in the respondents was longer (median duration 23 years, range 7–38) than that in the non-respondents (median duration 17.5 years, range 9–34). No significant differences were found in gender, diagnosis, age at diagnosis and health problems as registered at the LTFU clinic.

The demographic and clinical data of the 313 included LF and VLF survivors are shown in Table 1. The survivors had been treated for a variety of cancers or LCH. The most frequent diagnoses were leukaemia, malignant lymphoma, bone tumour and Wilms' tumour. Due to the inclusion criteria, VLF patients were older and the time since diagnosis was longer.

More VLF leukaemia patients had undergone cranial radiation (CR) (42.4%) than LF leukaemia patients (14.7%,

**Table 1 – Demographic and clinical data of 313 participating LF and VLF survivors**

	LF group (n = 129)	VLF group (n = 184)
<i>Patient characteristics</i>		
Age at study <sup>b</sup>	24 (19–45)	32 (21–60) <sup>a</sup>
Age at diagnosis <sup>b</sup>	10 (0–27)	5 (0–38) <sup>a</sup>
Time since diagnosis <sup>b</sup>	16 (7–20)	26 (21–38) <sup>a</sup>
Male <sup>c</sup>	68 (52.7)	94 (51.1)
<i>Type of cancer<sup>c</sup></i>		
Leukaemia	53 (41.1)	80 (43.5)
Malignant lymphoma	34 (26.4)	24 (13.0)
Bone tumour	12 (9.3)	26 (14.1)
Soft tissue sarcoma	7 (5.4)	16 (8.7)
Wilms' tumour	10 (7.8)	12 (6.5)
Langerhans cell histiocytosis	3 (2.3)	11 (6.0)
Other	10 (7.8)	15 (8.2)
<i>Treatment<sup>c</sup></i>		
Cranial radiation	19 (14.7)	78 (42.4) <sup>a</sup>
Chemotherapy only	70 (54.3)	65 (35.3) <sup>a</sup>
Radiotherapy only	6 (4.7)	7 (3.8)
Chemo-and radiotherapy	45 (34.9)	108 (58.7) <sup>a</sup>
<i>Late effects<sup>c</sup></i>		
No late effect	45 (34.9)	16 (8.7) <sup>a</sup>
Mild late effect	48 (37.2)	80 (43.5)
Severe late effect	36 (27.9)	88 (47.8) <sup>a</sup>

a  $P < 0.001$ .

b Years, median (range).

c Number (%).

$P < 0.001$ ) and they had received more often a combination of chemo-and radiotherapy (58.7% versus 34.9%,  $P < 0.001$ ). VLF patients had significant more severe late effects (47.8%) than LF patients (27.9%,  $P < 0.001$ ) (Table 1).

### 3.1. Quality of life (RAND-36)

The outcomes on the various subscales of the RAND-36 for the standard population, the LF patients, and the VLF patients are shown in Table 2. LF patients did not score significantly lower on the RAND-36 subscales compared to the standard population. On the subscale Bodily pain, they even scored significantly better ( $P < 0.01$ ). VLF survivors showed worse HRQoL scores in comparison to the standard population on the subscales physical functioning (PF,  $P < 0.01$ ), social functioning (SF,  $P < 0.001$ ), vitality (VT,  $P < 0.001$ ) and general health perception (GH,  $P < 0.001$ ).

Fig. 1 shows the differences on the various RAND dimensions between the LF and VLF patients in comparison with the age matched standard population. Difference scores were calculated by subtracting mean outcomes of the standard population from the results of the LF and VLF patients. Negative difference scores indicate worse outcomes than in the standard population. Compared with LF patients, VLF patients scored significantly worse on the subscales PF ( $P < 0.01$ ), RP ( $P < 0.05$ ), VT ( $P < 0.05$ ), BP ( $P < 0.001$ ) and GH ( $P < 0.05$ ).

In Fig. 2, the difference scores for the various RAND dimensions are shown for patients treated with chemotherapy

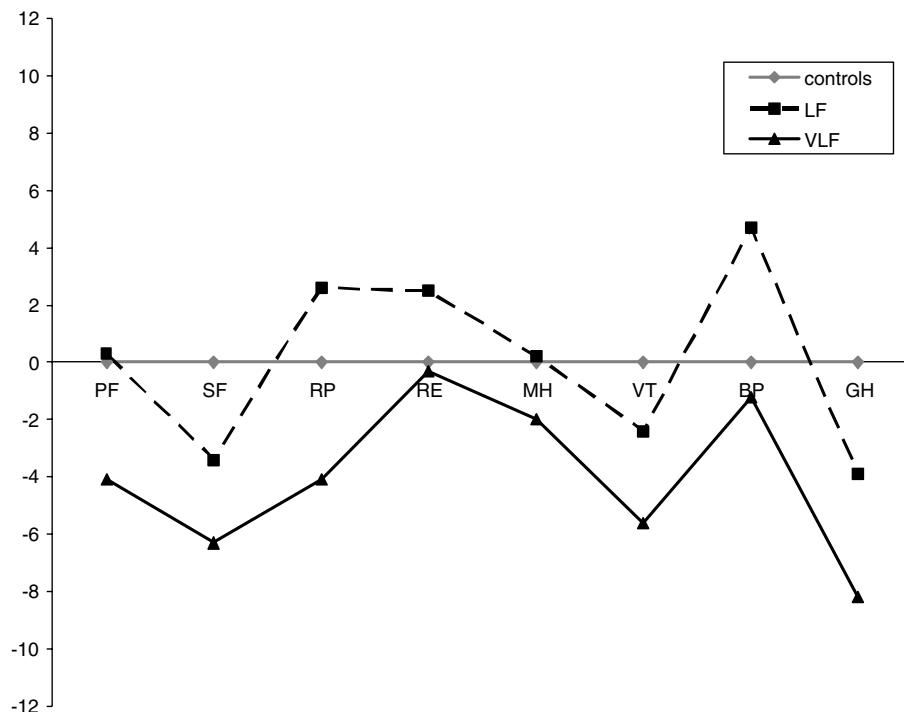
**Table 2 – Means and standard deviations for the RAND-36 subscales for LF patients, VLF patients and the Dutch comparison groups LF (18–34 years) and VLF (25–44 years)**

	LF patients (n = 129)		VLF patients (n = 184)		Comparison group LF (n = 356)		Comparison group V LF (n = 416)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PF	90.6	14.1	85.6 <sup>a</sup>	18.7	90.3	16.6	89.7	16.3
SF	85.2	22.8	83.0 <sup>b</sup>	21.1	88.7	18.3	89.4	17.0
RP	86.4	27.8	78.6	33.8	83.8	31.2	82.7	32.2
RE	87.1	30.2	84.3	32.2	84.6	31.5	84.6	31.5
MH	77.0	16.9	75.9	15.3	76.8	18.7	77.9	17.7
VT	66.7	19.6	62.6 <sup>b</sup>	19.6	69.1	18.8	68.2	18.9
BP	90.1 <sup>b</sup>	16.9	82.8	19.8	85.5	22.8	84.0	22.9
GH	73.5	18.0	67.7 <sup>b</sup>	22.6	77.4	20.0	75.9	20.2

LF: long term follow-up  $\leq 20$  years; VLF: very long-term follow-up  $> 20$  years; PF: physical functioning; SF: social functioning; RP: role limitations due to physical problems; RE: role limitations due to emotional problems; MH: mental health; VT: vitality; BP: bodily pain; GH: general health perceptions.

a  $P < 0.01$ : difference between survivors and comparison group.

b  $P < 0.001$ : difference between survivors and comparison group.

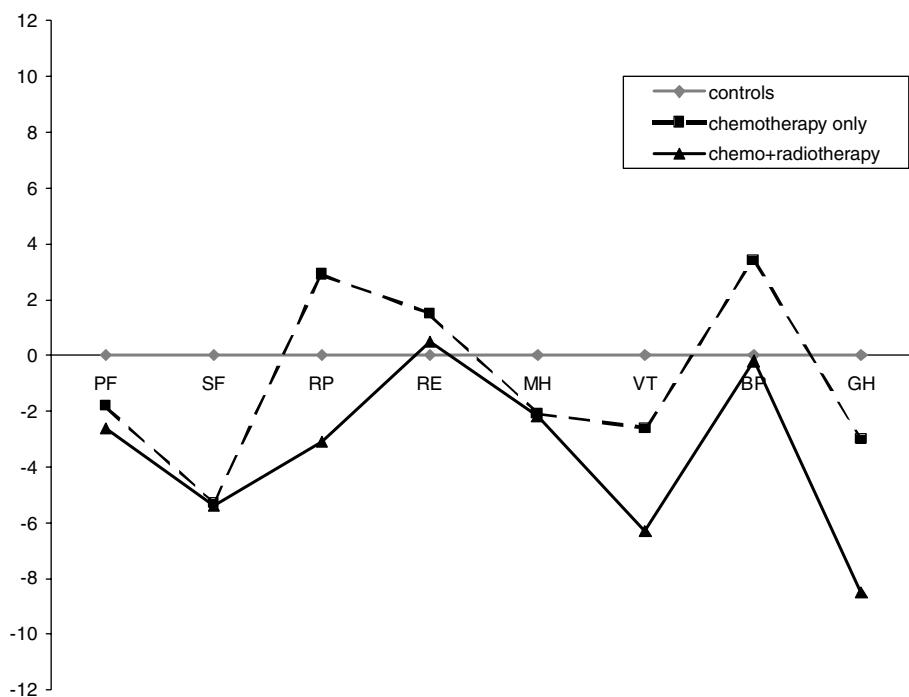
**Fig. 1 – Difference in mean RAND scores of LF- (long-term follow-up,  $\leq 20$  years) and VLF patients (very long-term follow-up,  $> 20$  years) compared with an age matched Dutch standard population PF, etc. see Section 2.1.**

only or a combination of chemotherapy with radiotherapy, in comparison with those of the Dutch norm population. Patients treated with a combination of radio- and chemotherapy showed lower scores on different subscales of the RAND but this was only significant for the subscale General health perception compared to those treated with chemotherapy only. Although leukaemia patients treated with cranial radiation ( $n = 85$ ) had lower scores on the RAND-36, they did not differ significantly from those who did not receive cranial radiation ( $n = 48$ ) (Fig. 3).

Except for the bone tumour patients who scored significantly lower on the subscale physical functioning (PF) (mean score PF 71.0 versus 87.4), no significant differences could be

detected between the different diagnoses concerning the results in the different RAND subscales.

Table 3 shows the regression coefficient  $b$  of gender, age at diagnosis, time since diagnosis and late effects per organ system for six subscales of the RAND-36. In general, males appreciate their HRQoL better than females. The presence of orthopaedic, neurological and psychosocial late effects is negative related with the subscale physical functioning of the RAND-36 ( $P < 0.001$ ). Psycho-social late effects are also negative related to the subscales social functioning ( $P < 0.001$ ), mental health ( $P < 0.001$ ), vitality ( $P < 0.001$ ), bodily pain ( $P < 0.05$ ) and general health perception ( $P < 0.05$ ). Gastro-intestinal late effects are neg-

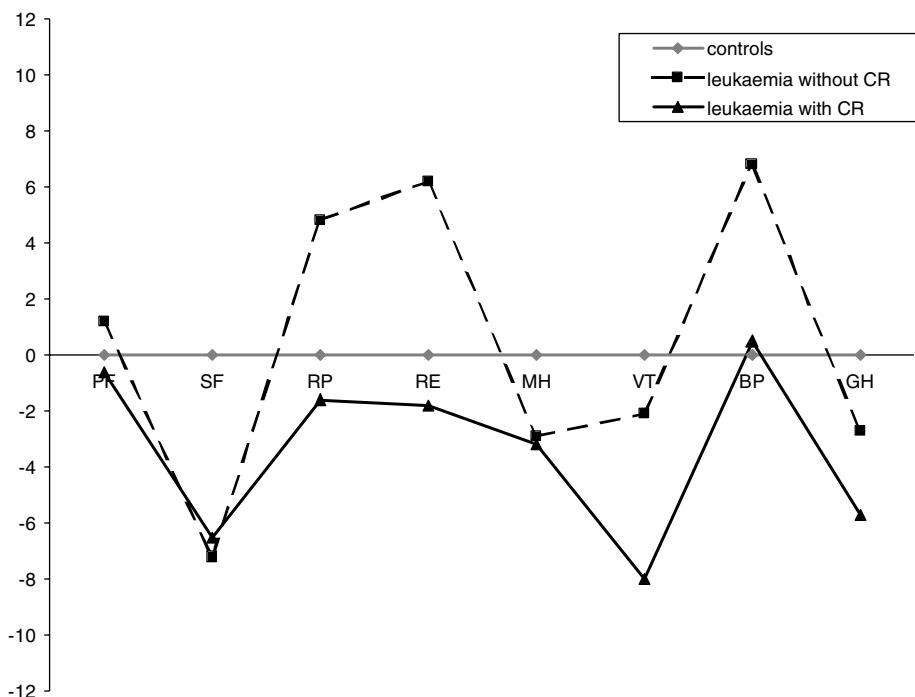


**Fig. 2 – Difference in mean RAND scores of patients treated with chemotherapy and patients treated with a combination of chemo-and radiotherapy compared with a Dutch standard population PF, etc. see Section 2.1.**

ative related to the subscales physical functioning ( $P < 0.05$ ), social functioning ( $P < 0.001$ ), vitality ( $P < 0.01$ ) and general health perception ( $P < 0.05$ ). Orthopaedic and cosmetically late effects are negative related to the subscale bodily pain ( $P < 0.05$ ) (Table 3).

### 3.2. Grading of late effects

Significant more patients in the VLF group had severe (grades 3 and 4) late effects (88/184, 47.8%) than in the LF group (36/129, 27.9%,  $P < 0.001$ ) (Table 1). The survivors



**Fig. 3 – Difference in mean RAND scores of leukaemia patients treated with cranial radiation (CR) and leukaemia patients treated without CR compared with a Dutch standard population PF, etc. see Section 2.1.**

**Table 3 – Regression coefficients b (95% confidence interval) of patient characteristics and late effects per organ system for six subscales of the RAND-36**

Variables <sup>a</sup>	PF	SF	MH	VT	BP	GH
Gender (male)	6.6 (3.4–9.9)	6.1 (1.3–10.9)	3.2 (−0.4 to 6.8)	9.0 (4.8–13.2)	6.9 (2.9–11.1)	6.2 (1.7–10.7)
Age at diagnosis	−0.1 (−4.5 to 0.2)	0.0 (−0.5 to 0.5)	0.1 (−0.3 to 0.5)	−0.5 (−0.9 to 0.4)	0.3 (−0.1 to 0.7)	0.2 (−0.2 to 0.7)
Time since diagnosis	−0.2 (−0.5 to 0.1)	−0.1 (−0.5 to 0.3)	0.2 (−0.2 to 0.5)	−0.4 (−0.7 to 0.0)	−0.3 (−0.65 to 0.8)	−0.2 (−0.6 to 0.2)
Late effects						
Auditory	3.8 (−3.1 to 10.7)	1.7 (−8.6 to 11.9)	−1.8 (−9.7 to 6.1)	0.0 (−9.1 to 9.2)	6.3 (−2.3 to 14.9)	4.1 (−5.6 to 13.9)
Cardiovascular	−11.7 (−20.1 to −3.3)	−7.0 (−19.5 to 5.5)	0.0 (−9.4 to 9.4)	−2.2 (−13.1 to 8.7)	−3.0 (−13.5 to 7.5)	−9.3 (−20.9 to 2.3)
Cosmetic	−1.5 (−5.7 to 2.7)	1.2 (−5.1 to 7.5)	0.2 (−4.6 to 4.9)	2.6 (−2.9 to 8.1)	−6.8 (−12.1 to −1.4)	−4.7 (−10.6 to 1.2)
Endocrine	3.0 (−1.9 to 7.8)	2.8 (−4.4 to 10.1)	0.6 (−4.9 to 6.1)	2.9 (−3.5 to 9.2)	−1.3 (−7.4 to 4.9)	−0.5 (−7.3 to 6.2)
Gastrointestinal	−10.1 (−19.3 to −0.8)	−16.6 (−30.3 to −2.8)	−1.3 (−11.7 to 9.0)	−17.9 (−29.9 to −5.9)	−9.8 (−21.8 to 2.2)	−16.2 (−28.9 to −3.4)
Neurology	−8.1 (−12.7 to −3.5)	−0.6 (−7.4 to 6.2)	−1.5 (−6.7 to 3.6)	1.6 (−4.4 to 7.6)	−5.1 (−10.9 to 0.6)	−7.6 (−13.9 to −1.2)
Ocular/visual	−2.9 (−11.1 to 5.4)	0.1 (−12.1 to 12.4)	3.8 (−5.4 to 13.0)	0.1 (−10.6 to 10.8)	−0.4 (−10.7 to 9.9)	−8.4 (−19.8 to 3.0)
Orthopaedic	−20.6 (−25.9 to −15.3)	1.6 (−6.3 to 9.5)	−0.4 (−6.5 to 5.6)	2.3 (−4.7 to 9.4)	−8.6 (−15.5 to −1.8)	−8.8 (−16.2 to −1.3)
Psycho/social	−8.8 (−13.4 to −4.1)	−15.6 (−22.5 to −8.7)	−9.8 (−15.0 to −4.6)	−11.5 (−17.6 to −5.5)	−6.2 (−12.0 to −0.4)	−6.4 (−12.8 to 0.1)
Pulmonary	−2.4 (−8.9 to 4.2)	−7.3 (−17.1 to 2.3)	−6.1 (−4.6 to 4.9)	−10.3 (−19.0 to −1.6)	−5.7 (−13.9 to 2.5)	−6.4 (−15.4 to 2.7)
Renal/urinary	−2.2 (−8.8 to 4.4)	−0.7 (−10.6 to 9.1)	1.8 (−5.7 to 9.2)	3.8 (−4.7 to 12.5)	−1.3 (−9.2 to 6.5)	5.1 (−4.1 to 14.3)
Sec. tumour	−1.6 (−7.9 to 4.7)	−4.0 (−13.4 to 5.4)	0.1 (−6.9 to 7.1)	−6.1 (−14.3 to 2.0)	−4.7 (−13.1 to 3.8)	−1.6 (−10.3 to 7.1)
Reproductive	−2.8 (−7.9 to 2.4)	2.8 (−4.8 to 10.5)	1.0 (−4.8 to 6.7)	2.7 (−4.0 to 9.3)	−3.1 (−9.6 to 3.3)	−7.5 (−14.6 to −0.4)
Adjusted R <sup>2</sup>	0.32	0.08	0.02	0.13	0.14	0.14

<sup>a</sup> Regression coefficient b, 95% confidence interval.

**Table 4 – Relation between severe late effects and diagnosis or treatment modalities**

Type of tumour and treatment	Number of patients	Severe late effect Grade 3 or 4	
		N	%
<i>Type of tumour</i>			
Leukaemia	133	48	36.1
Leukaemia with CR	85	40	47.1
Leukaemia without CR	48	8	16.7
Bone tumour	38	31	81.6
Malignant lymphoma	58	11	19.0
Soft tissue sarcoma	23	12	52.2
Wilms' tumour	22	5	22.7
Histiocytosis	14	6	42.9
Other	25	11	44.0
<i>Treatment</i>			
Survivors treated with chemotherapy	135	37	27.4
Survivors treated with RT and chemotherapy	153	74	48.4

who had been treated with a combination of chemo- and radiotherapy had more severe late effects (74/153, 48.4%) than those who had received chemotherapy only (37/135, 27.4%,  $P < 0.001$ ). Leukaemia patients treated with cranial radiation (CR) had more severe late effects (40/85, 47.1%) than those who did not receive CR (8/48, 16.7%,  $P < 0.001$ ).

Bone tumour and soft tissue sarcoma patients had the highest incidence of severe late effects (Table 4). The numbers of sequelae graded according to the CTCAEv3 represent cumulative data (survivors with multiple late effects).

#### 4. Discussion

Childhood cancer survivors with a follow-up of more than 20 years had significant lower scores on the RAND-36 subscales physical functioning, vitality, bodily pain and general health perception and have significantly more severe late effects than those with follow-up less than 20 years. In agreement with other studies, the LF group showed only small differences in HRQoL compared with the Dutch standard group. Patients treated with a combination of chemo-and radiotherapy had significant more late effects and lower HRQoL scores than those who were treated with chemotherapy alone. Female gender and late effects, especially psychosocial problems, were negatively related to HRQoL.

It has been stated that persons who have survived a life-threatening disease find their present life more satisfying as a result of psychological adaptation. This might occur in cancer patients as well as in patients with other chronic diseases.<sup>14,8</sup>

This could explain why LF patients score significantly better on the subscale bodily pain than the Dutch comparison group. It seems plausible that this mechanism may decline when time since diagnosis increases.

LF patients had different treatment protocols than VLF patients and the supportive care during treatment has improved over the years. The number of patients who received cranial radiation was higher in the VLF group, which might partly explain our finding that VLF patients have more severe late effects and lower scores on the RAND. But also if we exclude patients who received cranial radiation from the analyses,

we still find significant lower scores on various subscales of the RAND-36 in the VLF group compared with the LF group.

It seems likely that long-term effects in adults differ from those experienced in childhood or adolescence. New issues may come up, like worries about fertility, health of offspring and future health problems of their children. Negative consequences consistently reported in the literature concern job discrimination, difficulties in obtaining health and life insurance,<sup>21,22</sup> as well as lower rates of marriage and parenthood.<sup>23</sup> Also medical problems associated with aging may exhibit an earlier onset or more accelerated course following certain cancer therapies such as cardiovascular disease, osteoporosis or second malignancy.

Long-term follow-up of childhood cancer survivors is highly recommended by the American Cancer Society.<sup>6</sup> Regularly scheduled surveillance with early detection and treatment of late effects, combined with education concerning risk modification theoretically should have a positive impact on the quality of life and long term health of adult survivors.

From the literature, we know that the percentage of survivors involved in follow-up programs decreases with age of the survivor. Adult survivors do not fit in paediatric clinics, and when they grow up, marry and change their name and/or address, they are likely to be 'lost to follow-up'. In the CCSS analysis, only 31% of survivors who were 18–19 years of age at the time of interview had seen a health care provider at a childhood cancer centre in the previous two years. This percentage steadily decreased with age to 17% of those who were 35 years or older.<sup>24</sup>

Our study shows that survivors diagnosed more than 20 years ago have a higher percentage of severe late effects (47.8%) and perceive their QoL to be worse than survivors diagnosed more recently. In general, only a minority of VLF-survivors will attend a LTFU clinic. For these elder survivors it is important to establish new systems for follow-up, which are more flexible and appropriate to the needs of adult survivors.

Most survivors are in contact with a general practitioner (GP), but the average GP is not particularly aware of the risks of this population. GPs will increasingly come in contact with these patients, up to 8–9 in 2010.<sup>25</sup> Involving GPs in a shared

care program for long-term follow-up will increase their knowledge about the unique needs of childhood cancer survivors. It is important that GPs are well informed before their first interaction with a patient who is a childhood cancer survivor. Only then GPs will not miss the opportunities to recognise late effects and to intervene if possible. GPs are trained to promote good health practices and avoidance of risk-taking behaviours; this might help to decrease risky behaviour among cancer survivors. A Combined Model for long-term follow-up as described by Friedman,<sup>26</sup> in which long-term follow-up of childhood cancer survivors is a co-ordinated effort of the Cancer clinic and the patients own GP, might be successful, but is not yet studied.

Such a model could facilitate the necessary transition from paediatric-based care to adult care as childhood cancer survivors mature into adulthood. At the same time, GPs will become more prepared for the specific needs of the increasing number of adult survivors of childhood cancer.

Several limitations must be regarded in the interpretation of this study. Firstly, eight persons were older than 45 years, however, their exclusion did not change the outcome of this study.

Secondly brain tumour survivors were not included in this study and there is an over-representation of leukaemia patients. Compared with leukaemia survivors, survivors of brain tumours are more likely to report adverse health.<sup>27</sup> In addition the instrument used was the RAND-36, which is a generic outcome measure focusing on health-related quality of life. To investigate the functioning of survivors more thoroughly, more specific questionnaires are needed. There are also other important aspects of the functioning of survivors as educational achievement, employment, marital status, additionally experienced life events and comorbidities, which we left out of the current study.

### Conflict of interest statement

'All authors declare that they have nothing to declare'. Ethical approval was not required.

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