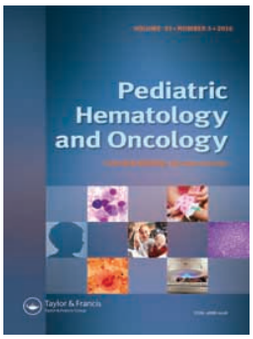

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Health-related quality of life and emotional problems in children surviving brain tumor treatment: A descriptive study of 2 cohorts

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ABSTRACT

The survival of childhood brain tumors has improved in the past 30 years, but acquired brain injury due to damage caused by tumor invasion and side effects of different treatment modalities frequently occurs. This study focused on residual impairments, health-related quality of life (HRQoL), and emotional and behavioral problems in 2 cohorts of survivors diagnosed and treated for various types of brain tumors. Survivors in the 2004 cohort visited the Erasmus Medical Centre for standardized follow-up between 2003 and 2004, and in the 2014 cohort, between 2012 and 2014. Data of neurologically impairments of all children were extracted from medical records. Parents and survivors filled out questionnaires on quality of life and emotional and behavioral problems. In both cohorts, approximately 55% of the survivors displayed neurologic impairments. In comparison with the healthy reference group, a reduced parent-reported quality of life was found on the Motor, Cognition, and Autonomy (Cohort 2004) scales. Comparison between the cohorts showed that parents in the 2004 cohort reported a higher HRQoL on the Motor and Cognitive functioning scales. In the 2014 cohort, children reported less negative emotions than healthy children. No increase in emotional or behavioral problems were reported by children in both cohorts, whereas parents reported problems in social functioning and isolation related to a delay in emotional development. Children surviving brain tumor treatment have a reduced quality of life. The authors therefore recommend regular screening of HRQoL and emotional and behavioral problems and referral to specific aftercare.

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Brain diseases; brain neoplasms; child behavior disorders; cohort study; quality of life

Introduction

Brain tumors account for approximately 20% of all cases of pediatric cancer in Europe. They are the second most common form of pediatric cancer, exceeded only by leukemia [1]. Survival has dramatically improved since the late 1970s. Currently in Europe, an overall 5-year survival rate of approximately 65% has been reached [1, 2]. Many survivors of childhood brain

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tumors experience neurologic and neuropsychological problems later in life due to brain damage from tumor invasion as well as treatment modalities and their side effects [3, 4]. Radiotherapy (RT) and chemotherapy (ChT) negatively affect attention and memory capacities and have adverse influence on mental and physical functioning [3, 5]. Also, age of presentation and location of the tumor in the brain are related to mental and physical functioning of childhood brain tumor survivors. Children diagnosed and treated at younger age show the greatest decline in IQ scores and academic achievements after long-term follow-up [6, 7]. Specific impairments in cognitive (e.g., linguistic difficulties) and emotional (e.g., anxiety and depression) functioning have been described in children with infratentorial tumors [7, 8].

These residual neurologic and neuropsychological side effects may hamper functioning in daily life and social participation. Monitoring of health-related quality of life (HRQoL) is done, for example, in childhood survivors who are treated for a pilocytic astrocytoma [9–11], low-grade glioma [12], high-grade glioma [13], craniopharyngioma [14,15], medulloblastoma [16, 17], and in heterogeneous groups [18–24]. In most of these studies, survivors reported a variety of degree of reduction in HRQoL compared with healthy age mates [9, 10, 13–16, 18–24]. This could be explained by the heterogeneity of brain tumors and their treatments. A part of the low-grade tumors can be treated by surgery only, or in combination with low-dose RT, in contrast to high-grade tumors, for which additional high-dose RT and ChT are parts of the treatment regimen. Multiple studies showed that intensive therapy is an important predictor of a lower HRQoL [18, 19]. Reimers et al. mentioned RT as an important predictor of HRQOL because of the effect on intelligence [18].

Between 2003 and 2004, we performed a standardized evaluation of all children who survived a brain tumor and who visited the Erasmus Medical Centre (Cohort 2004). After the first evaluation, a new evaluation was performed of all new children who survived a brain tumor and visited the Erasmus Medical Centre between 2012 and 2014 (Cohort 2014).

In 2005, we introduced a structured follow-up program in our clinic. The yearly follow-up consists of a neurologic, oncologic, radiotherapeutic, endocrine, and psychological evaluation including consultation with a psychologist and screening on behavioral and emotional problems by questionnaires. Standardized neuropsychological assessment is offered 1 and 3 years after diagnosis. Upon request, neuropsychological assessment is performed again at the start of primary school (age 6) and at the start of high school (age 12). The purpose is to detect physical, neurocognitive, and psychological sequelae as soon as possible and start timely interventions such as physical rehabilitation, remedial teaching at school or special education services, and acceptance and commitment therapy if indicated. Before 2005, these interventions were available but not offered in a structured and tailor-made routine to all patients.

The aim of this study was twofold. First, we evaluated the impairments, disabilities, HRQoL, and behavior and emotional problems of all brain tumor survivors in 2 cohorts. We compared the HRQoL and behavior and emotional problems between the 2 cohorts and the healthy reference group.

We hypothesized a decreased HRQoL and more behavior and emotional problems in both patient cohorts in comparison with healthy children due to brain damage from tumor invasion as well as treatment modalities and their side effects.

Secondly, we hypothesized an amelioration of HRQoL and a decrease of behavioral-emotional problems in the 2014 cohort in comparison with the 2004 cohort. The aim of cancer treatment in general is to optimize the balance between survival and toxicity. We could not find any publications that compare the toxicity of different treatment protocols that are used over the years in children with a brain tumor. We expected that in the 2014 cohort, lower doses of RT and less toxic ChT protocols were used. As intensive therapy is an important

predictor for a low HRQoL, we predicted that lower doses of RT and less toxic ChT would result in improved HRQoL in the 2014 cohort [18, 19]. In addition, the positive contribution of our follow-up program might have a positive effect on the HRQoL.

This study adds important information to the existing literature. With the increase in children surviving a brain tumor, a need for standardized follow-up of neurologic and neuropsychological well-being combined with assessment of HRQoL is necessary. Evaluation of these aspects in survivors of pediatric brain tumors can measure the impact of brain tumor survival in daily life.

Methods

Study design and participants

Comparison of HRQoL and emotional and behavioral problems between 2 cohorts of children who survived various types of brain tumors. A comparison is also made with healthy controls. Survivors visited the Erasmus Medical Centre at least once between April 1, 2003, and April 1, 2004 (2004 cohort; $n = 59$), and between May 1, 2012, and April 1, 2014 (2014 cohort; $n = 73$). The study was approved by the Medical Ethical Commission of Erasmus Medical Centre Rotterdam.

Children were eligible for study participation when they were treated for a brain tumor of any histology, had a complete remission or stable disease in the previous 3 months at follow-up, and were between 6 and 16 years old. Children included in the 2004 cohort are excluded for the 2014 cohort.

In the 2004 cohort, 35 (59%) children were eligible for study participation, of whom 83% of the children and/or their parents responded by filling out the questionnaires (Figure 1). In the 2014 cohort, 46 (63%) children were eligible for study participation, of whom 76% of the

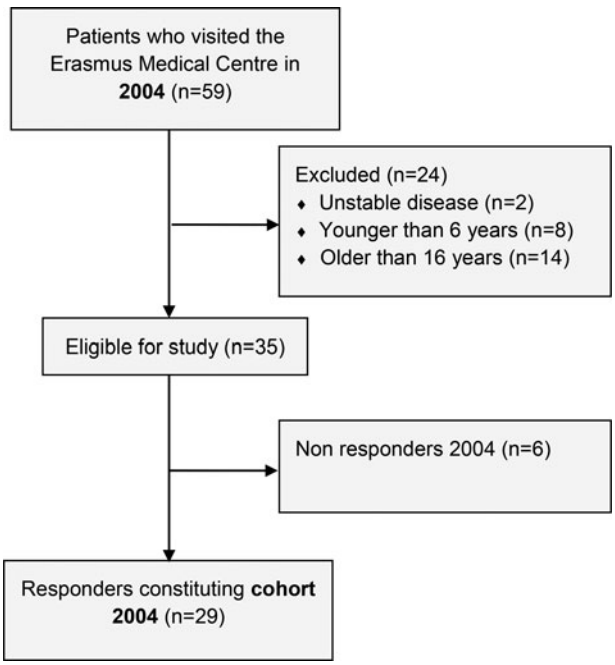

Figure 1. Exclusion and response in Cohort 2004.

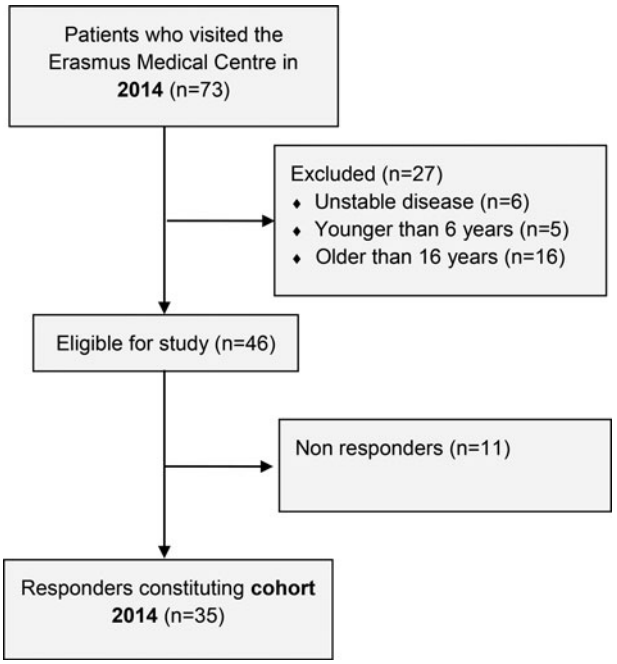

Figure 2. Exclusion and response in Cohort 2014.

children and/or their parents responded (Figure 2). Table 1 shows the characteristics of the survivors of both cohorts.

Data and measures

Data retrieval

The following data at follow-up were collected from survivors' medical records in Elpado, the center-wide electronic patient system used in the Erasmus Medical Centre: date of birth, gender, diagnosis, age at primary diagnosis, tumor histology, tumor site, information on treatment modalities (surgery, RT, ChT), neurologic impairments, endocrinopathy, and disability.

Disability

A simplified version of the pediatric modified Rankin Scale (mRS) was used to score the degree of disability. Data on motor disturbances and learning disabilities were extracted from medical records. Children were categorized in 3 categories by the school they attended: (1) mRS score 0, no motor or learning disabilities, regular school is attended; (2) mRS score 1 or 2, mild motor disturbances, mild learning disabilities, or a combination, remedial teaching is needed; and (3) mRS score 3–5, severe motor disturbances, severe learning disability, or a combination, special education services or a day care center is attended. The mRS is a frequently used measure to determine disability and neurologic impairment in stroke patients. The mRS interrater reliability (kappa = 0.78) and test-retest reliability (kappa = 0.81–0.95) can be considered good [25].

HRQoL

HRQoL was measured by the TNO-AZL (Netherlands Organisation for Applied Scientific Research Academic Medical Centre) Children's Quality of Life rating scale (TACQOL) [26], a

Table 1. Demographic an tumor characteristics of the 2004 and 2014 patient cohorts.

	Cohort 2004 ($n = 29$)		Cohort 2014 ($n = 35$)	
Characteristic	Median	Range	Median	Range
Age at diagnosis (years)	5.8	1.3–11.5	5.9	0.1–13.8
Age at study (years)	11.7	6.3–15.8	11.3	6.3–15.9
Time since diagnosis (years)[#]	4.1	1.5–14.3	5.9	1.8–11.0
	n	%	*n*	%
Gender				
Male	13	45%	24	69%
Female	16	55%	11	31%
Tumor type				
Low-grade astrocytoma	15	52%	11	31%
High-grade astrocytoma	1	3%	2	6%
Medulloblastoma	4	14%	8	23%
Ependymoma	4	14%	8	23%
Craniopharyngioma	4	14%	8	23%
Teratoma	—	—	2	6%
Meningioma	1	3%	—	—
Plexus carcinoma/papilloma	—	—	2	6%
Location tumor				
Hemispheric supratentorial	4	14%	8	23%
Midline supratentorial	11	38%	11	31%
Infratentorial	14	48%	16	46%
Neurofibromatosis	5	14%	1	4%
Relapse tumor				
Yes	9	31%	5	14%
Time since relapse (years)[#]	2.1	0.4–5.0	1.0	0.3–2.9
Type of treatment undergone				
Neurosurgery	25	86%	31	87%
Radiotherapy	19	66%	21	60%
Chemotherapy	11	38%	19	54%

[#]Time between diagnosis/relapse and April 1, 2004 (Cohort 2004), or April 1, 2014 (Cohort 2014).

generic measure for HRQoL in medical research. In the TACQOL, HRQoL is determined as a functional status weighted by the emotional reaction, resulting in a HRQoL status. Functional status items give information on the incidence of physical, psychological, and social problems. The TACQOL contains 57 questions, divided over 7 subscales of 8 items each: Physical complaints, Motor functioning, Autonomy, Cognitive functioning, Social functioning, and Negative and Positive emotions. Each item is scored on a 3-point Likert scale (0 = never, 1 = sometimes, 2 = often). If a problem in functional status is reported, the child is asked to indicate the suffering on a 4-point Likert scale (0 = good, 1 = not so good, 2 = rather bad, 3 = bad). Raw scores are transformed into *T*-scores using the means and standard deviations of the reference data [27]. Parental and child versions are available to collect dyadic data: the TACQOL—Parental Form (PF) need to be filled out by parents from children aged 6–16; the TACQOL—Child Form (CF) can be filled out by their children aged 8–16.

The TACQOL is validated in the Dutch population. Reference data are available from 1048 healthy Dutch children [26, 27]. The TACQOL is an excellent instrument to assess HRQoL in chronically ill or children surviving a brain tumor and compare findings with the reference population. Multiple studies using the TACQOL are published, including studies in children surviving a brain tumor [7, 9, 28]. Reliability and validity are sufficient for research purposes. Cronbach's alphas ranges from .65 to .79 for the TACQOL-CF and .67 to .84 for the TACQOL-PF [26, 27].

Behavior and emotional problems

Problems were assessed by the Child Behavior Checklist (CBCL/6–18), and the Youth Self Report (YSR) [29, 30]. The questionnaire consists of 113 items on behavior or emotional

problems, with 8 subscales containing 8–17 questions. Parents of children aged 6–18 and children or adolescents aged 11–17 are asked to evaluate their child's/their own behavior in the past 6 months on a 3-point Likert scale. The composite scale Internalization comprises items from the subscales Withdrawal, Somatic Complaints, and Anxious/Depressed. The Externalization scale comprises items from the Rule-breaking Behavior and Aggressive Behavior subscales. The Total Problems scale comprises of all items. Higher scores indicate more problems.

All checklists have been translated into Dutch, and reference data are available for the Dutch population. The psychometric properties of the Dutch questionnaires are excellent, Cronbach's alphas ranges from .83 to .97 for the CBCL and .79 to .95 for the YSR [31, 32].

Response

In the 2004 cohort, 29 (100%) parents filled out the CBCL and TACQOL-PF. Thirteen of 16 (81%) children aged 11 years and older completed the YSR. Twenty-one out of 29 (72%) children filled out the TACQOL-CF. In the 2014 cohort, 35 (100%) parents filled out the CBCL and TACQOL-PF. Seventeen out of 18 (94%) children aged 11 years and older returned the YSR. Thirty-one (89%) children filled out the TACQOL-CF.

Data analysis

Survivors' and parents' reports on the TACQOL and CBCL/YSR were compared with children's and parents' reports from the healthy reference groups [27, 29, 31–33]. Distributions of outcomes were checked for normality using the Shapiro-Wilk test. Responses on the HRQoL and behavior and emotional problems were not normally distributed. Therefore, differences between patient cohorts (2004, 2014) and healthy controls were tested with the nonparametric 1-sample Wilcoxon signed-rank test and the Mann-Whitney *U* test. Fisher's exact test was used to compare differences in nominal variables. $P < .05$ (2-sided) was considered significant.

The statistical analyses of the questionnaires and checklists were conducted using IBM Statistical Package for the Social Sciences, version 21.0.0.1 (IBM, Armonk, NY, USA).

Results

Impairments

Table 2 gives an overview of the neurologic and endocrine problems after treatment in both cohorts. Sixteen children (55%) in the 2004 cohort and 17 (49%) children in the 2014 cohort had neurologic disabilities at follow-up. Frequently observed problems were motor problems (Cohort 2004: 24%; Cohort 2014: 23%), visual disorders (Cohort 2004: 28%; Cohort 2014: 26%), and visual field deficits (Cohort 2004: 31%; Cohort 2014: 20%). Endocrine problems were seen in 11 (45%) children in Cohort 2004 and 18 (51%) in Cohort 2014. Growth hormone (GH) deficiency (Cohort 2004: 31%; Cohort 2014: 23%) was the most observed endocrine complication.

Disability

Table 2 presents the disability scores (mRS scores) of the cohorts. In the 2004 cohort, 16 children (55%) displayed no disability (mRS1), 6 a mild disability (21%) (mRS2), and 7 a severe

Table 2. Neurologic and endocrine deficiencies and impairments after treatment in the 2004 and 2014 cohorts.

	Cohort 2004 ($n = 29$)		Cohort 2014 ($n = 35$)	
Diagnosis	*n*	%	*n*	%
Neurologic complications[#]	16	55%	17	49%
Motor problem	7	24%	8	23%
Somatic sensory deficit	—	—	3	9%
Visual disorder	8	28%	9	26%
Visual field defect	9	31%	7	20%
Auditory sensory deficit	—	—	1	3%
Epilepsy	2	7%	1	3%
Endocrine problems[#]	11	38%	18	51%
GH deficiency	9	31%	8	23%
TSH deficiency	5	17%	6	17%
ACTH deficiency	4	14%	4	11%
Pubertas praecox	2	7%	8	23%
Diabetes insipidus	5	17%	2	6%
Modified Rankin Scale (mRS)				
mRS 1	16	55%	19	54%
mRS 2	6	21%	9	26%
mRS3	7	24%	7	20%

[#]Multiple neurologic and/or endocrine problems could be present in one survivor.

disability (24%) (mRS3). Thirteen (45%) children required remedial teaching or had been referred to schools for children with sensory or neurologic impairments.

In the 2014 cohort, 19 children (54%) displayed no disability, 9 a mild disability (26%), and 7 a severe disability (20%). Sixteen (46%) children required remedial teaching or special education.

HRQoL

Table 3 shows that in both cohorts, parents reported a lower quality of life on the Motor (Cohort 2004: median = 48.68, $Z = -3.86$, $P < .001$; Cohort 2014: median = 45.60, $Z = -4.02$, $P < .001$) and Cognition (Cohort 2004: median = 49.69, $Z = -2.24$: $P = .025$; Cohort 2014: median = 41.46, $Z = -3.36$, $P = .001$) functioning scales compared with the reference group of parents with healthy children. On the Autonomy scale, parents in the 2004 cohort also reported a lower quality of life (median = 49.04, $Z = -2.79$, $P = .005$). The children themselves did not report a reduction in quality of life. Children in the 2014 cohort reported less negative emotions than the healthy reference group (median = 54.72, $Z = 2.14$, $P = .032$).

Comparison between cohorts revealed that parents in the 2014 cohort reported a lower quality of life on the Motor (Cohort 2004: median = 48.68, Cohort 2014: median = 45.60, $U = 276$, $P = .003$) and Cognition (Cohort 2004: median = 49.69, Cohort 2014: median = 41.60, $U = 302$, $P = .015$) functioning scales than parents in the 2004 cohort. Children in the 2014 cohort reported a higher quality of life on the Social functioning scale (Cohort 2004: median = 50.09, Cohort 2014: median = 50.86, $U = 183$, $P = .007$) and less negative emotions (Cohort 2004: median = 50.10, Cohort 2014: median = 54.72, $U = 197$, $P = .016$) than children in the 2004 cohort.

Behavioral and emotional problems

Parents in the 2004 cohort reported more social isolation (Withdrawal, $P = .028$), somatic problems ($P < .001$), and more problems in social functioning because of infantile behavior

Table 3. Health-related quality of life in survivors of childhood brain tumors (Cohorts 2004 and 2014): parents' and survivors' evaluations.

Parents									
	Reference group (n = 1318)	Cohort 2004 (n = 29)	Cohort 2004 vs. Reference group		Cohort 2014 (n = 35)	Cohort 2014 vs. Reference group		Cohort 2004 vs. Cohort 2014	
TACQOL-PF 6–15	Mean (SD)*	Median (IQR)*	Z	P	Median (IQR)*	Z	P	U	P
Physical	50 (10)	51.08 (42.95–56.50)	−.51	.61	51.08 (42.95–56.50)	−.10	.92	477	.68
Motor		48.68 (47.03–50.00)	−3.86	**<.001**[y]	45.60 (27.97–50.00)	4.02	**<.001**[y]	276	**.003**[a]
Autonomy		49.04 (46.73–50.42)	−2.79	**.005**[y]	47.76 (34.94–54.17)	1.74	.08	474	.82
Cognition		49.69 (48.34–50.50)	−2.24	**.025**[y]	41.60 (33.35–52.27)	3.36	**.001**[y]	302	**.015**[a]
Social		49.57 (49.14–50.22)	−1.68	.09	50.04 (37.11–54.35)	−.77	.44	480	.71
Positive emotions		50.01 (48.07–50.57)	−.30	.77	50.11 (44.56–55.67)	.50	.62	445	.39
Negative emotions		49.71 (49.07–50.56)	−0.88	.38	51.37 (47.09–64.19)	1.41	.16	378	.08

Children									
	Reference group (n = 860)	Cohort 2004 (n = 21)	Cohort 2004 vs. Reference group		Cohort 2014 (n = 31)	Cohort 2014 vs. Reference group		Cohort 2004 vs. Cohort 2014	
TACQOL-CF 8–15	Mean (SD)*	Median (IQR)*	Z	P	Median (IQR)*	Z	P	U	P
Physical	50 (10)	51.39 (48.41–58.33)	1.48	.14	49.60 (43.65–55.56)	−.61	.54	275	.35
Motor		49.69 (48.89–50.32)	−1.79	.07	50.03 (37.33–56.38)	−.91	.37	325	.99
Autonomy		50.38 (49.04–50.38)	−.41	.68	53.82 (43.06–53.82)	.14	.89	272	.31
Cognition		49.86 (49.35–50.88)	−.40	.69	48.63 (35.27–56.26)	−1.00	.32	288	.60
Social		50.09 (49.15–50.65)	−.19	.85	50.86 (47.12–58.35)	1.64	.10	183	**.007**[b]
Positive emotions		49.75 (48.55–50.96)	−1.52	.07	51.53 (43.49–59.56)	.10	.92	230	.92
Negative emotions		50.10 (48.97–50.84)	−.61	.54	54.72 (47.23–62.21)	2.14	**.032**[x]	197	.032[b]

Note. Higher scores indicate higher quality of life. *Transformed scores. [a] = HRQoL Cohort 2004 > HRQoL Cohort 2014; [b] = HRQoL Cohort 2004 < HRQoL Cohort 2014; [y] = HRQoL cohort > HRQoL healthy reference group; [x] = HRQoL cohort < HRQoL healthy reference group.

($P = .004$) than parents in the reference group did. Consequently, also the composite domain Internalization showed a difference between groups ($P = .026$) (Table 4).

Somatic problems ($P = .045$) and problems in social functioning ($P = .045$) were reported more by parents in the 2014 cohort. These parents also reported problems in thinking and behavior ($P = .045$). Comparison between the 2004 and 2014 cohorts did not reveal any differences. Children did not report any suffering from behavioral or emotional problems.

Discussion

We described psychosocial well-being of children who survived brain tumor treatment in 2 cohorts. We determined proportions of impairments and disabilities in the 2 cohorts and compared quality of life and the prevalence of behavior and emotional problems between the

Table 4. Emotional and behavioral problems in survivors of childhood brain tumors (Cohorts 2004 and 2014): parents' and survivors' evaluations.

Parents					
		Cohort 2004 (n = 29)		Cohort 2014 (n = 35)	
CBCL 6–18	Reference group % of scores in clinical ranges	% of scores in clinical ranges	P value Cohort 2004 vs. Reference group	% of scores in clinical ranges	P value Cohort 2014 vs. Reference group
Withdrawal	2%	10%	**.028**[x]	6%	.19
Somatic complaints		21%	**<.001**[x]	9%	**.045**[x]
Anxious/Depressed		3%	.49	6%	.19
Social problems		14%	**.004**[x]	9%	**.045**[x]
Thought problems		3%	.49	9%	**.045**[x]
Attention problems		3%	.49	6%	.19
Rule-breaking behavior		0%	.51	0%	.45
Aggressive behavior		0%	.51	3%	.55
Internalization	8%	21%	**.026**[x]	17%	.06
Externalization		3%	.31	9%	.55
Total problems		14%	.20	14%	.15
Children					
		Cohort 2004 (n = 13)		Cohort 2014 (n = 17)	
YSR 11–18	Reference group % of scores in clinical ranges	% of scores in clinical ranges	P value Cohort 2004 vs. Reference group	% of scores in clinical ranges	P value Cohort 2014 vs. Reference group
Withdrawal	2%	0%	.74	0%	.68
Somatic complaints		8%	.26	0%	.68
Anxious/Depressed		8%	.26	0%	.68
Social problems		8%	.26	0%	.68
Thought problems		0%	.74	0%	.68
Attention problems		0%	.74	0%	.68
Rule-breaking behavior		0%	.74	0%	.68
Aggressive behavior		0%	.74	0%	.68
Internalization	8%	8%	.72	0%	.26
Externalization		0%	.34	6%	.63
Total problems		8%	.72	0%	.26

Note. [x] = Emotional and behavioral problems cohort > healthy reference group.

2 cohorts. In addition, we also compared findings with a reference group of healthy Dutch children.

These 2 cohorts include a large part of all the children who are seen in the Erasmus Medical Centre for regular follow-up after brain tumor treatment and are therefore representative of the heterogeneous population of brain tumor survivors. Neurologic impairments were seen in approximately 50% of the children of both cohorts, which is in line with findings in previous studies [9, 19]. Due to their impairments, 45% of the children experienced learning problems, received remedial teaching, or were referred to schools for special education. In comparison, only 6.9% of Dutch children visit special schools [34]. GH deficiency was the most observed endocrine complication. Mostoufi-Moab et al. [35] described that different hypothalamus-pituitary cell lines have a different sensitivity to radiation, with GH being the most vulnerable. Most of the children treated with radiation doses above 30 Gy will have decreased GH responses to insulin tolerance test within the next 5 years. Remarkable detail is the higher frequency of pubertas preacox in the 2014 cohort. As described by Mostoufi-Moab et al., lower doses of cranial irradiation paradoxically can result in early puberty, as a result of the decrease in inhibition of cortical influences on the hypothalamus and a lower

γ-aminobutyric acid (GABA)ergic tone [35]. It is likely that the increase in pubertas preacox in the 2014 cohort is a result of the decreasing intensity of RT over the past 10 years.

Parents of pediatric brain tumor survivors reported a reduced HRQoL with respect to the Motor functioning, Cognitive functioning, and Autonomy scales (2004 cohort only). However, the reduction in HRQoL compared with the healthy controls, especially the 2004 cohort, is very small. The clinical importance of this small difference is therefore questionable. However, our findings are in line with findings from other studies that described impaired HRQoL in similar domains, using other HRQoL measures [9, 10, 19–21]. The reduced HRQoL on the Motor and Cognitive functioning scales can be explained by the high proportion of neurologic impairments seen in these children. Studies carried out in children with neurologic impairments due to stroke, spina bifida, and traumatic brain injury also observed a reduced HRQoL in the physical domain [36, 37].

Parents and children evaluated their HRQoL differently: parents gave less optimistic HRQoL scores than their children. A moderate correlation between reports by patients and their parents have been observed before, and survivors of childhood cancer tend to judge their coping strategies as superior [21, 38, 39]. In a study by Aarsen et al. [9], children who were diagnosed during adolescence reported a lower HRQoL in social functioning than children who were diagnosed at a younger age. They suggested that behavioral, physical, and social problems become more prominent over the years. As an explanation for this phenomena, they mentioned that early brain damage may result in a cumulative effect on ongoing development, and increasing deficits may emerge through childhood as more brain functions are expected to mature [9].

On the behavioral and emotional questionnaires, parents reported more somatic complaints, problems in social functioning, and social isolation because of childish behavior and thought problems (2014 cohort only). This is in line with previous research [9, 40, 41]. Findings regarding somatic complaints need careful interpretation: the CBCL aims to measure somatic problems related to anxiety and depression, whereas parents may have emphasized their child's neurologic disabilities.

Comparison between the cohorts showed that parents in the 2004 cohort reported a better quality of life on motor and cognitive functioning than parents in the 2014 cohort. Children in the 2014 cohort reported a higher quality of life in social functioning and reported less negative emotions compared with children in the 2004 cohort. A possible explanation is the differences in clinical characteristics (Table 1) between the cohorts. The ratio of gender and tumor type is different between the 2 cohorts; however, we did not adjust for characteristics due to the small numbers of children per subgroup. Alternatively, it is possible that a structured follow-up program with more attention for optimization of autonomy, social functioning, and early recognition of impeding factors for rehabilitation had a positive influence in the past 10 years.

Compared with the 2004 cohort, parents in the 2014 cohort indicated more problems on the Thought Problems scale. The increase might be related to the survival of larger numbers of children who underwent intensive treatment strategies, despite the efforts to compose treatment modalities with less toxic effects. Additional research in larger study groups will be necessary to test this hypothesis.

A limitation of this study is the heterogeneity of tumor histology and tumor site. Our findings cannot be generalized to survivors of specific types of brain tumors. Furthermore, the sample size is relatively small and we did not adjust for multiple testing. For the same reason, we avoided multiple subgroup analyses to check whether the case mix of the cohorts had any meaningful impact on the outcome measures studied. Finally, HRQoL and behavior problems

were only examined in children who were able to fill out the questionnaires. Children with severe cognitive problems may experience a low HRQoL and more behavioral problems.

Conclusion

The impairments of brain tumor survivors influence quality of life particularly regarding motor, cognitive, and social functioning. Children impeded in their autonomy may develop a delay in their social capacities. This is affirmed by their parents, who reported more social problems. Early detecting of such problems is important, as timely interventions can prevent aggravation of such problems and will enhance the child's coping capacities. We therefore advocate a regular screening of physical, psychosocial, and behavioral problems and timely interventions in survivors of childhood brain tumors [42].

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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