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Children With Minimal Chance for Cure: Parent Proxy of the Child's Health-Related Quality of Life and the Effect on Parental Physical and Mental Health During Treatment

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Abstract

To assess health-related quality of life (HRQOL) from the time of diagnosis until disease progression in a cohort of children with diffuse intrinsic pontine glioma (DIPG). The assessment was collected from the perspectives of the child and their parents and evaluated the effect of the child's HRQOL on their parents' physical and mental well-being, thus providing insight into the optimal timing of palliative consultation, including anticipatory grief and bereavement services. This longitudinal study assessed 25 parents and their children, ages 2–17 years of age with DIPG across 5 time-points, baseline and weeks 2, 4, 6, 16, 24. Assessments included the PedsQL 4.0 Core Scales, PedsQL 3.0 Brain Tumor Scale, and Short-Form 36. HRQOL instruments were completed by the child (age ≥ 5 years) and parent-proxy (ages 2–17 years), with the parent completing the SF-36. Children's reports and parents' proxy of their child's HRQOL indicated poor physical functioning and increased anxiety at the initiation of therapy. A trending improvement in the children's HRQOL was reported by children and parents from baseline to week 6, with a decline at week 16. The children's parent proxy reported cognitive problems, procedural anxiety and lower overall brain tumor HRQOL were associated with poorer self-reported parental mental status. Palliative care consultation should be initiated at the time of diagnosis and is supported in the high physical and emotional symptom burden reported by our patients, with heightened involvement initiated at 16 weeks. Prompt palliative care involvement, mitigating anxiety associated with clinic visits and procedures, management of brain tumor specific symptoms, advanced care planning, anticipatory grief and bereavement services, and care

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coordination may maximize HRQOL for patients and ensure positive long-term outcomes for parents of children with DIPG.

Introduction

Survival among children with CNS tumors has steadily improved, with trends in 5-year survival rates for children younger than 15 years approaching 75%.¹ However, children diagnosed with diffuse intrinsic pontine glioma (DIPG) have minimal chance of survival, and this prognostic trajectory is shared with the family at the time of diagnosis.

It is clinically intuitive that children with minimal chance of cure at the time of diagnosis and their parents would have a lower health-related quality of life (HRQOL) during the treatment trajectory. In a cross-sectional survey of parents of children with no realistic chance of cure, parents whose children died within 6 months reported their children as having worse physical health, pain, and fatigue than did parents whose children survived for more than 6 months.² Another cross-sectional design demonstrated that parents caring for a child with active cancer reported significantly lower HRQOL than population norms across all domains and scores, except for physical function and the physical component summary score for fathers. Higher parental HRQOL scores were associated with the child having a better health status, lower treatment intensity, and surviving a longer time since diagnosis.³ In contrast a recent study assessed psychological distress in parents of children with advanced cancer and found that parents experience lower levels of distress, when prognostic understanding is aligned with treatment goals despite the understanding that the child's illness is incurable.⁴ We found no prospective longitudinal study that examined the HRQOL of parents and their children with DIPG. Given that description of HRQOL in this patient population may provide insight into the optimal timing of palliative consultation, including anticipatory grief and bereavement services, in the treatment plan, our study objectives were to assess HRQOL from the time of diagnosis until disease progression in a cohort of children with DIPG from the perspective of the children and parents and to examine the effect of the parent proxy reported children's HRQOL on their parents' physical and mental well-being.

Patients and methods

Patients

This prospective study followed 25 patients aged 2 years or older and their parents after they received information regarding diagnosis and prognosis. The HRQOL question was a secondary objective within the institution's front-line Phase I study to determine the maximum tolerated dose of the combination of vandetanib and dasatinib administered during and after local radiation therapy in children with DIPG.⁵ Dexamethasone was discontinued or significantly reduced prior to completion of radiation in all but one of the patients. Patients were removed from treatment at the time of progressive disease or unacceptable toxicity. At the time of this study, palliative care consultation was not initiated by the primary physician until disease progression.

Study design

This study was approved by the institutional review board, with consent obtained from all parents and assent obtained from children according to institutional guidelines. Child and parent demographic information was collected at baseline, with HRQOL questionnaires administered at baseline (prior to initiation of treatment) and weeks 2, 4, and 6 of radiation therapy. The majority of patients were from out of state and after the completion of radiation at week 6, the child and parent returned home for approximately 10 weeks. Each child presented for the first post-radiation evaluation at week 16, at which time HRQOL questionnaires were again completed and subsequently obtained every 8 weeks until treatment toxicity or progression of disease. The questionnaires were completed by each participating child and parent during a scheduled clinic visit, with the assistance of a research nurse. The primary caregiver of each enrolled child was responsible for completion of the parent proxy and parent HRQOL data.

Measures

HRQOL was assessed in children and adolescents using the Pediatric Quality of Life Inventory (PedsQL V.4), a 23-item Likert-type scale measuring (1) physical, (2) emotional, (3) social, and (4) school functions. This instrument has parallel forms for child and parent report. The instrument for both patients and parents are internally consistent (Cronbach alpha coefficients of 0.91 to 0.92, respectively) and clinically valid.⁶ The Likert scale scores are transformed to a 0, 25, 50 and 100 point scale, with higher scores reflecting a higher HRQOL. At all time-points, the PedsQL V. 4 was completed by parent proxy only for children 2–4 years and by children and adolescents aged 5 years and older. In an attempt to decrease the study burden, parent proxy was not completed in the older children.

The PedsQL brain tumor module is a 24-item Likert-type scale developed to measure health-related HRQOL in children and adolescents who are receiving treatment or are survivors of pediatric brain tumors. The module contains 6 scales and addresses cognitive function, pain and hurt, movement and balance, procedural anxiety, nausea, and worry. This instrument has parallel forms for child and parent report. The PedsQL brain tumor module is scored as the PedsQL V. 4, with higher scores reflecting a higher HRQOL. At all time-points, the brain tumor module was completed by parent proxy and by children and adolescents aged 5 years or older. The brain tumor module has been found to be internally consistent.⁷

The short form-36 health survey questionnaire (SF-36) is a generic measurement of adult HRQOL and is a 36-item Likert-type scale measuring physical functioning, role physical function (problems with work or daily activities as a result of physical health), bodily pain, general health perception which together comprise the physical component summary score. The scale also measures mental health, role emotional function (problems with work or daily activities as a result of emotional function), energy, and social functioning which together comprise the mental component summary score. The SF-36 questionnaires were scored for each domain; possible scores range from 0 to 100, with higher scores indicating better HRQOL. The normative scores have a mean of 50 and standard deviation of 10, which is representative of the mean and standard deviation of the findings in the general US population.⁸ The SF-36 was completed by the primary parent caregiver at all time-points.

The female US population norms were used since mothers overwhelmingly completed the SF-36 measure.

Statistical analysis

Patients' characteristics and HRQOL domain scores were summarized by descriptive statistics. The Wilcoxon signed-rank test was used to compare the change in HRQOL from baseline to week 6 of therapy and from week 16 to 24 of therapy for patients and parents. Patient (5 years of age) self-reported and parent proxy brain tumor specific HRQOL were compared at each time point using the Wilcoxon signed-rank test.

Z-scores were computed to estimate the statistical significance of the mean differences between sample and population norm scores on the SF-36. Effect sizes were computed to explore the clinical importance of the mean differences between sample and population norm scores of the SF-36. Effect sizes were calculated by dividing the mean difference in scores by the population standard deviation. Guidelines by Cohen⁹ were used to interpret effect sizes, as the magnitude of difference between the two groups (small 0.20, medium 0.50, large 0.80). The generalized estimating equations (GEE) model was used to examine the individual effects of parental age, time to child's death, time since initiation of therapy, and parent-proxy brain tumor specific HRQOL on physical and mental health (as measured by SF-36 physical and mental component summary scores). The compound symmetry working correlation structure was selected to account for the correlation among repeated measurements. Time to child's death was defined as the time between enrollment and death. All patients had died at the time of analyses and thus there was no censoring present in the data. All analyses included treatment time points up to week 24, due to small sample size and loss-to-follow-up secondary to disease progression. The false discovery rate adjustment was used to account for multiple testing when appropriate. A two-sided significance level of $P < .05$ was used for all statistical tests. Statistical analyses were conducted by using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Twenty-five patients and their parents were assessed for HRQOL, 24 patients with DIPG and 1 with medullary glioblastoma. Patients aged 2–4 years were only assessed by parent proxy ($n = 10$). In all, 80% of patients were white, and 52% were female. At study enrollment, the median age was 5.8 years (range, 2.3–17.2), and the median survival from enrollment was 13.8 months (95% CI: 9.3 to 19.2 months). The primary parental proxy included 24 mothers and 1 father with median age 35.2 years (range, 22.5 to 45.3).

At the week 24 evaluation, 8 (32%) of the patients were off treatment due to progressive disease. This decline continued with 16 (64%) off treatment at week 32 and only 6 patients remained on treatment by week 40. Due to the small sample size and loss-to-follow up secondary to disease progression, HRQOL was not reported beyond week 24. Because the patients were not attending school, school functioning, psychosocial functioning, and total score were not reported for the PedsQL V. 4.

Parent- and child-reported QOL

Table 1 compares children and adolescent outcomes for the PedsQL V. 4 and PedsQL brain tumor module domains over time, with measures reported only for those with data at the comparative time points. Thirteen of the 15 children and adolescents had comparative data and reported physical functioning to be low at baseline, with no significant change at week 6. Nine children and adolescents remained on study at week 16 and reported a non-significant decline in physical function from week 6. Procedural anxiety was the most concerning treatment specific symptom reported when compared to all other symptom domains. At week 16, 9 children and adolescents reported pain and hurt and movement and balance to worsen from week 6 to week 16; however, no significant difference was found. Table 2 details the change in the HRQOL brain tumor module scores as reported by parent proxy. From baseline to week 6, parents reported significant improvement in cognitive problems, movement and balance, procedural anxiety, and total score. In contrast, there were no significant changes in scores from week 6 to week 16. Table 3 details the child and adolescent self-reported HRQOL brain tumor scores as compared to parent proxy for the same patient. The only significant difference between the child and parent reported HRQOL was within the domain of movement and balance, with the patients reporting higher function at baseline through week 6.

Description of and predictor of parental SF-36

Table 4 details the mean normative scores of mothers as compared with those of the general female US population for the domains of the SF-36. When compared, mothers in our study had significantly higher HRQOL on five of the eight domains: physical functioning (baseline to week 24), physical role (baseline to week 6), bodily pain (baseline to week 24), general health perceptions (baseline to week 24), and energy/vitality (week 4 and 6). Mothers in our study only reported significantly lower HRQOL on two of the eight domains: social functioning (week 2) and mental health (baseline and week 2). Mothers reported lower emotional role function as compared to population norms; however, this was not statistically significant. The mental component summary score was only reported significantly lower for the mothers at baseline and week 2. Although not significant, at week 16, mothers had lower HRQOL scores within the domains of social functioning, emotional role, and mental health, than did the general population.

The clinical importance of the differences in HRQOL between the parents and populations norms is reported by effect size (Table 4). Effect sizes for the domains of physical health indicated small to moderate differences with the exception of bodily pain, which reflected a large difference and clinically higher parent reported HRQOL compared to the population norms. The effect sizes for domains of mental health indicated small to moderate differences with lower parent reported HRQOL compared to the population norms. The effect sizes for the physical component summary score were large, which reflected clinically important differences in the positive parental HRQOL (range 0.79 to 0.88), while the effect sizes for the mental component summary score indicated small to large differences negatively impacting parental HRQOL (−0.04 to −0.80).

Results from the GEE univariate model revealed that changes in brain tumor-specific HRQOL of the child as reported by the parents was associated with changes in parent's overall mental health HRQOL (Table 5). Specifically, parents reported higher mental health HRQOL if they reported their child as having less cognitive problems ($p=0.028$), less procedural anxiety ($p=0.001$) or higher total score brain tumor-specific HRQOL ($p<0.0001$). We did not find a relationship between the parents' age, time to their child's death, or time since diagnosis and the parents' reported HRQOL.

Discussion

During our prospective study of HRQOL in children with minimal chance of cure and the effect of their disease trajectory on their parents' HRQOL, we made several observations about the parents and their children. First, parents consenting to a Phase I study for their child were approachable and willing to complete the questionnaires at all designated time points. However, our participants sought this Phase I study and this level of participation cannot be generalized to other patients and parents offered Phase I participation after relapse. Surprisingly, we found emotional and social functioning to be higher as reported by the children and their parents than a previously published oncology sample.⁶ Children and adolescents reported a decline in physical function HRQOL at week 16, which may precede evidence of disease progression. Lastly, we observed that the children and adolescents reported their movement and balance HRQOL to be higher than that reported by parent proxy. This higher rated HRQOL by the children and adolescents may be a function of ego-resilience. Resilience may help patients adapt to the physical changes associated with illness, instead of reacting to the acute disease or treatment specific challenges. It has been suggested that specific challenges such as appearance may be perceived by the child as being outside the treatment context; therefore, the child may report their self-perception based on their ego-resilience.¹⁰

Contrary to a previous study,³ we did not find the child's illness to affect the parents reported physical functioning. This discrepancy may be related to the relatively young age of the parents in our study when compared to the general female population. In addition, parents were informed of their child's prognosis from the initiation of therapy, and many stated that they had to live each day to the fullest for their child. Contrary to reluctance to discuss prognosis with patients and their families at the risk of creating anxiety and depression, full prognostic disclosure has been found to give parents peace of mind and hope rather than increased anxiety.¹¹ Parents of a child not doing well, have reported hope of having more time with their child only if the child sustains a good quality of life, as well as hope for moments of grace and peace.¹² We did find that parents reporting their child as having heightened cognitive problems, procedural anxiety and poorer brain tumor-specific HRQOL, reported a lower mental health status. Our finding supports that of Rosenberg et al.⁴ who described parents having increased psychological distress when they felt their child had increased anxiety or sadness. Increased psychological distress among patients and their parents substantiates the need for integration of comprehensive, interdisciplinary HRQOL-directed care interventions and integration of palliative care to best support the patient and family throughout the course of illness and into the bereavement period. A landmark study of adult patients with high-risk cancer demonstrated that early palliative care integration

leads to improved HRQOL, mood and longer survival.¹³ Earlier palliative care integration may provide benefit for parents of children with incurable disease who are under emotional distress while navigating the care of their child. A barrier to early palliative care consultation is prognostic uncertainty and variable disease trajectory in pediatric patients; however, the diagnosis of DIPG and other high-grade gliomas is a notable exception because it has a predictable course and uniformly poor outcome and readily allows for integration of palliative care. For patients with DIPG, ideally palliative care integration would begin at diagnosis, providing optimal physical, spiritual, and emotional support to the patient and family to ensure the best possible QOL for the patient and caregivers.¹⁴ Anticipatory grief and bereavement support is an important aspect of quality palliative care for patients with prognoses that carry minimal chance for survival, as is the case in patients with DIPG. Data about the optimal timing and effect of interventions in this area are sparse. Parental grief from the loss of a child is known to be one of the most intense forms of grief and can result in poor long-term physical and psychological health effects that may lead to increased mortality. A study of bereaved parents found that open communication through the course of illness and availability of grief counseling services during their child's end-of-life leads to improved long-term caregiver outcomes.¹⁵ The results of our study are important in illuminating the typical timing of patients' and parents' HRQOL decline in the course of DIPG therapy and therefore may help to guide the timing of critically supportive palliative care measures.

As is common in similar studies that compare findings with population norms, we are limited in understanding the variability between our parent study sample and normative data. The parental reports were provided almost entirely by mothers, thus providing us only with the maternal QOL perspective during the patients' treatment trajectory. Mothers of children with cancer, who reported increased worry and lower personal-HRQOL, rated their child's HRQOL to be worse. Thus the maternal ratings of the child's HRQOL, especially for the very young child may be related to the mother's worries and concerns.¹⁶ These findings have limited generalizability due to the small sample size and the select parent population who made the decision to seek specialized treatment beyond the standard radiation. Lastly, these observations may not be generalizable to DIPG patients treated with radiation only, which is the current standard treatment in most of the world. While our patients did not receive palliative care referral until disease progression, palliative care should be integrated into the care of all children with DIPG at the time of diagnosis, which will allow for optimal symptom management at presentation and increase relationship-building with the family. The palliative care team may be especially helpful to assist in care coordination to help the patient and family make the most of their limited time. The decline in HRQOL scores seen at week 16 of therapy may precede progression of disease and should be a prompt for increased palliative care involvement, including aggressive symptom management, advanced care planning, anticipatory grief and bereavement services, and care coordination, to maximize HRQOL for the patient and help ensure positive long-term outcomes for the family.

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Table 1
Change in scores of patients' reports of PedsQL v.4.0 and PedsQL brain tumor module domains

	Change from baseline to week 6				Change from week 6 to week 16			
	N	Baseline	Week 6	FDR P	N	Week 6	Week 16	FDR P
		Median (IQR)	Median (IQR)	Median (IQR)		Median (IQR)		
PedsQL v.4.0								
Physical functioning	13	75 (50 – 90.6)	87.5 (75 – 96.9)	0.1406	9	87.5 (81.3 – 96.9)	65.6 (50 – 81.3)	0.3984
Emotional functioning	13	80 (70 – 90)	90 (70 – 100)	0.4258	9	90 (70 – 100)	100 (75 – 100)	0.9688
Social functioning	13	90 (60 – 95)	100 (80 – 100)	0.1406	9	100 (80 – 100)	95 (80 – 100)	0.9688
PedsQL brain tumor module								
Cognitive problems	12	79.2 (62.5 – 92.3)	91.7 (67.9 – 100)	0.9411	9	91.7 (89.3 – 100)	92.9 (83.3 – 100)	0.7500
Pain and hurt	12	100 (83.3 – 100)	100 (66.7 – 100)	0.9517	9	100 (83.3 – 100)	91.7 (50 – 100)	0.7500
Movement and balance	13	83.3 (66.7 – 91.7)	83.3 (66.7 – 100)	0.9516	9	91.7 (66.7 – 100)	83.3 (66.7 – 100)	0.7500
Procedural anxiety	13	16.7 (0 – 66.7)	33.3 (25 – 100)	0.0273 *	9	66.7 (33.3 – 100)	83.3 (33.3 – 100)	0.7500
Nausea	13	100 (80 – 100)	80 (70 – 90)	0.1709	9	80 (70 – 90)	90 (80 – 95)	0.7500
Worry	12	91.7 (83.3 – 100)	87.5 (83.3 – 100)	0.9516	9	91.7 (83.3 – 100)	91.7 (75 – 100)	0.7500
Total score	12	79.3 (67.4 – 88.2)	81.1 (67.9 – 90.2)	0.9517	9	81.8 (80.4 – 89.1)	84.8 (73.9 – 87)	0.7500

Higher scores indicate better HRQOL
IQR: interquartile range, FDR: false discovery rate
* Statistically significant, P<0.05

Table 2

Change in scores of parent proxy PedsQL brain tumor module domains

PedsQL brain tumor module	Change from baseline to week 6			Change from week 6 to week 16		
	N	Pre-study	Week 6	N	Week 6	Week 16
		Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)
Cognitive problems	13	70.8 (58.3 – 83.3)	83.3 (75 – 91.7)	10	85.4 (75 – 91.7)	79.2 (54.2 – 89.3)
Pain and hurt	23	91.7 (75 – 100)	91.7 (75 – 100)	17	100 (83.3 – 100)	100 (83.3 – 100)
Movement and balance	23	50 (12.5 – 83.3)	75 (50 – 75)	17	75 (58.3 – 100)	58.3 (33.3 – 83.3)
Procedural anxiety	22	25 (0 – 50)	58.3 (33.3 – 91.7)	17	58.3 (33.3 – 91.7)	58.3 (16.7 – 83.3)
Nausea	21	100 (90 – 100)	95 (70 – 100)	17	100 (80 – 100)	90 (70 – 100)
Worry	22	100 (75 – 100)	100 (83.3 – 100)	16	100 (95.8 – 100)	100 (75 – 100)
Total score	19	70.7 (62.5 – 80.9)	79.3 (75 – 91.2)	16	82.1 (77.9 – 91.8)	73.3 (68.5 – 82.4)

Questions related to cognitive problems are not asked of toddlers. Higher scores indicate better HRQOL

IQR interquartile range, *FDR* false discovery rate

* Statistically significant, $P < 0.05$.

Table 3
Difference in scores of patients', reports and parent proxy of PedsQL brain tumor module domains

PedsQL brain tumor module	Time point	N	Patient Median (IQR)	Parent Median (IQR)	FDR P
Cognitive problems	Baseline	14	79.2 (66.7 – 91.7)	70.8 (58.3 – 83.3)	0.4219
	Week 2	11	91.7 (85.7 – 100)	70.8 (66.7 – 87.5)	0.3926
	Week 4	13	89.3 (83.3 – 92.9)	85.7 (70.8 – 91.7)	0.7764
	Week 6	13	91.7 (75 – 100)	87.5 (75 – 91.7)	0.8135
	Week 16	9	92.9 (83.3 – 100)	83.3 (54.2 – 89.3)	0.3926
	Week 24	8	95.8 (82.1 – 100)	85.4 (77.1 – 93.8)	0.4219
Pain and hurt	Baseline	14	100 (83.3 – 100)	87.5 (66.7 – 100)	1.0000
	Week 2	13	91.7 (83.3 – 100)	83.3 (66.7 – 100)	1.0000
	Week 4	12	100 (83.3 – 100)	91.7 (83.3 – 100)	1.0000
	Week 6	13	100 (66.7 – 100)	100 (83.3 – 100)	1.0000
	Week 16	9	91.7 (50 – 100)	91.7 (58.3 – 100)	1.0000
	Week 24	8	95.8 (87.5 – 100)	95.8 (87.5 – 100)	1.0000
Movement and balance	Baseline	15	83.3 (50 – 91.7)	50 (0 – 66.7)	0.0078*
	Week 2	13	66.7 (50 – 91.7)	58.3 (25 – 75)	0.0498*
	Week 4	12	66.7 (66.7 – 100)	54.2 (50 – 75)	0.0078*
	Week 6	13	83.3 (66.7 – 100)	66.7 (50 – 75)	0.0078*
	Week 16	9	83.3 (66.7 – 100)	50 (25 – 75)	0.1500
	Week 24	8	50 (16.7 – 62.5)	25 (0 – 70.8)	0.3438
Procedural anxiety	Baseline	15	16.7 (0 – 66.7)	25 (0 – 58.3)	0.8906
	Week 2	13	50 (33.3 – 91.7)	50 (33.3 – 66.7)	0.8906
	Week 4	13	66.7 (33.3 – 100)	66.7 (33.3 – 75)	0.8906
	Week 6	13	33.3 (25 – 100)	58.3 (33.3 – 91.7)	0.8906
	Week 16	9	83.3 (33.3 – 100)	50 (16.7 – 83.3)	0.8906
	Week 24	8	50 (0 – 95.8)	50 (16.7 – 95.8)	0.8906
Nausea	Baseline	15	100 (80 – 100)	95 (75 – 100)	0.6523

PedsQL brain tumor module	Time point	N	Patient	Parent	FDR P
			Median (IQR)	Median (IQR)	
	Week 2	12	87.5 (60 – 90)	80 (70 – 97.5)	0.6523
	Week 4	13	90 (90 – 100)	90 (75 – 100)	0.6523
	Week 6	13	80 (70 – 90)	95 (70 – 100)	0.6523
	Week 16	9	90 (80 – 95)	80 (70 – 90)	0.6523
	Week 24	8	95 (78.8 – 100)	95 (62.5 – 100)	0.6523
Worry	Baseline	13	91.7 (83.3 – 100)	75 (75 – 100)	0.4922
	Week 2	12	87.5 (70.8 – 100)	100 (75 – 100)	0.6563
	Week 4	13	83.3 (50 – 100)	100 (75 – 100)	0.4922
	Week 6	12	95.8 (83.3 – 100)	95.8 (75 – 100)	1.0000
	Week 16	9	91.7 (75 – 100)	100 (75 – 100)	1.0000
	Week 24	6	100 (83.3 – 100)	100 (91.7 – 100)	1.0000
	Baseline	13	78.3 (65.2 – 84.8)	63.6 (62.5 – 71.9)	0.1641
	Week 2	10	83.7 (67.7 – 90.9)	76.6 (63.5 – 81.3)	0.4648
	Week 4	12	77.2 (72.3 – 94.7)	81.5 (75 – 82.5)	0.9097
	Week 6	12	81.1 (75.6 – 90.2)	79.3 (75.5 – 87.5)	0.9097
	Week 16	9	84.8 (73.9 – 87)	69.6 (67.4 – 74)	0.1641
	Week 24	6	79.7 (71.7 – 92.7)	82.6 (73.9 – 87)	0.9097
Total score					

Higher scores indicate better HRQOL
IQR interquartile range, *FDR* false discovery rate.
* Statistically significant, P<0.05.

SF-36 norm scores of parents of children with cancer and of the general U.S. population

Table 4

Scale	Time point	Female parent norms		Female U.S. population norms		z score	Effect size
		N	Mean (SD)	N	Mean (SD)		
Physical functioning	Baseline	24	54.40 (5.20)	40 32	48.70 (10.59)	5.30*	0.54
	Week 2	24	53.62 (8.98)			2.67*	0.46
	Week 4	22	55.68 (9.72)			3.36*	0.66
	Week 6	21	55.31 (3.24)			9.10*	0.62
	Week 16	18	56.40 (1.25)			22.74*	0.73
	Week 24	15	56.40 (1.30)			20.54*	0.73
Physical role	Baseline	24	54.73 (5.87)	40 32	49.09 (10.33)	4.66*	0.55
	Week 2	24	54.44 (4.77)			5.42*	0.52
	Week 4	22	53.00 (7.77)			2.35*	0.38
	Week 6	21	52.84 (6.55)			2.61*	0.36
	Week 16	18	52.28 (9.13)			1.48	0.31
	Week 24	15	51.97 (8.34)			1.33	0.28
Bodily pain	Baseline	24	57.69 (6.10)	40 32	49.11 (10.29)	6.83*	0.83
	Week 2	24	59.31 (6.58)			7.54*	0.99
	Week 4	22	58.65 (6.24)			7.12*	0.93
	Week 6	21	58.24 (6.34)			6.55*	0.89
	Week 16	18	58.17 (8.05)			4.76*	0.88

Scale	Time point	Female parent norms		Female U.S. population norms		z score	Effect size
		N	Mean (SD)	N	Mean (SD)		
General health perceptions	Week 24	15	58.29 (8.18)			4.33*	0.89
	Baseline	24	55.30 (7.76)	40 32	49.39 (10.22)	3.71*	0.58
	Week 2	24	55.59 (7.48)			4.04*	0.61
	Week 4	22	57.55 (6.34)			5.99*	0.80
	Week 6	21	57.02 (7.09)			4.91*	0.75
	Week 16	18	54.72 (8.01)			2.81*	0.52
	Week 24	14	56.34 (7.35)			3.53*	0.68
	Baseline	24	48.57 (9.20)	40 32	48.74 (10.19)	-0.09	-0.02
Energy/vitality	Week 2	24	47.89 (9.77)			-0.42	-0.08
	Week 4	22	53.59 (8.95)			2.53*	0.48
	Week 6	20	54.17 (7.69)			3.14*	0.53
	Week 16	18	50.26 (9.62)			0.67	0.15
	Week 24	15	53.53 (9.02)			2.05	0.47

Table 5

GEE univariate model results investigating predictors of parental physical and mental health

Predictor	SF-36			
	Physical health component summary		Mental health component summary	
	β (SE)	P	β (SE)	P
Parental age (years)	0.023 (0.086)	0.7883	-0.398 (0.246)	0.1061
Time to child's death (months)	0.023 (0.067)	0.7362	-0.085 (0.271)	0.7539
Time since initiation of therapy (weeks)	-0.052 (0.050)	0.2985	0.122 (0.133)	0.3576
Parent brain tumor module domains				
Cognitive problems ^a	0.028 (0.031)	0.3760	0.164 (0.075)	0.0285 *
Pain and hurt	0.015 (0.032)	0.6328	0.094 (0.050)	0.0612
Movement and balance	-0.020 (0.014)	0.1489	0.040 (0.030)	0.1711
Procedural anxiety	-0.002 (0.012)	0.8582	0.075 (0.023)	0.0015 *
Nausea	0.043 (0.046)	0.3478	0.101 (0.065)	0.1202
Worry	-0.001 (0.040)	0.9896	0.089 (0.060)	0.1366
Total score	0.018 (0.054)	0.7434	0.303 (0.077)	<0.0001 *

Higher scores indicate better HRQOL

 β beta coefficient, SE standard error^aSample size is based on n=15 as questions related to cognitive problems are not given for toddlers. All other models are based on a sample size of n=25

* Statistically significant, P<0.05