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Health related quality of life in the first year after diagnosis in children with brain tumours compared with matched healthy controls; a prospective longitudinal study

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ABSTRACT

This paper compares parent- and self-report health-related quality of life (HRQL) in children aged 2–16 years with brain tumours, one, six and twelve months after diagnosis with matched normal controls. HRQL was assessed using the PedsQL generic core scales. 37 tumour patients and 42 controls were included in analysis of parent-report, and 27 patients and 31 controls in self-report HRQL. Parent-report scores were significantly lower in patients than controls for all PedsQL scores at all time points (max $p = 0.002$). Differences in self-report PedsQL between patients and controls were variable. The relationship between self- and parent-report in patients and controls was inconsistent; varied over time; and did not consistently correlate with parental depressive symptoms, suggesting parents and their children do not regard HRQL in a similar way. Prospective, longitudinal assessment of HRQL is important, but should be supplemented with other outcome measures such as health status and behaviour in this population.

1. Introduction

Brain tumours are the second most common form of childhood cancer, accounting for over 20% of all cases in European children.[1] Prognosis for many childhood brain tumours has improved over the past two decades, with approximately 65% of all children treated for brain tumour now achieving long-term survival.[2]

Treatment, recovery and rehabilitation of children with cancer may be lengthy, and they may have difficulties re-integrating into normal life, maintaining peer relationships and attaining normal academic milestones.[3–7] This is particularly true for survivors of childhood brain tumours.[8–10] Measurement of quality of life (QOL) and more specifically Health-Related Quality of Life (HRQL) have therefore become increasingly important in quantifying morbidity in paediatric oncology.

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HRQL has been described as a multidimensional construct that incorporates both objective and subjective data. It includes, but is not limited to, the social, physical and emotional functioning of the child/ adolescent, and where indicated their family. HRQL must be sensitive to changes occurring throughout development.[11]

Research into QOL in childhood cancer has primarily focused on defining QOL in long-term survivors.[12–16] Studies of long-term survivors of childhood brain tumours have shown their QOL to be lower than that observed in normal peers and other childhood cancer survivors.[17–21]

To date there is only one study that assessed HRQL in children with cancer prospectively, at six weeks and one year after diagnosis. Patients had deficits in both physical and emotional HRQL at both time points, with significant improvements in HRQL over time. All tumour types were included, so findings may not represent the paediatric brain tumour population.[22] There are currently no published longitudinal data on HRQL in children with brain tumours. Measurement of HRQL early after diagnosis with childhood brain tumour may be important in predicting which children and families could benefit most from interventions aimed at improving both early and long-term outcome.

It is often stated that HRQL, being a subjective measure, is best reported by the individuals themselves. However, this may not be possible in children with brain tumours, where the tumour and its treatment may impair their ability to respond competently to questioning. Some authors have suggested that self-scored HRQL be used only as a secondary outcome measure in younger children due to lack of reliability.[23] It is also usually the parent's perception of their children's HRQL that determines health care utilization.[24,25] Others feel that any comprehensive assessment of HRQL should try to include information from both child and caregiver, as both views may provide valid results.[13,26] Parents of healthy children tend to overestimate, and parents of children with cancer tend to underestimate their children's HRQL in relation to self-report, further complicating analysis.[27,28]

In view of the paucity of published data on this subject, we aimed to measure HRQL in children with brain tumours one, six and twelve months after diagnosis, and compare HRQL with "normal" matched controls. In addition, we sought to assess the relationship between parent and self-report HRQL for patients and controls. As parental mental health may influence their rating of their child's health/ HRQL,[29,30] we also aimed to explore the relationship between parental depression and differences in parent- and self-report HRQL.

2. Patients and methods

This was a longitudinal prospective cohort study using matched controls. Ethical approval for the study was gained from Central and South Bristol Research Ethics Committee.

2.1. Subjects

All children and adolescents with primary intracranial tumours, referred to the regional neuro-surgical unit at Frenchay Hospital, Bristol, from April 2003 to April 2005, were approached to take part in the study.

HRQL and other outcome data were collected at interviews, approximately one (T1), six (T6) and twelve (T12) months after diagnosis. All patients alive one year after diagnosis, and all controls for which data was available were included in this analysis.

The 'best friends' model was used to recruit controls matched for socio-economic status and academic attainment.[31]

Interviews were face-to-face to avoid placing a high demand on children's expressive and receptive language skills and to maximize rapport building.[32] Parents and children were interviewed independently, to avoid possible influence on their separate responses by one another.

2.2. The Paediatric Quality of Life Inventory 4.0 (PedsQL)

The PedsQL generic core scale forms part of a modular system that includes both generic and disease-specific scales. It measures HRQL in patients and controls for the four-week period immediately prior to interview. Age specific versions of both parent-report (ages 2-18), and self-report (ages 5-18 years), are available. Items are scored on a 5-point Likert scale 'never a problem' to 4 'almost always a problem' with the exception of the self-report for children aged 5 to 7 years, where items are rated on a simplified 3-point scale. Items are reverse scored and linearly transformed to a 0-100 scale with higher scores representing better HRQL. There are four domains; namely the physical, emotional, social and school domains, and three summary scores; the psychosocial summary, a summary of the emotional, social, and school domains; the physical summary, which is identical to the physical domain score; and the total score, a summary of all four domains.[33]

The validity and reliability of the PedsQL for healthy children, and children with acute and chronic diseases, including those with cancer, have been established.[33–35,23]

2.3. Parental Depression: The BDI-II

We used the Beck Depression Inventory –Second Edition (BDI-II) to measure symptoms of depression in the primary caregivers of patients and controls. The BDII is a valid and reliable questionnaire, developed as an indicator of the presence and degree of depressive symptoms consistent with DSM-IV criteria. Higher scores represent more severe depressive symptoms.[36]

2.4. Statistical analysis

Comparisons between the patients and controls at the three time points were made using repeated measures Analyses of Variance (ANOVAs), using the 'Proc MIXED' procedure in SAS version 8.2 (SAS Inst. Inc., 1999–2001, Cary, NC, USA). The results reported below assume a compound symmetry model with different variance-covariance matrix for the two groups as this gave the best fit. All available data were included in the analysis conditional on the child's survival to 12 months. The analysis of each variable concluded with a comparison between the two groups made separately at each

time point, and a comparison of the three time points for each group.

Pearson correlation, intraclass correlation (ICC) and group means differences were used to assess the relationship between parent and child scores. ICC was estimated using the two-way random effects model .[37] The degree of correlation was categorised as small, medium and large when correlation coefficients were smaller than 0.3, between 0.3 an 0.5 or larger or equal to 0.5, respectively.[37,38] Spearman's correlation was used to assess the possible influence of maternal depressive symptoms on self/parent PedsQL differences. These analyses were carried out using the SPSS version 11 (SPSS inc, Chicago, IL).

3. Results

3.1. Participants

Of the 48 patients eligible for the study, 3 declined to participate. Seven patients died before T12 assessment, and one patient was too young for any HRQL assessment. Two patients withdrew following T1 assessment. Controls were successfully recruited for all but two patients in the study. Four controls having consented to the study declined further follow-up. Table 1 provides details about the patient population and reasons for missing data.

26 patients were included in the analysis of agreement/differences between parent- and child-rated HRQL at T1, 25 at T6, and 27 at T12. 28 controls were included in the analysis of agreement/differences between parent- and child-rated HRQL at T1, 27 at T6, and 31 at T12.

Mean time from definitive diagnosis to T1 assessment was 1.8 months (range 0.8–3.7 months), and to T12 assessment 14.0 months (range 12.0–18.7 months). The complexity of post-operative management was the main cause of delay in completing T1 assessments.

For patients at T1, median age was 9.4 years (range 1.8–16.6). For controls at T1, median age was 9.3 years (range 1.7–17.8).

3.2. Difference in HRQL between patients and matched controls

See Figs. 1 and 2 for details.

3.2.1. Parent-report

There was a significant difference between patients and controls in parent-report PedsQL scores at all three time-points (maximum $p = 0.002$).

3.2.2. Self-report

Results for the self-report PedsQL were more variable:

T1: While there was a significant difference between patients and controls for all summary scores and the school domain of the self-report (max $p = 0.028$), this was not true for the social or emotional domains (min $p = 0.120$).

T6: There was a significant difference between patients and controls for the total score, physical summary and school domain (max $p = 0.033$), while there was no significant difference for the psychosocial summary, or emotional and social domains (min $p = 0.412$).

T12: There was again, a significant difference between patients and controls for the physical summary score ($p = 0.016$), but no significant differences between patients and controls for any other PedsQL scores (min $p = 0.111$).

3.2.3. Changes in HRQL over time

Fig. 1 shows changes in HRQL for patients and controls.

Patients

Parent-report: There was a statistically significant improvement in HRQL over time for all summary scores and for the emotional and school domain for patients (max $p = 0.044$), but not for the social domain ($p = 0.113$).

Self-report: There was a statistically significant improvement in HRQL over time in patients for the total and physical summary scores (max $p = 0.013$), but not for the psychosocial summary, or the emotional, social or school domains (min $p = 0.283$).

Controls: There was no significant difference in HRQL over time for any parent- or self-report PedsQL scores for controls.

3.3. Relationships between self-rated and parent-rated HRQL

The relationship between self and parent-report PedsQL can be seen in Table 2.

3.3.1. Pearson's and intraclass correlation coefficients

ICC was identical or very similar to Pearson's correlation for all summary and domain scores of the PedsQL at all three time-points, and therefore only Pearson's correlation is discussed below.

T1, patients: Correlation between self- and parent-report HRQL for all summary scores and the social domain of the PedsQL were good (range $r = 0.65$ to $r = 0.79$). Agreement was similar for psychosocial and physical summary scores. The correlation between self-and parent-report in the emotional and school domains was moderate ($r = 0.36$ and 0.45 respectively).

T1, controls: Pearson's correlation for all PedsQL scores was good (range $r = 0.51$ to $r = 0.73$). Agreement was similar for psychosocial and physical summaries scores.

T6, patients: Pearson's correlation for all summary scores and the social domain of the PedsQL were good (range $r = 0.53$ to $r = 0.86$). The relationship between self-and parent-report was moderate for the emotional and the school domains ($r = 0.39$, $r = 0.30$ respectively). Agreement was better for the physical than the psychosocial summary score.

T6, controls: Pearson's correlation was moderate for the total score, psychosocial summary score, and emotional and school domains (range $r = 0.34$ to $r = 0.44$), but poor for the physical summary score and social domain ($r = -0.07$ and $r = 0.19$ respectively). Agreement was higher for the psychosocial summary than the physical summary score.

T12, patients: Pearson's correlation was good for the total and the physical summary scores($r = 0.66$ and $r = 0.87$ respectively), moderate for the social domain ($r = 0.32$) and poor for the psychosocial summary score, and the emotional and school domains (range, $r = 0.13$ to $r = 0.23$). Again, as for

Table 1 – Patient Characteristics

Age at t1	Age at t12	Sex	Tumour Type	PPedsQL t1	SPedsQL t1	PPedsQL t6	SPedsQL t6	PPedsQL t12	SPedsQL t12
6.4	7.4	F	Ependymoma	Y	Y	Y	N[2]	Y	Y
2.7	3.7	M	LG astrocytoma	Y	N[1]	Y	N[1]	Y	N[1]
2.0	2.9	M	Ependymoma	Y	N[1]	Y	N[1]	Y	N[1]
12.5	13.5	M	Germ-cell Tumour	Y	N[4]	Y	Y	Y	Y
7.7	8.8	F	LG astrocytoma	Y	Y	Y	Y	Y	Y
16.6	N[5]	M	Medulloblastoma	Y	Y	N[5]	N[5]	N[5]	N[5]
3.9	5.1	F	LG astrocytoma	Y	N[1]	Y	N[1]	Y	Y
12.8	13.9	F	LG astrocytoma	Y	Y	Y	Y	Y	Y
1.8	2.6	F	LG astrocytoma	N[1]	N[1]	Y	N[1]	Y	N[1]
12.2	13.1	M	Germ-cell tumour	Y	Y	Y	Y	Y	Y
11.3	12.4	M	Medulloblastoma	Y	Y	Y	Y	Y	Y
7.7	8.7	F	Medulloblastoma	Y	Y	Y	Y	Y	Y
15.0	16.3	M	HG astrocytoma	Y	Y	Y	Y	Y	Y
4.2	5.1	M	LG astrocytoma	Y	N[1]	Y	N[1]	Y	N[2]
13.9	14.9	M	LG astrocytoma	Y	Y	Y	Y	Y	Y
6.0	6.9	M	LG astrocytoma	Y	Y	Y	Y	Y	Y
2.7	3.2	M	Choroid plexus papiloma	Y	N[1]	N[3]	N[3]	Y	N[1]
16.5	17.3	M	Germ-cell Tumour	Y	Y	Y	Y	Y	Y
1.8	2.8	M	Ependymoma	N[1]	N[1]	Y	N[1]	Y	N[1]
14.2	15.3	F	Meningioma	Y	Y	Y	Y	Y	Y
13.7	14.6	M	Supratentorial PNET	Y	Y	Y	Y	Y	Y
9.3	10.3	M	Ependymoma	Y	Y	Y	Y	Y	Y
13.2	14.2	F	LG astrocytoma	Y	Y	Y	Y	Y	Y
6.4	7.7	F	Ependymoma	Y	Y	Y	Y	Y	Y
9.3	10.4	F	LG astrocytoma	Y	Y	Y	Y	Y	Y
4.3	5.3	F	LG astrocytoma	Y	N[1]	Y	N[1]	Y	N[2]
14.5	N[5]	F	Medulloblastoma	Y	Y	N[5]	N[5]	N[5]	N[5]
9.7	10.7	F	Craniopharyngioma	Y	Y	Y	Y	Y	Y
12.0	12.9	M	Craniopharyngioma	Y	Y	Y	Y	Y	Y
11.7	12.7	F	LG astrocytoma	Y	Y	Y	Y	Y	Y
16.6	17.6	M	HG astrocytoma	Y	Y	Y	Y	Y	Y
8.9	9.9	F	LG astrocytoma	Y	N[4]	Y	Y	Y	Y
16.0	17.0	F	LG astrocytoma	Y	Y	Y	Y	Y	Y
3.9	4.9	F	LG astrocytoma	Y	N[1]	Y	N[1]	Y	N[1]
7.8	8.8	M	LG astrocytoma	Y	Y	Y	Y	Y	Y
9.4	10.4	F	Medulloblastoma	Y	Y	Y	Y	Y	Y
15.3	16.3	M	LG astrocytoma	Y	Y	Y	Y	Y	Y

Abbreviations: t1, one month assessment; t6, six month assessment; t12, 12 month assessment; F, female; M, male; PPedsQL, parent-report PedsQL; SPedsQL, self-report PedsQL; LG, low-grade; HG, high-grade; PNET, primitive neuroectodermal tumour; Y, yes; N, no. Reasons for N: 1,too young; 2, unable/uncooperative; 3, missed interview/missing data; 4, too ill; 5, withdrew.

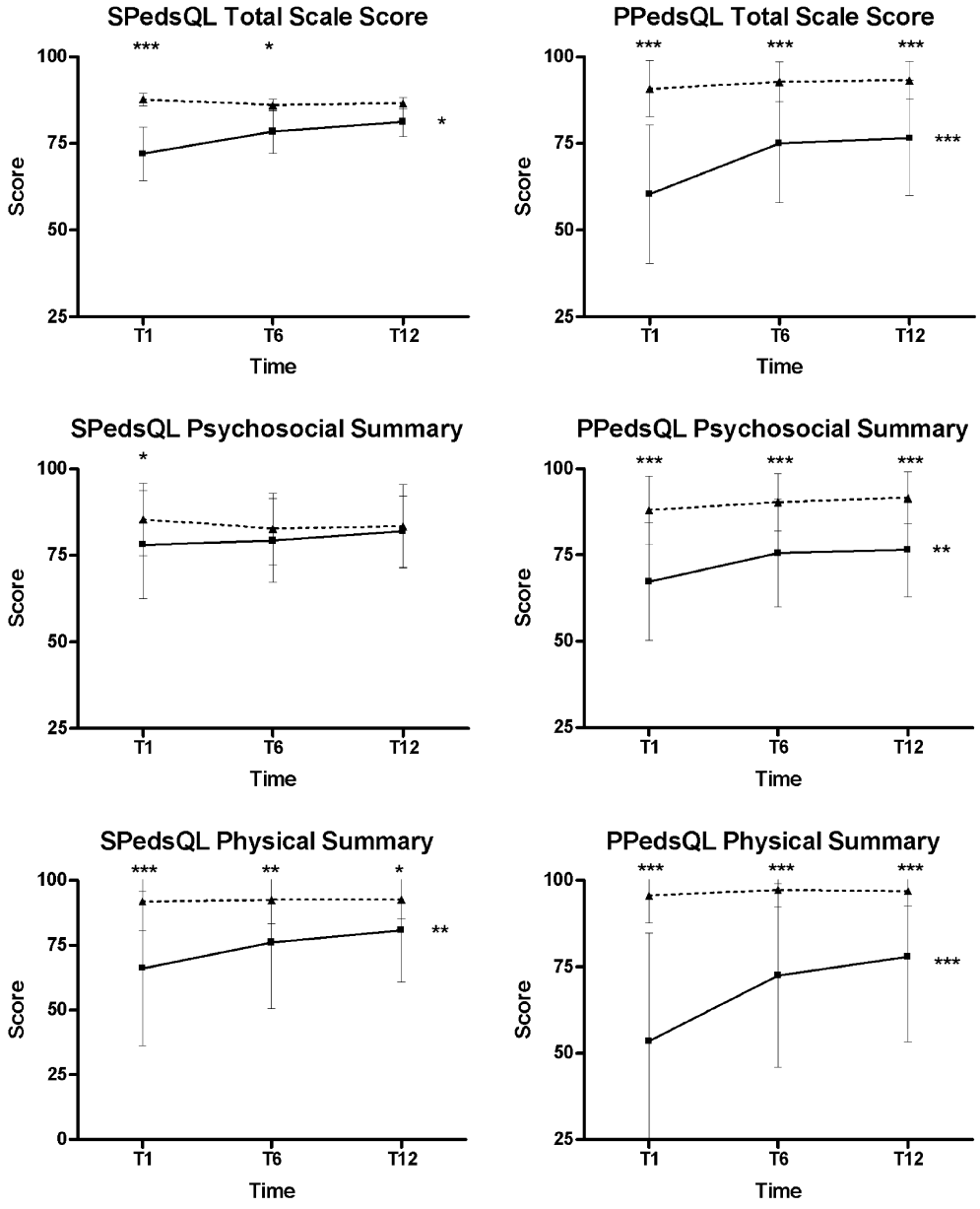

Fig. 1 – Self- and parent report PedsQL summary scores showing group means and standard deviations. —— Represents children with brain tumours, - - - represents controls. PPedsQL, parent-report PedsQL; SPedsQL, Self-report PedsQL; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

patients at t6, agreement was higher for the physical than the psychosocial summary score.

T12, controls: For controls, Pearson's correlation was moderate for the total, psychosocial summary score and school domain (range, r = 0.35 to r = 0.39), but poor for the physical summary score and emotional and social domains (range, r = –0.12 to r = 0.27). As for controls at T6, agreement was higher for the psychosocial summary than the physical summary score.

3.3.2. Relationship between maternal depressive symptoms (BDI) and difference between self- and parent-report PedsQL (self-parent report)

There was a statistically significant correlation between the BDI and the difference between self- and parent-report PedsQL in patients for the physical summary at T6 ($r_s = 0.54$, $p = 0.006$) and T12 ($r_s = 0.39$, $p = 0.042$), but not for any other PedsQL scores at any time-points. Correlation between the BDI and PedsQL difference for the psychosocial summary in patients does approach significance at T1 ($r_s = 0.36$, $p = 0.087$). There was a statistically significant correlation between the BDI and the difference between self- and parent-report PedsQL in controls for the psychosocial summary ($r_s = 0.49$, $p = 0.009$) and the social domain ($r_s = 0.41$, $p = 0.035$) at T6 only. Details of depressive symptoms in parents will be published in a separate manuscript.

3.3.3. Differences in group means

For patients, with the exception of the school domain at T6 and T12, parent-report was lower than self-report for all

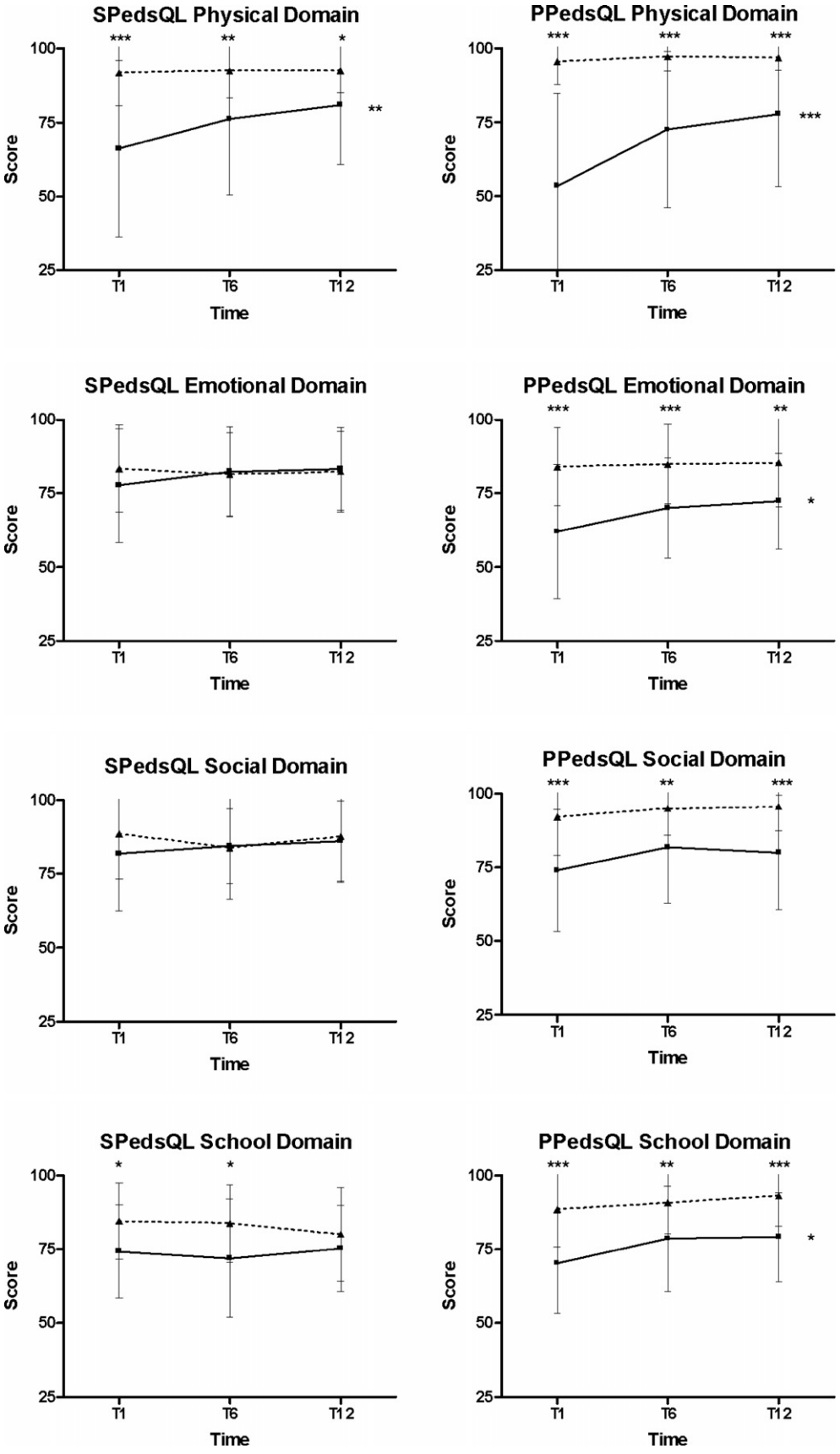

Fig. 2 – Self- and parent report PedsQL domain scores showing group means and standard deviations. —— Represents children with brain tumours, - - - represents controls. PPedsQL, parent-report PedsQL; SPedsQL, Self-report PedsQL; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

Table 2 – Relationship between self-report and parent-report for brain tumour patients and controls using the PedsQL

	T1				T6				T12			
PedsQL	N	Mean bias[a]	R	ICC	PedsQL	N	Mean bias[a]	R	ICC	PedsQL	N	Mean bias[a]	R	ICC
Brain Tumour Children					**Brain Tumour Children**					**Brain Tumour Children**				
Total scale score	26	10.52[d]	0.79[d]	0.78[d]	Total scale score	25	5.40[b]	0.76[d]	0.74[d]	Total scale score	27	3.28	0.66[d]	0.61[d]
Physical health	26	10.17[b]	0.79[d]	0.79[d]	Physical health	25	6.49[b]	0.86[d]	0.85[d]	Physical health	27	0.94	0.87[d]	0.85[d]
Psychosocial health	26	9.71[c]	0.73[d]	0.72[d]	Psychosocial health	25	5.56	0.54[c]	0.53[c]	Psychosocial health	27	4.26	0.13	0.13
Emotional function	26	14.04[b]	0.36[b]	0.35[b]	Emotional function	25	12.40[c]	0.39	0.39[b]	Emotional function	27	8.70[b]	0.23	0.23
Social function	26	7.11[b]	0.65[d]	0.64[d]	Social function	25	5.00	0.53[c]	0.48[c]	Social function	27	4.81	0.32	0.31
School function	12	3.75	0.45	0.45	School function	23	−2.39	0.30	0.29	School function	24	−3.33	0.16	0.16
Controls					**Controls**					**Controls**				
Total scale score	28	−2.79	0.73[d]	0.73[d]	Total scale score	27	−6.48	0.34	0.33[b]	Total scale score	31	−6.63	0.39[b]	0.35[b]
Physical health	28	3.00	0.74[d]	0.72[d]	Physical health	27	−5.21	−0.07	−0.05	Physical health	31	−4.42	−0.12	−0.10
Psychosocial health	28	−2.68	0.68[d]	0.68[d]	Psychosocial health	27	−7.16	0.42[b]	0.42[b]	Psychosocial health	31	−8.12	0.36	0.32[b]
Emotional function	28	−0.89	0.51[c]	0.50[c]	Emotional function	27	−3.15	0.37	0.37[b]	Emotional function	31	−4.19	0.24	0.24
Social function	28	−3.39	0.58[c]	0.58[c]	Social function	27	−10.20	0.19	0.16	Social function	31	−7.26	0.27	0.23
School function	28	−3.21	0.69[d]	0.68[d]	School function	27	−6.11	0.44[b]	0.44[b]	School function	31	−11.60	0.35	0.33[b]

Abbreviations: PedsQL, Pediatric Quality of Life inventory 4.0; R, Pearson Product-moment correlation; ICC, Intraclass correlation.

a Child group mean - parent group mean.

b $p < 0.05$.

c $p < 0.01$.

d $p < 0.001$.

scores. In general, the group mean difference was similar for psychosocial and physical summary scores, and greatest for the emotional domain.

For controls, self-report was lower than parent-report for all PedsQL scores at all time points. At T6 and T12, group mean difference was greater for the psychosocial than the physical summary score. In general, the biggest difference between self- and parent-report for controls was in the social and school domains.

4. Discussion

This is the first time that HRQL has been measured prospectively in children with brain tumours and controls over the first year after diagnosis. The study demonstrates the feasibility of engaging children with brain tumours, and their families, in longitudinal studies of quality of life soon after diagnosis.

Our data are generally in keeping with retrospective studies of more long-term survivors of childhood brain tumours, showing that parents report their child's HRQL, as lower than that in healthy controls.[17,21,23,39] However, although we found a statistically significant difference in self-report overall HRQL between tumour patients and controls at one and six months after diagnosis, this was not true at twelve months. This is in contrast to two retrospective studies that reported decreased overall self-rated HRQL in long-term survivors of primary brain tumours.[17,23] Limited self-report numbers may account in part for the lack of statistically significant difference in our study. Importantly, the difference between patients and controls did exceed the suggested minimum clinically important difference of 4.4 for the self- report total score at twelve months after diagnosis.[35]

Reduction in HRQL was most marked one month after diagnosis, and improved over time for both self- and parent-report for most HRQL domains and summaries. The most marked improvement for both physical and psychosocial health occurred between one and six-month assessments. Reduction in HRQL across a wide variety of domains in brain tumour patients is unsurprising considering the impact of recent diagnosis, initial surgical and adjuvant treatment (radiotherapy +/- chemotherapy). Physical health was scored lower than psychosocial health by parents and patients one month after diagnosis. This changed over time, parents and patients both reporting similar scores for physical and psychosocial health at six and twelve months. These findings are in agreement with Eiser *et al*, who, reported comparable physical and psychosocial health in children an average of seven years after brain tumour diagnosis.[17]

Despite the possible impact of time in hospital, separation from family and friends, painful procedures and neurological deficit, patients showed surprisingly high self-rating for psychosocial health at all time points. These children may not fully understand the consequence of their diagnosis, may be repressing symptoms of distress while adapting to their illness,[40,41] or may be reluctant to reveal their emotional state. This finding may change over time, since Bhat et al reported reduced self- and parent-rated psychosocial HRQL in such children a median of three years after diagnosis.[23]

The lack of agreement between child and parent-rated HRQL suggests that parents and their children do not regard HRQL in a similar way. This conclusion is in contrast to that of Bhat et al..[23] For patients, agreement between parent and child rated HRQL was better for the more observable (physical), compared with less observable (psychosocial) domains, in keeping with previously published data on childhood cancer and other chronic disorders.[26,42,43] Parents of children with cancer tended to rate their children's HRQL lower than the children themselves.[17,27,37] In contrast to parents of children with brain tumours, but in agreement with previous studies, parents of healthy controls estimated their child's HRQL as higher than the children themselves.[28,44,45] These discrepancies exaggerated the reported difference between brain tumour patients and controls in parent-rated HRQL and reduced the reported difference in self-rated HRQL.

Agreement between parent- and self-report among the controls was similar to that in the patients one month after diagnosis. This is a surprising finding as it has been suggested that agreement between parent and child ratings of HRQL is better in chronically sick than healthy children .[26] Agreement decreased over time, and was better for psychosocial than physical domains.

There are a number of possible explanations for the differences between self- and parent-rated HRQL. These include differences in child and parent's interpretation of events, adaptive style, response style, child personality and parental emotional status/QOL.[40,46–48] Children with cancer often utilize a repressive adaptive style. They consider themselves well adjusted, score high on defensive measures, and tend to report low levels of psychological and somatic distress.[40,41,49] Jurbergs et al reported that children with a repressor style reported better HRQL than their parents regardless of health status.[40]

Symptoms of depression in parents correlated with reported differences in physical aspects of HRQL in brain tumour children at six and twelve months, and with reported differences in psychosocial aspects of HRQL in controls at six months only. The absence of a consistent relationship between parental depressive symptoms and differences in self- and parent reported HRQL does not support the hypothesis that parental emotional status plays a significant role in rating their child's HRQL.

Our data pose a challenge to the use of proxy measures of HRQL and have important implications for the use of HRQL as an outcome measure in clinical trials where an observed difference between treatment arms may depend on who is rating the child's HRQL. We suggest that it is important to employ other outcome measures, such as health status, psychological status and behaviour, in addition to measures of HRQL, when quantifying quality of survival in children with brain tumours and other childhood cancers.

Conflict of interest statement

None declared.

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