THE EFFECT OF CHILDHOOD BRAIN TUMOURS ON THE CHILD AND FAMILY: A PROSPECTIVE MULTIDISCIPLINARY FOLLOW UP OF CHILDREN WITH INTRACRANIAL TUMOURS

Anthony Penn

This thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree of Doctor of Philosophy: Integrated Format

Johannesburg 2013

DECLARATION

I, Anthony Penn declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted for any degree or examination at this or any other University.

PUBLICATIONS AND PESENTATIONS:

Publications arising from this study in support of the PhD, integrated format

Penn A, Lowis SP, Shortman IR, McCarter RJ, Stevens M, Hunt LP, Curran AL, Sharples PM. 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. European Journal of Cancer, 2008, 44(9); 1243-1252.

Penn A, Lowis SP, Stevens MC, Hunt LP.; Shortman RI, McCarter RJ, Pauldhas D, Curran AL, Sharples PM. Family, demographic and illness related determinants of HRQL in children with brain tumours in the first year after diagnosis. Pediatric Blood and Cancer, 2009, 53(6); 1092-1099.

Penn A, Shortman IR, Lowis SP, Stevens MC, Hunt LP, McCarter RJ, Curran AL, Sharples PM. Child related determinants of Health Related Quality of Life (HRQL) in children with brain tumours in the first year after diagnosis. Pediatric Blood and Cancer, 2010, 55(7); 1377-1385**.**

Penn A, Lowis SP, Stevens M, Shortman IR, Hunt LP, McCarter RJ, Curran AL, Sharples PM. A detailed prospective longitudinal assessment of health status (HS) in children with brain tumours in the first year after diagnosis. Journal of Pediatric Hematology/ Oncology, 2011, 33(8); 592-599

Selected national and international presentations arising from this study

Oral presentations

Penn A, Lowis S, Shortman R, et al. A detailed prospective longitudinal assessment of HS in children with brain tumours in the first year after diagnosis. Oral presentation, Royal College of Paediatrics and Child Health (RCPCH) Annual Meeting, April 22, 2010, Warwick and poster presentation International Symposium for Pediatric Neuro-Oncology (ISPNO), 2010, Vienna, Austria.

Penn A, Lowis S, Shortman R, et al. Behavioural problems, adaptive behaviour, cognitive status, emotional status, health status and HRQL in the first 12 months after diagnosis in children with brain tumours: a prospective longitudinal study, Oral presentation, ISPNO, July 2, 2008, Chicago, USA. Presented at British Paediatric Neurology Association (BPNA) 2008 and RCPH Spring Meeting 2009 by Dr. PM Sharples.

Penn A, Lowis S, Shortman R, et al. HRQL in the first year after diagnosis in children with brain tumours and its determinants at twelve months. Oral Presentation, The Inaugural Meeting of the Academic Paediatrics Association, Institute of Child Health, May 25, 2007, London, UK and Oral Presentation, The 11th Spring Meeting of the RCPCH, March 29, 2007, York, UK.

Penn A, Lowis S, Shortman R, et al. HRQL early after diagnosis in children with brain tumours; how does the Pediatric Quality of Life Inventory compare with the Health Utilities Index? Oral presentation, the 6th World Congress on Brain Injury, May 6-8 2005, Melbourne, Australia.

Poster presentations

Penn A, Lowis S, Shortman R, et al. HRQL in the first year after diagnosis in children with brain tumours and its determinants at twelve months. The 38th International Society of Paediatric Oncology (SIOP) Congress, September 18-21 2006, Geneva, Switzerland and the 12th ISPNO congress, June 6-9 2006, Nara, Japan.

Penn A, Lowis S, Shortman R, et al. HRQL one and six months after diagnosis in children with brain tumours and its relationship to child and family variables. ISPNO 12, June 6-9 2006, Nara, Japan.

Related publications

Eiser C, **Penn A**, Katz, E, Barr R. Psychosocial Issues and Quality of Life in Young Adults with Cancer. Seminars in Oncology, June 2009, 36 (3); 275-280.

Zebrack B, Chesler M, **Penn A**, Katz E. Psychosocial Issues in Adolescent Cancer Patients and Survivors, Current Problems in Pediatric and Adolescent Health, 2005 May-June, 35(5); 195-201.

Penn A, Shortman IR, Lowis SP, McCarter RJ, Stevens M, Hunt LP, Curran AL, Sharples PM. Prospective assessment of quality of survival in the first year after diagnosis with brain tumour. Manuscript In preparation, 2011.

Shortman R I, Beringer A, **Penn A**, Malson H, Lowis P, & Sharples P. The Experience of Mothers Caring for a Child with a Brain Tumour. Child: Care, Health and Development, In Press, 2012.

ABSTRACT

Health Related Quality of Life and its Determinants in the First Year after Diagnosis in Children with Brain Tumours

Brain tumours are the second most common malignancy in childhood and account for approximately 20% of all childhood cancers. Children diagnosed with a primary brain tumour are at risk of significant morbidity. Measurement of quality of life (QOL) and health status (HS) are important in quantifying morbidity and identifying strategies to provide relevant support for patients.

We aimed to: (1) Measure QOL and HS, using the PedsQL and HUI3 in children with brain tumours one, six and twelve months after diagnosis.

(2) Compare QOL and HS with “normal” matched controls, and assess the relationship between parent- and self-report QOL and HS.

(3) Identify determinants of overall QOL one year after diagnosis.

A total of 45 patients and 43 controls were recruited to the study, with 37 patients and 42 controls and 27 patients and 31 controls eligible for comparison of QOL using parent-report and self-report PedsQL respectively. Thirty-five patients were eligible for analysis of determinants of parent-report and 26 for self-report QOL one year after diagnosis.

There were 29 patients and 29 controls, and 21 patients and 22 controls eligible for comparison of HS between patients and controls using the parent-report and self-report HUI3 respectively, one year after diagnosis. In addition, 29 and 21 patients were eligible for analysis of determinants of parent- and self-reported HS one year after diagnosis.

Children with a primary brain tumour have significantly lower QOL/ HS in the first year after diagnosis than normal controls. QOL/ HS improved significantly over time, most notably in the six months after diagnosis.

For patients, agreement between parent- and self-report was variable, with greater agreement for the more observable (physical), compared with less observable (psychosocial) domains. Agreement between parent- and self-report was better using the HUI3 than the PedsQL. Parents of patients rated their children's HRQL lower than their child did, while for controls this was reversed.

Selective attention one month after diagnosis and infratentorial tumour site are most important in predicting both parent- and self-report overall QOL at 1 year after diagnosis.

Larger multi-centre, prospective studies are needed to confirm these findings. Cognitive remediation and/ or pharmacological intervention, particularly aimed at children with infratentorial tumours may improve attention and subsequently QOL, and both merit further investigation.

THE CLIC SARGENT BRAIN TUMOUR STUDY

The study on QOL and its determinants as reported in this thesis was undertaken as part of a prospective longitudinal multidisciplinary study led by Dr Peta Sharples (Consultant Paediatric Neurologist) and Dr Stephen Lowis (Consultant Paediatric Oncologist), with support from Dr Renee McCarter (Consultant Neuropsychologist), Professor Mike Stevens (Professor of Paediatric Oncology), Dr Andrew Curran (Senior Registrar in Paediatric Neurology), Dr Linda Hunt (Senior Lecturer in Medical Statistics) and Mr Robert Shortman (Assistant Psychologist). The overall aim of the study was to investigate, in detail, the effects of childhood brain tumour on the child and family. More specifically, it was intended to investigate the effect of primary brain tumours on cognitive, neurological, behavioural and functional outcome by comparing children presenting with CNS tumours with matched normal controls. In addition, the study sought to assess the effect of the diagnosis and treatment on the primary carer's emotional status, family functioning and other family variables. Assessments were to be undertaken at an early stage (within 1 month of diagnosis) and at 6 and 12 months thereafter with the intention that the findings would define the early rehabilitation needs and rate of recovery of this patient population.

In collaboration with supervisors, particularly Dr. Sharples, the author of this thesis, after reviewing the literature on QOS in children diagnosed and treated for a primary intracranial tumour made the decision to use QOL as the primary outcome measure and dependent variable. During the study, the importance of assessment of the relationship between parent- and child-reported QOL using both the PedsQL and HUI3 became clear, and self- report HUI3, in addition to the PedsQL, was

incorporated into the study and became an important theme of two of the papers submitted in support of the author's thesis and the thesis itself.

In addition to the contribution to the direction of the study, as mentioned above, the PhD applicant's role in the study were (1) to recruit all patients and controls; (2) to collect, score and enter data relating to quality of life, behavioural/emotional functioning, neurological and physical outcome and family structure and function in patients, controls and their families; (3) to undertake preliminary data analysis for presentation at local, national and international meetings, and publication of results in the form of the four papers submitted in support of the PhD, Integrated Format; (4) to collate the data and divide it for publication in its current form; (5) to write and act as corresponding author for the four papers submitted in support of the PhD. Details of collection, handling and statistical analysis of data are covered below.

For the purpose of this manuscript, only data used in the papers submitted in support of the author's PhD are referred to, not other data arising from study.

ACKNOWLEDGEMENTS

Most importantly, to my wife Sophie for supporting me through the lengthy period required to complete the papers and thesis in support of this degree.

I am grateful to the CLIC Sargent Charity, and the Bowles Bequest who funded this research, and particularly Liz Hill, Fund Manager General Fund, North Bristol NHS Trust for supporting us in obtaining funding from the Bowles Bequest which made the study possible.

My thanks to Steve Lowis and Peta Sharples, my two UK supervisors, for their guidance and advice throughout the project, to Linda Hunt for her sometimes bewildering statistical explanations and support, and Rob Shortman for always ensuring lively ,entertaining debate in our office as well as on the road. To Professor Peter Cooper for his support and assistance in facilitating the submission of this body of work for the degree of PhD via the integrated format.

Finally, I wish to thank Professor Mike Stevens, without whose belief, guidance and red pen this submission would never have been completed.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

CCLG	Childhood Cancer and Leukaemia Group
CSI	Cranio-spinal irradiation
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory II
BDS	Birleson Depression Scale
BT	Brain tumour
CCSS	Childhood Cancer Survivor Study
CHIP	Coping Health Inventory for Parents
CLIC	Cancer and Leukaemia in Childhood
CMS	Children's Memory Scale
CNS	Central Nervous System
FSS	Family Support Scale
GCT	Germ cell tumour
GMI	General Memory Index
GTR	Gross total resection
Gy	Gray Units
HG	High grade
HGG	High grade glioma
HRQL	Health related quality of life
HS	Health status
HUI 2/3	Health Utilities Index Mark 2/3
IDACI	Income Deprivation Affecting Children Index
ICC	Intra-class correlations
ICD	International Classification of Disease
ICF	International Classification of Functioning, Disability and Health
ICF-CY	ICF-Children and Youth Version
ICIDH	International Classification of Impairments, Disabilities and Handicaps
IES	Impact of Events Scale
IFS	Impact on Family Scale
IQ	Intelligence Quotient
LG	Low grade
LGG	Low grade glioma
MAUF	Multi Attribute Utility Function
MCS	Mental Component Summary
NHS	National Health Service
MCS	Medical Component Summary
PedsQL	The Paediatric Quality of Life Inventory 4.0

PHUI	Parent-report HUI
PIQ	Performance IQ
PNET	Primitive neuroectodermal tumour
PPedsQL	Parent-report PedsQL
QOL	Quality of life
QOS	Quality of survival
RCMAS	Revised Children Manifest Anxiety Scale
SAUF	Single Attribute Utility Function
SHUI	Self-report HUI
SPedsQL	Self-report PedsQL
STR	Subtotal resection
T1	One month assessment
T12	Twelve month assessment
T6	Six month assessment
TEACH	Test of Everyday Attention in Children
TSS	Total Scale Score (For PedsQL)
UK	United Kingdom
USA	United States of America
VIQ	Verbal IQ
WHO	World Health Organisation
WHO-FIC	WHO Family of International Classifications (WHO-FIC)
WMS	Wechsler Memory Scale

1. INTRODUCTION: PRIMARY INTRACRANIAL TUMOURS IN CHILDREN

1.1. Incidence and Epidemiology

Brain and spinal cord tumours account for approximately 20% of childhood malignancies. They are the commonest solid tumours in developed countries, and the second commonest form of malignancy in childhood after acute leukaemia in children under 15 years of age (1). In developing countries they are the third commonest, after leukaemia and lymphomas.

The peak incidence is from ages 3 to 7 years, although all ages are affected. The incidence falls steadily to a minimum incidence at age 15 –19, before rising steadily through adulthood. However, the age distribution of central nervous system (CNS) tumours in children and adolescents differs depending on diagnostic group (2;3). The overall age-standardised incidence rate (ASR) for CNS tumours in children 0-14 in Europe, based on data from 59 population based cancer registries, was approximately 29.9 per million for all tumours, and 25.9 for malignant tumours between 1978 and 1997. The overall ASR for the British Isles was 30.3 per million (2). For European adolescents aged 15-19, a similar study found the overall age-standardised ASR for CNS tumours to be 24 per million (4). A similar incidence has been reported for the United States of America (5). The incidence of CNS tumours seems to be rising in Western industrialised countries, including the USA, and Europe (2;6). Peris Bonnet et al. concluded, in agreement with others, that improvements in diagnosis are unlikely to explain in full the increase in incidence of

CNS tumours over time, and that environment and other risk factors are likely to have played a part (2;7;8).

The aetiology of childhood brain tumours remains unclear, and as with other forms of childhood malignancy, known risk factors account for only a very small number of childhood primary intracranial tumours. Approximately 5% of primary intracranial tumours can be attributed to increased risk due to genetic disorders such as neurofibromatosis types 1(NF1) and 2, tuberous sclerosis, Gorlin Syndrome and Turcot syndrome (9). Boys are at higher risk than girls for getting tumours, particularly primitive neuroectodermal tumours (PNET's) (10). Ionizing irradiation is the only established environmental risk factor for childhood CNS tumours (11). Cranial irradiation for childhood leukaemia, CNS and other tumours, and whole body irradiation in bone marrow transplant (BMT) are significant risks for further CNS tumours (12-15). This increased risk, as well as other deleterious adverse effects of cranial irradiation, has led to increasing efforts aimed at decreasing the dose, or eliminating entirely the use of cranial irradiation in childhood cancer treatment regimes, without compromising survival. Currently national and international childhood cancer study groups are assessing the effect of cranial irradiation and other treatment modalities in children with brain tumours in the context of clinical trials (16).

1.2. Pathological and Molecular Classification of Primary Intracranial Tumours

Brain tumours in children and adolescents represent a heterogeneous and complex group of tumours, with variable biological behaviour. While light microscopy remains the cornerstone for the classification of primary brain tumours in children, molecular, genetic and immunohistochemistry now also play a role in the definition of tumour categories. Classification of tumours is important in dictating treatment strategies and in prognosis. Unfortunately interpretation of tumour pathology is subjective, and disagreement amongst experts can be considerable (17). As a result some patients may receive over-aggressive treatment or be under-treated for their type of tumour. Most paediatric oncologists accept the revised World Health Organisation (WHO) international histological classification for tumours (18), which incorporates light microscopy as well as some of the neurobiological changes seen in certain brain tumours, as the standard classification scheme.

While most brain tumours can and do occur in all age groups, some are more common in the childhood population. These include embryonal tumours such as medulloblastomas, mixed neuronal-glial tumours, germ cell tumours, craniopharyngiomas and specific types of astrocytomas such as pilocytic and desmoplastic astrocytomas. In addition, and in contrast to adults, infratentorial primary brain tumours are at least as common as supratentorial brain tumours in children (5).

Approximately 80% of tumours in children less than 18 years of age are of neuroepithelial origin; namely gliomas, ganglion cell tumours, mixed neuroglial tumours and embryonic tumours. Gliomas, the commonest, are then subdivided into astrocytomas, mixed gliomas, ependymomas, choroid plexus tumours, and oligodenrogliomas.

Non- neuroepithelial tumours, including germ cell tumours, craniopharyngiomas, meningiomas and a heterogeneous group of other, rare tumours make up the remainder. Some of the more common tumour types are discussed below.

1.3. Common Subtypes of Primary Intracranial Tumours

1.3.1. Neuroepithelial tumours

1.3.1.1. Astrocytomas

There are four histological sub-types of astrocytoma. These are graded from 1-4 using the Kernohan grading system. While there are other subtypes/ variants of astrocytoma, they are beyond the scope of this thesis. Pilocytic and fibrillary astrocytomas usually referred to as low grade gliomas (LGG)/ astrocytomas (grade 1 and 2 respectively) make up approximately 80% of all astrocytomas, and 60% of all childhood brain tumours. Pilocytic astrocytomas, occurring almost exclusively in childhood, account for just over one third of gliomas. Anaplastic astrocytomas (grade 3) and GBM (grade 4), the high grade astrocytomas/ gliomas (HGG) account for the

other 20%. HGGs are far less common in children than in adults accounting for approximately 5-10% of all childhood brain tumours. Grading of astrocytoma is important, as it is a determinant of prognosis, treatment stratification and subsequent late effects.

1.3.1.2. Ependymomas

Ependymomas are thought to arise from the lining of the ventricles and the central canal of the spine. They account for approximately 12% of all childhood glial tumours (19). They are the third commonest posterior fossa tumour after pilocytic astrocytoma and medulloblastoma. They are of variable morphological appearance, with the majority of ependymomas classified as either low grade ependymoma (grade II) or anaplastic ependymoma (grade III). However, the histological distinction between low grade ependymoma and anaplastic ependymoma is ambiguous, and open to interpretation (20), resulting in a reported frequency of 7% to 89% of ependymomas (21;22).

1.3.1.3. Embryonal tumours

Embryonal tumours constitute almost 25% of all childhood tumours. There are five distinct tumour entities, three of which, namely the ependymoblastomas, medulloblastomas and supratentorial primitive neuroectodermal tumours (sPNET) are characterised histologically as small round-cell tumours. The two other entities,

medulloepithelioma and atypical teratoid rhabdoid tumour (ATRT), have distinct histological features.

Medulloblastoma

Medulloblastoma is the most common malignant CNS tumour in children. It occurs in the cerebellum, with approximately 75% in the vermis in the roof of the fourth ventricle, and the other 25% in the cerebral hemispheres. There are a number of histological variants, some with different prognoses from classic medulloblastoma. Medulloblastoma with extreme nodularity have a better prognosis. In contrast, the large cell/ anaplastic variety has a poorer outcome, and requires more aggressive treatment (23).

In addition to histological variants, the prognostic significance of several biological markers has recently been investigated. C-myc/ n-myc over-expression or amplification, and ErbB2 over-expression have all been correlated with aggressive biological/ clinical behaviour in paediatric medulloblastoma (24-28). In contrast, activation of the canonical Wnt/Wingless (Wnt/Wg) signalling pathway associated with nuclear accumulation of the beta-catenin protein generally signifies longer survival (29;30). Prospective biological studies have been incorporated in current and future European PNET studies (PNET 4 and PNET 5) (31;32). Future, “real-time” biological classification of tumour material will allow for more precise stratification, ensuring that patients get the least toxic treatment without

compromising survival. This is of great importance in medulloblastoma, where aggressive treatment is the norm.

Supratentorial primitive neuroectodermal tumours (sPNET)

These malignant tumours are found above the tentorium, and generally have a worse prognosis than their infratentorial counterparts, medulloblastomas

Atypical teratoid/ rhabdoid tumour

AT/RT of the CNS is a rare and aggressive tumour of early childhood. The AT/RT as an entity was defined by Rorke et al in 1996, and prior to this was included in the PNET/ medulloblastoma group of tumours (33).

1.3.2. Non-neuroepithelial tumours.

1.3.2.1. Germ-cell tumours (GCT)

Intracranial GCTs are rare tumours of childhood and adolescence that are heterogeneous with respect to their primary site, histology and biological profile. They are usually found in the midline, most commonly in the pineal or sellar/ suprasellar regions, but do occur in the third ventricle, and hypothalamus. They are more common in boys with a sex ratio (2.4:1 for germinoma; 11:1 for Non germanomatous germ cell tumours (NGGCT)) (34).The histological classification of

CNS GCTs is the same as in extracranial GCTs. GCTs may show pure germ cell differentiation (seminomas (testes)/ dysgerminomas (ovarian)/ germinomas (CNS)), or somatic differentiation (NGGCTs).

1.3.2.2. Craniopharyngioma

Craniopharyngiomas are histologically benign epithelial tumours arising in the sellar region. It can occur at any age, but has a bimodal distribution with a peak between five and 14 years and in adults older than 65 years (35;36). The tumours are solid, but often contain cystic elements which tend to be thick and sticky as well as hard, calcified elements. This and their anatomical position make them challenging to resect completely without causing significant adverse effects.

1.4. Clinical Presentation

Childhood CNS tumours may present with a number of varied signs or symptoms in various combinations. These may vary, depending on the age and development of the child, tumour site, tumour biology and the rate of growth of the tumour. Many of these symptoms are also found in more common, and less life threatening diseases of childhood such as migraine or gastroenteritis, resulting in considerable latency between symptom onset and diagnosis of CNS tumours (37;38), which may effect treatment and subsequent survival and quality of life (39).

A recent systematic review and meta-analysis of the clinical presentation of children (papers published between 1991 and 2005) with CNS tumours, which included 4171 children and adolescents, identified some of the more common signs and symptoms In summary they conclude that symptoms related to hydrocephalus are only present in 40 % of all intracranial tumours, 40% of intracranial tumours in children under four years of age, 80% of posterior fossa tumours, 60% of hemispheric tumours, 30% of brainstem tumours and 7% of spinal tumours. Other than those associated with hydrocephalus, signs and symptoms indicative of a possible CNS tumour include abnormal gait and coordination, other motor system abnormalities, eye signs, weight loss, behavioural changes (including lethargy and irritability) and school difficulties, developmental delay, cranial nerve palsies, head tilt, macrocephaly, diabetes insipidus, and growth arrest (40).

1.4.1. Initial work-up and management

Initial evaluation and management depends on resources available and presenting signs and symptoms. Craniospinal imaging is mandatory, and while MRI is the optimum neuro-imaging modality available, computerised tomography (CT) is acceptable for initial identification of a space occupying lesion and confirmation of the presence of dilated ventricles with hydrocephalus. Detailed MRI scans with and without gadolinium contrast, (and possibly other MRI modalities) of the brain and spine are required for planning, prior to definitive surgery.

In patients with hydrocephalus/ raised intracranial pressure (ICP), it is important to control this before any permanent damage is done. Medical management of hydrocephalus includes high dose corticosteroids, relative fluid restriction with or without mannitol/ hypertonic saline and 30-degree head elevation. Current practice is for neurosurgical relief of hydrocephalus, prior to resection of the tumour, using either an external ventricular drain (EVD), third ventriculostomy or ventriculoperitonial shunt (VPS).

For intracranial tumours in childhood, definitive diagnosis is usually histological. While appearance of the tumour on neuro-imaging may be suggestive of tumour type, it is not usually specific enough for definitive diagnosis. There are however three situations where biopsy/ resection is not necessary for diagnosis, namely, diffuse intrinsic brain stem tumours and optic pathway tumours, where the diagnosis is usually HGG or LGG respectively, and in secreting GCTs, where either raised serum AFP or ß-HCG is diagnostic. However, the attainment of tissue for molecular and genetic assessment in order to improve understanding and subsequently treatment of such tumours, particularly brain stem gliomas, is being debated within tumour working groups in the UK, Europe and elsewhere.

In addition to neuro-imaging, initial lumbar puncture, blood tests, including pre-operation routine haematology and electrolyte analysis, as well as other more

specialised blood tests may be necessary depending on the likely tumour type and site.

All in all, many intrusive, painful and anxiety–provoking procedures are necessary for accurate diagnosis, relief of hydrocephalus and preparation for multimodality definitive treatment. Such procedures, in addition to the effect of presenting symptoms, hospitalisation and subsequent loss of independence are likely to have a significant impact on quality of survival (QOS) in brain tumour patients.

1.5. Principles of Treatment in Primary Intracranial Tumour

Standard therapeutic options for the treatment of childhood brain tumour include surgery, radiotherapy and chemotherapy. The modality or modalities utilised, and their combination, may depend on a number of variables, including tumour type, grade or site, and the age of the child. More recently, the use of novel, targeted drug therapy, predominantly in the trial setting, has become more common.

1.5.1. Principles of neurosurgery

Surgery is the initial and in many cases the primary treatment for the majority of paediatric brain tumours. It is used for relief of symptoms including hydrocephalus, for biopsy, and most importantly removal of the tumour. In children, unlike in adults with brain tumours, it may be the only treatment necessary for cure in a significant

subset of tumours, including most low-grade astrocytomas (41). For most tumours, most notably ependymoma, the extent of surgical removal of tumour plays a significant role in predicting outcome and determining further treatment (14;42;43). Improved surgical resection may result in some children being placed in lower risk treatment groups, potentially sparing them some additional adjuvant radiotherapy and/ or chemotherapy, and subsequent treatment related morbidity. The extent of resection needs to be balanced with the risk of permanent damage to eloquent brain structures during surgery resulting in impaired motor function, cognition and QOL.

Various surgical adjuncts have helped to increase the neurosurgeons ability to resect the tumour, while minimising damage to adjacent normal brain tissue. Better neuroimaging modalities such as CT and in particular MRI have contributed greatly to improvements in neurosurgical and overall outcome in both children and adults with primary intracranial tumours. Functional MRI helps in differentiating eloquent areas of the brain from tumour tissue pre-operatively in older children. Stereotactic, image guided surgery facilitates intra-operative localization of the tumour and its relationship to normal brain tissue. Intraoperative MRI allows for serial images to be taken during surgery. Intraoperative electrophysiological monitoring (including the measurement of sensory and motor evoked responses) may provide an early warning that functional brain tissue is being disturbed. Improvements in anaesthetic technique, use of the intraoperative microscope, safe forms of head fixation, self-retaining retractor systems, development of the ultrasonic aspirator and

improvements in post-operative care have also contributed to improvement in neurosurgical outcome (44).

1.5.2. Principles of radiotherapy

Radiotherapy has been accepted as an important treatment modality in paediatric oncology for over 50 years. It is mainly used as ancillary treatment, and the majority of children with high-grade tumours such as HGG, medulloblastoma, ependymoma and GCT will receive radiotherapy as part of their treatment. Depending on tumour type and the pattern of relapse/ progression, the tumour, tumour bed (post resection), the whole brain or the entire neuraxis (brain and spinal cord) may be irradiated.

Improved targeting of radiotherapy is important in limiting exposure of normal brain tissue, and other important intracranial organs while ensuring optimal tumour cover. Immobilization is of utmost importance in ensuring repeated delivery of radiotherapy to the same target field. Facemasks are often used to ensure children are immobile during therapy. Voluntary immobilization may be impossible for many children aged less than six years and for all children under three years. For these children, general anaesthesia is necessary to ensure optimum treatment (45). Extensive treatment planning is necessary to provide safe, effective irradiation (46). Three-dimensional conformal radiation therapy, standard in most UK centres allows the division of the total dose fraction into multiple intersecting beams (usually four to six) to conform to

the tumour target shape (47). Intensity-Modulated Radiation Therapy (IMRT) allows even greater precision in delivery of radiation therapy by moving radio-opaque leaves in and out of the radiation field during treatment (48). Hyperfractionated radiotherapy, where radiotherapy is given twice daily, allowing for increased dosing and decreased damage to normal brain issue, in conjunction with myeloablative therapy, is now being used in high risk medulloblastoma (49). Proton beam radiotherapy, characterised by a highly constricted radiotherapy dose, has the potential of delivering higher radiation doses than can be achieved with conventional radiotherapy, with less damage to surrounding tissue (50). However, detailed prospective cognitive and QOS evaluation have not yet been done to support the use of many of the new radiotherapeutic methods.

1.5.3. Principles of chemotherapy

The role of chemotherapy in childhood brain tumours varies depending on tumour type. Chemotherapy is mainly used as an adjuvant to surgery +/- radiotherapy in children with brain tumours. It has shown to improve survival in tumours such as medulloblastoma, and in some cases the use of chemotherapy as an adjunct to surgical resection in infants may be possible, thus avoiding, or postponing cranial radiation and ameliorating the neurocognitive effects of radiotherapy. GCTs, particularly non-secreting germinomas have been shown to be exquisitively sensitive to systemic chemotherapy, which forms a major part of treatment. However, the addition of chemotherapy has been shown to impact on QOS in survivors of childhood medulloblastoma (51), and infants treated for malignant brain tumours with

surgery and chemotherapy with radiotherapy omitted may still have significant neuro-cognitive deficit, and high treatment related mortality (52;53). For other tumours including HGG and ependymomas, there has been a lack of progress despite intensive investigation (54).

1.6. Measuring Outcome for Children with Primary Intracranial Tumours

1.6.1. Survival

Over the past thirty to forty years, advances in the diagnosis, treatment and support as well as centralisation of care of children with cancer have resulted in improvement in overall survival. Between 70 and 75% of children and adolescents treated for cancer in the United States and Western Europe will achieve long-term survival (55;56). The prognosis for many childhood brain tumours has lagged behind that for other childhood malignancies such as acute leukaemia (57), but this has improved over the past two decades. Approximately 60 to 70% of all children treated for brain tumour now achieve long-term survival (2). Mortality, expressed as overall survival (OS) and event free survival (EFS) are the commonest primary outcome measures in paediatric oncology clinical trials. OS is an indication of the proportion of people within a group who are expected to be alive after a specified time. It takes into account death due to any cause - both related and unrelated to the cancer in question. In the context of cancer, EFS usually refers to the proportion of people who remain free from recurrence/ relapse. Disease free survival, progression free survival

and relapse free survival rates are also sometimes used to describe mortality-related outcome in paediatric oncology.

Improvements in survival are primarily due to increasingly aggressive treatment protocols. Treatment, recovery and rehabilitation of such children may be lengthy, and children may have difficulties re-integrating into normal life, maintaining peer relationships and attaining normal academic milestones (58-62). This is particularly true for survivors of childhood brain tumours (63-65).This raises questions about the quality of survival as well as quantity or length of survival. In the past, children with brain tumours were often excluded from psychosocial research of survivors of childhood cancer (66), but this thankfully is no longer the case.

1.6.2. Outcome measures other than survival

1.6.2.1. Levels of measurement

There are many ways in which disease outcome assessment has been conceptualised, one of which has been used to describe outcome in paediatric neuro-oncology (67). Aarsen et al. (2006) used Van Gijn's proposal that outcomes in clinical research could be assessed at the following five levels: Disease process, impairment, disability, handicap and QOL (68). This classification is similar to and expands on the International Classification of Impairments, Disabilities and Handicaps (ICIDH), (69) now known as the International Classification of Functioning, Disability and Health (ICF). Importantly, QOL is included.

Disease process refers to the occurrence of biological events. In the context of brain tumours it may refer to the volume of tumour, or normal tissue damaged by treatment. As a small volume tumour in an eloquent region of the brain may cause significant disability, while a large, slow growing tumour in the cerebellum may not, this level of measurement has significant limitations.

Impairment refers to the general effect of the disease on the child at the organ level. In the context of childhood brain tumours this may include both neurological (tremor, power, ataxia) and endocrine impairments (hypothyroidism, diabetes insipidus, panhypopituitarism). The main problem with both disease process and impairment as outcome measures is that they are of little relevance to the patient in every day life.

Disability, according to the WHO, refers to “the restriction or lack of the ability to perform tasks within the physical and social environment” (69). It refers to performance at the level of the person. Most disability scales measure essential tasks in activities of daily living such as walking and managing stairs (mobility), eating, dressing and toileting (self-care) or comprehension, expression and problem solving (cognition) (68;70).

Handicap has been defined as a “loss or limitation of opportunities to take part in the life of the community on an equal level with others“ (69). While both impairment and disability can essentially be assessed objectively, handicap addresses the social consequences of impairments and disabilities in the domains of, for example, relationships, school and leisure activities (67).

The updated ICF is based on the integrative bio-psycho-social model of functioning, disability and health of the World Health Organization (WHO) and complements the International Classification of Disease (ICD) and together form the core classifications in the WHO Family of International Classifications (WHO-FIC). The advantage to this more recent approach is that functioning, with its components; Body Functions, Structures, Activities and Participation, is viewed in relation to the health condition under consideration, as well as personal and environmental factors. Thus, all aspects of a person’s life (development, participation, and environment) are incorporated instead of focusing exclusively on the disease diagnosis. This approach also acknowledges that not all people with the same disease, and even the same disability will experience the same functional limitations which. A Children and Youth Version (ICF-CY) has been developed in order to capture the impact of a particular condition on functioning throughout the growth and development trajectory of the child.

2. INTRODUCTION: QUALITY OF LIFE

Traditional measures of outcome, particularly survival or reduction of symptoms do not adequately quantify the extent to which patients may be affected by illness and its treatment (71). The inclusion of more holistic outcome measures such as QOL and HRQL aim to help quantify the impact of illness and treatment, and at this level of measurement it is the patient, and no longer the medical professionals who determine to what extent the disease and treatment has affected their lifestyle. This manuscript concentrates on QOL, and more specifically HRQL, the definitions of which will be explored in detail below.

2.1. Definitions of Constructs

2.1.1. Quality of life and health related quality of life

The definition of QOL is complicated. It is a hypothetical construct; an organising concept that exists to guide its users (72). There is no universal agreement on its definition, and it is often used interchangeably with a related, though crucially different construct; HRQL. A recent review on the impact of the conceptual framework of paediatric QOL instruments identified eleven types of definition of QOL and HRQL (73). Many studies in QOL research in children and young adults have extrapolated from adult research, and used adult values and expectations when defining QOL/ HRQL in children, which has added to the confusion (74). The World Health Organization (WHO) QOL Group (an international group originally based on representation from 15 nations worldwide) has defined QOL as follows: 'Quality of

Life is defined as individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns' It is a broad ranging concept affected in a complex way by the persons' physical health, psychological state, level of independence, social relationships, personal beliefs and their relationships to salient features of the environment' (The WHO QOL Group, 1995). QOL has been described as a broad construct, reflecting many aspects of life of which health is only one (75). Eiser (2003) suggested that some aspects of QOL such as a comfortable place to live, running water and food are basic requirements, as is good health. On the other hand, participation in sports may be extremely important to some but not others. QOL may therefore be conceptualised as a broad assessment of wellbeing across a variety of domains (76), and HRQL as a sub domain of overall QOL (77-79).

Bradlyn *et al.* described HRQL (In the context of paediatric oncology) 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 (80). This is particularly true for children, where the relative importance of certain attributes of QOL will change as they grow, develop and become more independent. Others consider HRQL purely as a subjective construct and therefore influenced by one's values and the importance attached to particular aspects of life. Aaronson et al. described HRQL as a

"multidimensional concept that includes the broad areas of functional status, psychological and social well-being, health perceptions, and disease and treatment-related symptoms" (81), thus emphasising the impact of health on QOL. Both of the above definitions identify the three core domains of HRQL, namely the physical, psychological (both emotional and cognitive) and social domains. Other (often related) domains identified when measuring HRQL include self-competence, independence/ autonomy, personal development, body image, leisure, future, behaviour, pain, family, school, rights, security and spirituality (73;80;82;83). In summary, QOL is a broader general term which encompasses non health-related aspects of life which are not amenable to medicinal products or healthcare services, while HRQL represents the patient's perception of the impact of an illness and its treatment (84).

2.1.2. Health status

A further concept used in defining outcome is Health status (HS). There are a wide variety of definitions for HS (85;86). The WHO has defined health as;" a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". This definition has some overlap with the more global definition of QOL and has been used in the development of QOL measures, which has added to the confusion that exists in defining the two constructs (87). A more narrow, "within the skin" concept focuses on the HS of the person and ability for living allowed by that HS (88). This is echoed by Pantell and Lewis' definition of child health as "the ability to participate fully in developmentally appropriate activities and

requires physical, psychological, and social energy" (89). This definition is closer to the concept of HRQL (85), and also has some overlap with the definition of functional status.

As a result of the abovementioned disagreement on its definition and that of QOL and HRQL, HS is commonly used interchangeably with HRQL and QOL, and while they are related, they are not the same construct, and are viewed as different by patients (90). For patients, there is greater emphasis on physical functioning rather than mental health when rating HS, and the reverse for QOL (87). In a study of 246 cancer survivors, HS measured by the Short form Health Survey (SF 36) had a weak influence on overall QOL using the Schedule for the Evaluation of Quality of Life-Direct Weighing (SEIQoL-DW). The authors conclusion was once again that HS and QOL are distinct constructs and should be evaluated as such (91). Vogels et al., in a manual for a HRQL instrument, differentiates HRQL from HS when defining HRQL, as "Health Status weighted by people's own emotional responses to Health Status problems they encounter " (92).HS is a modality commonly used to quantify disability and QOS in chronic illness including childhood brain tumours (51;93-99).

2.1.3. Functional status

The terms, QOL and HRQL have also commonly been used interchangeably with functional status when quantifying morbidity and quality of survival (73). Functional status has been defined as 'a child's ability to perform daily activities that are

essential to meet his or her basic needs, fulfil roles, and maintain health and well-being (90). There is no evidence that a child's perception of their life corresponds with the ability to perform various tasks/ activities, i.e. that what they feel is related to what they can do (73). It is therefore possible that some children with poor functioning may have a high QOL/ HRQL if they have they feel that they have adapted well to their current functional state (100;101).

2.2. Quality of life and Health Related Quality of Life: Conceptualisation

Schipper et al. (1996) identified five approaches to conceptualising HRQL, namely, the 'utility' approach, the psychological view, the community centred approach, opportunities for reintegration to normal living, and as a gap between what a person can do and what they want to do (102). These approaches have been summarised by Eiser (2004) (103), and are discussed below.

2.2.1. The utility approach

The "utility" approach emphasises the trade-offs or preferences that people may be willing to make or have respectively. Preference-based measures evaluate the patient's preference for a health state instead of measuring the frequency and the severity of symptoms or disabilities. Utility values are numbers that represent the degree of an individual's preference for particular outcomes under conditions of uncertainty. The three techniques most commonly used to determine utility values are rating scales, standard gamble and time-trade-off (104). Values usually range

from 0 to 1, with 0 representing death, and 1 perfect health. However, for some HRQL instruments, negative values can be accrued, and represent health states considered worse than death (105). The “utility” approach is favoured by economists as it facilitates estimation of quality-adjusted life years (QALYs) as outcome measures for cost-effectiveness analyses (106). Scales, such as the Health Utilities Index 2/3 (HUI 2/3), based on the utility approach using the standard gamble technique, rely on population preferences in their development. Preferences are made by people who have not experienced the health states themselves, and not at the individual level (i.e. not subjective at the level of each patient). Such individuals have to imagine such health states for the purpose of comparison of desirability. A reasonable individual may relate quality to the extent of restriction, or lack of ability in any health state to perform age specific activities, otherwise known as disability. There is therefore an argument that scales like the HUI do not measure QOL/HRQL but disability or health status only (107).

2.2.2. The psychological approach

The psychological approach emphasises the patient’s subjective view of their illness, and the interrelationship between physiological and psychological conditions. Psychological variables can contribute significantly to an individual’s approach to the disease process, disease and treatment effect and HRQL.

2.2.3. The community-centred approach

The community-centred approach emphasises the impact of disease on the wider community. It is best conceptualised as a hierarchy with physical illness in the centre of a circle, and its impact in terms of personal functioning, psychological distress or well-being, general health perceptions and finally social role functioning.

2.2.4. Opportunities for reintegration to normal living

The fourth approach: Opportunities for reintegration to normal living, is self-explanatory. Some clinicians and parents may consider reintegration into normal society as evidence of successful management of their physical illness. However, successful participation in normal society does not necessarily mean satisfaction with ones life status. This approach is very similar to that in conceptualising the construct of functional status as 'a child's ability to perform daily activities that are essential to meet his or her basic needs, fulfil roles, and maintain health and well-being (90).

2.2.5. The gap between what a person can do and what they would like to do

Finally, there is the approach of considering HRQL as a gap between what a person can do and what they would like to do. This approach implies that good HRQL occurs when patient's experiences meet their expectations. The difficulty making decisions on which expectations are reasonable and which are unrealistic when

considering attainment of goals has been identified as a major limitation of this approach (108). This approach is also most likely to be influenced by the phenomenon of response shift, or the change of internal standards in response to a change in health status, which may effect an individual's expectations.

2.3. Psychometric Properties of Measures

As with all constructs, QOL measures require satisfactory psychometric properties in order to be used for clinical or research purposes. A detailed account of reliability and validity prerequisites for HRQL measures can be found elsewhere (109), and are described briefly below.

2.3.1. Reliability

Internal reliability, quantified using Cronbach's alpha, is the most commonly reported test of reliability for QOL measures. Because QOL can change over time (and QOL measures need to be sensitive to such changes) and is subjective, test-retest and Inter-rater reliability are not applicable.

2.3.2. Validity

Assessments of validity test the ability of an instrument to measure what it purports to measure and whether it is useful for its intended purpose. Tests of validity are also complicated in QOL measurement as there is no agreement amongst practitioners or

researchers on the definition of QOL or HRQL (110). Validity has primarily been measured in terms of content validity, construct validity and criterion validity. Content validity is defined as the extent to which a specific set of items or questions constitutes a domain. Construct validity refers to whether an instrument is concerned with the theoretical relationship of a variable to other variables, or the extent to which a measure reflects the variability among subjects on an underlying continuum. Criterion validity determines whether the scale reflects the construct, which in this case is QOL (111;112). Construct validity may be estimated using factor analysis to identify an appropriate underlying structure or measuring the relationship or correlation of one instrument with another. Criterion validity is defined as the relationship between a scale and another measure which has been used and is accepted in the field. Again, as there is no agreement on the definition of HRQL/ QOL and therefore no gold standard to which to compare an instrument, assessment of construct validity is challenging when considering QOL.

2.4. Instrument Administration

QOL instruments may be self-completed or administered by a trained interviewer either face to face, or by telephone. Administration by a trained interviewer is more resource dependent, but there are usually fewer errors and missing responses. Self-completion in the home environment, may be easier for the patient, but there is a higher likelihood of patients' answers being influenced by parents and vice-versa (113). The return rate of questionnaires completed at home is also typically much lower than when they are administered face to face. This is particularly true in the

context of multi-centre trials where collection of QOL data is reliant on local clinicians providing and collecting completed questionnaires. One compromise is to have patients or parents complete questionnaires under supervision. The development of online biomedical informatics systems will facilitate web-based self completion of QOL instruments and may increase completion and return rates of QOL questionnaires (114). However, this method of administration may also be subject to contamination of individual's answers by family members or friends if completed at home. Further research, including psychometric analysis of web-based questionnaires is needed before they can be more widely applied.

2.5. Generic Versus Disease-Specific Instruments

HRQL measures are categorized as either generic or disease specific, and the decision to use either or both depends on the information one wishes to gain in a particular circumstance, as described above. Generic paediatric measures are designed to be used to assess HRQL in children with all types of illness and in well children. Their advantage is that they can be used to compare QOL across different illnesses or disease subtype (115). This is particularly important in paediatric oncology, where the effects of the disease and treatment may vary tremendously depending on the location, and type and grade of the cancer. Generic QOL measures are also most commonly used to assess QOL in more long-term survivors who are off treatment and being compared with normal controls/ population norms or when within group comparisons are being made. They are therefore broad based with items relevant to both ill and well children and adolescents, but their generalised

nature means that they might not be sensitive to subtle changes in QOL related to disease process or treatment in childhood cancer (86;116).

However, as in general, the paediatric oncology-specific and paediatric oncology disease-specific (i.e. brain tumour specific) instruments focus on health status and HRQL during therapy and are thus focused on symptoms directly related to treatment received, they are not generally suitable for assessment of QOL in survivors off treatment. It may therefore be prudent to use disease-specific measures along with generic measures that are also relevant for the assessment of long-term outcome, in the comparison of treatment regimes or observational studies of children taking part in clinical trials. The use of modular systems which include generic and disease-specific modules, such as that employed by Varni et al. for the PedsQL and the DISABKIDS group, allow for more comprehensive analysis of QOL (112;117;118).

One of the challenges in developing paediatric oncology-specific and paediatric oncology disease-specific HRQL measures is that the domains of importance may differ depending on the type of cancer and treatment used. Largely because of their site, and the vulnerability of the CNS to tumour and treatment-related damage, children with brain tumours have unique symptoms compared to those with non-CNS cancers, and are at greater risk of impairments. This may prove to be particularly important with new targeted therapy where investigational products are likely to have

adverse effect profiles which differ from those of traditional chemotherapy. To date there has been a dearth of HRQL measures aimed at children with brain tumours specifically. The PedsQL Brain Tumor Module is the only recognised HRQL questionnaire designed to measure brain tumour-specific HRQL, and this was only developed in 2007 (119). It is part of a modular system developed by Varni and colleagues mentioned above (118). A second brain tumour specific measure, the Pediatric Functional Assessment of Cancer Therapy - Childhood Brain Tumor Survivors Questionnaire, Version 2 (pedsFACT-BrS), is currently in development (120).

2.6. Issues Specific to Childhood

With QOL increasingly being used in preference to other more narrow measures of morbidity, recognition of the unique demands of measuring QOL in children compared with adults is increasingly being discussed (112).

2.6.1. Age and developmental stage

Some domains important in adult health QOL assessment may not be relevant to children. These include the impact of illness on income, employment and sexuality. One cannot therefore apply pre-existing QOL measures to the paediatric population. Children develop at different rates, as does the impact of illness and subsequent treatment and its effects. QOL measures must be sensitive to these changes in order

to provide meaningful results. Providing age appropriate versions of the instrument and using age-matched controls can overcome such challenges (121).

2.6.2. Self- versus proxy-report

It is often stated that HRQL, being a subjective measure, is best reported by the individuals themselves. A limitation of early paediatric oncology studies, identified in reviews of QOL in the paediatric oncology population, was that children's own views on QOL were generally underrepresented. Children were viewed as unreliable and lacking the necessary cognitive and linguistic skills to understand and respond to questionnaires (122). More recently, Bhat et al. suggested that self-scored HRQL be used only as a secondary outcome measure in younger children due to lack of reliability (123). However, a recent study by Varni et al. reported that children as young as five years of age were able to reliably and validly self-assess HRQL using the PedsQL 4.0 generic core scales (124). Participants included well children, children recruited from general paediatric clinics, sub-speciality clinics, and children attending hospital with mild acute illness or chronic illness. However, as brain tumours of childhood most commonly occur between the age of three and seven years (2;3), self-assessment of HRQL is not possible in the youngest group of patients. Self-assessment of QOL may also not be possible in older children with disabilities, including children with brain tumours, where the tumour and its treatment may impair their ability to respond competently to questioning. In such cases, proxy assessment is necessary in order to avoid excluding potentially the most vulnerable population from assessment. There is now a general feeling that comprehensive

assessment of HRQL should try to include information from both child and care-giver, as both views may provide valid results (112;122;125-127). It is also usually the parent's perception of their children's HRQL that determines health care utilization (128;129).

In addressing the "proxy problem", much effort has been spent in analysing the relationship between self and proxy assessment of QOL in many different childhood diseases, including cancer. For the purpose of this manuscript, paediatric oncology literature will predominantly be used.

Initial studies looked predominantly at Pearson product-moment correlations (PPMC) to measure agreement between patients and proxies(122). However strong correlations between patient and proxy data may hide large differences in mean scores, and patient and proxy data are therefore not interchangeable. Intra-class correlations (ICC) may be preferable as they measure the proportion of variability accounted for by variability among individuals (130). It is also important that self and proxy-report versions of HRQL questionnaires be evaluated separately for reliability and validity as limited reliability may contribute to poor correlation between patients and proxies (131). Median or mean difference (i.e. child group mean/median-proxy group mean/ median) has also been used to assess agreement, usually in combination with PPMC and/ or ICC (132-134). Not surprisingly, the use of varied

methods to assess agreement can produce different results, making it difficult to meaningfully compare data.

In general, parents, particularly mothers, have been employed most commonly as proxy assessors of their child's QOL. Proxy assessment by medical staff, including doctors and nurses, has also occasionally been reported, with mixed results (135-138). Billson and Walker assessed HRQL/ HS of survivors of different cancers (n=48) using the HUI. Doctors identified fewer deficits than either parents or patients, and the degree of correlation between patient self-assessment and their doctor or parent were similar (135). Phipps et al. found more significant correlations between parent-child pairs than nurse-child pairs in children hospitalised for bone marrow transplant, though most correlations were only low or moderate (137). Fluchel et al. found better ICC between patient and parent scores than between patient and physician scores for 95 childhood cancer survivors in Uruguay (138). In contrast, Klaasens et al. in a longitudinal study of HRQL in children with Hodgkin disease (n=51) found substantial correlation between nurses and patients ratings at each of the four time points (intraclass correlation coefficient >0.6), with similar findings for parents and patients ratings. One exception to these findings was when patients were receiving inpatient chemotherapy where correlation was only low to moderate, suggesting that medical staff may contribute valuable additional information as proxy respondents in certain circumstances (136). However, medical and nursing only observe patients in restrictive situations, limiting their usefulness as proxies (122).

In childhood cancer and other chronic disorders, agreement between parent and child rated HRQL tends to be better for the more observable (physical), compared with less observable (psychosocial) domains (118;122;139). Method of administration, as mentioned above, may also be important, with home completion of questionnaires more likely to result in collaborative completion and closer agreement (113). Parents of children with cancer tend to rate their children's HRQL lower than the children themselves (132;140;141). It has been suggested that agreement between parent and child ratings of HRQL is better in chronically sick than healthy children, given the increased dependence that occurs between sick children and their parents (122). In addition, parents of healthy controls tend to estimate their child's HRQL as higher than the children themselves (133;142;143). These discrepancies may exaggerate the reported difference between patients and controls in parent-rated HRQL and reduce the reported difference in self-rated HRQL.

2.6.3. Agreement between self- and parent-reported quality of life in the paediatric brain tumour population

To date, few studies have measured agreement between parent- and self report in the brain tumour population (95;123;144). Bhat et al. using the PedsQL generic core scales, found moderate to good correlation (r range 0.34-0.73) between parent- and self-report for children (mean= 11yrs +/-4.5yrs) an average of 3.2 years after diagnosis, and concluded that children and parents viewed the child's HRQL in a similar way (123). However, no measure of ICC or group mean/ median difference was reported, limiting their conclusions with respect to agreement. Cardarelli and

colleagues reported on the HS and HRQL of 50 children and young adults aged between eight and thirty years at least six months off treatment for brain tumour using the HUI mark 2 (HUI2) (95). No formal assessment of agreement was reported, although it was noted that in general children rated their HS and HRQL lower than their parents did. Finally, Yoo et al. using a brain tumour specific instrument currently in development (the pedsFACT-BrS) comprehensively measured agreement in children both on and off treatment (n=351, age range 7-18) (144). Agreement was moderate to good in general with agreement better in children (aged 7-12 years) compared with adolescents (aged 13-18 years) and for physical and social well-being in comparison with emotional well-being. Poorer agreement for emotional aspects of QOL mirrors that found in other studies of children with cancer as mentioned above (118;122;139).

2.6.3.1. Putative reasons for lack of agreement for self- and parent-report

There are a number of possible explanations for the differences between self- and parent-rated QOL. These include differences in child and parent's interpretation of events, adaptive style, response style, child personality and parental emotional status/QOL. (145-148). Davis et al., using qualitative methods concluded that possible reasons for differences in reporting of QOL by the child and parent was due to differences in reasoning and different response styles, rather than differences in interpretation of items. They found that children tended to provide extreme scores (highest or lowest score) and to base their response on a single example (146). Eiser et al., in a study of the QOL of 87 children recently diagnosed with cancer and

their mothers found a significant correlation between mother's worries and their reporting of their own and their child's QOL (147). Parental emotional status needs therefore to be taken into account when considering their reporting of their child's QOL. This is particularly true early after diagnosis when parents are at significant risk of depression and anxiety symptoms (149).

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 (145;150;151). Jurbergs et al reported that children with a repressive adaptive style reported better HRQL than their parents regardless of health status (145), and is one pathway to resilience in survivors of childhood cancer (152).

2.6.4. The utility of quality of life measurement in paediatric oncology

2.6.4.1. Efficacy of clinical trials

HRQL can be used for assessing the efficacy of clinical trials, with a number of measures being developed specifically for such use (82;153;154). The Medical Research Council (UK) and the National Cancer Institutes (United States and Canada) insist that all clinical trials requiring sponsorship must include quality-of-life (QOL) measures (155;156). In most cases, HRQL has been used as a secondary outcome measure. However, for equivalence, or non-inferiority trials in some types of childhood cancer such as certain types of germ cell tumours and acute lymphoblastic

leukaemia where survival is very good or in brain stem tumours and HGGs where outcome is very poor, HRQL may be used as the primary outcome measure when comparing two different treatment regimes (157).

2.6.4.2. The impact of diagnosis and treatment

Measurement of HRQL has been extensively used to help understand the impact cancer (and other health conditions) and its treatment may have on the quality of lives of children and adolescents both during and after treatment.

2.6.4.3. Efficacy of intervention

HRQL may also be used to evaluate intervention programmes. For instance, an improvement in HRQL after a rehabilitation programme to improve attention or memory for children irradiated as part of brain tumour treatment would be more meaningful than an improvement in attention or memory alone.

2.6.4.4. Screening for patients at risk

In the context of clinical practice, regular assessment of HRQL in individual patients may help in screening for patients at risk of psychosocial and other problems (158). At the personal level, feedback and discussion of results of such HRQL assessments may be helpful to the patients receiving treatment, as it may identify problems not raised in direct consultation either due to reluctance or inability of patients to voice

such problems. Identification of patients in particular need or at high risk of requiring intervention/ rehabilitation is also important in the context of limited financial resources, as is present in most national health care institutions.

2.6.4.5. Identification of patients likely to survive

HRQL measures have also been used to help identifying which cancer patients are most likely to survive their illness. Two reviews of the adult cancer literature identified a positive relationship between quality of life data or some quality of life measures and the survival duration of cancer patients (159;160). It seems likely that this largely reflects more severe disease being associated with poorer QOL and also with lower survival rates, but it is tempting to speculate that there may also be other factors relating survival and QOL.

2.6.4.6. Cost utility analysis

Some HRQL measures have been used in cost utility analysis in the context of health economics (161;162). The quality-adjusted life-year (QALY) is a measure of the value of health outcomes. As health is a function of both length and quality of life, the QALY was developed in order to provide a single index number from both attributes (163).

2.7. Quality of Survival and Survivorship

The term “QOL” has, in the past, been used erroneously to include all and any psychosocial aspects of survival. The term does include physical, social and emotional domains of life, and is a construct in its own right. In preference to QOL, the use of Quality of Survival (QOS) as an umbrella term is gaining credence in paediatric oncology, and includes all of the abovementioned outcomes with the exception of mortality (i.e. quantity of survival). The Children’s Cancer and Leukemia Group (CCLG) and the International Society of Paediatric Oncology (SIOP) brain tumour working groups are in the process of adopting QOS as an umbrella term for describing outcome in the context of paediatric oncology and particularly paediatric neuro-oncology (164). The CCLG is an association of healthcare professionals involved in the treatment and care of children and younger teenagers with cancer, and underpins all the activity in paediatric oncology in the United Kingdom. SIOP is the major global organisation concerned with the issues of children and young people who have cancer, and co-ordinates multi-national studies, predominantly within Europe.

QOS is therefore a term that can be used to describe the overall morbidity experienced by survivors of childhood cancer; with QOL, HRQL and HS questionnaires forming part of the tool kit available to measure aspects of QOS. The vast majority of paediatric oncology (including neuro-oncology) QOL data collected to date focuses on outcomes in children or adults some time after diagnosis and treatment for childhood cancer. Further definitions of the terminology in use when

describing children treated for cancer are therefore required. In the context of childhood and adult cancer, a person may be considered a survivor from the day that he/ she is diagnosed with cancer. The phrase: “long-term survivor” usually applies to people who are alive five years after diagnosis. Cancer-related complications that persist or develop 5 years after cancer diagnosis are termed “late effects” and include adverse effects on organ function and psychosocial complications related to the cancer experience, both of which influence the long-term survivor’s quality of life (165).

3. LITERATURE REVIEW: QUALITY OF LIFE IN CHILDREN WITH PRIMARY INTRACRANIAL TUMOURS

3.1. Preamble and Framework of Review

The following chapter aims at providing a comprehensive review of all papers that have examined QOL in children with brain tumours. For the purpose of the review, only studies that used standardised measures were included. Studies focusing on QOL in children with brain tumours only, or on childhood cancers in general in which those with brain tumours were analysed separately were included. Studies focusing purely on agreement between self- and proxy versions of questionnaires were excluded as they are discussed above.

Both Wallander et al. (166) and Davis et al. (73) conducted reviews on the conceptual framework and methodological issues related to QOL and concluded that HRQL should not be differentiated from the broader notion of QOL. Due to lack of clarity between the constructs of QOL and HRQL, McDougall and Tsonis (2009) considered patients reporting on either construct in a recent systematic review of QOL in survivors of childhood cancer (167). Because of the overlap, and interchangeable use of HRQL and QOL in the literature, both HRQL and QOL are referred to as QOL where they are used to describe health-specific QOL. Papers reporting on both outcomes are considered together and not as separate entities. Regarding the use of the HUI as an outcome measure, some studies have referred to HS and others HRQL/QOL when measuring outcome using the HUI. As an overall

measure of HRQL is attained (The Multi-attribute Utility Function), studies that used the HUI as an outcome measure have been included in this review. Table 3.2 summarises all the studies included in the review.

3.2. Study Details

Seven of the studies were large, multi-centre cohort studies including all cancer types, and included within group analysis of QOS in BT patients in some way (93;99;168-172). Three further studies compared QOL in children with brain tumours with children with ALL +/- other non CNS solid tumours (+/- normal controls) (95;173-175). The majority of studies compared QOL in BT patients with published (119;123;170;172;176-182) or unpublished(67) scale norms, or matched controls (99;144;168;171;183-187). Zeltzer et al. also included siblings as controls (172). Study numbers varied immensely, and ranged from nine to 556 for BT studies, and 7147, including 886 primary CNS tumours for studies of survivors of all childhood cancers. Eight studies looked primarily at predictors or correlates of QOL in children with brain tumours (51;96;98;173;185;188-190), and 15 papers focused on aspects of QOL in a specific sub-type of childhood and adolescent BT or compared QOL between two or more BT sub-types (51;67;98;177-182;185-187;189;191;192). Two papers focused primarily on the development of a new Paediatric BT specific QOL instrument (119;144).

3.3. Instruments Used To Measure Quality of Life

The description of whether QOL, HRQOL or HS was being measured varied substantially. Some authors described outcome as HS and others QOL/HRQL or both or even functional disability when the same measure was used, illustrating the lack of agreement on definitions of the constructs and the instruments designed to measure them. This was common for the HUI (51;93-95;183), and SF-36 (168-170;172).

Ten different instruments were used to measure outcome in total. These instruments are listed in Table 3.1. The HUI 2/3 system was most commonly used, followed by the Short-Form Health survey (SF-36), PedsQL and the Child Health Questionnaire (CHQ). The Minneapolis-Manchester Quality of Life Instrument (MMQL), TNO-AZL Questionnaires for Children's Health-Related Quality of Life (or TACQOL), Ferrans and Powers Quality of Life Index (QLI), The Adult GH-Deficient Assessment (AGHDA) and Psychological General Well-Being (PGWB) questionnaires, and the Pediatric Functional Assessment of Cancer Therapy-Childhood Brain Tumor Survivors Questionnaire, Version 2 (pedsFACT-BrS) were each used in a single study. All instruments are generic instruments other than the following: The MMQL was designed to assess HRQL in survivors of childhood cancer. The PedsQL has cancer specific and fatigue modules in addition to the Generic Core Scales. The pedsFACT-BrS and PedsQL Brain tumour module are the only BT specific instruments/ modules in development and used in this review. The AGHDA was designed to asses QOL in adults with growth hormone deficiency.

Table 3.1 Summary of instruments used to measure QOL, HRQL and HS in children with CNS tumours

Instruments		Age range limits (years)	Summary Scales	Domains (used by investigators in the studies reviewed)
AGHDA		Adult self-report	Total score	Mobility, pain, energy, sleep, emotional reactions and social isolation
CHQ (parent report: 50 item)		parent 5-18 Self 10-18	Physical and psychosocial scores	General behaviour, mental health, self-esteem, bodily pain, general health, role limitations-emotional, role limitations-physical and physical functioning
QLI		Adult self-report	Overall QOL	Health and functioning, social and economic, psychological/spiritual, and family
HUI	HUI2	Proxy $\geq$ 8 Self $\geq$ 5	Overall HRQL HUI2 MAUF	Sensation, mobility, self-care, emotion, cognition, pain, fertility
	HUI3		HUI3 MAUF	Vision, hearing, speech, ambulation, dexterity, emotion, cognition, pain
MMQL (youth, adolescent & young adult form)		Self 8-45	None	Physical symptoms, physical functioning and energy, psychological functioning, social functioning, cognitive functioning, body image, outlook of life and intimate relations.
PedsFACT-BrS		Parent 7-18 Self 7-18	None	Physical well-being, emotional well-being and illness experience, Social/family well-being and BT specific concerns
PedsQL	Generic Core Scale	Parent 2-18	TSS Physical Summary Score Psychosocial Summary Score	Physical (Same as Physical summary), emotional, social, school
	Cancer Module	Self 5-18	None	Treatment and procedure anxiety, cognitive ability, patient worry, physical self-appearance and communication
	Brain Tumour Module		None	Cognitive problems, pain and hurt, movement and balance, procedural anxiety, nausea and worry

	Fatigue Module		None	General fatigue, sleep/rest fatigue and cognitive fatigue
PGWB questionnaires		Adult self-report	None	Anxiety, depression, vitality, positive well-being, self-discipline and general health
SF-36		Adult self-report	Physical Health Mental Health	Physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, vitality
TACQOL		Parent 6-15 Child 8-18	None	Problems/limitations concerning: general physical functioning/ complaints, motor functioning, independent daily functioning, cognitive functioning and school performance, social contacts with parents and peers. The occurrence of positive moods, the occurrence of negative moods

AGHDA, Adult GH-Deficiency Assessment; CHQ, Child Health Questionnaire; QLI, Ferrans and Powers Quality of Life Index; QOL, quality of life; HRQL, health related quality of life; HUI2/3, Health Utilities Index 2/3; MAUF, Multi-Attribute Utility Function; MMQL, Minneapolis-Manchester Quality of Life Instrument; PedsFACT-BrS, Pediatric Functional Assessment of Cancer Therapy-Childhood Brain Tumor Survivors Questionnaire, Version 2; PedsQL, Paediatric Quality of Life Inventory; TSS, Total Scale Score; PGWB, Psychological General Well-Being; SF-36, Short-Form Health survey; TACQOL , TNO-AZL Questionnaires for Children's Health-Related Quality of Life

3.4. Quality of Life in Children With Brain Tumours in Comparison With Non-Cancer and Cancer Controls

3.4.1. Overall quality of life

Conflicting results have emerged when comparing overall QOL/HS in childhood cancer survivors with that in normal controls, with some studies reporting better HRQL in survivors (125;193), and some reporting worse (194). Most studies on children with brain tumours report lower overall QOL in children with brain tumours (including BT sub-types) compared with normal, or other cancer controls (94;99;119;123;168;173-175;183;185;195). In the only large study of all tumour types, included in this review in which an overall QOL/HS score was obtained, a statistically and clinically poorer overall QOL/HS was found in childhood cancer survivors compared with normal controls. Pogany et al., using the parent or self-report HUI3 (depending on the individual's age) in a study of 2152 childhood cancer survivors also found that survivors were more likely than controls to have scores in the bottom quartile of responses for the HUI3 MAUF summary score. In this study, survivors of brain and bone tumours had the lowest mean summary scores (99). Similar results were found in a large Italian multi-centre study (93).

In contrast to this, Carderelli et al. in a much smaller study found no statistically significant differences in parent- or self-report HUI3 MAUF between BT patients at least six months off treatment compared with lymphoma/ leukaemia patients or non-CNS tumour patients. A trend for lower HUI2 MAUF for BT patients was noted (95).

Only two small studies of survivors of medulloblastoma (176;177) and one of cerebellar astrocytoma (182) found no difference in overall QOL compared with controls or published norms. All three studies were extremely small, so results should be viewed with caution.

In the largest study (n=556) of outcome in childhood BT, Boman et al. again found statistically significant, large deficits in overall QOL in BT patients at least five years from diagnosis compared with matched normal controls using the HUI2/3 MAUF. In addition, BT patients reported disabilities in more single attributes than controls (183).

In a study of children both on and off treatment for brain tumour or ALL, parent proxy-report scores for overall QOL in children with brain tumours were statistically and clinically lower (indicating poorer QOL) than for ALL patients. Additionally, 63% of BT patients off treatment for more than 12 months had scores at least one standard deviation below the published population mean for the Total Scale Score (overall QOL) (174). Pogorzala et al. and Bhat et al, both reported similar results for BT patients a median time of three and four years respectively from end of treatment. Again, using the PedsQL Generic Core Scales, BT patients had significantly lower overall QOL than ALL patients and/or healthy controls for both parent- and self-report (123;175).

Some scales such as the Self Report Short Form Health Survey (SF-36) and the Child Health Questionnaire (CHQ) do not have an overall QOL summary score, but two component scores for physical and mental/ psychological QOL (196;197). Most of the large studies of all childhood cancer survivors included in this review have used such scales (168-172).

Table 3.2 Summary of studies included in the review

Study	**Sample (n)**	**Age at study (years)** Mean (SD) Range unless not reported/ stated	**Tumour type**	**Country and nature of sample**	**Age at diagnosis (years)** Mean (SD) Range unless not reported/ stated	**Time since diagnosis (years)** Mean (SD) Range unless not reported/ stated	**Controls**	**Instrument and informant**	**Major findings as reported in the study** (With respect to QOL/ HRQL/ HS)
Aarsen et al.(67)	38	-	LG astrocytoma	Nether-lands SC	7 1.3-14.6	7.6 3.6-11.3	Scale norms	TACQOL-P and TACQOL-C parent and self report	QOL decreased for all scales (motor, cognition, social, physical and autonomy problems) except for emotions for parent report. QOL decreased for motor, cognition and social problems for self report.
Alessi et al.(93)	644 for all cancers 133 for BT	15<	All cancers	Italy MC CCRP	0-14	Survived 5 years<	Scale norms and Within group analysis	HUI2/3 self-report	Most survivors reported good overall HRQL. No statistical comparison with norms. CNS tumours (and retinoblastoma and bone tumours) had greater impairment of overall HRQL, vision, ambulation, dexterity, cognition and pain than in other cancers.
Barr et al.(188)	19	5.5-17.8	BT treated with radiotherapy	Canada SC	7 1,5-12.8	7 0.9-10.6	Within group analysis	HUI2/3 proxy- report	HRQL was lower and pain more frequent in those with low BMD scores.
Barr et al.(94)	44	9.5 1.7-17.9	All BT	Canada SC	6.2 0-14.2	2.6 <0.1-8.6	None	HUI2/3 Nurse (1ry	Nurse report HUI2 MAUF lower in those irradiated at

								assessor (n=41) parent (n=23) physician (n=12) self (n=15)	less than 5 years of age. >50% had disabilities in ≥2 attributes. Greatest burden of morbidity in attributes of cognition and pain. Children with demonstrable disease had lower scores than those without. Levels of agreement between raters reported as good.
Bhat et al.(123)	134	11.8 (5.4)	All BT	USA SC	7.6 (5.0)	4.3 (4.4)	Scale norms	PedsQL 4.0 Generic core scales & cancer module self and parent report	Core: Patient self and parent-report scores lower than controls for all sub-scales and summary scores. Lower HRQL in patients with shunt and radiotherapy with no chemotherapy. LGG had best HRQL Cancer module: Older children had worse perception of self-appearance for self and parent-report.
Boman et al.(183)	531 (self) 556 (parent)	>18 26.1 (5.0)	All BT	Sweden MC	10.4 (4.5) 0-19	>5 15.7 (5.1)	Random general population matched for age & gender (n=996)	HUI2/3 Self-report & parent-report	Most severe disability for cognition, sensation and overall HRQL. Risks for poor HRQL were female, young age at diagnosis and time since diagnosis for overall HRQL (MAUF): GCTs, oligodendrogliomas unspecified gliomas and medulloblastomas did

									worst.
Bull et al.(51)	108	-	MBL	UK MC	2.8-14.9	7.2	Compared CSI alone vs. CSI + CT	HUI3 self(n=86) and proxy (n=97) PedsQL, CHQ-PF28, QLQ-C30 and BN-20	Statistically and clinically lower overall self reported HS for CSI compared with CSI+CT. Similar trend for parent report. No statistically significant difference for PedsQL/ QLQ-C30, BN-20 or CHQ.
Cardarelli et al. (95)	50	13.3 8-28	All BT	Italy SC	8.8 0.6-20	> 6 months off treatment	Acute leukaemia / lymphoma (n=89). Non-CNS Tumours (n=74) > 6 months off treatment	HUI2 self- and parent-report	No significant differences for self/ parent report MAUF. More BT patients in the severe range for self & parent-report MAUF. Self- and parent-report emotion, pain, sensation and cognition were effected most commonly in decreasing frequency.
Eiser et al.(173)	BT =26 ALL=51	CNS+GH 13.5(3.56) CNS-GH 13.9(1.97) 8-18	ALL BT	UK SC	CNS +GH 5.96(3.13) CNS-GH 8.75(2.45)	$\geq$ 4 years off treatment	ALL and published scale norms	Self and parent report	Self: Survivors of BT reported worse QOL than ALL and norms. GH did not moderate HRQL Parent: Those prescribed GH had lower QOL than those not on GH.
Forman et al.(96)	52	16.4 12.3-20.3	All BT	USA SC	8.1 1.1-15.3		No controls. Within group analysis	Modified HUI2 parent report	No statistical differences in HS for tumour site, type, age, recurrence, gender. No formal statistical analysis of HS(overall HRQL), but reported as low.
Frange et	34	Median 24.5	Average & high risk	France SC	Median 8.8 1.4-17	Median 14.4	No controls	Self report HUI2/3	Impairments in vision, pain, cognition, emotion

al.(191)		13-39	MBL treated with CSI					15% with help or by parent	and ambulation reported most commonly (35 %<). Mean MAUF = 0.731.
Gerberet al.(176)	9	12.7 4-22	All BT	Swiss SC	0.4 0-0.9	12.3	Published Scale norms	Parent and self report PedsQL generic core scales	No sign. Difference in TSS. Lower HRQL in patient's psychosocial health and social sub-scale.
Glaser et al.(195)	30	10.5 6-16	All BT	UK SC	6.4 1-13	4.1 1-10 Off treatment ≥1 year	Historical controls	HUI2/3 self (n=28) proxy(parent, physio, physician) (n=30)	Physiotherapist was designated as primary assessor. Greatest burden of morbidity in emotion & cognition. Pain also surprisingly common. HUI2/3 MAUF completed by all was lower than historical controls. Linguistic modification must be taken with caution.
Glaser et al.(198)	27	10.8 6-17	All BT	UK SC	6.1 1-13	Off treatment ≥1 year	Matched controls (n=25) and siblings (n=21)	HUI2/3 teachers (n=27) parent (n=21) self (n=13),	Teacher report: more pain, less mobile, lower cognition and emotion. Radiotherapy not identified as risk for poor HS by any respondents.
Maddrey et al.(177)	16	21.9 (3.6) 13.6-27.9	MBL	USA SC	7.2 (4.5) 1-15	14.6 (3.5)	Published scale norms	Ferrans and Powers QOL Index (QLI)self-report	Self reported QOL not decreased despite significant cognitive & functional deficits.
Kennedy and Leyland(107)	30	Median 8.6 6.4-15.2	All BT	UK SC	Median 5 2.1-10.9	Median 3.4 2.7-4.9	No controls	HUI2 <16 years: Parent report	Those with statement of special educational needs had lower HUI2 MAUF than those without.

								>16 years: Self-report	Emotion followed by pain was affected most frequently.
Maunsell et al.(168)	1334 cancers 238 BT	15-37	All cancers	Canada MC CCCSP	<20	>5 years after diagnosis 5-19	Age and sex matched controls (n=1477)	Self-report SF-36	Small statistically, but probably not clinically significant decrease in QOL in survivors in physical component summary (PCS), general health, role physical and social function. No clinically important sex differences. Survivors of CNS & bone tumours had lower QOL than controls for general health, physical function and role limitations due to physical health problems. CNS survivors reported poorer QOL in psychosocial dimensions. Treatment with cranial radiation predicted poor PSC, but not MSC.
Meeske at al.(174)	86 BT	9.7 (4.4) 2-18	All BT	USA Two centres	5.0 (3.7)	On treatment, off treatment for > or <12 months	Childhood ALL (n=170) & Scale norms	PedsQL generic core, cancer and fatigue modules Parent-report only	BT patients scored lower than ALL for TSS, physical health psychosocial health summary scores, social, school, cognitive and fatigue domains. BT patients were more fatigued and had lower TSS than scale norms.
Mulhern	22	Not	MBL- No	USA	Median 8.9	Median 8.2	No	HUI2-proxy	Moderate to strong

(98)		documented	brainstem involvement	SC	4.1-19	6.1 to 9.9	controls	psychologist report only	correlations between HUI 2 Cognition utility and IQ accounting for 22% to 36% of the variance in IQ.
Ness et al.(169)	7147 all cancer 886 BT	18-35+	All cancers	USA MC CCSS	0-20	>5 yrs after original treatment	Within group analysis. leukaemia survivors used as baseline	Self-report SF-36	CNS malignancies, HD, NBL and bone tumour survivors have poorest HRQL in physical summary score. Previous surgery or cranial radiation also predicted poor Physical HRQL.
Odame et al. (189)	25	15.6 (4.8) 4.8-23.5	PF tumours (MBL, LGG) and hypo-thalamic LGG	Canada SC	8.5 (4.6) 0.6-18	6.5 (3.8) 2.3-16.6	Within group analysis	HUI2/3 parent-report	Significant correlation between HUI3 MAUF, SAUFs for pain and ambulation/ mobility and z scores for bone mineral density of lumbar spine. No difference in HS between radiated and non-radiated patients.
Palmer et al.(119)	PPeds QL 99 SPeds QL 51	PPedsQL: 9.8 (4.5) 2-18 SPedsQL: 12.2 (3.9) 5-18	All BT	USA SC	Not documented	On treatment, off treatment </>12 months	Published scale norms	PedsQL BT Module, GCS and Fatigue Module	significantly impaired generic HRQL and fatigue-related symptoms (for all summary and scale scores).
Pedreira et al.(185)	N=18	21.2 14.5-27.9	Cranio	Australia SC	Not documented	LTS	Age and sex matched controls	AGHDA and PGWB	Patient General Health score significantly lower than controls (using PGWB). Subjective QOL (using AGHDA) in patients with GH deficiency on GH was lower than those not

									GH deficient.
Pogany et al.(99)	2152 all cancers 345 BT	5-37	All cancers	Canada MC CCCSP	0-19	5 year ≤ survivors	Randomly selected from population	HUI3 self report (>16 yrs=60%) Parent-report (<16 40%)	Survivors of BT were most likely to report impairments over multiple domains. Impairment in cognition, the domain most commonly reported by all survivors, was most common in those exposed to CSR at a young age. Children with BT or bone tumour, diagnosed in early school years or those having received radiotherapy had the lowest mean MAUF scores.
Pogorzala et al.(175)	36	Median 15.7 7.9-18.9	All BT	Poland SC	Median 8.7 1.7-15.8	Off treatment median 3.0 0.7-11.8	Acute leukaemia (n=35) & random healthy school children (n=60)	Polish version of PedsQL GCS self and parent report	All domains of QOL of BT and leukaemia was lower than healthy controls, BT was lower than leukaemics for self and parent report. Treatment with radiotherapy led to lower physical health. Time after treatment was associated with increased overall QOL.
Poretti et al.(178)	21	20.6 (7.3) 4.5-32.4	Cranio	Swiss SC	9 (4.5) 2.8-15.9	Not documented	Published scale norms	PedsQL GCS and cancer module self- & parent-report	HRQL was rated lower in patients, but no statistics reported.
Reimers	126	21 (7.9)	All BT	Denmark	8.3 (3.8)	>1yr off	Within	Danish	Radiotherapy was the

et al.(190)		7.9-40.4		SC	Range 0-15	treatment 12.8 (7.1)	group analysis	version MMQL Self report+/- parental assistance	most important predictor of HRQL, primarily due to its effect on intelligence. PF tumour site was associated with lower scores for physical functioning & energy. Third ventricular tumours were associated with lower scores for body image. Seven patients were too debilitated to complete questionnaires.
Reulen et al.(170)	10189 all cancers 2188 BT	30.4 (10.3)	All cancers	UK MC	6.7(4.4)	16-50+	Standardised UK scale norms	Self-report UK version SF-36	No difference in mental health between cancer survivors and norms. For physical health survivors aged >19 years were statistically and clinically lower than norms. Survivors of CNS tumours scored lower than norms. Survivors of CNS and bone tumours scored lower than norms for physical health. Treatment with radiotherapy in CNS tumours was associated with lower physical HS.
Ribi et al.(187)	16	18.9 8.5-31.9	MBL	Switzerland SC	6.8 1.1-14.7	12.2 3 - 24	healthy controls	Parent and self-report	Statistically significant differences for social domain only. Parent report were generally lower than self-report.
Roncadi	AST 29	AST:	AST	Canada	AST 7.3(3.4)	AST	Within	HUI2	MBL had lower overall

n at al.(192)		23.5(8.3) 9.8–36	(Surgery only) and	SC	1.2–15	16.3 (7.2) 5.2–31.4	group analysis	Self>18 years, Parent<18 years	HRQL than AST patients. CSI most important in predicting outcome in MBL. For AST, older age at diagnosis and higher perioperative and short-term survival scores(i.e. medical events) predicted lower overall HRQL.
	MBL 29	MBL 17.4 (7.1) 7.5–31.3	MBL (surgery + CSI +/- chemo)		MBL:6.4(3.8) 1.2–15.9	MBL 11.1 (6.1) 4.8–22.2			
Sands et al.(180)	29		Cranio	USA SC	8 0.9-15.2	Median=6 0.7-14.9	Published norms	>19y self-report SF-36 (n=7) 19yrs< Parent-report CHQ-PF50 (n=22)	For all patients: overall physical functioning in the low average range. Overall psychosocial functioning in the average range.
Sands et al.(179)	43	20.7 (7.5)	GCT	USA, Argentina, Australia MC	14.4 (7.3)	6.2 (1.1) Median 6.1 4.5-8.8	Published norms	>19y self-report SF-36 (n=24) 19yrs< parent-report CHQ-PF50 (n=19)	Self-report physical and psychosocial functioning was in the normal range. Parent-report physical functioning in the low average range and psychosocial functioning in the borderline range. Younger age at diagnosis correlated with poor physical and psychological health. Lower physical, but not psychosocial health was found in irradiated children.
Speechley et al.(171)	800 all cancers 122 BT	9.5 6-16	All cancers	Canadian MC CCCSP	2.2 0-9	>5 years after diagnosis	Randomly selected, age- and sex-	Parent-report CHQ-PF50	Survivors' physical and psychosocial summary health was lower than controls. Differences were

							matched controls (n=923)		more marked for physical health. Survivors of CNS tumours, lymphoma, and leukaemia and those treated with cranial radiation were reported to have poorest HRQL (CNS had poorest HRQL). CNS tumour survivors were the only ones with appreciable negative effects for psychosocial health.
Sutton et al.(181)	22	27.1 16-47	Germinoma (irradiated)	USA SC	16.9 11-42	Not documented	SF-36 Published scale norms FACT- BT patients from a different study	SF-36 and FCAT	SF-36: Physical functioning, general health and physical composite scales were lower in patients. Mental composite scale was higher in patients than published norms. FACT: No difference to adults diagnosed with BT.
Yoo et al.(144)	Self 351 Mother 351 Child 166 Adolesc ent 185	7-18 Child 9.9 7-12 Adolescen t 15.0 13-18	All BT	South Korea MC	Child 6.9 Adolescent 12.3 No range	On and off treatment	Child: 2 primary schools, non-matched (n=97) Adolescen ts: No controls	pedsFACT-BrS	Primarily assessed agreement between self and parent-report QOL. The correlation between paediatric self and parent scores were significant (r=.59-.84), while that for adolescent patients was weaker (r=.47-.78). With the exception of the emotional well-being score, the self- and parent-reports showed

									moderate-to-good agreement and similar mean scores in both the child and adolescent BT groups.
Zeltzer at al.(172)	7147 all cancers 886 BT	Median 32 18-54	All cancers	USA MC CCSS	Median 7 0-20	Median 23 15-34	Siblings (n=388) and published norms	Self report SF-36	Survivors and siblings reported better mental health than population norms. Survivors scored lower than norms on all other aspects of HRQL, and lower than siblings for physical summary, but not for mental summary scores. CNS tumour, lymphoma, soft tissue or bone tumours reported more problems in physical function, role physical, general health and social function domains than siblings. Survivors of astrocytomas scored lower than siblings for mental health.
Zuzak et al.(182)	21	Median 15.8 8.3–41.0	LG cerebellar AST	Swiss SC	Median 7.8 2.4–14.3	Median 7.9 5.6-27.4	Published norms	German version of parent and self-report PedsQL GCS	HRQL is similar in AST to that of published scale norms. Patients rated physical health higher than did healthy controls.

Abbreviations: QOL, quality of life; HRQL, health related quality of life; HS, health status; SC, single centre; MC, multi-centre; CNS, central nervous system, BT, brain tumour; LG, low grade; PF, posterior fossa; MBL, medulloblastoma; AST, astrocytoma; GCT, germ cell tumour; cranio, craniopharyngioma; HD, Hodgkin Disease; NBL Neuroblastoma; LTS, long term survivor; GH, growth hormone; BMD, bone marrow density; IQ, Intelligence Quotient; CCSS; Childhood Cancer Survivor Study; CCCSP, Canadian Childhood Cancer Surveillance and Control Programme; CCRP, Childhood Cancer Registry of

Piedmont; AGHDA, Adult GH-Deficiency Assessment; CHQ, Child Health Questionnaire; QLI, Ferrans and Powers Quality of Life Index; HUI2/3, Health Utilities Index 2/3; MAUF, Multi-Attribute Utility Function; MMQL, Minneapolis-Manchester Quality of Life Instrument; PedsFACT-BrS, Pediatric Functional Assessment of Cancer Therapy-Childhood Brain Tumor Survivors Questionnaire, Version 2; PedsQL, Paediatric Quality of Life Inventory; GCS, Generic Core scales; TSS, Total Scale Score; PGWB, Psychological General Well-Being; SF-36, Short-Form Health survey; TACQOL , TNO-AZL Questionnaires for Children's Health-Related Quality of Life

3.4.2. Physical quality of life

Long-term survivors of childhood cancer have consistently been shown to have, on average, lower physical health than normal controls using proxy report, self-report, or both (99;168;170-172). In the same childhood cancer survival studies, children with CNS tumours were more compromised with regards to physical health, when compared with other childhood cancer survivors and normal controls (99;168;170-172). The finding of decreased physical health (when aspects of physical health were analysed), in comparison to normal or other childhood cancer controls was also true for all the other papers in this review (67;119;123;144;174;175;180;181;183;191;195;198), with the exception of a few small studies (95;176;177;182).

In the Meeske et al. paper, physical QOL in BTs was lower than children with ALL using PedsQL parent-proxy rating. The differences in physical aspects of QOL were, in general, more marked in comparison with differences in psychosocial aspects of QOL. Significant differences were found for the PedsQL Core Physical Health Summary Score and the Multi-dimensional fatigue scale and the fatigue subscales, confirming findings of other studies of QOL/HS in children with cancer. There was a quadratic (inverted U) trend for BT patients where peak scores for the Physical Health Summary Score were attained in those off treatment for less than 12 months and lowest for those for patients that had not received treatment for more than 12 months. Means for Psychosocial Summary Scores lay between the two for BT patients receiving treatment (174).

While Cardarelli et al. found no significant difference between children treated for BT compared with other childhood cancers, the attributes most commonly affected were emotion, pain and sensation, rather than cognition and the physical attributes of mobility, ambulation and dexterity. The authors acknowledge that their study may not be representative of the BT population as some long-term patients may not have been recruited from clinic in the time period of the study, patients being not as long off treatment as in other studies, and because of small numbers (95).

Glaser et al. found the greatest burden of morbidity for cognition and emotion, followed by pain, though self-care and dexterity were also significantly affected. Again, the numbers were small, and patients were not as far off treatment as in other studies (195).

The study by Gerber et al. is interesting as it examined QOL (and other outcome measures) in survivors of brain tumours diagnosed at younger than one year of age, a population traditionally thought to be at high risk of negative outcome in terms of survival and QOS (199-205). While both self and parent-report showed deficits in overall QOL and some psychosocial aspects of QOL, none was found for physical health (176). Again, the study was small (n=11), and only three received focal cranial radiation and none CSI. This fits in with the nature of the tumours represented, with

six of the survivors having low grade tumours (four choroid plexus papilloma and two LGG).

The study on outcome of children with low-grade cerebellar astrocytomas by Zuzack et al. is invalidated by the use of the PedsQL in patients over 18 years of age (182). According to Table 1 data, nine of the 21 patients evaluated would have been over 18 years of age at time of assessment, and therefore beyond the upper age limit for the instrument.

3.4.3. Psychosocial quality of life

In general, investigation of psychosocial QOL (as for symptoms of depression, anxiety and self esteem) in survivors of childhood cancer has shown little difference between BT patients and controls. While some investigators have found small or no differences (99;168;170;171), others have reported better psychological health for childhood cancer survivors in general (172). One would expect, given the high morbidity experienced by a large number of children with brain tumours that their psychological health would be reported as lower than that in normal controls and other childhood cancer patients. However, while most studies have shown deficits or impairments in psychosocial aspects of QOL (67;95;119;123;144;175-179;182;187;191;195;198), others have not (180;181;183). In some cases, deficits in social aspects of QOL appear more common in BT patients than emotional aspects of QOL (174).

Speechley et al., using the CHQ-PF50 found that survivors of CNS tumours were reported by their parents as the only childhood cancer survivors with clinically significant negative psychosocial health (171). In comparison with children with ALL, Meeske et al. found that children with BTs scored lower for the parent-report PedsQL Core Psychosocial Health Summary Score, Social Function and School Function subscales, and the Cancer Worry and Cognitive subscales. Interestingly, there was no difference between BT and ALL patients with regard to the PedsQL Core Emotional Function or Acute Cancer Worry subscales. Patients treated for ALL require more invasive procedures and investigations over a more prolonged treatment period, which may explain the lack of difference between the two patient groups. Lack of insight or worry due to cognitive deficit in BT patients on behalf of the parents may also have contributed. There was again a quadratic (inverted U) trend for the Psychosocial Health Summary Score for BT patients, though differences weren't as marked as for physical health (174).

Bhat et al., again using the PedsQL in children a mean of 4.3 years after diagnosis found significant differences between BT patients and scale norms for the emotional, social and school subscales and the Psychosocial Health Summary (123). Cardarelli et al. using the HUI2, found that emotion, pain, cognition and sensation were most commonly affected in the brain tumour cohort, and appeared to be affected to a greater degree than survivors of leukaemia and other solid tumours, though no formal statistical comparison was made (95).

Boman et al. using the HUI 2/3 (primarily self-report) in the largest QOL study specific to BT survivors found lower scores in BT survivors for all domains with the exception of emotion and pain. In a sample of 38 children with LG astrocytomas, the majority of which were treated with surgery alone (n=24/38) a mean of 7.6 years after diagnosis, HRQL was decreased for most physical and social subscales of the TACQOL parent and self-report, when compared with scale norms, there was no significant decrease in the emotion subscales (positive or negative moods) (67). Adult survivors of intracranial germinomas diagnosed at a mean age of 16.9 years (range 11-42 years) scored higher than normal controls for the mental composite score of the SF-36 (181;191). No reasons for this are given in the paper, though the relatively older age at diagnosis of patients included in the study and the less intensive nature of treatment for germinomas may have contributed. Finally, Sands et al., in a small study, reported overall psychosocial QOL in the average range in a small cohort of 29 survivors of craniopharyngioma a median of 6 years after diagnosis (180).

3.4.4. The attributes of cognition and pain

Cognition (94-96;99;107;183;184) and pain (94-96;99) are consistently reported by brain tumour patients and their proxies as being impaired, particularly by researchers using the HUI. The high incidence of cognitive impairment is not surprising, as cognition is well known to be affected in a high proportion of brain tumour survivors. Direct (i.e. face to face) testing of neuropsychological function using instruments such as the age appropriate versions of the Wechsler for IQ and more specific tests for memory and attention require expertise, time and money. The HUI cognitive sub-scale/ attribute has been by some to correlate significantly with IQ, and has been suggested as a screening test prior to formal neuropsychological assessment (94;99;191).

It is unclear why pain should be so commonly reported as a problem in both long-term brain tumour survivors and in those not long off treatment (94-96;191). Foreman et al. attributed the relatively high frequency of parent-reported pain (19% of patients) to association with headache and craniotomy scars (96), though neither the data on headache/craniotomy nor their association with the SAUF of pain is documented in the manuscript. Emotional distress (somatisation) and the burden of undiagnosed chronic pain are also cited as possible reasons for the report of pain by mothers of childhood cancer survivors (96). Frange et al. suggest that chronic back pain and/or osteopaenia may explain in part the high (58% of medulloblastoma survivors) incidence of pain in their cohort (191).

Neither of the other two papers referenced contain information on why pain is prevalent in this population. Odame et al., in a cohort of childhood brain tumour survivors a median of 6.5 years after completing treatment, found more severe pain in those with low bone mineral density (BMD) scores (189). While low BMD was also associated with cranial radiation, no consideration of the causal pathway of the pain is made. A brief survey of the non-QOL literature revealed a complete lack of data relating to the prevalence, anatomical origin or severity of pain in survivors of childhood brain tumours. It is also not possible to ascertain from questionnaires such as the HUI, the anatomical origin or nature of the pain. More in depth, qualitative research into pain in survivors of childhood brain tumours, and the extent to which it impacts on QOL is thus necessary.

Boman et al. found no difference between BT survivors a mean of 15.7 years after diagnosis and controls for the HUI attribute of pain. The reason given for this lack of difference between the groups, which contrasts with the results of other studies was that some late effects, such as pain, may decrease or cease over time while others become more pronounced (sensation, cognition and overall HRQL) (183). However, no reason is given in the discussion for why pain should decrease over time.

3.5. Predictors of Quality of Life

The heterogeneity in recovery and adjustment seen in children with cancer, and more specifically those with brain tumours, makes identification of risk and resilience predictive factors of QOL both important and complex.

3.5.1. Socio-demographic predictors of quality of life

3.5.1.1. Age at diagnosis

Data on the influence of age at diagnosis on later QOL in children with all types of cancer suggests that children diagnosed at a younger age are at higher risk of poorer overall QOL than older children and adolescents. In a large study by Alessi et al., survivors diagnosed between ten and fourteen years had better overall HRQL (significantly less children in this age group scored in the lowest quartile for HUI3 MAUF) and less morbidity for the attributes of emotion, cognition and pain than those diagnosed at a younger age (93). Pogany et al., again using the HUI, reported similar results (99). Some studies adjusted for age when considering predictors of QOL in long-term childhood cancer survivors, and have not commented on the effect of age on QOL (93;169).

Findings on the effect of age at diagnosis on QOL in children with brain tumours vary. The relationship between age at diagnosis and QOL is complicated by recent efforts to avoid cranial radiation in very young children in an attempt to avoid its

effect on cognitive function and development. In one of the earlier studies, Barr et al. found the highest burden of morbidity in children who received radiotherapy before the age of five years (94). Similar findings were reported in a more recent study of survivors of all types of childhood cancer, highlighting the vulnerability of the immature brain to damage secondary to cranial radiation (190). Older age at diagnosis was found to be positively correlated with both physical and psychosocial QOL in survivors of intracranial GCTs, using self-report for over 19 year olds and parent reports for those 18 years and younger (179).

In a study of outcomes limited to infants treated for brain tumour in the first year of life at a mean follow up time of 12.3 years, Gerber et al. did not find a significant difference between patients and controls, though sample size, with only nine out of 11 survivors completing self-report PedsQL, makes interpretation difficult (176).

In contrast, in one study of five year survivors of cerebellar astrocytomas and medulloblastomas, older age at diagnosis predicted lower QOL, possibly as a result of greater disruption and psychological trauma (192). This finding is supported by the study of Bhat et al. Although this study found no relationship between overall QOL and age at diagnosis, it showed that parent-report suggested patients diagnosed above the median age (7.2 years) worried more about their illness than younger children did (123). Meeske et al. also found no significant relationship between age at diagnosis and QOL with the exception of the PedsQL

Multidimensional Fatigue total score which was inversely related to age at diagnosis (174).

Aarsen et al. found that age at diagnosis correlated significantly with parent- and self-report QOL in social functioning, with children diagnosed in adolescence reporting significantly lower social QOL than those diagnosed at a younger age (67). This reflects the importance of establishing meaningful relationships and socialising with peers in adolescence and highlights the differential effects brain tumour diagnosis may have, depending on the key age-dependent developmental tasks of the person affected (206). In contrast, younger age at diagnosis was found to predict poorer peer relationship and intimate relations. This finding was attributed to younger patients not acquiring basic social skills normally acquired in early childhood (190), a similar explanation to that given by Aarsen et al. to explain their contrasting results.

Several other studies found no relationship between age at diagnosis and later QOL (96;175;198). There is thus no consensus in the literature that QOL is affected by age at diagnosis.

3.5.1.2. Age at assessment and time since diagnosis

Age at assessment, and time since diagnosis, are likely to be related in survivors treated in childhood, and therefore have been grouped together. Improvements in

surgery and radiotherapy techniques, as well as refinement of chemotherapy protocols over time may well confound findings related to time since diagnosis, as there is likely to be a relationship between time from diagnosis and era of treatment.

An interesting finding by Reulen et al. was that while younger survivors (16-19 years) reported no deficit in physical function compared with normal controls, older survivors (>19 years) did (170). Speechley et al. and Zeltzer et al. reported that, for children with all cancers, longer time from diagnosis correlated with greater survivor-control group differences and effect sizes (171;172). Several reasons are suggested for this difference including the possibility that survivors became less repressive regarding their cancer history over time, lost the enhanced appreciation of life over time, or that survivors age faster, and that this is related to the increased appearance of adverse health conditions at an earlier age (170).

In agreement with studies of childhood cancer survivors in general, QOL in BT survivors tended to get worse with time post treatment. Those patients further from diagnosis demonstrated more difficulty with communication and social functioning, using the parent-report PedsQL, than those closer to diagnosis, suggesting that they may become more isolated from their peers over time (207). This is in contrast to that found in other childhood cancer survivors.

Bhat et al. found that children below the median age at assessment (11.3 years) had worse self- and parent-report scores for procedural anxiety, while those above the median age at assessment had worse parent-report perceptions of self-appearance (123). Aarsen et al. also found that the TACQOL-P physical, motor, cognitive and social domains, as with the behaviour domain of withdrawal, correlated negatively with age at assessment in survivors of childhood LG astrocytomas at a mean of 7.6 (range 3.6-11.3) years after diagnosis. Similar results were found in BT and ALL patients on and off treatment with patients older at interview scoring worse for the PedsQL generic core total scale score, physical health summary and the overall multidimensional fatigue total score (174). The authors suggest that physical, motor and social problems in particular appear to become more significant over time. Moreover Aarsen et al. suggest that such problems may suddenly become apparent years after diagnosis as patients become unable to meet the increasing expectations of society as they age and mature (67). They cite two examples where this appeared to be the case. However, it is unclear whether these examples represent the brain tumour population as a whole and the authors do not elaborate whether the correlations were for parent- or self-report or both, which makes interpretation more difficult.

When comparing their results with other studies of younger survivors of childhood brain tumours, Boman et al. came to the conclusion that some late effects impacting on sensation, cognition and overall HRQL may become more pronounced later in life, while others such as pain and emotion may decrease or cease. Era of diagnosis

was also identified as a predictor of QOL, with those diagnosed later reporting less disability than those diagnosed earlier (183). This evolution of the effects of deficits over time impacting on aspects of QOL is similar to that made by Aarson et al., above (67).

These results, discussed above, contradict findings from a large Canadian study of childhood cancer survivors where older age at assessment was strongly correlated with reports of poor emotion (99).

Moreover, it is difficult to substantiate such conclusions based on comparison between different cross sectional studies. The quadratic trend reported by Meeske et al. for BT patients, where peak scores for both physical and psychosocial QOL were attained in those off treatment for less than 12 months and lowest for those for patients that had not received treatment for more than 12 months, is interesting and contrasts with findings for ALL patients where QOL improved for those off treatment for more than 12 months (174). These findings are most likely due to differences between treatment regimes, with many BT patients receiving intensive treatment throughout their therapy course, and ALL patients receiving less intensive maintenance therapy for a long period before therapy is completed. However, Meeske et al.'s findings are limited by the sole use of parent proxy report.

In contrast to the previous studies, Reimers et al., in a Danish study of BT survivors a mean of 12.8 years after diagnosis, found that younger age at assessment significantly correlated with more physical symptoms. As age at assessment correlated strongly with duration of follow up, the authors concluded that survivors may be more aware of, and worried about, symptoms the closer they are to treatment. Another possible reason given is the relative importance that children, rather than adults, place on physical prowess (190). Unfortunately, the authors did not compare their findings in relation to age at assessment with other published results.

Finally, Sands et al. also found that while psychosocial and physical functioning in survivors of intracranial GCTs over 19 years of age at assessment fell within normal ranges, for 18 years and younger they were low average and borderline respectively (179). However, as QOL was measured using self-report for those over 19 (SF-36) and using parent-report for those 18 years and younger, valid conclusions are difficult to reach, particularly as parents tend to underestimate their children's QOL.

As with the Childhood Cancer Survivor Studies, all the abovementioned studies were cross-sectional, and assessed QOL in survivors of BT a variable time from diagnosis or assessed children and young people at variable ages. Furthermore, some researchers found no significant correlations between age at assessment or time

since diagnosis and QOL (96;175;192;198). However, there was general agreement that time since diagnosis/ older age at assessment is associated with lower QOL.

3.5.1.3. Gender

For all childhood cancer survivors, in general, when differences related to gender were found, female survivors tended to report lower QOL than males (93;99;168;172;208). Alessi et al. found lower self-reported overall HRQL and more morbidity in the attributes of dexterity, emotion and pain in females for all cancer types (93). Boman et al. reported similar results in survivors of BT for overall HRQL and pain, with a trend towards significantly higher disability for all single attributes with the exception of hearing and dexterity. Thirty-three percent of females and 22% of males reported MAUF scores in the severe range (183). Bhat et al. reported higher QOL for school functioning in female survivors (123). For brain tumour and ALL patients, both on and off treatment, females scored significantly lower for parent-report PedsQL scale for overall QOL and physical summary score (174). In general, females have consistently been shown to report greater symptoms than males, and this is the most likely reason for differences in the brain tumour literature. However, females are also more vulnerable to cognitive changes secondary to cranial irradiation than males, (209) which may contribute to gender differences in QOL.

For some studies, gender was not a significant predictor of QOL (96;175;190;192;198), and again, for many studies its potential effect on later QOL was not assessed.

Unfortunately, few authors have published the relationship between QOL and demographic predictors in their normal control group which makes it difficult to distinguish brain tumour specific from general population predictors of QOL in this population.

3.5.1.4. Socio-economic status

Very few studies have investigated the impact of socio-economic status on QOL in children with brain tumours. There is some evidence that lower educational attainment, being unmarried and lower annual household income are all risk factors for psychological distress and poor QOL for adult survivors of childhood cancer (172;210). Similar findings regarding lower educational attainment and unemployment have been reported elsewhere (211). These findings seem to make sense and are likely to be true for the non-cancer population as well. In the brain tumour literature, few studies conducted within group analysis of the relationship between socio-economic status at assessment and QOL (174;183). Boman et al. found a significant relationship between lower educational attainment, greater remedial support in school, lower employment status, greater use of social support/ government subsidies and those who less frequently became parents and lower

overall QOL/ HS(183). Meeske et al., using parent-report, found no relationship between socio-economic status at assessment, ethnicity or parent's level of education and QOL(174). The patients in this study were, however much younger at assessment than those in the Boman et al. study, and this as well as the use of different methodological tools used in quantify Socio-economic status, makes comparison between the two difficult. To date, there are no published data relating socio-economic factors at diagnosis with QOL.

3.5.2. Tumour and treatment related predictors of quality of life

Because of the heterogeneity of childhood brain tumours and differences in treatment protocols, it is difficult to distinguish important tumour and treatment related predictors of quality of life. As a result, results are mixed and difficult to interpret.

With regard to tumour type, Bhatt et al. found that children diagnosed with LGG had higher parent-reported overall QOL, better emotional functioning, physical functioning and communication of all BT types. This is unsurprising, as standard treatment for low grade astrocytomas consists of surgery alone. Interestingly, this relationship was not found for child-reported QOL (123).

In a study by Roncadin et al. comparing outcome between posterior fossa astrocytomas and medulloblastoma, QOL measured using the HUI2 was significantly lower in long-term survivors of medulloblastoma. This finding was true for most other outcomes assessed. In this retrospective study, the incidence of specific medical events in four time periods: diagnosis, peri-operative (initial inpatient hospitalisation), short-term-survival (first five years post-initial hospitalisation) and long term survival (beyond five years post-initial hospitalisation) were examined, and using multiple regression models, used to evaluate predictors of neurobehavioral outcome, including QOL. For astrocytomas patients only, higher peri-operative, short-term survival scores and an older age at diagnosis predicted lower QOL. The same pattern was not found for medulloblastoma patients where cranial radiation is likely to supersede other medical events (192).

The invasive pattern of malignant tumours, particularly with respect to brainstem involvement, as seen in medulloblastoma, may also play a role in moderating QOL by damaging normal tissue and complicating surgical resection. Differences in tumour site, with medulloblastomas more commonly occurring in the vermis, than hemispheres of the cerebellum, as is the case of astrocytomas, may also be important. A study similar to that of Roncadin et al., on children with low grade posterior fossa astrocytomas using comparable outcome measures, but not including QOL, did not find an association between outcome and adverse medical events (212).

Surprisingly, and in contrast to earlier studies (181;213), Boman et al. reported that survivors of intracranial GCTs reported poorest overall health, followed by those with oligodendroglioma, mixed/ unspecified glioma and medulloblastoma (183). Patients with GCTs do not in general receive as high a cranial radiation dose or as intense chemotherapy as other malignant tumours such as medulloblastoma, ependymoma and high grade astrocytomas. Contemporary treatment does not usually require aggressive surgery and in general, GCTs occur in older children than other brain tumours. However, treatment for GCTs has changed over time, with children treated in earlier eras more likely to have had aggressive surgery. In addition, GCTs have a relatively high incidence of neuro-endocrine dysfunction with resultant obesity and body image problems as well as visual dysfunction due to their tendency to occur in the pituitary and pineal regions (214-216), which are likely to account for significant detriment in QOL. Due to their anatomical site, there is also a relatively high incidence of hydrocephalus in pineal tumours.

Bomen et al. also found that the overall HS/ QOL measure (HUI2/3 MAUF) did not reflect the specific deficits found in different tumour types. Low overall HS/ QOL in the mixed/ unspecified glioma group was due to marked deficits in motor and visual attributes, with other single attributes being largely unaffected (183). Such findings are likely due to overrepresentation of optic pathway gliomas in this group. This finding emphasizes the importance of considering single attributes/ subscales as well as multi attributes/ summary scores when assessing health status and QOL. Survivors of craniopharyngioma have also been found to have lower QOL than

norms, and they too are at risk of neuro-endocrine and visual dysfunction due to tumour site and difficulty in achieving local tumour control without compromising function (180;185).

The presence of a ventriculoperitonial shunt has been associated with lower total, psychosocial, social and physical QOL (123). This may be because larger, more aggressive tumours are more likely to result in shunt dependent hydrocephalus. The presence of hydrocephalus was one of the “peri-operative medical events” used by Roncadin et al. in their analysis (192).

Meeske et al. found no relationship between tumour location and QOL, though no detail of how patients were stratified was given (174). A trend towards better QOL for infratentorial tumours ($p=0.07$) in comparison with supratentorial was found by Pogorzala et al. (175). Foreman et al. however, found no relationship between tumour site, type or recurrence and QOL (96).

The literature on the impact of different treatment modalities used in children with brain tumour is inconsistent. Studies focussing on QOL in survivors of childhood low grade astrocytomas, treated by surgery alone have shown decreased QOL in comparison with normal controls or population norms (67;172;183;192). The relative influence of radiotherapy and chemotherapy on QOL is less clear, though both appear to impact adversely on QOL. Bhat et al., in a study of all brain tumour types,

found that the patients treated with chemotherapy in addition to cranial radiation did not have lower QOL (measured using the PedsQL) than those treated with radiotherapy alone, and suggest that, where feasible, radiotherapy doses and fields may be reduced and chemotherapy added without adversely effecting QOL. However, as assessment was cross sectional and performed a median of 3.2 years after treatment, it does not reflect QOL of children undergoing treatment or QOL of long-term survivors of childhood brain tumours. The study included all childhood brain tumour types, for which chemotherapy regimes may differ significantly. Treatment with radiotherapy with or without chemotherapy resulted in lower QOL than in those treated with surgery alone (123). In contrast to this, Bull et al., in a fairly large study of children treated in a uniform manner for medulloblastoma in the UK (PNET 3), found that children treated with chemotherapy and cranial radiation had worse HS/ QOL (measured using the HUI3) than those treated with radiotherapy alone. There was also a trend towards poorer outcomes for behaviour and QOL measured using the PedsQL (51). Patients on the chemotherapy arm received pre-radiotherapy chemotherapy consisting of vincristine 1.5 mg/m^2 weekly for 10 weeks, carboplatin 500 mg/m^2 daily for 2 days in weeks 1 and 7, cyclophosphamide 1,500 mg/m^2 once in weeks 4 and 10, and etoposide 100 mg/m^2 daily for 3 days on weeks 1, 4, 7, and 10. The conclusions of this study are potentially weakened because treatment allocation was not randomised for all patients, as in some cases parent or physician choice determined treatment arm.

One would expect to find that children on treatment would tend to have lower QOL than those off treatment, and this has been found in a study focusing on the development of a brain tumour specific QOL instrument (144). However, the quadratic trend reported by Meeske et al. for BT patients, as discussed in detail above suggests that this is not always necessarily true (174).

3.5.3. Family related variables as predictors of quality of life

Demographic and medical variables only explain QOL to a limited extent (65;208;217-219). The author has found no published data on the influence of family variables, such as family functioning, family support, the impact of the disease on the family or parental mental health on either parent- or child-reported QOL in the paediatric brain tumour population. However, there is some evidence that such variables may modify outcome in children with cancer and other chronic disorders. Socio-ecological theories, such as the bio-ecological systems theory suggest that a person's wellbeing is dependent on the social system and resources around them as well as personal characteristics (220). The family system and its resources is a proximal and important factor in a child's development and may influence the child's adjustment to a stressor (221). A number of global variables, including family and parental functioning, have been defined as resistance factors that may moderate the negative effect of risk factors such as the disease, its treatment, and parental stress in children with chronic health conditions (222). Further application of this "risk-resistance theoretical framework" to children with cancer in a prospective longitudinal study, identified perceived family cohesion and expressiveness as the best

predictors of psychological and social adjustment in the first nine months after diagnosis with all types of cancer (223). This study only included two children with brain tumours, however, and therefore the results may not be generalisable to the brain tumour population.

There is evidence that parental mental health may influence their rating of their child's health/ HRQL (147;224;225). Of particular relevance, Eiser et al., in a study of children with acute lymphoblastic leukaemia three to five months after diagnosis, found a significant correlation between mothers rating of their own QOL and their rating of their child's QOL (147). However, as the study was cross sectional, no information about the direction of the relationship can be made.

Robinson et al. again found significant correlations between both mothers' and fathers' rating of their own and their child's distress. Using hierarchical regression analysis, family environment, child age and sex, treatment severity, were identified as possible moderators of the relationship between father and child distress. The same relationship was not found for mothers. Social support was not found to significantly moderate the relationship between parent and child distress (221). However, there was no significant relationship between parent distress and child, self-reported outcomes; shared source variance cannot be excluded as the reason for significant correlations between parent distress and their rating of their child's distress. Further longitudinal studies on the same cohort of patients showed similar

results. While there was again a significant relationship between mother and father distress during treatment and their rating of their subsequent proxy rating of their child's internalising symptoms soon after they reached 18 years of age, parent distress was not found to be predictive of self-report outcomes. Neither social support nor family environment during treatment moderated parent or self reported mood in cancer survivors on follow up. Severity of initial treatment and late effects were found to be important moderators between parent and young adult survivor distress (226). Children with brain tumours were excluded from this cohort, making generalisations to the brain tumour population difficult. Moreover, predictors of psychological outcome measures, such as adjustment or distress as in the studies mentioned above, may not be the same as that for the more global outcome of QOL.

3.5.4. Child-related variables as predictors of quality of life

To date, there are very few data on the moderating/ mediating effect of child-related variables such as cognition, behaviour and emotional status on QOL in children with brain tumours. Insight into these psychosocial variables that may predict QOL may be helpful in directing interventions, and is therefore important (208). Possible neurocognitive factors which have been shown to be compromised in children with CNS tumours and may be important in modulating QOL include Intelligence (PIQ and VIQ), memory, attention and executive functioning (227-229). Through its effect on general intelligence, radiotherapy has been shown to be important in predicting QOL in long-term survivors of childhood brain tumours.

A linear regression model, with scales and sub-scales of an early version of the Minneapolis-Manchester Quality of Life (MMQL) as outcome variables, considered six potential predictive factors of QOL: gender, age at diagnosis, age at follow up, tumour location, treatment with radiotherapy and the presence or absence of hydrocephalus requiring shunt. To investigate the potential moderating effects of general IQ, a supplementary analysis using Full-scale IQ as a covariate was conducted. A significant relationship between treatment with radiotherapy and poorer physical functioning and energy, social functioning (poorer relationship with peers, but not family), cognitive functioning, body image, outlook on life and intimate relations was found. When full scale IQ was included as a covariate, the relationship remained significant for relationship to peers and intimate relations.

Survivors of tumours in the third ventricular region reported significantly lower scores for feelings about body, and this remained significant when IQ was added to the model. This was attributed to such patients being at higher risk of having pituitary and/ or hypothalamic dysfunction, which may result in an altered bodily appearance. Tumour location in the posterior fossa was significantly associated with more tiredness and unsteadiness in the arms and legs which was attributed to the role of the cerebellum in balance and co-ordination. This relationship was not significant when IQ was included in the model. The insertion of shunt for hydrocephalus was the only predictor associated with a better QOL. This was found for the subscale of feelings about body in both models utilised. No reason for this association could be

found and it was therefore attributed to a type I error (190). Importantly, age at diagnosis, a potential confounding factor when considering radiotherapy induced cognitive effects, was included in the multivariate analysis, strengthening the study findings.

A recent study by Papazoglou et al. (2009) identified that parent reported attention problems within 3 years of diagnosis predicted adaptive behaviour three to five years later (230). In addition, a child's emotional and behavioural status may contribute to feelings of worthlessness, isolation and subsequently impact on QOL. There is some evidence that methylphenidate may improve the establishment of social relationships with peers in children with ADHD (231). It is possible that the use of stimulants such as methylphenidate may be useful in improving attention and potentially social interactions in selected childhood brain tumour survivors. This may in turn, impact positively on QOL.

In adult survivors of childhood brain tumours, those who had lower educational attainment, received more remedial assistance in school, had lower employment status and to a greater extent utilised social insurance or government financial support, and who less frequently became parents, had poorer overall health using the HUI 2/3 (183). However, with the possible exception of the requirement of remedial assistance in school, these associations are not relevant when considering QOL in the paediatric population.

3.6. Criticism of Current Available Literature

In general, children with brain tumours have significantly lower QOL than normal controls and other children with cancer. However, most studies have concentrated on measuring QOL in long term survivors, and not in newly diagnosed children or in the first year after treatment when children are particularly vulnerable to the deleterious effects of tumour and its treatment, and where identification of patients at risk, and the application of appropriate interventions, may be most relevant.

To the author's knowledge there have been no prospective longitudinal QOL studies of children diagnosed with primary brain tumours, resulting in a lack of understanding regarding the process of adjustment that takes place throughout the cancer experience, and the mediating factors that may effect adjustment. There have however been some longitudinal studies in the childhood cancer population (232;233). There have also been some studies where controls were not assessed, and in which population norms were used for comparison of QOL. However, because QOL may change over time as children age and develop or during times of stress (during exam time for example), utilization of matched controls is of utmost importance for longitudinal studies.

Most studies included children with all brain tumour types, while some concentrated on specific tumour types (with resultant small numbers). This is most likely because of the rarity and heterogeneity of brain tumours in children. Patient's treatment and

subsequent medical events may vary substantially depending on tumour type, grade and site, making identification of mediating factors challenging. There was also a large degree of heterogeneity regarding the primary research question, sample size and the QOL/ HS measure used. Most studies were descriptive studies of the cancer population, with inclusion of brain tumour patients or in children with brain tumours alone. Some studies focused on specific tumour types, some in specific age ranges, while a few looked at predictors/ moderators of quality of life. All were quantitative in nature.

A total of ten different QOL instruments were used, most of which were generic in nature. The abundance of available QOL instruments makes comparisons between studies challenging. Perhaps more concerning is the interchangeable use of QOL, HRQL and HS to define measures. This issue is discussed in depth in section 1.3 above. Encouragingly, most studies reported self-report QOL, with some providing parent-report only and a few using self- and parent report interchangeably, despite concerns regarding differences in interpretation self- and parent-report. Very few studies used self- and parent-report in parallel, or used more than one QOL or similar measure to validate their outcome.

Study methodology, with regard to analysis of data, varied widely. The use of means, medians and centiles as descriptive measures varied. In studies that considered

possible predictors of QOL, there was, in general, a lack of multivariate analysis to avoid confounding factors. This may have been due to limitations in case numbers.

When considering predictive variables, most studies concentrated on demographic and treatment related variables, with very little data available on family and child-related determinants available to date.

3.7. Study Aims

In order to explore QOL in children with brain tumours at / soon after diagnosis and in the first year thereafter, and to address some of the limitations of previous studies, the work submitted for this PhD aimed to:

1) Measure the health related quality of life of children presenting with primary brain tumours to a regional neurosurgical centre, at 1, 6 and 12 months after diagnosis using two QOL/ HS measures.

2) Compare heath related quality of life in children with brain tumours to those of normal controls matched for age, sex, socio-economic status, geographic location and pre-morbid academic achievement in the first year after diagnosis.

3) Identify medical and non-medical predictors of health related quality of life in children with brain tumours one year after diagnosis.

4) Identify possible targets for intervention aimed at improving health related quality of life in this patient population.

4. MATERIALS AND METHODS

4.1. Study Sample

4.1.1. Patients

All children and young people with primary intracranial tumours, aged between 0 and 18 years, referred to the regional paediatric neuro-surgical unit (Frenchay Hospital, Bristol, UK) from April 2003 to April 2005, were approached to take part in the study. Once a pathological diagnosis (or radiological evidence in cases where tissue diagnosis was deemed unsuitable or unnecessary) was made, the child and family were approached by the author, who explained the purpose and nature of the project. When the author was not present, consent for the overarching study was obtained by my colleague RS. Information sheets were provided for parents and separately for children over 8 years of age. Families were given time to consider and discuss the proposal (in all cases at least overnight), before consent was obtained.

4.1.1.1. Inclusion criteria

1. All children aged less than 18 years with primary brain tumours who were admitted to the regional neurosurgical unit (RNSU) at Frenchay Hospital, Bristol over the two-year enrolment period.

2. Written informed parental consent and child consent/ assent when appropriate.

4.1.1.2. Exclusion criteria

1. History of pre-existing major neurological impairment.

2. Parental refusal to consent to enrolment.

4.1.2. Controls

The “best friends” model was used to recruit controls matched for socio-economic status and academic attainment (234). Older children, or parents in the case of younger children, were asked to identify same sex controls in the same school year as the patient. Potential controls were then provided with written information regarding the study with a reply slip confirming whether or not they were willing to be contacted by telephone to discuss possible participation in the study. If the first parent or child refused, another friend of the same age was identified and approached in the same manner. For very young patients, where no appropriate controls were identified by the parent, the patient’s health visitor was approached to identify an appropriate control.

4.1.3. Ethical approval

Ethical approval for the entire study was gained from Central and South Bristol Research Ethics Committee and ethical approval for aspects of the study relating to this manuscript was obtained from the University of the Witwatersrand Committee for

Research on Human Subjects. All parents provided written consent, and children gave assent to take part in the entire study where appropriate.

4.2. Timing of Interviews

Assessments were intended to take place at home at one (t1), six (t6) and 12 (t12) months after diagnosis in patients. For patients who were hospitalised but able to take part at time of t1 assessment, the assessment was done in a room away from the neurosurgery ward. It was expected that, at one month post diagnosis, most patients would have had primary surgical intervention and would have commenced / be about to commence cranial radiotherapy or chemotherapy as required; at six months post diagnosis, radiotherapy would have been completed; and at 12 months after diagnosis, for patients without relapse / progression, the initial treatment regime would normally been completed. Controls were assessed at the same time periods, in parallel with, but geographically separate from the patients. During these visits the research psychologist (RS) attached to the project also performed an age appropriate cognitive assessment of each patient. The same assessments were to be performed at each time-point allowing for identification of changes over time.

4.3. Details of collection and handling of data

The following description refers to collection and handling of data used in the papers submitted in support of the author's PhD. All QOL and family related data and data on executive function, behaviour and adaptive behaviour were collected, scored and

entered onto a secure database (FileMaker Pro 6.0 v04, 1984-2002 FileMaker inc.) by the author. Completed questionnaires were kept in a secure cabinet in a locked room in Frenchay Hospital. A sample of the completed questionnaires was checked by RJM for quality control purposes. Cognitive assessment and supervision of the completion of the remaining child related variables (BDS, RCMAS, and IES) was done by RS. All socio-demographic data was collected by the author from the patient's notes and during the one month interview. Data was exported from the data base to Excel and from there to SPSS or SAS for analysis.

4.4. Dependent Variables: Quality of Life Measures

4.4.1. The Pediatric Quality of Life Inventory 4.0 (PedsQL)

The PedsQL was used in papers 1-3. 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. Developmentally appropriate, age specific versions of both parent-report (ages 2-18), and self-report (ages 5-18 years) are available. These versions are specific for ages 2-4 (parent-report only), 5-7, 8-12, and 13-18 years. Items are scored on a 5-point Likert scale from 0, "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 (physical, emotional, social and school domains), three summary

scores (the psychosocial summary, a summary of the emotional, social, and school domains, and a physical summary which is identical to the physical domain score) and the total score (a summary of all four domains) (121). We used both parent- and self-report PedsQL at all three time-points.

The validity and reliability of the PedsQL for healthy children, and children with acute and chronic diseases, including those with cancer and, more specifically, brain tumours have been established (121;207;235) (123).

4.4.2. The Health Utilities Index Mark 3 (HUI3)

The HUI3 is used in papers 3 and 4. The HUI is a generic, preference based system designed to measure ability or disability for health status attributes. We used the more recently developed HUI3, rather than the HUI2, as it is the more descriptive system, and has full structural independence. The HUI3 has been used to estimate health status at the population level and in survivors of childhood cancer (236) (99). It has also been used to evaluate HS in survivors of central nervous system tumours in Canada and the UK (51;94;195).

The HUI3 consists of eight attributes (domains) selected according to the importance placed on them by the general population (237). The domains comprise vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. Measures of

disability for each attribute are converted into single attribute utility function (SAUF) scores with interval scale properties. The multiplicative Multi Attribute Utility Function (MAUF) incorporates all eight attributes, and represents overall HS. SAUF scores range from 0.00 to 1.00, with higher scores representing better HS. HUI3 MAUF scores ranges from –0.36 to 1.00, defined as 0.00 = death and 1.00 = perfect health. Negative scores therefore represent health states considered worse than death by the general public. Differences of 0.03 or greater for HUI overall HS (MAUF) and 0.05 or greater for mean single attribute (SAUF) represent meaningful changes (105).The HUI3 proxy-report, reported by parents in this study and referred to as such, can be used for children aged five and over. The self-report HUI3 can be used by children aged eight years and over.

Both the overall MAUF and single attribute levels can be aggregated into levels of disability (none, mild, moderate and severe). For the purpose of this study, HUI3 levels of disability were grouped as either none/ mild or moderate/ severe in order to identify those patients with more than minor disability (such as near- or farsightedness, which would be classified as “mild” disability) (238).

4.5. Independent Variables

The range of independent variables we could consider was limited due to the relatively small patient numbers and the heterogeneity of diagnoses amongst our unselected population. Our principal focus was on child and family-related variables

as we felt that these would provide generic targets for intervention, independent of potential future adjustments to treatment regimes and / or the application of new technologies in surgery and radiotherapy which would be better explored in the context of a studies restricted to patients with specific diagnoses.

4.5.1. Demographic variables

These included gender and age of the child at diagnosis and socio-economic status (SES). SES was assessed using the Income Deprivation Affecting Children Indices (IDACI) of the Index of Multiple Deprivation (IMD), a measure widely used by British government departments. The IDACI represents the proportion of children aged 0-15 living in income deprived households as a proportion of all children 0–15. (defined as either households receiving Income support/ Job seekers allowance-Income Based/ Pensions Credit or those not in receipt of these benefits but in receipt of Working Tax Credit/ Child Tax Credit with an equivalised income below 60 per cent of the national median before housing costs) in an area and the score for each study participant was identified from post code of residence, using data provided by the South West Public Health Observatory (239). Scores are converted to rank scores with lower scores representing higher levels of deprivation.

4.5.2. Tumour and treatment related variables

Illness related variables included the site (supra- vs. infratentorial) and grade of the tumour (high vs. low grade) based on the revised WHO classification system (240),

the presence or absence of hydrocephalus at diagnosis, confirmed radiologically, and the use of cranial irradiation and/ or chemotherapy. Previous research suggests that higher tumour grade, presence of hydrocephalus and exposure to cranial irradiation and/or chemotherapy may be associated with poorer quality of survival (51;178;209;241-245).

4.5.3. Family related variables

All measures are well established, have good validity and reliability. All measures were questionnaire based. These measures were used in paper 2, and the Beck Depression Index (BDI-II) was used in paper 1 as a moderator of parent-reported QOL.

4.5.3.1. Symptoms of depression and anxiety in the primary carer

BDI-II (246;247) and Beck Anxiety Inventory (BAI) (248) were used to assess state mental health in the main carer. Both are 21 item scales that assess various symptoms of depression and anxiety, respectively, via a self report questionnaire.

4.5.3.2. The impact of brain tumour diagnosis and treatment on the family

The Impact on Families Scale (IFS) is an easily administered, reliable, and valid measure of a family member's perception of the effect of a child's condition on the family (249). The overall family impact summary scale was used in our analysis.

4.5.3.3. Family functioning

Family Assessment Device (FAD) was used to assess global family functioning. This is a 60 item questionnaire designed to evaluate families according to the McMaster Model of Family Functioning (250) and is made up of seven scales measuring Problem Solving, Communication, Roles, Affective Responsiveness, Affective Involvement, Behaviour Control and General Functioning. The General Functioning subscale was used in our analysis.

4.5.3.4. Coping strategies in the primary carer

Coping Health Inventory for Parents (CHIP) (251) is a 45-item self-report checklist that required parents to indicate the helpfulness of family, social and medical resources used in coping with their child with a CNS tumour. The summative total scale score was used in this analysis (252). Higher scores for this measure indicate the parent reported a greater number of coping strategies. The CHIP has been widely used to evaluate parental coping in the childhood cancer population (252-254).

4.5.3.5. Perceived helpfulness of family support

The Family Support Scale (FSS) is an instrument used to measure the degree to which different sources of support are perceived as helpful to families (255). The scale consists of 18 items across 5 weighted subscales relating to different types of support: partner-spouse (PS), relatives/ formal kinship (FK), friends/ informal kinship

(IK) and others in the family's social network; social organisation (SO); and specialised and generic professional services (PS). There is also a summative total scale score. All scores were used in the multivariate analysis.

4.5.4. Child related variables

These included measures of cognitive and behavioural/emotional outcome. All measures are well established, have good validity and reliability and have been previously used in studies of childhood cancer. Measures were either direct, face to face assessments of function or questionnaire based. These measures were used in paper 3.

Directly observed measures

4.5.4.1. Performance and verbal Intelligence quotients

Age appropriate Wechsler Intelligence scales were used to measure performance and verbal IQ (PIQ and VIQ). Wechsler Intelligence Scale for Children–Third Edition (WISC-III^{UK}) (256) was used to measure Performance and Verbal IQ in participants aged six to 16. Participants over 16 were tested with the Wechsler Abbreviated Scale of Intelligence (WASI) (257), and children ages three to five years, the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) (258). We measured VIQ and PIQ using a short form of the full IQ battery for two reasons. Firstly, we wanted to measure more specific aspects of neuropsychological

functioning such as attention and memory. Secondly, energy (on behalf of the patients) and time (on behalf of patients and testers) constraints prevented us from performing the full IQ battery. We utilised published short form norms to derive the standard scores. Second, most forms of brain damage, including that suffered by children treated for brain tumour, tend to affect performance measures more than verbal measures (though both are affected) particularly for older children/ adults and younger children in the short term(212;259). Younger children, over time, may fail to progress on the verbal scale due to impaired memory and other functions necessary for development of verbal functioning. Measuring Performance and Verbal IQ separately therefore allows for comparison between presumed 'hold tests' (those holding up better after acquired brain injury), with those more sensitive. Sensitivity of the PIQ measure is therefore not lost, which may be the case if it were to be amalgamated with VIQ in a measure of overall full-scale IQ.

4.5.4.2. Selective attention

The Test of Everyday Attention for Children (TEA-Ch) (260) was used to measure selective attention. The TEA-Ch provides measures of selective, sustained and divided attention and attention control and switching. We used the “Sky Search-visual selective attention” age scaled score which is relatively free from the influence of motor slowness in the analysis.

4.5.4.3. General memory

The Children's Memory Scale (CMS) (261) provides a measure of a child's visual and verbal learning, recall and recognition; its summary score, the General Memory Index (GMI), was used in this analysis as a global measure of memory function in children aged 5-16 years. The Wechsler Memory Scale (WMS) was used for children aged over 16 years. This is closely related to the CMS and also produces a summary GMI.

Questionnaire based measures

4.5.4.4. Executive Functioning

The Behaviour Rating Inventory of Executive Functioning (BRIEF) (262) parent questionnaire was used to measure executive functioning in children aged 5 years and older. The summary "Global Executive Composite" score was used for this analysis.

4.5.4.5. Behaviour

The Child Behaviour Checklist (CBCL) (263;264) is a well validated and widely used measure of child behaviour, can be used in children and adolescents from the age of 1.5-18 years, and was used to obtain parental rating of externalising and internalising behaviour problems in their child. It was completed by the main caregiver. The CBCL externalising scale provides a measure of under-controlled

behaviours such as aggression; the internalising scale a measure of over-controlled behaviours such as unhappiness, and withdrawal. There is a Youth Self report for self completion, but as only children and young adults from 11-18 years of age can complete it, it was not used in my analysis.

4.5.4.6. Adaptive behaviour

The Vineland Adaptive Behaviour Scales (VABS), Survey Form (265) is a parent report questionnaire and was used to attain a general measure adaptive behaviour, i.e., the daily activities required for personal and social sufficiency for all children. There are three functional domains: Communication, Daily Living Skills, and Socialization, and for children younger than 6 years an additional Motor Skills domain. We used the Adaptive Behaviour composite score, a summary of the four domains in this study.

4.5.4.7. Symptoms of depression in the child

The Birleson Depression Scale (BDS) (266;267) was used to assess symptoms of depression in the child. It is a self-report questionnaire, and can be used in children aged > 8 years. The children indicate how often they have experienced various depressive feelings, thoughts and behaviours over the past week as ‘most’, ‘sometimes’ or ‘never’.

4.5.4.8. Symptoms of anxiety in the child

The Revised Children's Manifest Anxiety Scale (RCMAS) (268) was used to assess symptoms of general anxiety. It is a 37-item self-report inventory evaluating apprehensive, oversensitivity/concentration, and physiological factors of anxiety, and can be used in children aged > 7 years.

4.5.4.9. Event related stress

The Children's Impact of Events Scale (IES) (269) is a self-report instrument that was developed to assess intrusive re-experiencing of the trauma and avoidance of trauma-related stimuli. The Impact of Events scale was initially developed for adults, but the Children's IES has proven useful for children aged > 8 years (270-272).

4.6. Statistical Analysis

4.6.1. Overview of statistical analyses

Initial statistical analysis was performed by the student using SPSS version 11-15 (SPSS inc, Chicago, IL) using appropriate parametric or non-parametric methodology. As the HUI3 MAUF had near normal distribution, while the SAUFs did not, both parametric and non-parametric analyses were applied when analysing MAUF outcomes. In some cases either patients or controls withdrew from the study, or missed a single assessment, resulting in incomplete patient-control pairing. Our policy, was to be inclusive, at the risk of causing confusion for readers. We

considered only including complete cases, but this would have meant discarding data for a significant number of patients and controls. For this reason, and for different age limits for individual measures, “n” varied, depending on the analysis performed. Because the SPSS programme did not allow for missing values (i.e. a missing t6 QOL value) without exclusion of the entire patient-control pair using repeated measures, Analyses of Variance (ANOVAs), SAS version 8.2 (SAS Inst. Inc., 1999-2001, Cary, NC, USA) was used in final analysis of PedsQL outcome. This was performed by the study statistician (LH). For the same reason un-paired analysis using Mann-Whitney U-tests was used in final analysis of HUI3 outcome. All final statistical analyses were done following advice from and under supervision of LH.

4.6.2. Comparisons between patients and controls, and changes in QOL over time

For the PedsQL, 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 assume a compound symmetry model with different variance-covariance matrix for the two groups as this gave the best fit (273). 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 (273). A 5% level of significance was used for comparison between patients and controls using the PedsQL.

When using the HUI3, in order to include all data, irrespective of complete pairing, Mann-Whitney U-tests, rather than Wilcoxon matched pairs signed rank tests were used to compare patients and controls with respect to parent and child-report SAUF. Changes in HUI3 MAUF with time were assessed using Friedman's test (3 time points) followed by Wilcoxon matched pairs signed rank tests (pairwise comparisons) (274). Although the HUI3 SAUF scores were not normally distributed, because of their interval scale properties and in keeping with other studies, means, standard deviations and ranges were used for their data summary (94;238).

To adjust for multiple testing, bearing in mind that the HUI3 has eight sub-scales/ SAUFs we chose to use a 1% significance level (275).

4.6.3. Comparison between parent- and self-report QOL

Pearson correlation, intraclass correlation (ICC) and group means differences were used to assess the relationship between parent and child PedsQL scores (273). ICC was estimated using the two-way random effects model (132). 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 (132;276).

Spearman's rank correlation, and group means differences were used to assess the relationship between parent and child reported outcomes using the HUI3 at t12. Once again, the degree of correlation was categorised as small, medium and large as detailed above (274).

4.6.4. Moderation of carer's depressive symptoms on differences between self- and parent report QOL

Spearman's correlation was used to assess the possible influence of maternal depressive symptoms on self/parent PedsQL differences (273). These analyses were carried out using the SPSS version 11 (SPSS inc, Chicago, IL). A 5% level of significance was utilised.

4.6.5. Predictors of QOL

We focused on family predictors of QOL in the first instance because of the data available on the relationship between family factors and adjustment in children with chronic disease (222;277;278) and more importantly in the context of this study, childhood cancer (including brain tumours) (223;252). We therefore prospectively investigated the relationship between parent- and child-report QOL using the PedsQL and demographic, tumour and family related variables, and then explored the predictive value of child related variables such as IQ, attention, memory,

behaviour and emotional status early after diagnosis and QOL measured using the PedsQL and HUI3 at twelve months after diagnosis. In multivariate analysis, HRQL at t1 strongly predicted HRQL at t12 (279), and was therefore carried forward in our analysis of child related variables.

Only overall QOL measured using the PedsQL Total Scale Score and HUI3 MAUF was considered when investigating the relationship between independent variables and QOL at t12

4.6.5.1. Family, demographic and illness related predictors of QOL

Univariate analyses

Separate repeated measures Analyses of Variance (ANOVAs) were used to compare the following subgroups with respect to their mean profiles of both parent and self-report PedsQL at one, six and twelve months after diagnosis: age (<13yrs vs. 13yrs≤), gender, IDACI (below vs. above median score), hydrocephalus (no vs. yes), tumour site (supra vs. Infratentorial), tumour grade (low vs. high), radiotherapy (no vs. yes), and chemotherapy (no vs. yes). Analyses were carried out using the 'mixed models' procedure in SAS (SAS Inst. Inc., 1999-2001, Cary, NC, USA) and were followed by between-group comparisons at each time point. Main effects were also calculated if no group x time interaction was suggested. Separate Pearson's correlation coefficients (r) were calculated at each time point to relate HRQL with all family variables except for the Beck Depression and Beck Anxiety Indices, which

were not normally distributed; and for which Spearman's rank correlation coefficients (r_s) were used.

Multivariate analysis

Multiple regression analysis was used to determine which variables were independently related to QOL measured using the PedsQL at t12. Given the relatively small sample size, we included only variables suggested in the univariate analyses. A 5% level of significance was used.

4.6.5.2. Child related predictors of QOL

A series of univariate regression analyses were undertaken to determine which of the child variables measured at t1 were most strongly related to QOL at t12. Variables significant at the 10% level were considered appropriate for inclusion into a multiple regression model, together with tumour site and QOL at t1, as these had been shown to be related to QOL in our previous paper (279). We then eliminated non-significant variables in a backwards fashion, but using all available cases at each step. Model checking included individually adding in all the other predictor variables (i.e., not just those identified from the univariate analysis), to check that none would significantly "improve" the model.

5. RESULTS

5.1. Summary of results

5.1.1. Participants

Of the 48 patients eligible for the study, three declined to participate. 45 patients were recruited to the CLIC Sargent Brain Tumour Study. Table 5.1 contains selected demographic, disease and treatment characteristics of all patients recruited to the study. Of those patients recruited, seven died before t12 assessment and one patient was too young for HRQL using the PedsQL assessment at any time-point. There were therefore 37 patients used to compare parent report QOL using the PedsQL in patients with that in controls. Because the lower age limit for self report was 5 years, compared with two years for parent report, there were 27 patients for self-report PedsQL(273). Two patients withdrew following t1 assessment. For investigation of predictors of QOL at t12, only those patients who completed t12 assessment were included. There were therefore 35 patients included in this analysis using the PedsQL. Numbers included for other analyses, as well as demographic, diagnosis and treatment details for patients eligible for analysis for the four papers from the study are available in table form in the published papers (273;274;279;280)

The median age at diagnosis was 9.1 years (range 1.5-16.4), 9.3 years (range 1.8-16.6) at t1 and 10.4 (2.6-17.6) at t12. Median time from definitive diagnosis to t1 assessment in the tumour patients was 1.8 months (range 0.8 – 5.0 months), and to

t12 assessment 13.8 months (range 11.2 – 18.7 months). The complexity of post-operative management was the main cause of delay in completing t1 assessments. Follow up assessments were undertaken approximately 6 and 12 months after t1 to avoid practice effects for cognitive measures (i.e., performance and verbal IQ, attention and memory).

Table 5.1: Demographic, disease and treatment characteristics of all patients recruited to the CLIC Sargent Brain Tumour Study

Age at Diag.	Age at t1	Age at t12	Gender	Tumour type	Surgery	Hydro-cephalus	Tumour site	Tumour grade	Radio-therapy	Chemo-therapy	Rank of IDACI
6.2	6.4	7.4	F	Right occipital ependymoma	GTR	N	S	H	Y	Y	7096
2.6	2.7	3.7	M	Cerebellar LG astrocytoma	GTR	Y	I	L	N	N	28254
15.3	15.5	N[2]	F	Cerebellar LG astrocytoma	STR	Y	I	L	Y	Y	19529
1.9	2.0	2.9	M	Cerebellar ependymoma	STR	N	I	H	N	Y	11757
12.3	12.5	13.5	M	Pineal germ cell tumour	Biopsy	Y	S	H	Y	Y	28768
7.6	7.7	8.8	F	Cerebellar LG astrocytoma	STR	Y	I	L	Y	N	30129
16.5	16.6	N[1]	M	Medulloblastoma	STR	Y	I	H	Y	Y	16400
3.6	3.9	5.1	F	Cerebellar LG astrocytoma	STR	Y	I	L	N	N	10713
0.6	0.8	N[2]	M	Fourth ventricle choroid plexus carcinoma	STR	N	I	H	N	Y	27209
12.7	12.8	13.9	F	Pineal LG astrocytoma	Biopsy	Y	S	L	N	N	17408
1.5	1.8	2.6	F	Cerebellar LG astrocytoma	GTR	Y	I	L	N	N	8
12.0	12.2	13.1	M	Pineal germ cell tumour	Biopsy	Y	S	H	Y	N	31853
11.1	11.3	12.4	M	Medulloblastoma	STR	Y	I	H	Y	Y	20569
7.5	7.7	8.7	F	Medulloblastoma	STR	Y	I	H	Y	Y	12869
14.8	15.0	16.3	M	Right parietal HG astrocytoma	STR	Y	S	H	Y	Y	10914
4.0	4.2	5.1	M	Hypothalamic LG astrocytoma	STR	Y	S	L	N	N	23852

13.8	13.9	14.9	M	Right parietal LG astrocytoma	STR	N	S	L	N	N	23391
1.6	1.7	N[2]	F	Atypical teratoid rhabdoid tumour	GTR	Y	S	H	N	Y	21213
5.8	6.0	6.9	M	Left peri-ventricle LG astrocytoma	Biopsy	N	S	L	Y	N	23783
2.2	2.7	3.2	M	Left lateral ventricle choroid plexus papilloma	GTR	Y	S	L	N	N	17838
16.2	16.5	17.3	M	Pituitary germ cell tumour	Biopsy	N	S	H	Y	N	12533
6.4	6.8	N[2]	F	Right lateral ventricle HG astrocytoma	GTR	Y	S	H	Y	Y	19850
12.0	12.2	N[2]	M	Left thalamic HG astrocytoma	STR	Y	S	H	Y	Y	23217
1.5	1.8	2.8	M	Left frontal-parietal ependymoma	GTR	N	S	H	N	Y	18551
14.1	14.2	15.3	F	Left frontal parafalcine atypical meningioma	STR	N	S	L	N	N	18985
3.6	3.8	N[2]	F	Bithalamic HG astrocytoma	Biopsy	Y	S	H	N	Y	3095
13.5	13.7	14.6	M	Pineoblastoma	STR	Y	S	H	Y	Y	6311
9.1	9.3	10.3	M	Right frontal-parietal ependymoma	GTR	N	S	H	N	N	23910
0.2	0.4	1.3	F	Right lateral ventricle choroid plexus papilloma	GTR	Y	S	L	N	N	20576
13.1	13.2	14.2	F	Optic nerve LG astrocytoma	STR	N	I	L	Y	N	25870
6.4	6.4	7.7	F	Fourth ventricle ependymoma	GTR	Y	I	H	Y	N	NA
9.2	9.3	10.4	F	Hypothalamic LG astrocytoma	STR	Y	S	L	Y	N	28860
4.2	4.3	5.3	F	Cerebellar LG astrocytoma	GTR	Y	I	L	N	N	28912
14.4	14.5	N[1]	F	Medulloblastoma	GTR	Y	I	H	Y	Y	9176

9.6	9.7	10.7	F	Craniopharyngioma	STR	N	S	L	Y	N	10220
11.8	12.0	12.9	M	Craniopharyngioma	STR	Y	S	L	Y	N	25251
11.6	11.7	12.7	F	Hypothalamic LG astrocytoma	STR	Y	I	L	Y	Y	28240
16.4	16.6	17.6	M	Cerebellar HG astrocytoma	STR	Y	I	H	Y	Y	NA
8.7	8.9	9.9	F	Cerebellar LG astrocytoma	STR	Y	I	L	N	N	16160
15.9	16.0	17.0	F	Cerebellar LG astrocytoma	STR	Y	I	L	Y	N	12614
3.7	3.9	4.9	F	Cerebellar LG astrocytoma	GTR	N	I	L	N	N	12733
7.6	7.8	8.8	M	Cerebellar LG astrocytoma	GTR	Y	I	L	N	N	3963
7.8	8.1	N[2]	M	Right lateral ventricle HG astrocytoma	STR	Y	S	H	Y	Y	25108
9.2	9.4	10.4	F	Medulloblastoma	STR	Y	I	H	Y	Y	16723
15.2	15.3	16.3	M	Cerebellar LG astrocytoma	STR	Y	I	L	Y	N	21504

Abbreviations: Diag, diagnosis; t1, one month assessment; t12, 12 month assessment; female; M, male; LG, low grade; HG, high grade; GTR, gross total resection; STR, sub-total resection; S, supratentorial; I, infratentorial; Y, yes; N, No .Reasons for N: 1,withdrew from study; 2, died before t12 assessment; NA, Not available

5.1.2. Details of patients excluded from analysis

Of the three families unwilling to take part in the study, one declined to participate as their child was already enrolled on a longitudinal cohort study (the Avon Longitudinal Study of Parents and Children (ALSPAC) study) in which the health and development of the children enrolled have been followed in great detail since birth, and the family did not feel able to participate in another study. No reason was given for refusal to enrol for the other two eligible patients.

The characteristics of the seven patients who died following t1 assessment, but before t12 assessment, were as follows: median age 6.4 years (range 0.6-15.3 years); four female patients; three patients with high grade astrocytomas, one with fibrillary astrocytoma of the posterior fossa, one with bi-thalamic grade 2 oligo-astrocytoma, one parietal ATRT and one with choroid plexus carcinoma. All died as a result of disease progression.

The ages of the patients who withdrew from the study after t1 assessment were 16.5 and 14.4 years at diagnosis. One was female, and both were diagnosed with medulloblastoma.

5.1.3. Summary of published papers submitted in support of the authors PhD

5.1.3.1. Paper 1: 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 (273).

Objectives: The objective of this manuscript was to measure HRQL in children with brain tumours one, six and twelve months after diagnosis and compare HRQL with normal controls. In addition, we aimed to investigate the relationship between parent- and self-reported HRQL in both brain tumour patients and controls. We also aimed to assess the relationship between parental depression and differences in parent- and self-reported HRQL

Patients and Methods: This was a prospective, longitudinal study of children sequentially diagnosed with a primary brain tumour at a regional neuro-oncology unit in South West England (Frenchay Hospital) from April 2003 to April 2005. All patients alive one year after diagnosis and all controls for which data was available were included in the analysis. HRQL in patients and controls was assessed using the PedsQL core parent- and self-report inventories.

For both parent- and self-report, HRQL in patients was compared to controls using repeated measures analysis of variance, compound symmetry model using the 'Proc

MIXED' procedure in SAS version 8.2 (SAS Inst. Inc., 1999-2001, Cary, NC, USA). Product moment correlation, intraclass correlation and comparison of group mean were used to evaluate the relationship between self- and parent-report. Spearman's correlation was used to moderate for parental depressive symptoms when comparing self- and parent-rated HRQL. These analyses were carried out using the SPSS version 11 (SPSS inc, Chicago, IL).

Results: For comparison of HRQL between patients and controls, 37 tumour patients and 42 controls were included in analysis of parent-report, and 27 tumour patients and 31 controls in self-report. Fig 5.1 shows differences in HRQL between patients and controls for PedsQL summary scores. 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 were variable and less marked. While statistically significant differences were present for all summary scores and the school domain at t1, only the physical summary score was statistically significantly decreased for patients at t12.

There was a statistically significant improvement in parent- and self-report HRQL over time for all summary scores with the exception of the self-report psychosocial summary score. The most marked improvement in HRQL for patients was seen in the first six months after diagnosis (between t1 and t6). There was no significant

difference in HRQL over time for any parent- or self-report PedsQL scores for controls.

Agreement between self- and parent-rated HRQL for patients was variable. Agreement was best at t1, and worst at t12. For patients, agreement between parent and child rated HRQL was better for the more observable (physical), compared with less observable (psychosocial) domains. In contrast with patients, agreement between self- and parent-reported HRQL was better for the psychosocial than physical domains. Parents rated their child's HRQL lower than their child did, with group means scores, in general lower for parent-report than self-report HRQL for patients. The opposite was true for controls.

There was no consistent relationship between parental depressive symptoms and differences in self- and parent-reported HRQL for patients or controls.

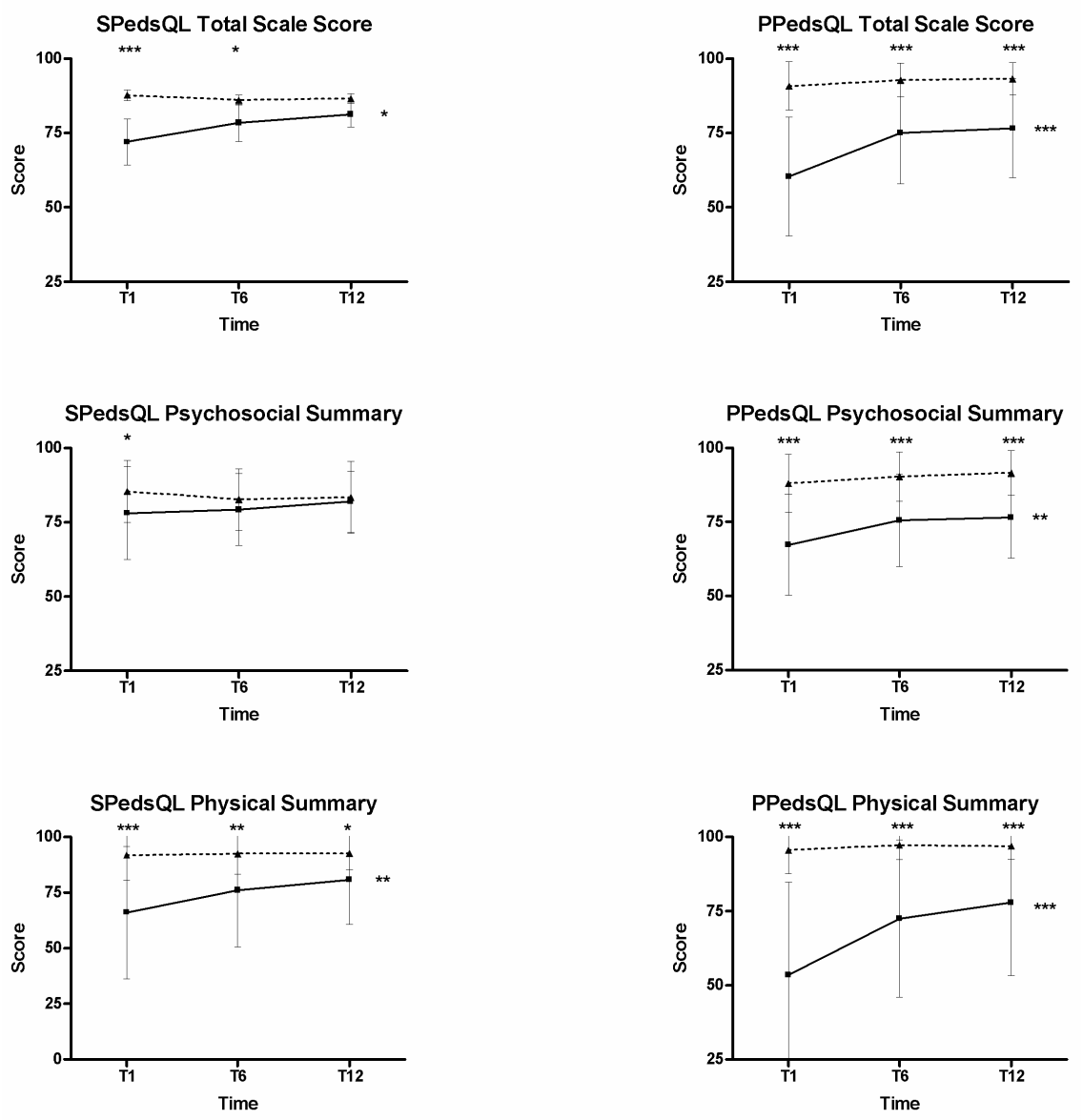

Figure 5.1 Self and parent-report PedsQL summary showing group means and standard deviations. — Represents children with brain tumours, --- represents controls;*, p<0.05; **, p<0.01; ***, p<0.001.

Table 5.2 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*	R	ICC	PedsQL	N	Mean bias[a]	R	ICC
Brain Tumour Children					**Brain Tumour Children**					**Brain Tumour Children**				
Total scale score	26	10.52***	0.79***	0.78***	Total scale score	25	5.40*	0.76***	0.74***	Total scale score	27	3.28	0.66***	0.61***
Physical health	26	10.17*	0.79***	0.79***	Physical health	25	6.49*	0.86***	0.85***	Physical health	27	0.94	0.87***	0.85***
Psychosocial health	26	9.71**	0.73***	0.72***	Psychosocial health	25	5.56	0.54**	0.53**	Psychosocial health	27	4.26	0.13	0.13
Emotional function	26	14.04*	0.36*	0.35*	Emotional function	25	12.40**	0.39	0.39*	Emotional function	27	8.70*	0.23	0.23
Social function	26	7.11*	0.65***	0.64***	Social function	25	5.00	0.53**	0.48**	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***	0.73***	Total scale score	27	-6.48	0.34	0.33*	Total scale score	31	-6.63	0.39*	0.35*
Physical health	28	-3	0.74***	0.72***	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***	0.68***	Psychosocial health	27	-7.16	0.42*	0.42*	Psychosocial health	31	-8.12	0.36	0.32*
Emotional function	28	-0.89	0.51**	0.50**	Emotional function	27	-3.15	0.37	0.37*	Emotional function	31	-4.19	0.24	0.24
Social function	28	-3.39	0.58**	0.58**	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***	0.68***	School function	27	-6.11	0.44*	0.44*	School function	31	-11.60	0.35	0.33*

Abbreviations: T1, One month assessment, T6, six month assessment; T12, twelve month assessment; PedsQL, Pediatric Quality of Life inventory 4.0; R, Pearson Product-moment correlation; ICC, Intraclass correlation

a Child group mean - parent group mean;

* p<0.05

** p<0.01

*** p<0.001

Conclusions: HRQL was, for the first time measured prospectively in brain tumour patients, demonstrating the feasibility of performing such assessments in the first year after diagnosis. Unsurprisingly, HRQL in patients was compromised, but improved over time. Agreement between self- and parent-rated HRQL was inconsistent and varied over time, confirming that parents and their children do not regard HRQL in a similar way. Possible reasons for this lack of agreement include differences in child and parent's interpretation of events, adaptive style, response style, child personality and parental emotional status. Because of such disagreement, additional outcomes, such as cognition, HS, psychological status and behaviour should be measured in order to better quantify QOS in this population.

Paper 2: Family, demographic and illness related determinants of HRQL in children with brain tumours in the first year after diagnosis (279).

Aims: The aims were to evaluate the relationship between parent- and child-report HRQL and demographic, tumour and family variables in children with a brain tumour in the first year after diagnosis and to identify family, demographic and illness related determinants of HRQL at twelve months after diagnosis.

Patients and Methods: This was a prospective, longitudinal study of children sequentially diagnosed with a primary brain tumour at a regional neuro-oncology unit in South West England (Frenchay Hospital) from April 2003 to April 2005. Semi-structured interviews took place approximately one, six and twelve months after diagnosis. All patients who completed the twelve month assessments were included in the analysis. Overall HRQL, dependant variable for the study, was measured using the self- and parent-report PedsQL 4.0 Total Scale Score.

Univariate analyses were used at all three time points, and to identify potential early demographic, tumour and family predictors of HRQL at one year. Separate repeated measures Analyses of Variance (ANOVAs) were used to compare the following subgroups with respect to their mean profiles of both parent and self-report PedsQL at t1, t6 and t12: age (<13yrs vs. 13yrs$\leq$), gender, IDACI (below vs. above median score), hydrocephalus (no vs. yes), tumour site (supra vs. Infratentorial), tumour grade (low vs. high), radiotherapy (no vs. yes), and chemotherapy (no vs. yes).

Analyses were carried out using the 'mixed models' procedure in SAS (SAS Inst. Inc., 1999-2001, Cary, NC, USA) and were followed by between-group comparisons at each time point. Main effects were also calculated if no group x time interaction was suggested. Separate Pearson's correlation coefficients (r) were calculated at each time point to relate HRQL with all family variables except for the Beck Depression and Beck Anxiety Indices, which were not normally distributed; and for which Spearman's rank correlation coefficients (r_s) were used.

Regression analysis was then used to identify independent early determinants of HRQL at one year after diagnosis. A 5% level of significance was used throughout.

Results: Thirty-five patients and their caregivers completed the twelve month interviews.

There were no significant relationships between parent- or self-report HRQL at twelve month assessment and gender, age at diagnosis or IDACI score at any time point. Treatment with radio- or chemotherapy correlated with child–report HRQL only at some time points.

Figure 5.2 illustrates the relationship between tumour and treatment variables and HRQL over time. Correlates between family/ carer related-variables and HRQL in patients can be seen in Table 5.3. There were consistent significant negative

correlations between concurrent family impact of illness and parent and self-report HRQL, and positive correlations between concurrent family support and parent-report HRQL. HRQL at one month correlated significantly with HRQL at twelve months for both parent- and self-report.

Multivariate analysis showed infratentorial tumour site, and poor HRQL at one month best predicted poor self- and parent-report HRQL at twelve months.

Conclusions: Children with infratentorial tumours and poor HRQL early after diagnosis tend to have poor HRQL at one year. While family factors are important modulators of concurrent HRQL, they do not appear important in predicting HRQL twelve months after diagnosis in children with primary intracranial tumours.

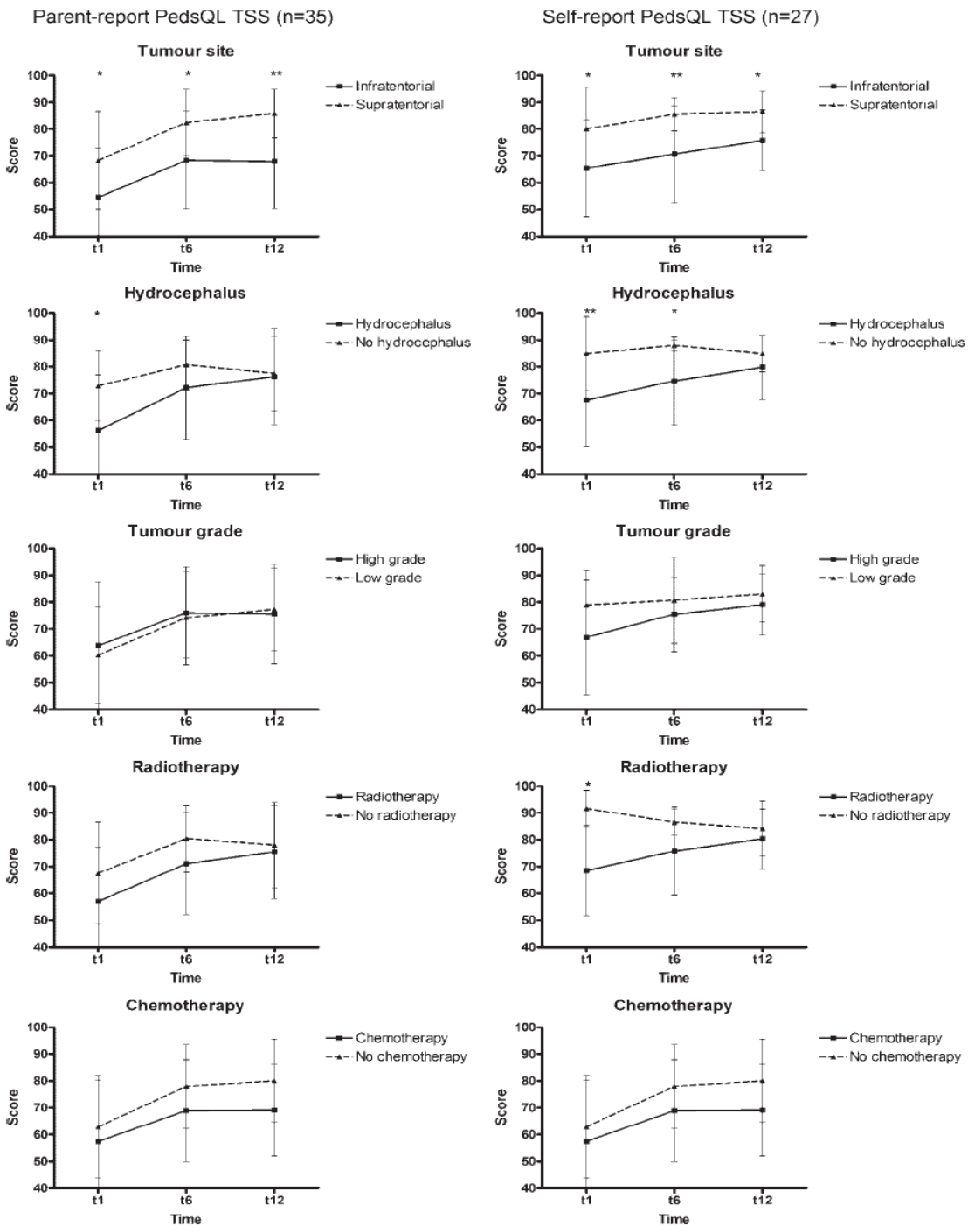

Figure 5.2 Self- and parent-report PedsQL total scale score showing group means and standard deviations for tumour and treatment variables. *, p<0.05; **, p<0.01; ***, p<0.001

Table 5.3 Correlates between family/ carer variables and HRQL in patients: r, unless r_s indicated

	BDI II (r_s)	BAI (r_s)	IFS	CHIP total	FAD general functioning	FSS total	FSS Partner/ spouse	FSS Informal kinship	FSS Formal kinship	FSS Social organisations	FSS Professional services
Concurrent correlations between family and carer variables and HRQL at t1, t6 and t12											
t1 variables and t1 HRQL											
PPedsQL	-0.21	-0.24	-0.45*	0.25	0.09	0.17	0.15	0.08	0.06	0.30	-0.05
	n=33	n=31	n=30	n=33	n=31	n=33	n=33	n=33	n=33	n=33	n=33
SPedsQL	-0.03	-0.14	-0.53**	0.21	0.07	0.02	0.04	-0.13	-0.02	0.30	0.05
	n=24	n=23	n=23	n=24	n=23	n=23	n=24	n=24	n=24	n=24	n=24
t6 variables and t6 HRQL											
PPedsQL	-0.45**	-0.43*	-0.47**	-0.02	-0.02	0.59***	0.25	0.65***	0.35*	0.60***	0.18
	n=33	n=33	n=34	n=33	n= 32	n=33	n=33	n=33	n=33	n=33	n=33
SPedsQL	-0.25	-0.19	-0.54**	-0.20	0.15	0.43*	0.23	0.47*	0.02	0.38	0.29
	n=25	n=25	n=25	n=25	n=25	n=25	n=25	n=25	n=25	n=25	n=25
t12 variables and t12 HRQL											
PPedsQL	-0.25	-0.00	-0.55***	0.21	-0.13	0.58***	0.29	0.55**	0.46**	0.39*	0.17
	n=34	n=34	n=35	n=34	n=33	n=34	n=34	n=34	n=34	n=34	n=34
SPedsQL	-0.35	0.08	-0.42*	0.09	-0.20	0.34	0.27	0.34	0.16	0.32	-0.00
	n=27	n=27	n=27	n=27	n=27	n=27	n=27	n=27	n=27	n=27	n=27
Early family and carer correlates of HRQL at one year											
t1 variables and t12 HRQL											
PPedsQL	-0.07	-0.20	-0.16	0.016	0.04	0.12	0.13	0.05	0.01	0.14	0.03
	n=35	n=33	n=32	n=34	n=33	n=35	n=35	n=35	n=35	n=35	n=35
SPedsQL	0.06	-0.17	-0.17	0.04	-0.07	0.08	0.24	-0.11	-0.30	0.15	0,18
	n=27	n=26	n=26	n=27	n=26	n=27	n=27	n=27	n=27	n=27	n=27

*P<0.05, **p<0.01, ***p<0.001. Abbreviations: HRQL, health related quality of life; r, Pearson's correlation coefficient; r_s, Spearman's correlation coefficient; t1, one month assessment; t6, six month assessment; t12, 12 month assessment; PPedsQL, parent-report PedsQL; SPedsQL, self-report PedsQL; BDI II, Beck Depression Inventory II; BAI, Beck Anxiety Inventory; IFS, Impact on Family Scale; CHIP, Coping Health Inventory for Parents; FAD, Family Assessment Device; FSS, Family Support Scale.

Paper 3: Child related determinants of Health Related Quality of Life in children with brain tumours in the first year after diagnosis (280).

Aims : Infratentorial tumour site and health related quality of life (HRQL) one month after diagnosis were shown to predict HRQL one year after diagnosis in children with brain tumours. This manuscript described additional early child- related potential determinants of parent- and child-report HRQL.

Patients and methods: The methodology was the same as in paper 2. In addition to the self- and parent-report PedsQL Total Scale Score, the HUI3 MAUF was used to measure overall HRQL. Early child-related variables included performance and verbal IQ, general memory, selective attention, executive function, behaviour problems, adaptive behaviour, symptoms of depression and anxiety and event related anxiety. Univariate analyses were used to identify potential early predictors of HRQL. Regression analysis was then used to identify the most important determinants of HRQL at one year.

Table 5.4 Univariate regression analysis using one month child-related variables to predict overall HRQL at one year.

	Dependent variables at one year after diagnosis			
	PPedsQL t12	**SPedsQL t12**	**PHUI3 t12**	**SHUI3 t12**
Independent variables (all measured at t1)	B Coefficient (SE) n p			
PPedsQL t1	0.48 (0.12) n=33 p=0.001	NA	NA	NA
SPedsQL t1	NA	0.36 (0.10) n=24 p=0.002	NA	NA
PHUI3 t1	25.6 (8.0) n=26 P=0.004	NA	0.46 (0.15) n=26 p=0.004	NA
Performance IQ	0.41 (0.18) n=29 p=0.027	0.22 (0.11) n=26 p=0.052	0.0087 (0.0028) n=28 p=0.004	0.0063 (0.0020) n=21 p=0.005
Verbal IQ	0.40 (0.19); n=29 p=0.048	0.22 (0.12); n=26 0.076	0.0063 (0.0032); n=28 p=0.062	0.0032 (0.0028); n=21 p=0.26
TEA-Ch (Sky search) Selective attention	2.23 (0.95) n=20 p=0.030	1.23 (0.60) n=20 p=0.054	0.0489 (0.0148) n=20 p=0.004	0.016 (0.008) n=18 p=0.072
CMS/ WMS General memory	0.25 (0.14) n=21 p=0.090	0.17 (0.09) n=21 p=0.064	0.0017 (0.0026) n=21 p=0.52	0.0011 (0.0010) n=19 p=0.28
BRIEF GEC Executive Function	-0.08 (0.36) n=20 p=0.83	-0.24 (0.20) n=20 p=0.26	-0.0010 (0.0061) n=20 p=0.88	-0.0012 (0.0031) n=18 p=0.70
VABS composite Adaptive behaviour	0.50 (0.15) n=34 p=0.003	0.20 (0.12) n=26 p=0.11	0.0059 (0.0028) n=28 p=0.045	0.0019 (0.0016) n=20 p=0.26
CBCL Internalising behaviour problems	-0.41 (0.31) n=33 p=0.20	-0.24 (0.23) n=25 p=0.30	-0.0049 (0.0058) n=27 p=0.41	-0.0009 (0.0030) n=20 p=0.77

CBCL externalising behaviour problems	-0.10 (0.26) n=33 p=0.69	-0.26 (0.18) n=25 p=0.17	0.0002 (0.0049) n=27 p=0.96	-0.0001 (0.0026) n=20 p=0.97
BDS Depressive symptoms	-0.68 (0.84) n=20 p=0.43	-0.40 (0.52) n=20 p=0.45	-0.0020 (0.0148) n=20 p=0.89	0.0007 (0.0061) n=19 p=0.91
RCMAS Anxiety symptoms	-0.87 (0.33) n=21 p=0.015	-0.43 (0.21) n=21 p=0.057	-0.0102 (0.0062) n=21 p=0.12	-0.0025 (0.0029) n=19 p=0.41
IES Event related stress	0.26 (0.40) n=21 p=0.53	0.07 (0.25) n=21 p=0.78	0.0076 (0.0068) n=21 p=0.28	-0.0012 (0.0030) n=19 p=0.69

Abbreviations: SE, Standard error; t1, one month assessment; t12, 12 month assessment; PedsQL, Pediatric Quality of Life Inventory; HUI3, Health Utilities Index Mark 3; PPedsQL, parent-report PedsQL; SPedsQL, self-report PedsQL; PHUI3, parent-report HUI3; SHUI, self-report HUI3; PIQ, Performance Intelligence Quotient; VIQ, Verbal Intelligence Quotient; TEA-Ch, Test Of Everyday Attention for Children; CMS, Children's Memory Scales; WMS, Wechsler Memory Scale; BRIEF GEC; The Behaviour Rating Inventory of Executive Functioning Global Executive Composite; VABS, Vineland Adaptive Behaviour Scales; BDS, Birleson Depression Scale; RCMAS, Revised Children's Manifest Anxiety Scales; IES, (Children's) Impact of Events Scale.

Results: Thirty-five patients completed the twelve month interviews. The results for univariate analysis can be seen in Table 5.4.

Multivariate analysis, details of which can be seen in Table 5.5, showed that infratentorial tumour site remained an important determinant of HRQL one year after diagnosis. Infratentorial tumour site and selective attention at one month generally best predicted poor self- and parent-report HRQL at one year. Adaptive behaviour was important in predicting parent report HRQL using both the PedsQL total scale score and the HUI3 MAUF. For self-report HUI3 MAUF at one year, only Performance IQ was statistically significant.

Conclusions: Selective attention and infratentorial tumour site were most important in predicting both parent- and self-report HRQL one year after diagnosis. Both selective attention and adaptive behaviour early after diagnosis may be more important determinants of HRQL at one year than HRQL early after diagnosis. Shared method variance may account for this as the VAB is parent reported.

Measuring emotional health and cognitive outcomes in children is challenging: for many of their constructs (i.e. RCMAS, BDS, TEA-Ch and CMS), questionnaires are not suitable or available for those most likely to be most affected, namely the younger children and infants. One is therefore forced to either ignore these children, or rely on proxy-report measures. In our study we have tried to be inclusive, and therefore recruited children of all ages, despite there being, for some constructs, no age appropriate measures.

The power of this study was reduced by the patient sample size and the heterogeneous nature of the sample, but the findings were strengthened by the similar results using two different parent- and child report HRQL measures.

Larger prospective studies are needed to confirm these findings. Cognitive remediation and/ or pharmacological intervention, particularly aimed at children with infratentorial tumours may improve attention and subsequently HRQL and both merit further investigation.

Table 5.5 Multivariate regression model for child-related predictors of HRQL at one year after diagnosis

	Variable	Regression coefficient (SE)	p
PPedsQL t12	Tumour site (0=infra, 1= supra)	18.7 (4.3)	p=0.001
Final model (n=20)	TEA-Ch SS (selective attention) t1	2.05 (0.57)	p=0.002
	VABS (adaptive composite) t1	0.32 (0.14)	p=0.034
	Constant	23.7 (12.4)	
SPedsQl t12	Tumour site (0=infra, 1= supra)	13.9 (2.9)	p<0.001
Final model (n=20)	TEA-Ch SS (selective attention) t1	1.19 (0.40)	p=0.009
	Constant	64.9 (3.8)	
PHUI3 t12	Tumour site (0=infra, 1= supra)	0.16 (0.09)	p=0.089
Final model (n=20)	TEA-Ch SS (selective attention) t1	0.0459 (0.0116)	p=0.001
	VABS (adaptive composite) t1	0.0067 (0.0028)	p=0.031
	Constant	-0.28 (0.25)	
SHUI3 t12	PIQ t1	0.0063 (0.0020)	p=0.005
Final model (n=21)	Constant	0.26 (0.18)	

t1, one month assessment; t12, 12 month assessment; PedsQL, Pediatric Qualitiy of Life Inventory; HUI3, Health Utilities Index Mark 3; PPedsQL, parent-report PedsQL; SPedsQL, self-report PedsQL; PHUI3, parent-report HUI3; SHUI, self-report HUI3; PIQ, Performance Intelligence Quotient; TEA-Ch, Test Of Everyday Attention for Children; VABS, Vineland Adaptive Behaviour Scales

Paper 4: A detailed prospective longitudinal assessment of health status in children with brain tumours in the first year after diagnosis (274)

Aims: The aims were to compare HS and overall HRQL in children with brain tumours one, six and twelve months after diagnosis with normal controls and to assess the relationship between parent- and self-report HS for patients at t12.

Patients and methods: HS was assessed using the HUI3 parent-report at all time points and self-report at 12 months after diagnosis. Self-report HUI3 was not utilised at t1 or t6. The importance of attaining both parent-and self-report measures of outcome emerged over time and at t12 both were utilised where applicable. All patients and controls who completed t12 interviews were included in the analyses. 29 patients and 32 controls were included in analysis of parent-report, and 21 patients and 22 controls in self-report HS at t12. Non-parametric analyses were used throughout as none of the SAUFs were normally distributed.

Results: Overall HRQL using the HUI3 MAUF. Patients scored significantly lower than controls for global overall HRQL using the HUI3 MAUF at all time-points for parent-report and at one year after diagnosis for self-report (p max 0.009). Table 5.6 shows parent-report for all time points and self-report for twelve month HUI3 MAUF scores for patients and controls.

There were significant changes in parent-report HUI3 MAUF for patients across the 3 time points with a statistically significant increase between t1 and t6 (p=0.006, n=26 pairs), but not

between t6 and t12 (p=0.74, n=26 pairs). There was no significant change in overall HS with time in controls (P=0.12, n = 26 complete sets).

A higher percentage of patients than controls had scores in the moderate/ severe levels of disability for overall HRQL at all time points using parent, and at twelve months using self-report HUI3 MAUF.

Differences in single attributes of HS between patients and controls. Table 5.7 shows parent-report for all time points and self-report for t12 HUI SAUF scores for patients and controls. For parent-report, patients scored significantly lower than controls in the attributes of emotion, cognition and pain at one and six months, in ambulation at one month and in dexterity at six months. At one year, the difference was statistically significant for parent-report cognition only (all $p<0.01$). No attributes reached significance for self-report at one year.

The incidence of moderate/ severe levels of disability for single attributes in patients and controls can be seen in Table 5.7. A higher percentage of patients than controls had scores in the moderate/ severe levels of disability for SAUFs. In general, there were fewer scores in the moderate or severe range at t12 than at t1 or t6.

Table 5.6 HUI3 MAUF parent-report scores one, six and twelve months and self-report at twelve months after diagnosis.

HUI3 MAUF	N	Mean	SD	Range	Moderate/severe N (%)	P value (patients vs. Controls)
Parent-report						
Brain tumours t1	26	0.53	0.36	-0.22-1.00	21 (81)	<0.001
Controls t1	29	0.95	0.08	0.70-1.00	6 (29)	
Brain tumours t6	26	0.72	0.28	0.13-1.00	16 (62)	<0.001
Controls t6	28	0.98	0.06	0.68-1.00	1 (4)	
Brain tumours t12	29	0.74	0.29	-0.15-1.00	18 (62)	<0.001
Controls t12	32	0.96	0.09	0.63-1.00	4 (13)	
Self-report						
Brain tumours t12	21	0.84	0.21	0.06-1.00	10 (48)	0.009
Controls t12	22	0.94	0.13	0.56-1.00	3 (14)	

Abbreviations: HUI3, Health Utilities Index Mark 3; MAUF, Multi Attribute Utility Function; t1, one month assessment; t12, 12 month assessment.

Table 5.7 Comparison of HUI3 Single Attribute Utility Functions between brain tumour patients and controls and the prevalence of moderate/ severe disability

	Brain tumour children				Controls				
HUI/3 SAUF	N	Mean	SD	Moderate/ severe N (%)	N	Mean	SD	Moderate/ severe N (%)	P value (patients vs. Controls)
Parent-report t1									
Vision	26	0.96	0.11	2 (8)	29	0.99	0.02	0	0.521
Hearing	26	1.00	0.00	0	29	1.00	0.00	0	1.00
Speech	26	0.93	0.21	3 (12)	29	0.99	0.05	0	0.275
Ambulation	26	0.74	0.37	8 (31)	29	1.00	0.00	0	<0.001
Dexterity	26	0.88	0.28	4 (15)	29	1.00	0.00	0	0.014
Emotion	26	0.93	0.10	4 (15)	29	0.99	0.02	0	<0.001
Cognition	26	0.85	0.20	8 (31)	29	0.98	0.07	1 (3)	0.002
Pain	26	0.75	0.34	11 (42)	29	0.98	0.07	3 (10)	<0.001
Parent-report t6									
Vision	26	1.00	0.01	0	28	0.99	0.02	0	0.705
Hearing	26	1.00	0.00	0	28	1.00	0.00	0	1.00
Speech	26	0.97	0.08	1 (4)	28	1.00	0.00	0	0.033
Ambulation	26	0.85	0.32	5 (19)	28	1.00	0.00	0	0.016
Dexterity	26	0.90	0.23	4 (15)	28	1.00	0.00	0	0.008
Emotion	26	0.96	0.08	2 (8)	28	1.00	0.00	0	0.004
Cognition	26	0.92	0.09	2 (8)	28	1.00	0.00	0	<0.001
Pain	26	0.89	0.15	8 (31)	28	0.98	0.10	1 (4)	0.002
Parent-report t12									
Vision	29	0.97	0.09	2 (7)	32	1.00	0.01	0	0.330
Hearing	29	0.96	0.13	2 (7)	32	1.00	0.00	0	0.134
Speech	29	0.98	0.07	1 (3)	32	1.00	0.00	0	0.064
Ambulation	29	0.91	0.26	3 (10)	32	1.00	0.00	0	0.031
Dexterity	29	0.95	0.14	2 (7)	32	0.98	0.10	1 (3)	0.141
Emotion	29	0.97	0.07	2 (7)	32	0.99	0.05	1 (3)	0.056
Cognition	29	0.86	0.19	8 (28)	32	0.98	0.06	1 (3)	<0.001
Pain	29	0.90	0.21	6 (21)	32	0.98	0.06	2 (6)	0.018
Self-report t12									
Vision	21	0.98	0.09	1 (5)	22	0.99	0.02	0	0.904
Hearing	21	0.98	0.11	1 (5)	22	1.00	0.00	0	0.306
Speech	21	0.98	0.05	0	22	1.00	0.00	0	0.143
Ambulation	21	0.94	0.19	1 (5)	22	1.00	0.00	0	0.069
Dexterity	21	0.95	0.12	1 (5)	22	0.98	0.12	1 (5)	0.045
Emotion	21	0.97	0.04	0	22	0.98	0.06	1 (5)	0.487
Cognition	21	0.92	0.11	3 (14)	22	0.97	0.09	2 (9)	0.012
Pain	21	0.94	0.22	1 (5)	22	0.99	0.03	0	0.369

Abbreviations: HUI3, Health Utilities Index Mark 3;SAUF, Single Attribute Utility Function; t1, one month assessment; t6, six month assessment; t12, 12 month assessment.

We have previously reported a significant relationship between tumour site and parent-and self-report HUI3 MAUF at t12 (280). There were no significant correlations between HUI3 SAUFs and any other independent variables analysed ($p>0.01$ for all, data not shown).

For patients, correlations between parent and self-report were good ($r_s>0.73$) for all HUI3 scores with the exception of emotion and pain. This can be seen in Table 5.8.

Conclusions: HS is significantly compromised in children with brain tumours over the first year after diagnosis, but improves with time. Nevertheless, the number of parent- and self-report overall HS (HUI3 MAUF) in the moderate/ severe range, indicating a moderate or severe level of overall global disability, remained high at 62% and 48% respectively at twelve months after diagnosis.

While clinically meaningful differences of 0.05 (105) between mean scores for patients and controls were present for the parent-report SAUFs of pain and ambulation an average of twelve months after diagnosis, differences did not reach statistical significance. This is most likely due to the relatively small sample size in this study. This was also true for the SAUFs of ambulation, cognition and pain for self-report HS.

The relatively high reporting of moderate/ severe levels of disability for single attributes, particularly that of pain at one and six months after diagnosis is concerning, and supports the incorporation of patient reported outcome measures, such as the HUI, in clinical practice to identify and facilitate discussion and increase clinicians' awareness of their patients' symptoms and health status.

Agreement between parent- and self-report for brain tumour patients was better for physical rather than psychosocial attributes (pain and emotion), and both parent- and self-report should be considered in assessing outcomes or defining interventions.

Further longitudinal research on HS and HRQL in children with brain tumours in larger multicentre studies is necessary in the development of timely, targeted interventions to ensure optimal developmental trajectories and quality of survival.

Table 5.8 The relationship between self-report and parent-report at twelve months after diagnosis for brain tumour patients using the HUI3 MAUF and SAUFs

HUI3 t12	n	Mean bias [95%CI]*	r_s	p
MAUF(overall score)	21	0.07 [0.00 to 0.14]	0.76	<0.001
Vision	21	0.02 [-0.01 to 0.04]	0.73	<0.001
Hearing	21	0.00**	1.00	-
Speech	21	0.01 [-0.01 to 0.02]	1.00	-
Ambulation	21	0.02 [-0.05 to 0.09]	0.82	<0.001
Dexterity	21	0.01 [-0.04 to 0.06]	0.79	<0.001
Emotion	21	0.02 [-0.02 to 0.06]	0.30	0.192
Cognition	21	0.04 [-0.00 to 0.09]	0.75	<0.001
Pain	21	-0.03 [-0.14 to 0.08]	0.20	0.393

Abbreviations: HUI3, Health Utilities Index Mark 3; MAUF, Multi Attribute Utility Function; SAUF, Single Attribute Utility Function; t12, 12 month assessment, r_s, Spearman's correlation coefficient; p, significance for r_s.
* Child group mean - parent group mean
**Child results were identical to respective parent

6. DISCUSSION AND CONCLUSIONS

6.1. Overall Findings/ Key Messages

This is the first time that HRQL has been measured prospectively and longitudinally in children with brain tumours and controls in the first year after diagnosis.

Assessment of QOL and other outcome measures early after diagnosis with childhood brain tumour is feasible. Despite our use of an exhaustive battery of assessment tools, including direct neuropsychological tests and indirect questionnaires, both parent- and self-report QOL assessment was possible at all time points for the vast majority of those eligible for assessment. Only three out of a possible 48 eligible patients declined participation and controls were found for 43 of the 45 patients entered into the study as a whole. Only three patients and four controls withdrew from the study before t12 assessment, suggesting that participants and their carers did not find the assessments unduly taxing. The vast number of assessments were performed in the participants' homes, avoiding unnecessary travel to the primary care centre, which in some cases was over 3 hours drive away.

Using both the PedsQL and HUI, children diagnosed with a primary brain tumour have significantly lower QOL, in the first year after diagnosis than normal controls. This is not surprising, considering the impact of tumour, its treatment, hospitalisation and isolation from peers in such patients. Assessment of other aspects of QOS in the same cohort of patients, including parent-reported internalising and total behavioural problems, and adaptive

behaviour, as well as cognitive function (VIQ, PIQ, attention and memory), revealed similar findings (manuscript in preparation and unpublished data).

For both measures, differences between patients' and controls' QOL decreased over time in the first year after diagnosis, with the most significant improvement occurring in the first six months. Once again outcomes using other QOS measures in our cohort showed similar trajectories, with marked improvement in the first six months after diagnosis (manuscripts in progress). This suggests that potential interventions may be most effective during this time period.

Comparison between parent- and self-report QOL in patients revealed mixed results. There was in general, a lack of agreement using the PedsQL, with greater agreement for the more observable (physical), compared with less observable (psychosocial) domains. Agreement between parent- and self-report was better using the HUI. However, the HUI is widely regarded as a measure of HS rather than QOL, and is heavily weighted towards physical functioning, with only one psychosocial single attribute (SAUF); namely that of emotion. Parent-report tended to be lower than self-report in patients using both the PedsQL and HUI. Taken overall, and in the light of the existing literature, comprehensive assessment of QOL should try to include information from both child and care-giver, as both views may provide valid results. However, this may not always be possible due to lower age limits for QOL and other direct and indirect measures.

Self-rated psychosocial health (PedsQL Psychosocial Health Summary score and emotion, social and school domains) was surprisingly high in patients. Decreased reporting of emotional symptoms by the patients themselves may be due to utilization of a repressive adaptive style, an emerging finding in children with cancer. Using the BDS and RCMAS, patients reported similar levels of depressive and general anxiety to that of controls at all time points. This was in contrast with an increase in parent-reported internalising and total behavioural problems, in comparison with normal controls (manuscript in progress), suggesting that issues related to proxy-ratings are likely to apply to all of the less observable aspects of child health.

We found no correlation between socio-economic status, using the IDACI scoring system, or any other socio-demographic factors and QOL in the first year after diagnosis. Previous research in the brain tumour population regarding the potential effect of socio-economic status is sparse and results inconclusive (174;183). A potential reason for the lack of relationship in our cohort may be due in part to the availability of psychosocial and financial support early after the diagnosis of cancer. Such support wains over time, potential moderating effect of such support

We found no consistent relationship between illness-related variables, most notably radiotherapy, and QOL in the first year after diagnosis. This may be due to a lag in cognitive deficit following cranial radiotherapy.

For the parent- and self-report PedsQL and for the parent-report HUI3, selective attention and infratentorial tumour site appear most important in determining HRQL one year after diagnosis. While there was a contemporaneous relationship between QOL at one year (using the PedsQL) and aspects of family and carer function, most notably using the IFS, we found no relationship between family-related variables early after diagnosis and QOL at one year. We were therefore unable to establish causality using family variables as predictors of QOL.

6.2. Limitations of the Study

The power of this study is reduced by the patient sample size and the heterogeneous nature of our sample. The CLIC Sargent Brain Tumour Study aimed to perform a comprehensive assessment of the effects of brain tumour and its treatment on the child and family, and to assess the interaction between tumour, treatment, family and child variables on QOL. We therefore performed a large number of direct and indirect assessments on a small number of patients and controls. The sheer number of assessments and varied results make interpretation challenging, and modelling of such interactions in a small population statistically unfeasible.

Patients enrolled on our study have undergone extremely varied treatment, based primarily on tumour type and site. Treatment ranged from biopsy only to resection, radiotherapy (either focal only or craniospinal with a boost to the primary) and chemotherapy. Chemotherapy

regimes were also extremely variable, again depending on tumour type. Numbers precluded us from stratifying potential variables such as treatment into smaller sub-groups for analysis. The same is true for tumour-related variables where we were restricted to considering supra- versus infratentorial tumours. We have therefore included children with hypothalamic LGGs and cerebellar LGGs in the same group, despite differences in their behaviour, treatment and prognosis. For the same reasons, we have also been limited in the depth to which we were able to investigate the impact of socio-economic variables on QOL in this cohort. However, the findings are strengthened by the similar results using two different parent- and child report HRQL measures.

While our patient cohort was unselected, their distribution is not representative of the childhood brain tumour population with underrepresentation of patients with medulloblastoma and overrepresentation of children with germ-cell tumours. Both patients who withdrew from the study had a diagnosis of medulloblastoma, which in part explains the underrepresentation of its sub-type, though variances in incidence in a relatively short period for an extremely uncommon disease is not unexpected and likely due to chance. We therefore caution generalising our results to those which may emerge after longer periods of follow-up in larger cohorts of patients.

Self-report HUI was not used at t1 or t6. When designing the study, analysis of differences between self- and parent-report was not a primary aim, though the importance of it emerged over time. The HUI is generally accepted to be primarily a measure of health status, with less

emphasis on psychosocial aspects of health than other HRQL measures like the PedsQL. We assumed that differences between parent- and self-report would be less likely to occur and we initially did not elect to use the self-report. In retrospect, we recognise that t1 and t6 self-report HUI data would have been useful.

The inherent problem with QOL and more specifically HRQL assessment is the lack of agreement on construct definition and the increasing number of questionnaires emerging purporting to measure the abovementioned constructs. This makes comparison between studies challenging. We have used two questionnaires, namely the PedsQL Generic Core Scale and HUI2/3 to measure HRQL. Both scales identified differences between BT patients and controls to a similar degree. However, as the HUI is not subjective/preference based at the individual level, and does not have a social domain the author feels that it is not a true measure of HRQL.

The absence of validated paediatric BT specific HRQL measures, such as the PedsQL Brain Tumour Module at the time of our study, precluded assessment of BT-specific HRQL in our cohort. Such assessment would likely have added an extra dimension to this study, particularly as we were evaluating patients during and shortly after treatment when BT specific symptoms were likely to be present. A BT specific measure would have been particularly useful in evaluating within group differences for the BT patients.

Measuring QOL, emotional health and cognitive outcomes in children is challenging: for many of their constructs (i.e. HRQL, HS, RCMAS, BDS, TEA-Ch and CMS), questionnaires are not suitable or available for those most likely to be most affected, namely the younger children and infants. One is therefore forced to either ignore these children, or rely on proxy-report measures. This accounts for differences in "n" for different statistical analyses. In our study we have tried to be inclusive, and therefore recruited children of all ages, despite their being, for some constructs, no age appropriate measures. Regarding the measurement of HRQL in particular; the lower age limit for PedsQL of two years, compared with that of the HUI allowed us to measure HRQL in a number of young children too young for HUI assessment.

6.3. Recommendations for Further Research

Further follow up of our patient cohort is important and will be aimed at identifying those patients and their families for whom the outcome has been poor, and to identify those elements of the earlier assessments which may be of predictive value. In this way, specific interventions may be targeted to achieve (it is hoped) the greatest benefit. However, as our cohort is small and taking account of the potential for further relapse and death, as well as potential drop out from the study, such a project is unlikely to yield robust results, so further, larger studies are required.

While home visits involving both direct and indirect assessment may be suitable for future in depth studies, this may not be feasible in the context of large multi-national clinical trials,

where trial numbers, funding, geographic spread and availability of neuropsychological expertise are limited. Posted, booklet-based assessment has been used successfully in a cross sectional study of health status, behaviour, and quality of life in UK medulloblastoma patients treated on the PNET 3 Trial (51). The application of this methodology to a prospective longitudinal study (PNET 4) has not been as successful, with significant drop-out of patients over time. The use of computer-based, online assessment of HRQL, HS and behaviour using platforms such as HealthTracker is already being explored by international childhood cancer groups such as SIOP in Europe for longitudinal assessment of QOS in children with medulloblastoma on future trials (PNET 5 and PNET6). It is hoped that this will facilitate continued participation by patients over time. Development of valid, reliable computer-based assessment of cognitive function in children, including that of attention is on-going (281;282).

Agreement on the definition of QOL and HRQL is unlikely to occur. However, further qualitative research is needed to determine which variables are important to children with brain tumours with regard to HRQL/ QOL, and in developing conceptually sound, valid and reliable measures of QOL in this population.

Further investigation for possible explanations for the differences between self- and parent-rated HRQL is merited, particularly for the health consequences of repressive adaptive style in this population.

Larger, longitudinal, multi-centre trials, ideally of patients with specific subsets of paediatric brain tumours treated in a uniform manner, such as pilocytic astrocytomas or medulloblastoma will be necessary to confirm or refute our results and establish the relative importance of tumour, treatment, family and child predictors of HRQL in this population. International collaboration will be necessary for accrual of suitable numbers for ensure robust results.

Whilst every effort is being made to improve risk stratification, surgical expertise, limit exposure to the potentially harmful effects of radiotherapy, and fine tune chemotherapeutic regimes to provide maximal chance of cure with minimal adverse effects, it is likely that progress will continue to be slow .The development of timely, targeted interventions to ensure optimal developmental trajectories for children diagnosed with and treated for a primary intracranial tumour are sorely needed. Early cognitive rehabilitation, and particularly attention training, which has been used in children with other disorders such as traumatic brain injury with promising early results (283-285), may be useful. It is important that potential interventions are first investigated in a research setting so that all may benefit from successful interventions. Using QOL as an outcome measure in addition to investigating potential improvement in the cognitive function being remediated would strengthen the findings of such studies.

7. REFERENCES

Reference List

(1) Parkin DM, Kramarova E, Draper GJ, Masuyer E, m, Michaelis J, et al. International Incidence of Childhood Cancer. Lyon: International Agency for Research on Cancer; 1998.

(2) Peris-Bonet R, Martinez-Garcia C, Lacour B, Petrovich S, Giner-Ripoll B, Navajas A, et al. Childhood central nervous system tumours--incidence and survival in Europe (1978-1997): report from Automated Childhood Cancer Information System project. Eur J Cancer 2006 Sep;42(13):2064-80.

(3) Stiller CA, Nectoux J. International incidence of childhood brain and spinal tumours. Int J Epidemiol 1994 Jun;23(3):458-64.

(4) Stiller CA, Desandes E, Danon SE, Izarzugaza I, Ratiu A, Vassileva-Valerianova Z, et al. Cancer incidence and survival in European adolescents (1978-1997). Report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006 Sep;42(13):2006-18.

(5) Surveillance, Epidemiology and End Results (SEER) Programme. SEER*Stat Database: Incidence - SEER 9 Regs Public-Use, Nov 2003 Sub (1973-2001). 2004. Bethesda, MD, National Cancer Institute, DCCPS, Surveillance Research Programme, Cancer Statistics Branch.

(6) Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al. SEER Cancer Statistics Review, 1975-2001. 2004. National Cancer Institute. Bethesda, MD.

(7) Hjalmars U, Kulldorff M, Wahlqvist Y, Lannering B. Increased incidence rates but no space-time clustering of childhood astrocytoma in Sweden, 1973-1992: a population-based study of pediatric brain tumors. Cancer 1999 May 1;85(9):2077-90.

(8) McNally RJ, Kelsey AM, Cairns DP, Taylor GM, Eden OB, Birch JM. Temporal increases in the incidence of childhood solid tumors seen in Northwest England (1954-1998) are likely to be real. Cancer 2001 Oct 1;92(7):1967-76.

(9) Bondy ML, Lustbader ED, Buffler PA, Schull WJ, Hardy RJ, Strong LC. Genetic epidemiology of childhood brain tumors. Genet Epidemiol 1991;8(4):253-67.

(10) Stiller CA, Allen MB, Eatock EM. Childhood cancer in Britain: the National Registry of Childhood Tumours and incidence rates 1978-1987. Eur J Cancer 1995 Nov;31A(12):2028-34.

(11) Little MP, de Vathaire F, Shamsaldin A, Oberlin O, Campbell S, Grimaud E, et al. Risks of brain tumour following treatment for cancer in childhood: modification by genetic factors, radiotherapy and chemotherapy. Int J Cancer 1998 Oct 29;78(3):269-75.

(12) Kantar M, Cetingul N, Kansoy S, Anacak Y, Demirtas E, Ersahin Y, et al. Radiotherapy-induced secondary cranial neoplasms in children. Childs Nerv Syst 2004 Jan;20(1):46-9.

(13) Ortega JJ, Olive T, de Heredia CD, Llort A. Secondary malignancies and quality of life after stem cell transplantation. Bone Marrow Transplant 2005 Mar;35 Suppl 1:S83-S87.

(14) Stavrou T, Bromley CM, Nicholson HS, Byrne J, Packer RJ, Goldstein AM, et al. Prognostic factors and secondary malignancies in childhood medulloblastoma. J Pediatr Hematol Oncol 2001 Oct;23(7):431-6.

(15) Walter AW, Hancock ML, Pui CH, Hudson MM, Ochs JS, Rivera GK, et al. Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children's Research Hospital. J Clin Oncol 1998 Dec;16(12):3761-7.

(16) Calaminus G, Nicholson J. SIOP CNS GCT II prospective trial for the diagnosis and treatment of children, adolescents and young adults with intracranial germ cell tumours. 2011.

(17) Pollack IF, Boyett JM, Yates AJ, Burger PC, Gilles FH, Davis RL, et al. The influence of central review on outcome associations in childhood malignant gliomas: results from the CCG-945 experience. Neuro -oncol 2003 Jul;5(3):197-207.

(18) Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, et al. The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol 2002 Mar;61(3):215-25.

(19) Rorke-Adams LB, Biegel J. Pathology and Molecular Oncology of Childhood CNS Tumours. In: Estlin E, Lowis SP, editors. Central Nervous System Tumours of Childhood.London: Mac Keith Press; 2005. p. 107-28.

(20) Robertson PL, Zeltzer PM, Boyett JM, Rorke LB, Allen JC, Geyer JR, et al. Survival and prognostic factors following radiation therapy and chemotherapy for ependymomas in children: a report of the Children's Cancer Group. J Neurosurg 1998 Apr;88(4):695-703.

(21) Grill J, Le Deley MC, Gambarelli D, Raquin MA, Couanet D, Pierre-Kahn A, et al. Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: a multicenter trial of the French Society of Pediatric Oncology. J Clin Oncol 2001 Mar 1;19(5):1288-96.

(22) Schiffer D, Chio A, Cravioto H, Giordana MT, Migheli A, Soffietti R, et al. Ependymoma: internal correlations among pathological signs: the anaplastic variant. Neurosurgery 1991 Aug;29(2):206-10.

(23) Giangaspero F, Bigner SH, Kleihues P, Pietsch T, Trojanowski JQ. Medulloblastoma. In: Kleihues P, Cavanee WK, editors. Pathology and Genetics of Tumours of the Nervous System.Lyon: IARC Press; 2000. p. 129-37.

(24) Aldosari N, Bigner SH, Burger PC, Becker L, Kepner JL, Friedman HS, et al. MYCC and MYCN oncogene amplification in medulloblastoma. A fluorescence in situ hybridization study on paraffin sections from the Children's Oncology Group. Arch Pathol Lab Med 2002 May;126(5):540-4.

(25) Gilbertson RJ, Pearson AD, Perry RH, Jaros E, Kelly PJ. Prognostic significance of the c-erbB-2 oncogene product in childhood medulloblastoma. Br J Cancer 1995 Mar;71(3):473-7.

(26) Gilbertson RJ, Perry RH, Kelly PJ, Pearson AD, Lunec J. Prognostic significance of HER2 and HER4 coexpression in childhood medulloblastoma. Cancer Res 1997 Aug 1;57(15):3272-80.

(27) Grotzer MA, Hogarty MD, Janss AJ, Liu X, Zhao H, Eggert A, et al. MYC messenger RNA expression predicts survival outcome in childhood primitive neuroectodermal tumor/medulloblastoma. Clin Cancer Res 2001 Aug;7(8):2425-33.

(28) Leonard JR, Cai DX, Rivet DJ, Kaufman BA, Park TS, Levy BK, et al. Large cell/anaplastic medulloblastomas and medullomyoblastomas: clinicopathological and genetic features. J Neurosurg 2001 Jul;95(1):82-8.

(29) Clifford SC, Lusher ME, Lindsey JC, Langdon JA, Gilbertson RJ, Straughton D, et al. Wnt/Wingless pathway activation and chromosome 6 loss characterize a distinct molecular sub-group of medulloblastomas associated with a favorable prognosis. Cell Cycle 2006 Nov;5(22):2666-70.

(30) Ellison DW, Onilude OE, Lindsey JC, Lusher ME, Weston CL, Taylor RE, et al. beta-Catenin status predicts a favorable outcome in childhood medulloblastoma: the United Kingdom Children's Cancer Study Group Brain Tumour Committee. J Clin Oncol 2005 Nov 1;23(31):7951-7.

(31) Brain Tumour Committee of the International Society of Paediatric Oncology (SIOP). HIT-SIOP PNET 4. SIOP and UKCCSG; 2004.

(32) Protocol SIOP PNET5a, Synopsis. Preliminary document. 2006.

(33) Rorke LB, Packer RJ, Biegel JA. Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity. J Neurosurg 1996 Jul;85(1):56-65.

(34) Keene D, Johnston D, Strother D, Fryer C, Carret AS, Crooks B, et al. Epidemiological survey of central nervous system germ cell tumors in Canadian children. J Neurooncol 2007 May;82(3):289-95.

(35) Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM. The descriptive epidemiology of craniopharyngioma. J Neurosurg 1998 Oct;89(4):547-51.

(36) Haupt R, Magnani C, Pavanello M, Caruso S, Dama E, Garre ML. Epidemiological aspects of craniopharyngioma. J Pediatr Endocrinol Metab 2006 Apr;19 Suppl 1:289-93.

(37) Mehta V, Chapman A, McNeely PD, Walling S, Howes WJ. Latency between symptom onset and diagnosis of pediatric brain tumors: an Eastern Canadian geographic study. Neurosurgery 2002 Aug;51(2):365-72.

(38) Punt JAG. Clinical Syndromes. In: Walker DA, Perilongo G, Punt JAG, Taylor RE, editors. Brain and spinal tumours in childhood.London: Arnold; 2004. p. 99-106.

(39) Halperin EC, Watson DM, George SL. Duration of symptoms prior to diagnosis is related inversely to presenting disease stage in children with medulloblastoma. Cancer 2001 Apr 15;91(8):1444-50.

(40) Wilne S, Collier J, Kennedy C, Koller K, Grundy R, Walker D. Presentation of childhood CNS tumours: a systematic review and meta-analysis. Lancet Oncol 2007 Aug;8(8):685-95.

(41) Pollack IF. Brain tumors in children. N Engl J Med 1994 Dec 1;331(22):1500-7.

(42) Pollack IF, Gerszten PC, Martinez AJ, Lo KH, Shultz B, Albright AL, et al. Intracranial ependymomas of childhood: long-term outcome and prognostic factors. Neurosurgery 1995 Oct;37(4):655-66.

(43) Wisoff JH, Boyett JM, Berger MS, Brant C, Li H, Yates AJ, et al. Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group trial no. CCG-945. J Neurosurg 1998 Jul;89(1):52-9.

(44) Chumas PD, Tyagi A. Neurosurgical techniques. In: Walker DA, Perilongo G, Punt JAG, Taylor RE, editors. Brain and Spinal Tumors of Childhood.New York: Arnold; 2004. p. 177-87.

(45) Kortmann RD, Freeman CR, Taylor RE, Abercromby C, Ingle A. Radiotherapy techniques. In: Walker DA, Perilongo G, Punt JAG, Taylor RE, editors. Brain and Spinal Tumors in Children.New York: Arnold; 2004. p. 188-212.

(46) Estlin E, Lowis SP. General principles of radiotherapy. In: Estlin E, Lowis SP, editors. Central Nervous System Tumours of Childhood.London: Mac Keith Press; 2005. p. 163-77.

(47) Kirsch DG, Tarbell NJ. Conformal radiation therapy for childhood CNS tumors. Oncologist 2004;9(4):442-50.

(48) Levy AS. Brain tumors in children: evaluation and management. Curr Probl Pediatr Adolesc Health Care 2005 Jul;35(6):230-45.

(49) Gandola L, Massimino M, Cefalo G, Solero C, Spreafico F, Pecori E, et al. Hyperfractionated accelerated radiotherapy in the Milan strategy for metastatic medulloblastoma. J Clin Oncol 2009 Feb 1;27(4):566-71.

(50) Yock TI, Tarbell NJ. Technology insight: Proton beam radiotherapy for treatment in pediatric brain tumors. Nat Clin Pract Oncol 2004 Dec;1(2):97-103.

(51) Bull KS, Spoudeas HA, Yadegarfar G, Kennedy CR. Reduction of health status 7 years after addition of chemotherapy to craniospinal irradiation for medulloblastoma: a follow-up study in PNET 3 trial survivors on behalf of the CCLG (formerly UKCCSG). J Clin Oncol 2007 Sep 20;25(27):4239-45.

(52) Dhall G, Grodman H, Ji L, Sands S, Gardner S, Dunkel IJ, et al. Outcome of children less than three years old at diagnosis with non-metastatic medulloblastoma treated with chemotherapy on the "Head Start" I and II protocols. Pediatr Blood Cancer 2008 Jun;50(6):1169-75.

(53) Ward C, Phipps K, de Sousa C, Butler S, Gumley D. Treatment factors associated with outcomes in children less than 3 years of age with CNS tumours. Childs Nerv Syst 2009 Jun;25(6):663-8.

(54) Gottardo NG, Gajjar A. Chemotherapy for malignant brain tumors of childhood. J Child Neurol 2008 Oct;23(10):1149-59.

(55) Gloeckler Ries LA, Reichman ME, Lewis DR, Hankey BF, Edwards BK. Cancer survival and incidence from the Surveillance, Epidemiology, and End Results (SEER) program. Oncologist 2003;8(6):541-52.

(56) Steliarova-Foucher E, Stiller C, Kaatsch P, Berrino F, Coebergh JW, Lacour B, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study. Lancet 2004 Dec 11;364(9451):2097-105.

(57) Linet MS, Ries LA, Smith MA, Tarone RE, Devesa SS. Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. J Natl Cancer Inst 1999 Jun 16;91(12):1051-8.

(58) Haupt R, Fears TR, Robison LL, Mills JL, Nicholson HS, Zeltzer LK, et al. Educational attainment in long-term survivors of childhood acute lymphoblastic leukemia. JAMA 1994 Nov 9;272(18):1427-32.

(59) Langeveld NE, Ubbink MC, Last BF, Grootenhuis MA, Voute PA, de Haan RJ. Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. Psychooncology 2003 Apr;12(3):213-25.

(60) Mitby PA, Robison LL, Whitton JA, Zevon MA, Gibbs IC, Tersak JM, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 2003 Feb 15;97(4):1115-26.

(61) Stam H, Grootenhuis MA, Last BF. The course of life of survivors of childhood cancer. Psychooncology 2005 Mar;14(3):227-38.

(62) Robison LL, Green DM, Hudson M, Meadows AT, Mertens AC, Packer RJ, et al. Long-term outcomes of adult survivors of childhood cancer. Cancer 2005 Dec 1;104(S11):2557-64.

(63) Lannering B, Marky I, Lundberg A, Olsson E. Long-term sequelae after pediatric brain tumors: their effect on disability and quality of life. Med Pediatr Oncol 1990;18(4):304-10.

(64) Mostow EN, Byrne J, Connelly RR, Mulvihill JJ. Quality of life in long-term survivors of CNS tumors of childhood and adolescence. J Clin Oncol 1991 Apr;9(4):592-9.

(65) Zebrack BJ, Gurney JG, Oeffinger K, Whitton J, Packer RJ, Mertens A, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study. J Clin Oncol 2004 Mar 15;22(6):999-1006.

(66) Last BF, Grootenhuis MA, Eiser C. International comparison of contributions to psychosocial research on survivors of childhood cancer: past and future considerations. J Pediatr Psychol 2005 Jan;30(1):99-113.

(67) Aarsen FK, Paquier PF, Reddingius RE, Streng IC, Arts WF, Evera-Preesman M, et al. Functional outcome after low-grade astrocytoma treatment in childhood. Cancer 2006 Jan 15;106(2):396-402.

(68) Van Gijn J, Vermeulen M. The clinical trial in efficacy research in neurological diseases. Investigating neurological disease. epidemiology for clinical neurology.Cambridge: Cambridge University Press; 2001. p. 113-33.

(69) World Health Organization. International classification of Impairments, disabilities and handicaps. 1980.

(70) Msall ME, DiGaudio K, Rogers BT, LaForest S, Catanzaro NL, Campbell J, et al. The Functional Independence Measure for Children (WeeFIM). Conceptual basis and pilot use in children with developmental disabilities. Clin Pediatr (Phila) 1994 Jul;33(7):421-30.

(71) Eiser C, Morse R. A review of measures of quality of life for children with chronic illness. Arch Dis Child 2001 Mar;84(3):205-11.

(72) Silva F. Psychometric foundations of behavioural assessment. Newbury Park, CA: Sage; 1993.

(73) Davis E, Waters E, Mackinnon A, Reddihough D, Graham HK, Mehmet-Radji O, et al. Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes. Dev Med Child Neurol 2006 Apr;48(4):311-8.

(74) Koot HM. The Study of Quality of Life: Concepts and Measures. In: Koot HM, Wallander JL, editors. Quality of Life in Child and Adolescent Illness.Hove, East Sussex: Brunner-Routledge; 2001. p. 3-20.

(75) Feldman BM, Grundland B, McCullough L, Wright V. Distinction of quality of life, health related quality of life, and health status in children referred for rheumatologic care. J Rheumatol 2000 Jan;27(1):226-33.

(76) Bjornson KF, McLaughlin JF. The measurement of health-related quality of life (HRQL) in children with cerebral palsy. Eur J Neurol 2001 Nov;8 Suppl 5:183-93.

(77) Harding L. Children's Quality of Life assessments: A review of generic and health Related Quality of Life Measures completed by Children and adolescents. Clin Psychol Psychother 2001;8:79-96.

(78) Sherman EM, Slick DJ, Connolly MB, Steinbok P, Camfield C, Eyrl KL, et al. Validity of three measures of health-related quality of life in children with intractable epilepsy. Epilepsia 2002 Oct;43(10):1230-8.

(79) Spilker B, Revicki D. Taxonomy of quality of life. In: Spilker B, editor. Quality of life and pharmacoeconomics. 2nd ed. New York: Lippincott-Raven; 1996. p. 25-31.

(80) Bradlyn AS, Ritchey AK, Harris CV, Moore IM, O'Brien RT, Parsons SK, et al. Quality of life research in pediatric oncology. Research methods and barriers. Cancer 1996 Sep 15;78(6):1333-9.

(81) Aaronson NK, Meyerowitz BE, Bard M, Bloom JR, Fawzy FI, Feldstein M, et al. Quality of life research in oncology. Past achievements and future priorities. Cancer 1991 Feb 1;67(3 Suppl):839-43.

(82) Armstrong FD, Toledano SR, Miloslavich K, Lackman-Zeman L, Levy JD, Gay CL, et al. The Miami pediatric quality of life questionnaire: parent scale. Int J Cancer Suppl 1999;12:11-7.

(83) Verdugo MA, Schalock RL, Keith KD, Stancliffe RJ. Quality of life and its measurement: important principles and guidelines. J Intellect Disabil Res 2005 Oct;49(Pt 10):707-17.

(84) FDA. Guidance for Industry: Patient-reported outcome measures: Use in medicinal product development to support labelling claims. 2006. Rochville, MD, Centre for Drug Evaluation and Research, Food and Drug Administration.

(85) Feeny D, Furlong W, Mulhern RK, Barr RD, Hudson M. A framework for assessing health-related quality of life among children with cancer. Int J Cancer Suppl 1999;12:2-9.

(86) Patrick DL, Erickson P. Health Status and Health Policy: Quality of Life in Health Care Evaluation and Resource Allocation. New York: Oxford University Press; 1993.

(87) Smith KW, Avis NE, Assmann SF. Distinguishing between quality of life and health status in quality of life research: a meta-analysis. Qual Life Res 1999 Aug;8(5):447-59.

(88) Ware JE, Jr., Brook RH, Davies AR, Lohr KN. Choosing measures of health status for individuals in general populations. Am J Public Health 1981 Jun;71(6):620-5.

(89) Pantell RH, Lewis CC. Measuring the impact of medical care on children. J Chronic Dis 1987;40 Suppl 1:99S-115S.

(90) Drotar D. Validating measures of pediatric health status, functional status, and health-related quality of life: key methodological challenges and strategies. Ambul Pediatr 2004 Jul;4(4 Suppl):358-64.

(91) Sundberg KK, Doukkali E, Lampic C, Eriksson LE, Arvidson J, Wettergren L. Long-term survivors of childhood cancer report quality of life and health status in parity with a comparison group. Pediatr Blood Cancer 2010 Aug;55(2):337-43.

(92) Vogels TC, Verrips GWH, Koopman HM, Theunissen NCM, Fekkes M, Kamphuis RP. TACQOL Manual Parent Form and Child Form 6-11 years. Revised version (2004) ed. Leiden: Leiden Center for Child Health and Pediatrics LUMC-TNO ; 2004.

(93) Alessi D, Dama E, Barr R, Mosso ML, Maule M, Magnani C, et al. Health-related quality of life of long-term childhood cancer survivors: a population-based study from the Childhood Cancer Registry of Piedmont, Italy. Eur J Cancer 2007 Nov;43(17):2545-52.

(94) Barr RD, Simpson T, Whitton A, Rush B, Furlong W, Feeny DH. Health-related quality of life in survivors of tumours of the central nervous system in childhood--a preference-based approach to measurement in a cross-sectional study. Eur J Cancer 1999 Feb;35(2):248-55.

(95) Cardarelli C, Cereda C, Masiero L, Viscardi E, Faggin R, Laverda A, et al. Evaluation of health status and health-related quality of life in a cohort of Italian children following treatment for a primary brain tumor. Pediatr Blood Cancer 2006 Jan 18;46(5):637-44.

(96) Foreman NK, Faestel PM, Pearson J, Disabato J, Poole M, Wilkening G, et al. Health status in 52 long-term survivors of pediatric brain tumors. J Neurooncol 1999 Jan;41(1):47-53.

(97) Glaser A, Kennedy C, Punt J, Walker D. Standardized quantitative assessment of brain tumor survivors treated within clinical trials in childhood. Int J Cancer Suppl 1999;12:77-82.

(98) Mulhern RK. Correlation of the Health Utilities Index Mark 2 cognition scale and neuropsychological functioning among survivors of childhood medulloblastoma. Int J Cancer Suppl 1999;12:91-4.

(99) Pogany L, Barr RD, Shaw A, Speechley KN, Barrera M, Maunsell E. Health status in survivors of cancer in childhood and adolescence. Qual Life Res 2006 Feb;15(1):143-57.

(100) Shelly A, Davis E, Waters E, Mackinnon A, Reddihough D, Boyd R, et al. The relationship between quality of life and functioning for children with cerebral palsy. Dev Med Child Neurol 2008 Mar;50(3):199-203.

(101) Vitale MG, Levy DE, Moskowitz AJ, Gelijns AC, Spellmann M, Verdisco L, et al. Capturing quality of life in pediatric orthopaedics: two recent measures compared. J Pediatr Orthop 2001 Sep;21(5):629-35.

(102) Schipper H, Clinch JJ, Olweny CLM. Quality of life studies: Definitions and conceptual issues. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials.Philadelphia: Lippincott-Raven; 1996. p. 11-23.

(103) Eiser C. Quality of life. In: Eiser C, editor. Children With Cancer, The Quality of Life.London: Lawrence Erlbaum Associates; 2004. p. 245-74.

(104) Nord E. Methods for quality adjustment of life years. Soc Sci Med 1992 Mar;34(5):559-69.

(105) Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI(R)): concepts, measurement properties and applications. Health Qual Life Outcomes 2003 Oct 16;1(1):54.

(106) Dolan P. Output measures and valuation in health. In: Drummond M, McGuire A, editors. Economic evaluation in health Care. Merging theory with Practice.Oxford: Oxford University Press; 2001.

(107) Kennedy CR, Leyland K. Comparison of screening instruments for disability and emotional/behavioral disorders with a generic measure of health-related quality of life in survivors of childhood brain tumors. Int J Cancer Suppl 1999;12:106-11.

(108) Carr AJ, Gibson B, Robinson PG. Measuring quality of life: Is quality of life determined by expectations or experience? BMJ 2001 May 19;322(7296):1240-3.

(109) Hays DM, Revicki D. Reliability and validity (including responsiveness). In: Fayers PM, Hays DM, editors. Assessing quality of life in clinical trials. Second ed. Oxford: Oxford University Press; 2005. p. 25-41.

(110) De Civita M, Regier D, Alamgir AH, Anis AH, Fitzgerald MJ, Marra CA. Evaluating health-related quality-of-life studies in paediatric populations: some conceptual, methodological and developmental considerations and recent applications. Pharmacoeconomics 2005;23(7):659-85.

(111) Connolly MA, Johnson JA. Measuring quality of life in paediatric patients. Pharmacoeconomics 1999 Dec;16(6):605-25.

(112) Eiser C, Jenney M. Measuring quality of life. Arch Dis Child 2007 Apr;92(4):348-50.

(113) Glaser AW, Davies K, Walker D, Brazier D. Influence of proxy respondents and mode of administration on health status assessment following central nervous system tumours in childhood. Qual Life Res 1997 Jan;6(1):43-53.

(114) Gringras P, Santosh P, Baird G. Development of an Internet-based real-time system for monitoring pharmacological interventions in children with neurodevelopmental and neuropsychiatric disorders. Child Care Health Dev 2006 Sep;32(5):591-600.

(115) Varni JW, Limbers CA, Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: A comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQLTM 4.0 Generic Core Scales. Health Qual Life Outcomes 2007 Jul 16;5(1):43.

(116) Levi RB. Quality of Life in Childhood Cancer. In: Brown RT, editor. Comprehensive Handbook of Childhood Cancer and Sickle Cell Disease. A Biopsychosocial Approach.New York: Oxford University Press; 2006. p. 170-88.

(117) Baars RM, Atherton CI, Koopman HM, Bullinger M, Power M. The European DISABKIDS project: development of seven condition-specific modules to measure health related quality of life in children and adolescents. Health Qual Life Outcomes 2005;3:70.

(118) Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care 1999 Feb;37(2):126-39.

(119) Palmer SN, Meeske KA, Katz ER, Burwinkle TM, Varni JW. The PedsQL Brain Tumor Module: initial reliability and validity. Pediatr Blood Cancer 2007 Sep;49(3):287-93.

(120) Lai JS, Cella D, Tomita T, Bode RK, Newmark M, Goldman S. Developing a health-related quality of life instrument for childhood brain tumor survivors. Childs Nerv Syst 2007 Jan;23(1):47-57.

(121) Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001 Aug;39(8):800-12.

(122) Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. Qual Life Res 2001;10(4):347-57.

(123) Bhat SR, Goodwin TL, Burwinkle TM, Lansdale MF, Dahl GV, Huhn SL, et al. Profile of daily life in children with brain tumors: an assessment of health-related quality of life. J Clin Oncol 2005 Aug 20;23(24):5493-500.

(124) Varni JW, Limbers CA, Burwinkle TM. How young can children reliably and validly self-report their health-related quality of life?: an analysis of 8,591 children across age subgroups with the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes 2007;5:1.

(125) De Clercq B, De Fruyt F, Koot HM, Benoit Y. Quality of life in children surviving cancer: a personality and multi-informant perspective. J Pediatr Psychol 2004 Dec;29(8):579-90.

(126) Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value Health 2004 Jan;7(1):79-92.

(127) Pickard AS, Topfer LA, Feeny DH. A structured review of studies on health-related quality of life and economic evaluation in pediatric acute lymphoblastic leukemia. J Natl Cancer Inst Monogr 2004;(33):102-25.

(128) Campo JV, Comer DM, Jansen-Mcwilliams L, Gardner W, Kelleher KJ. Recurrent pain, emotional distress, and health service use in childhood. J Pediatr 2002 Jul;141(1):76-83.

(129) Varni JW, Limbers C, Burwinkle TM. Literature Review: Health-Related Quality of Life Measurement in Pediatric Oncology: Hearing the Voices of the Children. J Pediatr Psychol 2007 Mar 8.

(130) Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986 Feb 8;1(8476):307-10.

(131) Sneeuw KC, Aaronson NK, Sprangers MA, Detmar SB, Wever LD, Schornagel JH. Comparison of patient and proxy EORTC QLQ-C30 ratings in assessing the quality of life of cancer patients. J Clin Epidemiol 1998 Jul;51(7):617-31.

(132) Chang PC, Yeh CH. Agreement between child self-report and parent proxy-report to evaluate quality of life in children with cancer. Psychooncology 2005 Feb;14(2):125-34.

(133) Cremeens J, Eiser C, Blades M. Factors influencing agreement between child self-report and parent proxy-reports on the Pediatric Quality of Life InventoryÖ 4.0 (PedsQLÖ) generic core scales. Health and Quality of Life Outcomes 2006;4(1):58.

(134) Sawyer M, Antoniou G, Toogood I, Rice M. A comparison of parent and adolescent reports describing the health-related quality of life of adolescents treated for cancer. Int J Cancer Suppl 1999;12:39-45.

(135) Billson AL, Walker DA. Assessment of health status in survivors of cancer. Arch Dis Child 1994 Mar;70(3):200-4.

(136) Klaassen RJ, Barr RD, Hughes J, Rogers P, Anderson R, Grundy P, et al. Nurses provide valuable proxy assessment of the health-related quality of life of children with Hodgkin disease. Cancer 2010 Mar 15;116(6):1602-7.

(137) Phipps S, Dunavant M, Jayawardene D, Srivastiva DK. Assessment of health-related quality of life in acute in-patient settings: use of the BASES instrument in children undergoing bone marrow transplantation. Int J Cancer Suppl 1999;12:18-24.

(138) Fluchel M, Horsman JR, Furlong W, Castillo L, Alfonz Y, Barr RD. Self and proxy-reported health status and health-related quality of life in survivors of childhood cancer in Uruguay. Pediatr Blood Cancer 2008;50(4):838-43.

(139) Parsons SK, Barlow SE, Levy SL, Supran SE, Kaplan SH. Health-related quality of life in pediatric bone marrow transplant survivors: according to whom? Int J Cancer Suppl 1999;12:46-51.

(140) Eiser C, Vance YH, Horne B, Glaser A, Galvin H. The value of the PedsQLTM in assessing quality of life in survivors of childhood cancer. Child Care Health Dev 2003 Mar;29(2):95-102.

(141) Levi RB, Drotar D. Health-related quality of life in childhood cancer: discrepancy in parent-child reports. Int J Cancer Suppl 1999;12:58-64.

(142) Russell KM, Hudson M, Long A, Phipps S. Assessment of health-related quality of life in children with cancer: consistency and agreement between parent and child reports. Cancer 2006 May 15;106(10):2267-74.

(143) Theunissen NC, Vogels TG, Koopman HM, Verrips GH, Zwinderman KA, Verloove-Vanhorick SP, et al. The proxy problem: child report versus parent report in health-related quality of life research. Qual Life Res 1998 Jul;7(5):387-97.

(144) Yoo HJ, Ra YS, Park HJ, Lai JS, Cella D, Shin HY, et al. Agreement between pediatric brain tumor patients and parent proxy reports regarding the Pediatric Functional Assessment of Cancer Therapy-Childhood Brain Tumor Survivors questionnaire, version 2. Cancer 2010 May 17.

(145) Jurbergs N, Russell KM, Long A, Phipps S. Adaptive style and differences in parent and child report of health-related quality of life in children with cancer. Psychooncology 2007 Apr 4;17(1):83-90.

(146) Davis E, Nicolas C, Waters E, Cook K, Gibbs L, Gosch A, et al. Parent-proxy and child self-reported health-related quality of life: using qualitative methods to explain the discordance. Qual Life Res 2007 Jun;16(5):863-71.

(147) Eiser C, Eiser JR, Stride CB. Quality of life in children newly diagnosed with cancer and their mothers. Health Qual Life Outcomes 2005 Apr 28;3(1):29.

(148) Goldbeck L, Melches J. Quality of life in families of children with congenital heart disease. Qual Life Res 2005 Oct;14(8):1915-24.

(149) Grootenhuis MA, Last BF. Predictors of parental emotional adjustment to childhood cancer. Psychooncology 1997 Jun;6(2):115-28.

(150) Canning EH, Canning RD, Boyce WT. Depressive symptoms and adaptive style in children with cancer. J Am Acad Child Adolesc Psychiatry 1992 Nov;31(6):1120-4.

(151) Phipps S, Steele RG, Hall K, Leigh L. Repressive adaptation in children with cancer: a replication and extension. Health Psychol 2001 Nov;20(6):445-51.

(152) Phipps S. Adaptive style in children with cancer: implications for a positive psychology approach. J Pediatr Psychol 2007 Oct;32(9):1055-66.

(153) Goodwin DAJ, Boggs SR, Graham-Pole J. Development and validation of the Pediatric Oncology Quality of Life Scale. Psychological Assessment 1994;6:321-8.

(154) Varni JW, Katz ER, Seid M, Quiggins DJ, Friedman-Bender A, Castro CM. The Pediatric Cancer Quality of Life Inventory (PCQL). I. Instrument development, descriptive statistics, and cross-informant variance. J Behav Med 1998 Apr;21(2):179-204.

(155) MRC. The assessment of MRC trials 1996/1997. 1996. London, Medical Research Council.

(156) Nayfield SG, Ganz PA, Moinpour CM, Cella DF, Hailey BJ. Report from a National Cancer Institute (USA) workshop on quality of life assessment in cancer clinical trials. Qual Life Res 1992 Jun;1(3):203-10.

(157) Cullen M, Stenning S. Clinical trials with moving targets: a commentary on a non-inferiority trial in testicular cancer. Lancet Oncol 2004 Feb;5(2):129-32.

(158) Fitzpatrick R, Fletcher A, Gore S, Jones D, Spiegelhalter D, Cox D. Quality of life measures in health care. I: Applications and issues in assessment. BMJ 1992 Oct 31;305(6861):1074-7.

(159) Montazeri A. Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008. Health Qual Life Outcomes 2009;7:102.

(160) Sprangers MA. Quality-of-life assessment in oncology. Achievements and challenges. Acta Oncol 2002;41(3):229-37.

(161) Barr RD, Feeny D, Furlong W. Economic evaluation of treatments for cancer in childhood. Eur J Cancer 2004 Jun;40(9):1335-45.

(162) Barr RD, Sala A. Quality-adjusted survival: a rigorous assessment of cure after cancer during childhood and adolescence. Pediatr Blood Cancer 2005 Mar;44(3):201-4.

(163) Prieto L, Sacristan JA. Problems and solutions in calculating quality-adjusted life years (QALYs). Health Qual Life Outcomes 2003;1:80.

(164) Kennedy C, Glaser. Quality of survival. In: Walker DA, Perilongo G, Punt JAG, Taylor RE, editors. Brain and spinal tumours of childhood.London: Arnold; 2004. p. 493-500.

(165) Hudson MM. A model for care across the cancer continuum. Cancer 2005 Dec 1;104(S11):2638-42.

(166) Wallander JL, Schmitt M, Koot HM. Quality of life measurement in children and adolescents: issues, instruments, and applications. J Clin Psychol 2001 Apr;57(4):571-85.

(167) McDougall J, Tsonis M. Quality of life in survivors of childhood cancer: a systematic review of the literature (2001-2008). Support Care Cancer 2009 Oct;17(10):1231-46.

(168) Maunsell E, Pogany L, Barrera M, Shaw AK, Speechley KN. Quality of life among long-term adolescent and adult survivors of childhood cancer. J Clin Oncol 2006 Jun 1;24(16):2527-35.

(169) Ness KK, Gurney JG, Zeltzer LK, Leisenring W, Mulrooney DA, Nathan PC, et al. The impact of limitations in physical, executive, and emotional function on health-related quality of life among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Arch Phys Med Rehabil 2008 Jan;89(1):128-36.

(170) Reulen RC, Winter DL, Lancashire ER, Zeegers MP, Jenney ME, Walters SJ, et al. Health-status of adult survivors of childhood cancer: A large-scale population-based study from the British childhood cancer survivor study. Int J Cancer 2007 Aug 1;121(3):633-40.

(171) Speechley KN, Barrera M, Shaw AK, Morrison HI, Maunsell E. Health-related quality of life among child and adolescent survivors of childhood cancer. J Clin Oncol 2006 Jun 1;24(16):2536-43.

(172) Zeltzer LK, Lu Q, Leisenring W, Tsao JC, Recklitis C, Armstrong G, et al. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev 2008 Feb;17(2):435-46.

(173) Eiser C, Vance YH, Glaser A, Galvin H, Horne B, Picton S, et al. Growth hormone treatment and quality of life among survivors of childhood cancer. Horm Res 2005;63(6):300-4.

(174) Meeske K, Katz ER, Palmer SN, Burwinkle T, Varni JW. Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. Cancer 2004 Nov 1;101(9):2116-25.

(175) Pogorzala M, Styczynski J, Kurylak A, Debski R, Wojtkiewicz M, Wysocki M. Health-related quality of life among paediatric survivors of primary brain tumours and acute leukaemia. Qual Life Res 2010 Jan 14.

(176) Gerber NU, Zehnder D, Zuzak TJ, Poretti A, Boltshauser E, Grotzer MA. Outcome in children with brain tumours diagnosed in the first year of life: long-term complications and quality of life. Arch Dis Child 2008 Jul;93(7):582-9.

(177) Maddrey AM, Bergeron JA, Lombardo ER, McDonald NK, Mulne AF, Barenberg PD, et al. Neuropsychological performance and quality of life of 10 year survivors of childhood medulloblastoma. J Neurooncol 2005 May;72(3):245-53.

(178) Poretti A, Grotzer MA, Ribi K, Schonle E, Boltshauser E. Outcome of craniopharyngioma in children: long-term complications and quality of life. Developmental Medicine and Child Neurology [NLM - MEDLINE] 2004 Apr;46(4):220.

(179) Sands SA, Kellie SJ, Davidow AL, Diez B, Villablanca J, Weiner HL, et al. Long-term quality of life and neuropsychologic functioning for patients with CNS germ-cell tumors: from the First International CNS Germ-Cell Tumor Study. Neuro Oncol 2001 Jul;3(3):174-83.

(180) Sands SA, Milner JS, Goldberg J, Mukhi V, Moliterno JA, Maxfield C, et al. Quality of life and behavioral follow-up study of pediatric survivors of craniopharyngioma. J Neurosurg 2005 Oct;103(4 Suppl):302-11.

(181) Sutton LN, Radcliffe J, Goldwein JW, Phillips P, Janss AJ, Packer RJ, et al. Quality of life of adult survivors of germinomas treated with craniospinal irradiation. Neurosurgery 1999 Dec;45(6):1292-7.

(182) Zuzak TJ, Poretti A, Drexel B, Zehnder D, Boltshauser E, Grotzer MA. Outcome of children with low-grade cerebellar astrocytoma: long-term complications and quality of life. Childs Nerv Syst 2008 Dec;24(12):1447-55.

(183) Boman KK, Hoven E, Anclair M, Lannering B, Gustafsson G. Health and persistent functional late effects in adult survivors of childhood CNS tumours: a population-based cohort study. Eur J Cancer 2009 Sep;45(14):2552-61.

(184) Glaser AW, Nik Abdul Rashid NF, Walker C, Walker DA. School Behaviour and health status after central nervous system tumours in childhood. British Journal of Cancer 1997;76(5):643-50.

(185) Pedreira CC, Stargatt R, Maroulis H, Rosenfeld J, Maixner W, Warne GL, et al. Health related quality of life and psychological outcome in patients treated for craniopharyngioma in childhood. J Pediatr Endocrinol Metab 2006 Jan;19(1):15-24.

(186) Pompili A, Caperle M, Pace A, Ramazzotti V, Raus L, Jandolo B, et al. Quality-of-life assessment in patients who had been surgically treated for cerebellar pilocytic astrocytoma in childhood. J Neurosurg 2002 Feb;96(2):229-34.

(187) Ribi K, Relly C, Landolt MA, Alber FD, Boltshauser E, Grotzer MA. Outcome of medulloblastoma in children: long-term complications and quality of life. Neuropediatrics 2005 Dec;36(6):357-65.

(188) Barr RD, Simpson T, Webber CE, Gill GJ, Hay J, Eves M, et al. Osteopenia in children surviving brain tumours. Eur J Cancer 1998 May;34(6):873-7.

(189) Odame I, Duckworth J, Talsma D, Beaumont L, Furlong W, Webber C, et al. Osteopenia, physical activity and health-related quality of life in survivors of brain tumors treated in childhood. Pediatr Blood Cancer 2006;46(3):357-62.

(190) Reimers TS, Mortensen EL, Nysom K, Schmiegelow K. Health-related quality of life in long-term survivors of childhood brain tumors. Pediatr Blood Cancer 2009 Dec;53(6):1086-91.

(191) Frange P, Alapetite C, Gaboriaud G, Bours D, Zucker JM, Zerah M, et al. From childhood to adulthood: long-term outcome of medulloblastoma patients. The Institut Curie experience (1980-2000). J Neurooncol 2009 Nov;95(2):271-9.

(192) Roncadin C, Dennis M, Greenberg ML, Spiegler BJ. Adverse medical events associated with childhood cerebellar astrocytomas and medulloblastomas: natural history and relation to very long-term neurobehavioral outcome. Childs Nerv Syst 2008 Jun 25;24(9):995-1002.

(193) Shankar S, Robison L, Jenney ME, Rockwood TH, Wu E, Feusner J, et al. Health-related quality of life in young survivors of childhood cancer using the Minneapolis-Manchester Quality of Life-Youth Form. Pediatrics 2005 Feb;115(2):435-42.

(194) Grant J, Cranston A, Horsman J, Furlong W, Barr N, Findlay S, et al. Health status and health-related quality of life in adolescent survivors of cancer in childhood. J Adolesc Health 2006 May;38(5):504-10.

(195) Glaser AW, Furlong W, Walker DA, Fielding K, Davies K, Feeny DH, et al. Applicability of the Health Utilities Index to a population of childhood survivors of central nervous system tumours in the U.K. Eur J Cancer 1999 Feb;35(2):256-61.

(196) Landgraf JM, Abla O, Ware JE, Jr. Child Health Questionnaire (CHQ): A User's Manual. Boston, MA: The Health Institue, New England Medical Center; 1996.

(197) Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992 Jun;30(6):473-83.

(198) Glaser AW, Abdul Rashid NF, CL U, Walker DA. School behaviour and health status after central nervous system tumours in childhood. Br J Cancer 1997;76(5):643-50.

(199) Cervoni L, Cantore G. Medulloblastoma in pediatric age: a single-institution review of prognostic factors. Childs Nerv Syst 1995 Feb;11(2):80-4.

(200) Chan MY, Teo WY, Seow WT, Tan AM. Epidemiology, management and treatment outcome of medulloblastoma in singapore. Ann Acad Med Singapore 2007 May;36(5):314-5.

(201) Ris MD, Noll RB. Long-term neurobehavioral outcome in pediatric brain-tumor patients: review and methodological critique. J Clin Exp Neuropsychol 1994 Feb;16(1):21-42.

(202) Ris MD, Packer R, Goldwein J, Jones-Wallace D, Boyett JM. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. J Clin Oncol 2001 Aug 1;19(15):3470-6.

(203) Riva D, Giorgi C. The neurodevelopmental price of survival in children with malignant brain tumours. Childs Nerv Syst 2000 Nov;16(10-11):751-4.

(204) Stiller CA, Bunch KJ. Brain and spinal tumours in children aged under two years: incidence and survival in Britain, 1971-85. Br J Cancer Suppl 1992 Aug;18:S50-S53.

(205) Tseng JH, Tseng MY. Survival analysis of children with primary malignant brain tumors in England and Wales: a population-based study. Pediatr Neurosurg 2006;42(2):67-73.

(206) Eiser C, Penn A, Katz E, Barr R. Psychosocial issues and quality of life. Semin Oncol 2009 Jun;36(3):275-80.

(207) Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. Cancer 2002 Apr 1;94(7):2090-106.

(208) Maurice-Stam H, Oort FJ, Last BF, Grootenhuis MA. A predictive model of health-related quality of life in young adult survivors of childhood cancer. [References]. European Journal of Cancer Care 2009 Jul;Vol.18(4):339-49.

(209) Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol 2004 Jul;5(7):399-408.

(210) Crom DB, Chathaway DK, Tolley EA, Mulhern RK, Hudson MM. Health status and health-related quality of life in long-term adult survivors of pediatric solid tumors. Int J Cancer Suppl 1999;12:25-31.

(211) Langeveld NE, Grootenhuis MA, Voute PA, de Haan RJ, van den BC. Quality of life, self-esteem and worries in young adult survivors of childhood cancer. Psychooncology 2004 Dec;13(12):867-81.

(212) Beebe DW, Ris MD, Armstrong FD, Fontanesi J, Mulhern R, Holmes E, et al. Cognitive and adaptive outcome in low-grade pediatric cerebellar astrocytomas: evidence of diminished cognitive and adaptive functioning in National Collaborative Research Studies (CCG 9891/POG 9130). J Clin Oncol 2005 Aug 1;23(22):5198-204.

(213) Kiltie AE, Gattamaneni HR. Survival and quality of life of paediatric intracranial germ cell tumour patients treated at the Christie Hospital, 1972-1993. Med Pediatr Oncol 1995 Dec;25(6):450-6.

(214) Benesch M, Lackner H, Schagerl S, Gallistl S, Frey EM, Urban C. Tumor- and treatment-related side effects after multimodal therapy of childhood intracranial germ cell tumors. Acta Paediatr 2001 Mar;90(3):264-70.

(215) Haupt C, Ancker U, Muller M, Herrmann HD, Schulte FJ. Intracranial germ-cell tumours--treatment results and residuals. Eur J Pediatr 1996 Mar;155(3):230-6.

(216) Schmugge M, Boltshauser E, Pluss HJ, Niggli FK. Long-term follow-up and residual sequelae after treatment for intracerebral germ-cell tumour in children and adolescents. Ann Oncol 2000 May;11(5):527-33.

(217) Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer. Support Care Cancer 2002 Nov;10(8):579-600.

(218) Stam H, Grootenhuis MA, Caron HN, Last BF. Quality of life and current coping in young adult survivors of childhood cancer: positive expectations about the further course of the disease were correlated with better quality of life. Psychooncology 2006 Jan;15(1):31-43.

(219) Zebrack BJ, Chesler MA. Quality of life in childhood cancer survivors. Psychooncology 2002 Mar;11(2):132-41.

(220) Bronfenbrenner U. The ecology of human development. Cambridge, MA: Harvard University Press; 1979.

(221) Robinson KE, Gerhardt CA, Vannatta K, Noll RB. Parent and family factors associated with child adjustment to pediatric cancer. J Pediatr Psychol 2007 May;32(4):400-10.

(222) Wallander JL, Varni JW, Babani L, Banis HT, Wilcox KT. Family resources as resistance factors for psychological maladjustment in chronically ill and handicapped children. J Pediatr Psychol 1989 Jun;14(2):157-73.

(223) Varni JW, Katz ER, Colegrove R, Jr., Dolgin M. Family functioning predictors of adjustment in children with newly diagnosed cancer: a prospective analysis. J Child Psychol Psychiatry 1996 Mar;37(3):321-8.

(224) Steele RG, Dreyer ML, Phipps S. Patterns of maternal distress among children with cancer and their association with child emotional and somatic distress. J Pediatr Psychol 2004 Oct;29(7):507-17.

(225) Waters E, Doyle J, Wolfe R, Wright M, Wake M, Salmon L. Influence of parental gender and self-reported health and illness on parent-reported child health. Pediatrics 2000 Dec;106(6):1422-8.

(226) Robinson KE, Gerhardt CA, Vannatta K, Noll RB. Survivors of Childhood Cancer and Comparison Peers: The Influence of Early Family Factors on Distress in Emerging Adulthood. Journal of Family Psychology 2009;23(1):23-31.

(227) Aarsen FK, Van Dongen HR, Paquier PF, Van Mourik M, Catsman-Berrevoets CE. Long-term sequelae in children after cerebellar astrocytoma surgery. Neurology 2004 Apr 27;62(8):1311-6.

(228) Anderson V, Godber T, Smibert E, Ekert H. Neurobehavioural sequelae following cranial irradiation and chemotherapy in children: an analysis of risk factors. Pediatr Rehabil 1997 Apr;1(2):63-76.

(229) Mulhern RK, Palmer SL, Reddick WE, Glass JO, Kun LE, Taylor J, et al. Risks of young age for selected neurocognitive deficits in medulloblastoma are associated with white matter loss. J Clin Oncol 2001 Jan 15;19(2):472-9.

(230) Papazoglou A, King TZ, Morris RD, Krawiecki N. Parent report of attention problems predicts later adaptive functioning in children with brain tumors. Child Neuropsychol 2009 Jan;15(1):40-52.

(231) Brown RT, Dingle A, Dreelin B. Neuropsychological effects of stimulant medication in children's learning and behaviour. In: Reynolds CR, Fletcher-Janzen E, editors. Handbook of clinical child pharmacology.New York: Wiley; 1997.

(232) Landolt MA, Vollrath M, Niggli FK, Gnehm HE, Sennhauser FH. Health-related quality of life in children with newly diagnosed cancer: a one year follow-up study. Health Qual Life Outcomes 2006;4:63.

(233) Maurice-Stam H, Oort FJ, Last BF, Brons PP, Caron HN, Grootenhuis MA. Longitudinal assessment of health-related quality of life in preschool children with non-CNS cancer after the end of successful treatment. Pediatr Blood Cancer 2008 May;50(5):1047-51.

(234) Yule W, Bolton D, Udwin O, Boyle S, O'Ryan D, Nurrish J. The long-term psychological effects of a disaster experienced in adolescence: I: The incidence and course of PTSD. J Child Psychol Psychiatry 2000 May;41(4):503-11.

(235) Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr 2003 Nov;3(6):329-41.

(236) Manuel DG, Schultz SE, Kopec JA. Measuring the health burden of chronic disease and injury using health adjusted life expectancy and the Health Utilities Index. J Epidemiol Community Health 2002 Nov;56(11):843-50.

(237) Feeny D, Furlong W, Boyle M, Torrance GW. Multi-attribute health status classification systems. Health Utilities Index. Pharmacoeconomics 1995 Jun;7(6):490-502.

(238) Furlong WJ, Feeny DH, Torrance GW. Health Utilities Index (HUI) Procedures Manual. 2000. Dundas, ON, Canada, Health Utilities Inc.

(239) Office of the Deputy Prime Minister. The English Indices of Deprivation 2004: Summary (revised). Communities and Local Government 2008 [cited 2008 Oct 2];Available from: URL: http://www.communities.gov.uk/documents/communities/pdf/131206.pdf

(240) Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007 Aug;114(2):97-109.

(241) Desai KI, Nadkarni TD, Muzumdar DP, Goel A. Prognostic factors for cerebellar astrocytomas in children: a study of 102 cases. Pediatr Neurosurg 2001 Dec;35(6):311-7.

(242) Grill J, Viguier D, Kieffer V, Bulteau C, Sainte-Rose C, Hartmann O, et al. Critical risk factors for intellectual impairment in children with posterior fossa tumors: the role of cerebellar damage. J Neurosurg 2004 Nov;101(2 Suppl):152-8.

(243) Mabbott DJ, Spiegler BJ, Greenberg ML, Rutka JT, Hyder DJ, Bouffet E. Serial evaluation of academic and behavioral outcome after treatment with cranial radiation in childhood. J Clin Oncol 2005 Apr 1;23(10):2256-63.

(244) Merchant TE, Lee H, Zhu J, Xiong X, Wheeler G, Phipps S, et al. The effects of hydrocephalus on intelligence quotient in children with localized infratentorial ependymoma before and after focal radiation therapy. J Neurosurg 2004 Nov;101(2 Suppl):159-68.

(245) Reimers TS, Ehrenfels S, Mortensen EL, Schmiegelow M, Sonderkaer S, Carstensen H, et al. Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. Med Pediatr Oncol 2003 Jan;40(1):26-34.

(246) Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess 1996 Dec;67(3):588-97.

(247) Beck AT, Steer RA, Brown GK. BDI-II Manual. San Antonio, Tx: The Psychological Corporation, Harcourt Brace and Company; 1996.

(248) Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988 Dec;56(6):893-7.

(249) Stein RE, Jessop DJ. The impact on family scale revisited: further psychometric data. J Dev Behav Pediatr 2003 Feb;24(1):9-16.

(250) Epstein NB, Baldwin LM, Bishop DS. The McMaster Family Assessment Device. J Marital Fam Therapy 1983;9:171-80.

(251) McCubbin H, McCubbin MA, Patterson JM, Cauble AE, Wilson LR, Warwick W. CHIP-Coping Health Inventory for Parents: An assessment of parental coping patterns in the care of the chronically ill child. Journal of Marriage and the Family 1983;45(2):359-70.

(252) Carlson-Green B, Morris RD, Krawiecki N. Family and illness predictors of outcome in pediatric brain tumors. J Pediatr Psychol 1995 Dec;20(6):769-84.

(253) Eiser C, Havermans T, Eiser JR. Parents' attributions about childhood cancer: implications for relationships with medical staff. Child Care Health Dev 1995 Jan;21(1):31-42.

(254) Patistea E. Description and adequacy of parental coping behaviours in childhood leukaemia. Int J Nurs Stud 2005 Mar;42(3):283-96.

(255) Dunst CJ, Trivette CM, Deal AG. Enabling and Empowering Families: Principles and Guidelines for Practice. Cambridge, MA: Brokklyn Books; 1988.

(256) Wechsler D. Wechsler Intelligence Scale for Children III (WISC-III). New York: The Psychological Corporation; 1991.

(257) Wechsler D. WASI Wechsler abbreviated scale of intelligence. San Antonio: Harcourt Assessment; 1999.

(258) Wechsler D. Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R)-Manual. New York: The Psychological Corporation; 1989.

(259) Briere ME, Scott JG, McNall-Knapp RY, Adams RL. Cognitive outcome in pediatric brain tumor survivors: Delayed attention deficit at long-term follow-up. Pediatr Blood Cancer 2007 Apr 25.

(260) Manley T, Robertson IH, Anderson V, Nimmo-Smith I. The Test of Everyday Attention for Children (TEA-Ch). Bury St Edmunds, UK: Thames Valley Test Company; 1999.

(261) Cohen M. Children's Memory Scale Manual. San Antonio: The Psychological Corporation; 1997.

(262) Giola GA, Isquith PK, Guy SC, Kenworthy L. Brief- Behavior Rating Inventory of Executive Function- Parent Form Professional Manual. Psychological Assessment Resources, Inc.; 2000.

(263) Achenbach TM, Rescorla LA. Manual for the ASEBA Preschool Forms and Profiles. Burlington, VT: University of Vermont, Research Centre for Children, Youth and Families; 2000.

(264) Achenbach TM, Rescorla LA. Manual for the ASEBA School-Age Forms and Profiles. Burlington, VT: University of Vermont, Research Centre for Children, Youth and Families; 2001.

(265) Sparrow SS, Balla DA, Cicchetti DV. Vineland Adaptive Behaviour Scalse, Survey Form Manual. International Edition ed. Circle Pines: American Guidance Service Inc.; 1984.

(266) Birleson P. The validity of depressive disorder in childhood and the development of a self-rating scale: a research report. J Child Psychol Psychiatry 1981 Jan;22(1):73-88.

(267) Birleson P, Hudson I, Buchanan DG, Wolff S. Clinical evaluation of a self-rating scale for depressive disorder in childhood (Depression Self-Rating Scale). J Child Psychol Psychiatry 1987 Jan;28(1):43-60.

(268) Reynolds CR, Richmond BO. Manual for the Revised Children's Manifest Anxiety Scale. Los Angeles: Western Psychological Services; 1985.

(269) Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. Psychosom Med 1979 May;41(3):209-18.

(270) Shemesh E, Keshavarz R, Leichtling NK, Weinberg E, Mousavi A, Sadow K, et al. Pediatric emergency department assessment of psychological trauma and posttraumatic stress. Psychiatr Serv 2003 Sep;54(9):1277-81.

(271) Dyregrov A, Gjestad R, Raundalen M. Children exposed to warfare: a longitudinal study. J Trauma Stress 2002 Feb;15(1):59-68.

(272) Dyregrov A, Kuterovac G, Barath A. Factor analysis of the impact of event scale with children in war. Scand J Psychol 1996 Dec;37(4):339-50.

(273) Penn A, Lowis SP, Hunt LP, Shortman RI, Stevens MC, McCarter RL, et al. 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. Eur J Cancer 2008 Jun;44(9):1243-52.

(274) Penn A, Lowis SP, Stevens MC, Shortman RI, Hunt LP, McCarter RJ, et al. A detailed prospective longitudinal assessment of health status in children with brain tumors in the first year after diagnosis. J Pediatr Hematol Oncol 2011 Dec;33(8):592-9.

(275) Altman DG, Machin D, Bryant TN. Statistics With Confidence. 2nd ed. London, England: BMJ Books; 2000.

(276) Cohen L, Holiday M. Statistics for Social Scientists. London: Harper and Row; 1982.

(277) Hamlett KW, Pellegrini DS, Katz KS. Childhood chronic illness as a family stressor. J Pediatr Psychol 1992 Feb;17(1):33-47.

(278) Wallander JL, Thompson RJ. Psychosocial adjustment of children with chronic physical conditions. In: Roberts MC, editor. Handbook of pediatric psychology. 2nd Edition ed. New York: Guildford; 1995. p. 124-41.

(279) Penn A, Lowis SP, Stevens MC, Hunt LP, Shortman RI, McCarter RJ, et al. Family, demographic and illness-related determinants of HRQL in children with brain tumours in the first year after diagnosis. Pediatr Blood Cancer 2009 Dec;53(6):1092-9.

(280) Penn A, Shortman RI, Lowis SP, Stevens MC, Hunt LP, McCarter RJ, et al. Child-related determinants of health-related quality of life in children with brain tumours 1 year after diagnosis. Pediatr Blood Cancer 2010 Dec 15;55(7):1377-85.

(281) Berger I, Goldzweig G. Objective measures of attention-deficit/hyperactivity disorder: a pilot study. Isr Med Assoc J 2010 Sep;12(9):531-5.

(282) Bush G. Neuroimaging of attention deficit hyperactivity disorder: can new imaging findings be integrated in clinical practice? Child Adolesc Psychiatr Clin N Am 2008 Apr;17(2):385-404, x.

(283) Penkman L. Remediation of attention deficits in children: a focus on childhood cancer, traumatic brain injury and attention deficit disorder. Pediatr Rehabil 2004 Apr;7(2):111-23.

(284) Rabiner DL, Murray DW, Skinner AT, Malone PS. A randomized trial of two promising computer-based interventions for students with attention difficulties. J Abnorm Child Psychol 2010 Jan;38(1):131-42.

(285) Sjo NM, Spellerberg S, Weidner S, Kihlgren M. Training of attention and memory deficits in children with acquired brain injury. Acta Paediatr 2010 Feb;99(2):230-6.

8. APPENDICES

EUROPEAN JOURNAL OF CANCER 44 (2008) 1243–1252

available at www.sciencedirect.com

journal homepage: www.ejconline.com

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

Anthony Penn[a,c,d,*], *Stephen P. Lowis*[c], *Linda P. Hunt*[e], *Robert I. Shortman*[b], *Michael C.G. Stevens*[c,e], *Renee L. McCarter*[b], *Andrew L. Curran*[a], *Peta M. Sharples*[a]

[a]*Department of Paediatric Neurology, Frenchay Hospital, Bristol, UK*
[b]*Department of Neuropsychology, Frenchay Hospital, Bristol, UK*
[c]*Department of Paediatric Oncology, Bristol Royal Hospital for Children, Upper Maudlin Street, Bristol, UK*
[d]*University of the Witwatersrand, Johannesburg, South Africa*
[e]*Institute of Child Life and Health, University of Bristol, Upper Maudlin Street, Bristol, UK*

ARTICLE INFO

Article history:
Received 4 September 2007
Accepted 20 September 2007
Available online 7 November 2007

Keywords:
Central nervous system tumours
Childhood
Brain tumours
Paediatric
Health related quality of life
PedsQL
HRQL
Quality of life
Longitudinal
Prospective

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.

* Corresponding author. Present address: Room 2 Academic Centre, Frenchay Hospital, Frenchay Hospital, Frenchay Park Road, Frenchay, Bristol BS16 1LE, United Kingdom. Mobile: +44 7866501769.
E-mail address: antpenn@doctors.org.uk (A. Penn).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.09.015

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.

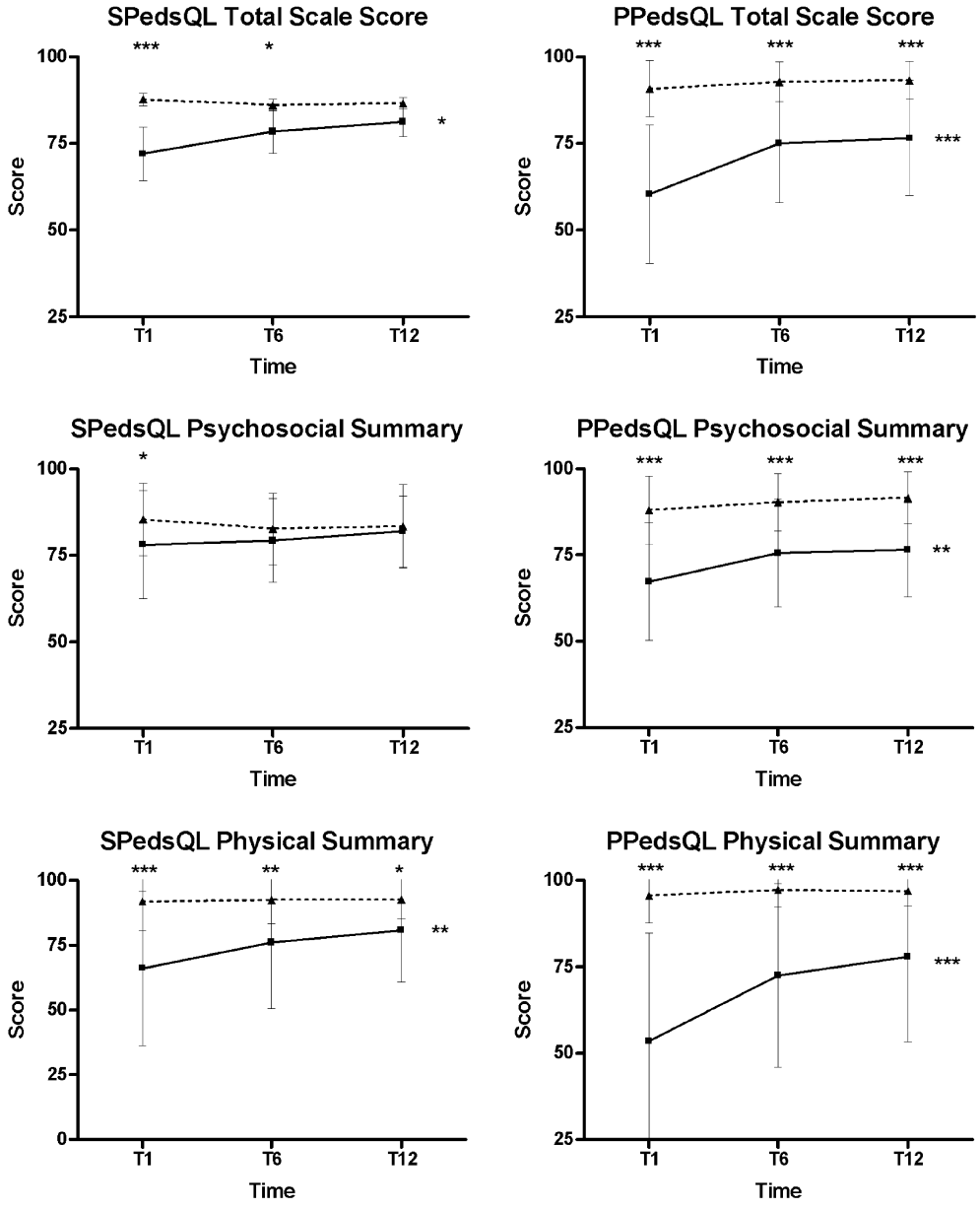

Fig. 1 – Self- and parent report PedsQL summary scores showing group means and standard deviations. —— Represents children with brain tumours, - - - represents controls. PPedsQL, parent-report PedsQL; SPedsQL, Self-report PedsQL; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

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

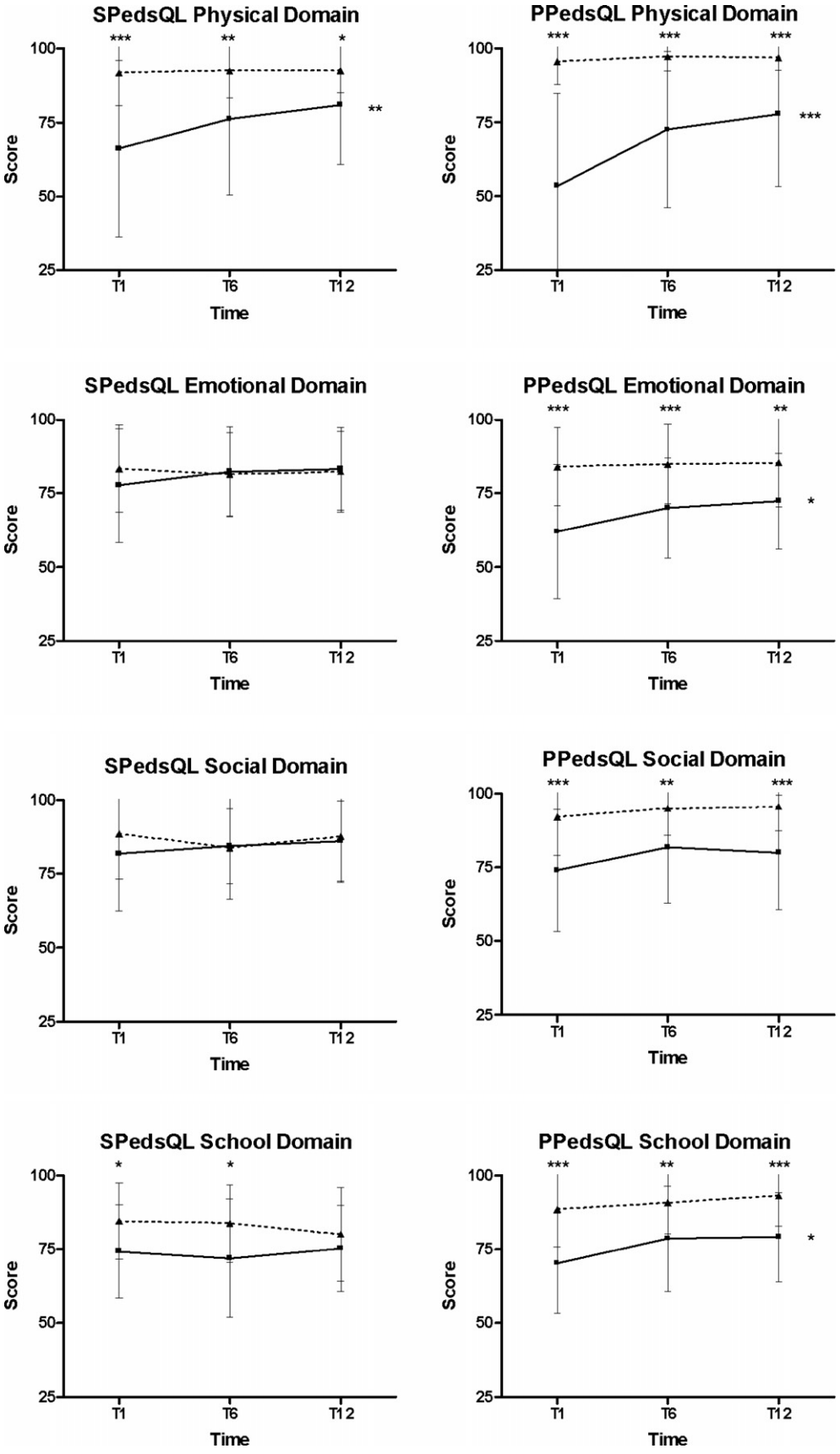

Fig. 2 – Self- and parent report PedsQL domain scores showing group means and standard deviations. —— Represents children with brain tumours, - - - represents controls. PPedsQL, parent-report PedsQL; SPedsQL, Self-report PedsQL; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

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.

Acknowledgement

We acknowledge the financial support from the CLIC Sargent Child Cancer Foundation, and the Bowles Bequest. We acknowledge the advice and support of Professor Peter Cooper, Consultant Paediatrician, Department of Paediatrics, University of the Witwatersrand.

REFERENCES

1. Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study. *Lancet* 2004;**364**(9451):2097–105.
2. Peris-Bonet R, Martinez-Garcia C, Lacour B, et al. Childhood central nervous system tumours–incidence and survival in Europe (1978-1997): report from Automated Childhood Cancer Information System project. *Eur J Cancer* 2006;**42**(13):2064–80.
3. Haupt R, Fears TR, Robison LL, et al. Educational attainment in long-term survivors of childhood acute lymphoblastic leukemia. *JAMA* 1994;**272**(18):1427–32.
4. Langeveld NE, Ubbink MC, Last BF, et al. Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. *Psychooncology* 2003;**12**(3):213–25.
5. Mitby PA, Robison LL, Whitton JA, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer* 2003;**97**(4):1115–26.
6. Stam H, Grootenhuis MA, Last BF. The course of life of survivors of childhood cancer. *Psychooncology* 2005;**14**(3):227–38.
7. Robison LL, Green DM, Hudson M, et al. Long-term outcomes of adult survivors of childhood cancer. *Cancer* 2005;**104**(S11):2557–64.
8. Lannering B, Marky I, Lundberg A, et al. Long-term sequelae after pediatric brain tumors: their effect on disability and quality of life. *Med Pediatr Oncol* 1990;**18**(4):304–10.
9. Mostow EN, Byrne J, Connelly RR, et al. Quality of life in long-term survivors of CNS tumors of childhood and adolescence. *J Clin Oncol* 1991;**9**(4):592–9.
10. Zebrack BJ, Gurney JG, Oeffinger K, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2004;**22**(6):999–1006.
11. Bradlyn AS, Ritchey AK, Harris CV, et al. Quality of life research in pediatric oncology. Research methods and barriers. *Cancer* 1996;**78**(6):1333–9.
12. Calaminus G, Weinspach S, Teske C, et al. Quality of life in children and adolescents with cancer. First results of an evaluation of 49 patients with the PEDQOL questionnaire. *Klin Padiatr* 2000;**212**(4):211–5.
13. De Clercq B, De Fruyt F, Koot HM, et al. Quality of life in children surviving cancer: a personality and multi-informant perspective. *J Pediatr Psychol* 2004;**29**(8):579–90.
14. Langeveld NE, Stam H, Grootenhuis MA, et al. Quality of life in young adult survivors of childhood cancer. *Support Care Cancer* 2002;**10**(8):579–600.
15. Pemberger S, Jagsch R, Frey E, et al. Quality of life in long-term childhood cancer survivors and the relation of late effects and subjective well-being. *Support Care Cancer* 2005;**13**(1):49–56.
16. Zebrack BJ, Chesler MA. Quality of life in childhood cancer survivors. *Psychooncology* 2002;**11**(2):132–41.
17. Eiser C, Vance YH, Horne B, et al. The value of the PedsQLTM in assessing quality of life in survivors of childhood cancer. *Child Care Health Dev* 2003;**29**(2):95–102.
18. Cardarelli C, Cereda C, Masiero L, et al. Evaluation of health status and health-related quality of life in a cohort of Italian children following treatment for a primary brain tumor. *Pediatr Blood Cancer* 2006.
19. Jenkin D, Danjoux C, Greenberg M. Subsequent quality of life for children irradiated for a brain tumor before age four years. *Med Pediatr Oncol* 1998;**31**(6):506–11.
20. Odame I, Duckworth J, Talsma D, et al. Osteopenia, physical activity and health-related quality of life in survivors of brain tumors treated in childhood. *Pediatr Blood Cancer* 2005.
21. Barr RD, Simpson T, Whitton A, et al. Health-related quality of life in survivors of tumours of the central nervous system in childhood–a preference-based approach to measurement in a cross-sectional study. *Eur J Cancer* 1999;**35**(2):248–55.
22. Landolt M, Vollrath M, Niggli F, et al. Health-related quality of life in children with newly diagnosed cancer: a one year follow-up study. *Health and Quality of Life Outcomes* 2006;**4**(1):63.
23. Bhat SR, Goodwin TL, Burwinkle TM, et al. Profile of daily life in children with brain tumors: an assessment of health-related quality of life. *J Clin Oncol* 2005;**23**(24):5493–500.
24. Campo JV, Comer DM, Jansen-Mcwilliams L, et al. Recurrent pain, emotional distress, and health service use in childhood. *J Pediatr* 2002;**141**(1):76–83.
25. Varni JW, Limbers C, Burwinkle TM. Literature Review: Health-Related Quality of Life Measurement in Pediatric Oncology: Hearing the Voices of the Children. *J Pediatr Psychol* 2007:28.
26. Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. *Qual Life Res* 2001;**10**(4):347–57.
27. Levi RB, Drotar D. Health-related quality of life in childhood cancer: discrepancy in parent-child reports. *Int J Cancer Suppl* 1999;**12**:58–64.
28. Russell KM, Hudson M, Long A, et al. Assessment of health-related quality of life in children with cancer: consistency and agreement between parent and child reports. *Cancer* 2006;**106**(10):2267–74.
29. Eiser C, Eiser JR, Stride C. Quality of life in children newly diagnosed with cancer and their mothers. *Health and Quality of Life Outcomes* 2005;**3**(1):29.
30. Waters E, Doyle J, Wolfe R, et al. Influence of parental gender and self-reported health and illness on parent-reported child health. *Pediatrics* 2000;**106**(6):1422–8.
31. Yule W, Bolton D, Udwin O, et al. The long-term psychological effects of a disaster experienced in adolescence: I: The incidence and course of PTSD. *J Child Psychol Psychiatry* 2000;**41**(4):503–11.
32. Wallander JL, Schmitt M, Koot HM. Quality of life measurement in children and adolescents: issues, instruments, and applications. *J Clin Psychol* 2001;**57**(4):571–85.
33. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 2001;**39**(8):800–12.
34. Varni JW, Burwinkle TM, Katz ER, et al. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer* 2002;**94**(7):2090–106.
35. Varni JW, Burwinkle TM, Seid M, et al. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr* 2003;**3**(6):329–41.
36. Beck AT, Steer RA, Brown GK. BDI-II Manual. San Antonio, Tx, The Psychological Corporation, Harcourt Brace and Company, 1996.

37. Chang PC, Yeh CH. Agreement between child self-report and parent proxy-report to evaluate quality of life in children with cancer. *Psychooncology* 2005;**14**(2):125–34.
38. Cohen L, Holiday M. *Statistics for Social Scientists*. London: Harper and Row; 1982.
39. Meeske K, Katz ER, Palmer SN, et al. Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. *Cancer* 2004;**101**(9):2116–25.
40. Jurbergs N, Russell KM, Long A, et al. Adaptive style and differences in parent and child report of health-related quality of life in children with cancer. *Psychooncology* 2007.
41. Canning EH, Canning RD, Boyce WT. Depressive symptoms and adaptive style in children with cancer. *J Am Acad Child Adolesc Psychiatry* 1992;**31**(6):1120–4.
42. Parsons SK, Barlow SE, Levy SL, et al. Health-related quality of life in pediatric bone marrow transplant survivors: according to whom? *Int J Cancer Suppl* 1999;**12**:46–51.
43. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. *Med Care* 1999;**37**(2):126–39.
44. Theunissen NC, Vogels TG, Koopman HM, et al. The proxy problem: child report versus parent report in health-related quality of life research. *Qual Life Res* 1998;**7**(5):387–97.
45. Cremeens J, Eiser C, Blades M. Factors influencing agreement between child self-report and parent proxy-reports on the Pediatric Quality of Life InventoryÖ 4.0 (PedsQLÖ) generic core scales. *Health and Quality of Life Outcomes* 2006;**4**(1):58.
46. Davis E, Nicolas C, Waters E, et al. Parent-proxy and child self-reported health-related quality of life: using qualitative methods to explain the discordance. *Qual Life Res* 2007;**16**(5):863–71.
47. Eiser C, Eiser JR, Stride CB. Quality of life in children newly diagnosed with cancer and their mothers. *Health Qual Life Outcomes* 2005;**3**(1):29.
48. Goldbeck L, Melches J. Quality of life in families of children with congenital heart disease. *Qual Life Res* 2005;**14**(8):1915–24.
49. Phipps S, Steele RG, Hall K, et al. Repressive adaptation in children with cancer: a replication and extension. *Health Psychol* 2001;**20**(6):445–51.

Pediatr Blood Cancer 2009;53:1092–1099

Family, Demographic and Illness-Related Determinants of HRQL in Children With Brain Tumours in the First Year After Diagnosis

Anthony Penn, MBBCh, MRCPCH,[1,2,3]* Stephen P. Lowis, BA (Hons), BM, BCh, MRCP, PhD,[2] Michael C.G. Stevens, MD, FRCP, FRCPCH, FRCR,[2,4] Linda P. Hunt, BSc, MSc, PhD, Cert Ed (Tech), CStat,[4] Robert I. Shortman, BSc (Hons), MPhil,[5] Renee J. McCarter, BA (Hons), MA CPsychol, AFBPsS, PhD,[5] Darwin Pauldhas, MBBS, DCH, MRCPCH,[1] Andrew L. Curran, MBBCh, BaO, MRCP, MRCPCH, DipCH, DRCOG,[1] and Peta M. Sharples, MB BS, DCH, MRCP, PhD, MRCPCH, FRCP, FRCPCH[1]

Aims. To evaluate the relationship between parent- and child-report Health-Related Quality of Life (HRQL) and demographic, tumour and family variables in children with a brain tumour in the first year after diagnosis and to identify determinants of HRQL at 12 months. ***Procedure.*** Longitudinal prospective study: Semi-structured interviews took place approximately 1, 6 and 12 months after diagnosis. HRQL was measured using the self- and parent-report PedsQL 4.0 Total Scale Score. Tumour and treatment variables considered included tumour site and grade, hydrocephalus at diagnosis, chemotherapy and radiotherapy. Family variables included measures of family function, family support and family stress, the primary carer's coping strategies and symptoms of depression and anxiety. Univariate analyses were used at all three time points, and to identify potential early predictors of HRQL at 1 year. Regression analysis was then used to identify the most important determinants of HRQL at 1 year. ***Results.*** Thirty-five patients completed the 12-month interviews. There were consistent significant negative correlations between concurrent family impact of illness and parent and self-report HRQL, and positive correlations between concurrent family support and parent-report HRQL. Treatment with radio- or chemotherapy correlated with child-report HRQL only at some time points. Multivariate analysis showed infratentorial tumour site, and poor HRQL at 1 month best predicted poor self- and parent-report HRQL at 12 months. ***Conclusion.*** Children with infratentorial tumours and poor HRQL early after diagnosis tend to have poor HRQL at 1 year. While family factors are important modulators of concurrent HRQL, they do not appear important in predicting HRQL. Pediatr Blood Cancer 2009;53:1092–1099. © 2009 Wiley-Liss, Inc.

Key words: brain tumour; CNS tumour; family; health-related quality of life; HRQL; paediatric

INTRODUCTION

Brain tumours are the second most common form of paediatric 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].

Survivors of childhood brain tumours may have difficulties re-integrating into normal life, maintaining peer relationships and attaining normal academic milestones [3–5]. Measurement of quality of life (QOL) and more specifically Health-Related Quality of Life (HRQL) has therefore become increasingly important in quantifying morbidity in children with brain tumours and in identifying strategies to provide relevant support.

Studies of long-term survivors of childhood brain tumours have shown that their QOL is lower than that observed in either normal peers or in other childhood cancer survivors [6–12]. Research by our group showed clinically significant reductions in parent and child-reported HRQL at 1, 6 and 12 months after diagnosis of a brain tumour [13]. A wide range of risk and resistance factors have been postulated to moderate outcome in children with brain tumours [14]. A number of global variables, including family and parental functioning, have been defined as resistance factors that may moderate the negative effect of risk factors such as the disease, its treatment and parental stress in children with chronic health conditions [15]. Further application of the risk-resistance theoretical framework to children with cancer in a prospective longitudinal study, identified perceived family cohesion and expressiveness as the best predictors of psychological and social adjustment in the first 9 months after diagnosis with all types of cancer [16]. This study only included two children with brain tumours, however, and therefore the results may not be generalisable to the brain tumour population. Moreover, few data are available concerning the disease-specific and family determinants of HRQL [10], particularly in the first year after diagnosis.

Previous studies have also tended to focus on parent-report measures although it is now generally accepted that any comprehensive assessment of HRQL should include, when possible, information from both child and parent, since each view may provide valid, but differing, results [13,17,18]. This study reports a prospective investigation of the relationship between parent- and child-report HRQL and demographic, tumour and family variables using a comprehensive battery of investigations in a cohort of children with a brain tumour evaluated at 1, 6 and 12 months after diagnosis.

PATIENTS AND METHODS

This was part of a longitudinal prospective cohort study using matched controls. Only the tumour patients are discussed here.

[1]Department of Paediatric Neurology, Frenchay Hospital, Bristol, UK; [2]Department of Paediatric Oncology, Bristol Royal Hospital for Children, Bristol, UK; [3]University of the Witwatersrand, Johannesburg, South Africa; [4]Institute of Child Life and Health, University of Bristol, Bristol, UK; [5]Department of Neuropsychology, Frenchay Hospital, Bristol, UK

The authors declared no potential conflicts of interest.

Grant sponsor: CLIC Sargent Charity.

*Correspondence to: Anthony Penn, C/o Rosy Bousfield, Institute of Child Life and Health, 6th Floor, UBHT Education Centre, Upper Maudlin Street, Bristol BS2 8AE, UK.
E-mail: antpenn@doctors.org.uk

Received 13 April 2009; Accepted 22 May 2009

DOI 10.1002/pbc.22157
Published online 17 July 2009 in Wiley InterScience (www.interscience.wiley.com)

Ethical approval for the study was gained from Central and South Bristol Research Ethics Committee. All parents provided written consent, and children gave assent where appropriate [13].

Participants

All children and young people with primary intracranial tumours, referred to a regional neuro-surgical unit (Frenchay Hospital, Bristol) from April 2003 to April 2005, were approached to take part in the study (Table I).

HRQL and other outcome data were collected at interviews conducted approximately 1 (t1), 6 (t6) and 12 (t12) months after diagnosis. All patients who completed t12 interviews were included in this analysis.

Interviews were face-to-face to avoid placing a high demand on children's expressive and receptive language skills and to maximise rapport building [19]. Parents and children were interviewed independently to avoid possible influence on their separate responses by one another. All interviews were undertaken by the same researcher (AP).

Dependent Variable

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 4-week period immediately prior to interview. Age-specific versions of both parent-report (applicable for ages 2–18) and self-report (applicable for ages 5–18 years) are available. There are four domains: physical, emotional, social and school; and three summary scores: the psychosocial summary is a summary of the emotional, social and school domains; the physical summary is identical to the physical domain score; and the total scale score (TSS), a summary of all four domains. Higher scores represent better HRQL [20]. The TSS was used in this analysis. The relationship between parent- and self-report HRQL has been reported in a previous article [13].

TABLE I. Demographics, Disease and Treatment Characteristics of Brain Tumour Patients

Total N (%)	35 (100)
Age at diagnosis: median (range) in years	9.1 (1.5–16.4)
Time to t1: median, (range) in months	1.8 (0.8–5.0)
Time to t12: median (range) in months	13.8 (11.2–18.7)
Gender	
Male	18 (51)
Female	17 (49)
Diagnosis, N (%)	
Low-grade astrocytoma	16 (46)
Medulloblastoma	3 (9)
Ependymoma	4 (11)
Germ cell tumour	3 (9)
Craniopharyngioma	2 (5)
Other	7 (20)
Tumour site, N (%)	
Infratentorial	18 (51)
Supratentorial	17 (49)
Presence of hydrocephalus, N (%)	
Yes	24 (69)
No	11 (31)
Tumour grade, N (%)	
Low grade	21 (60)
High grade	14 (40)
Treatment, N (%)	
Radiotherapy	20 (57)
Chemotherapy	11 (31)

t1, 1-month assessment; t6, 6-month assessment; t12, 12-month assessment.

Independent Variables

Demographic variables. These included gender and age of the child at diagnosis and socio-economic status (SES). SES was assessed using the Income Deprivation Affecting Children Indices (IDACI) of the Index of Multiple Deprivation (IMD), a measure widely used by British government departments. The IDACI represents the proportion of children aged 0–15 living in income-deprived households in an area and the score for each study participant was identified from post code of residence, using data provided by the South West Public Health Observatory [21].

Illness-related variables. Illness-related variables were limited due to relatively small patient numbers, and included the site (supra- vs. infratentorial) and grade of the tumour (high vs. low grade) based on the revised WHO classification system [22], the presence or absence of hydrocephalus at diagnosis, confirmed radiologically, and the use of cranial irradiation and chemotherapy. Previous research suggests that higher tumour grade, presence of hydrocephalus and exposure to cranial irradiation and/or chemotherapy may be associated with poorer outcome [23–30].

Family-related variables. *Beck Depression Index (BDI-II)* [31,32] and *Beck Anxiety Index (BAI)* [33] were used to assess state mental health in the main carer. Both are 21-item scales that assess various symptoms of depression and anxiety, respectively, via a self-report questionnaire. Both scales are reliable and well validated.

Impact on Families Scale (IFS) is an easily administered, reliable, and valid measure of a family member's perception of the effect of a child's condition on the family [34]. The overall family impact summary scale was used in this analysis.

Family Assessment Device (FAD) was used to assess global family functioning. This is a 60-item questionnaire designed to evaluate families according to the McMaster Model of Family Functioning [35] and is made up of seven scales measuring Problem Solving, Communication, Roles, Affective Responsiveness, Affective Involvement, Behaviour Control and General Functioning. The General Functioning subscale was used in this analysis.

Coping Health Inventory for Parents (CHIP) [36] is a 45-item self-report checklist that required parents to indicate the helpfulness of family, social and medical resources used in coping with their child with a CNS tumour. The summative TSS was used in this analysis [37]. Higher scores for this measure indicate the parent reported a greater number of coping strategies. The CHIP has been widely used to evaluate parental coping in the childhood cancer population [37–39].

Family Support Scale (FSS) is an instrument used to measure the degree to which different sources of support are perceived as helpful to families [40]. The scale consists of 18 items across five weighted subscales relating to different types of support: partner–spouse (PS), relatives/formal kinship (FK), friends/informal kinship (IK) and others in the family's social network; social organisation (SO); and specialised and generic professional services (PS). There is also a summative TSS. All scores were used in the multivariate analysis.

Statistics

Univariate analyses. Separate repeated measures analyses of variance (ANOVAs) were used to compare the following subgroups with respect to their mean profiles of both parent and self-report PedsQL at t1, t6 and t12: age (<13 years vs. ≤13 years), gender, IDACI (below vs. above median score), hydrocephalus (no vs. yes), tumour site (supra vs. infratentorial), tumour grade (low vs. high), radiotherapy (no vs. yes) and chemotherapy (no vs. yes). Analyses were carried out using the 'mixed models' procedure in SAS (SAS Inst., Inc., 1999–2001, Cary, NC) and were followed by between-group comparisons at each time point. Main effects were also calculated if no group × time interaction was suggested. Separate Pearson's correlation coefficients (r) were calculated at each time point to relate HRQL with all family variables except for the Beck Depression and Beck Anxiety Indices, which were not normally distributed; and for which Spearman's rank correlation coefficients (r_s) were used.

Multivariate analysis. Multiple regression analysis was used to determine which variables were independently related to HRQL at t12. Given the relatively small sample size, we included only variables suggested in the univariate analyses. A 5% level of significance was used throughout.

RESULTS

Participants

Of the 48 patients eligible for the study, 3 declined to participate, 7 patients died before t12 assessment and 1 patient was too young for HRQL assessment at any time-point. Two patients withdrew following t1 assessment, leaving 35 patients who completed t12 assessment and who formed the basis of this analysis. Table I provides demographic, diagnosis and treatment details.

The median age at diagnosis was 9.1 years (range 1.5–16.4), at t1 9.3 years (range 1.8–16.6) and t12 10.4 (2.6–17.6). Median time from definitive diagnosis to t1 assessment in the tumour patients was 1.8 months (range 0.8–5.0 months), and to t12 assessment 13.8 months (range 11.2–18.7 months). The complexity of postoperative management was the main cause of delay in completing t1 assessments. Follow-up assessments were undertaken approximately 6 and 12 months after t1 to avoid practice effects for other measures not reported in this article (i.e., performance and verbal IQ). The mean scores for HRQL (defined by PedsQL TSS) at the three time points are shown in Table II.

The Relationship Between HRQL (PedsQL TSS) and Demographic, Tumour and Family Variables

Demographic variables. There were no significant relationships between parent- or self-report HRQL and gender, age at diagnosis or IDACI score at any time point.

Tumour and treatment variables. The relationship between tumour and treatment variables can be seen in Figure 1.

The mean parent-report and self-report HRQL was lower for infratentorial tumours than supratentorial tumours at all time points (parent, main effect $P < 0.001$; self, main effect $P = 0.003$) and the overall mean difference was 14.6 (95% CI = 5.1–24.2) for parent-report and 13.3 (95% CI = 5.0–21.7) for self-report. It should be noted however that more children with infratentorial tumours had hydrocephalus than those with supratentorial tumours (83% vs. 53%).

There was a group × time interaction for parent- and self-report HRQL and hydrocephalus. Children with hydrocephalus had significantly lower parent- and self-report HRQL at t1 (parent, $P = 0.017$; self, $P = 0.005$) and lower self-report HRQL at t6 (self, $P = 0.027$). However, HRQL improved over time for these children and differences at t12 were not statistically significant.

Mean parent-report HRQL increased with time irrespective of grade of tumour and there was no difference overall between low- and high-grade tumours (main effect $P = 0.89$). Mean self-report HRQL was lower for high-grade tumours compared with the low grade at t1, although the difference was not significant (main effect $P = 0.053$). Improvement in mean self-report HRQL with time was more marked in those with high-grade tumours.

Mean parent-report HRQL for children who received radiotherapy was lower than children who did not receive it, at each time point. The overall mean difference was 8.8 (95% CI −3.0 to 18.5), although this was not statistically significant (main effect $P = 0.15$). Mean child-report HRQL was significantly lower for radiotherapy cases at t1. Relatively few children did not receive radiotherapy, so the comparison group is small.

Mean parent-report HRQL for children who received chemotherapy was lower than children who did not receive it, at each time point. The overall mean difference was 8.4 (95% CI −3.0 to 19.7), but was not statistically significant (main effect $P = 0.14$). Mean child-report HRQL was lower for chemotherapy cases at all time points, and the difference was significant at t1 ($P = 0.027$) and at t6 ($P = 0.002$).

Family variables. Mean/median scores for carer and family variables can be seen in Table III, and the correlation between HRQL and family/carer variables in Table IV. There was a significant negative relationship between parent-report HRQL and BDI-II ($r_s = -0.45$, $P = 0.005$) and BAI ($r_s = -0.43$, $P = 0.012$) at t6 only. Both parent and self-reported HRQL were negatively correlated with IFS at all time points: t1 (parent: $r = -0.45$, $P = 0.013$; self: $r = -0.53$, $P = 0.009$), t6 (parent: $r = -0.47$, $P = 0.004$; self: $r = -0.54$, $P = 0.005$) and t12 (parent: $r = -0.55$, $P < 0.001$; self: $r = -0.42$, $P = 0.030$). There were no significant correlations between the CHIP TSS or FAD general functioning and HRQL at any time point but there was a statistically significant correlation between parent-report HRQL and FSS TSS at

TABLE II. PedsQL TSS for Parent- and Self-Report for Brain Tumour Patients

PedsQL TSS	t1	t6	t12
Mean (SD) parent-report	61.2 (20.1) (n = 33)	75.0 (17.1) (n = 34)	76.6 (16.6) (n = 35)
Mean (SD) self-report	73.4 (18.0) (n = 24)	78.4 (15.1) (n = 25)	81.3 (10.9) (n = 27)

t1, 1-month assessment; t6, 6-month assessment; t12, 12-month assessment; PPedsQL, parent-report PedsQL; SPedsQL, self-report PedsQL; TSS, total scale score.

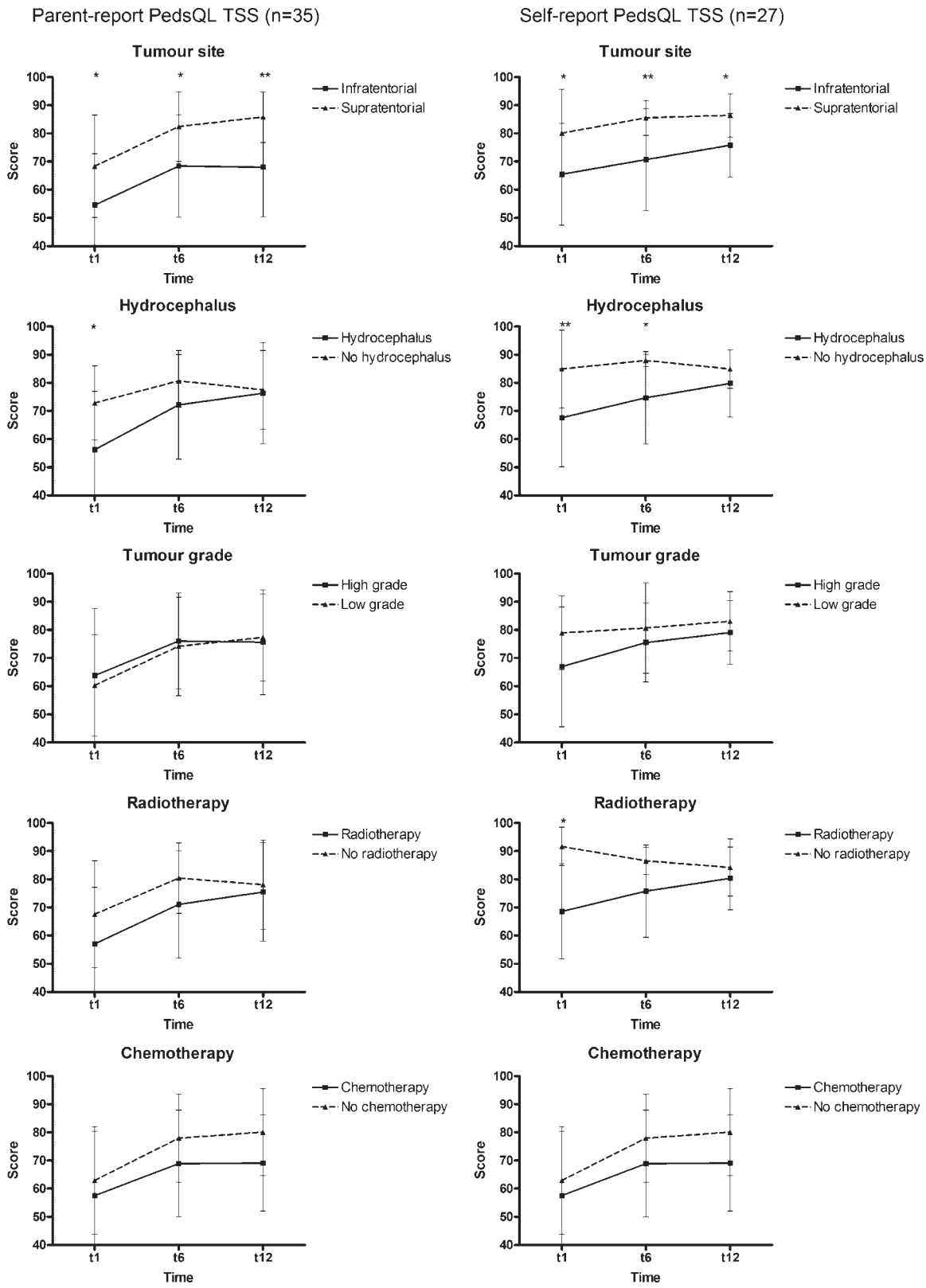

Fig. 1. Self- and parent-report PedsQL total scale score showing group means and standard deviations for tumour and treatment variables. PPedsQL, parent-report PedsQL; SPedsQL, self-report PedsQL; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

TABLE III. Mean/Median and Standard Deviation/Ranges for Family Variables at t1, t6 and t12, With Changes Over Time

Variables	t1	t6	t12	Changes over time (*P*-value)	Pairwise comparisons
BDI (median)	12 (range 0–51; n = 35)	9 (range 0–26; n = 33)	3.5 (range 0–28; n = 34)	<0.001**	t1 vs. t6, $P < 0.015$; t1 vs. t12, $P < 0.001$; t6 vs. t12, $P = 0.006$
BAI (median)	7 (range 0–53; n = 33)	5 (range 0–32; n = 33)	5 (range 0–26; n = 34)	0.024**	t1 vs. t6, $P = 0.009$; t1 vs. t12, $P = 0.019$; t6 vs. t12, $P = 0.31$
IFS (mean)	35.2 (SD 6.6; n = 32)	31.1 (SD 9.5; n = 34)	30.0 (SD 8.1; n = 35)	<0.001*	t1 vs. t6, $P < 0.001$; t1 vs. t12, $P < 0.001$; t6 vs. t12 $P = 0.46$
CHIP (mean)	82.9 (SD 12.9; n = 34)	84.4 (SD 13.8; n = 33)	83.1 (SD 15.2; n = 34)	0.81*	All ns
FAD (mean)	1.86 (SD 0.37; n = 33)	1.80 (SD 0.43; n = 32)	1.71 (SD 0.37; n = 33)	0.006*	t1 vs. t6, $P = 0.27$; t1 vs. t12, $P = 0.002$; t6 vs. t12, $P = 0.037$
FSS total (mean)	46.8 (SD 12.0; n = 35)	44.3 (SD 11.0; n = 33)	43.6 (SD 10.9; n = 34)	0.21*	t1 vs. t6, $P = 0.20$; t1 vs. t12, $P = 0.09$; t6 vs. t12, $P = 0.69$
			Components (mean)		
FSS partner/spouse	2.8 (SD 1.3)	2.5 (SD 1.2)	2.5 (SD 1.2)	0.45*	All ns
FSS informal kinship	3.1 (SD 0.8)	2.8 (SD 0.7)	2.7 (SD 0.8)	0.012*	t1 vs. t6, $P = 0.029$; t1 vs. t12, $P = 0.004$; t6 vs. t12, $P = 0.50$
FSS formal kinship	3.5 (SD 1.2)	3.1 (SD 1.2)	3.0 (SD 1.3)	0.031*	t1 vs. t6, $P = 0.035$; t1 vs. t12, $P = 0.016$; t6 vs. t12, $P = 0.76$
FSS social organisations	2.0 (SD 1.0)	2.0 (SD 0.8)	2.1 (SD 0.9)	0.79*	All ns
FSS professional services	2.8 (SD 1.0)	2.9 (SD 1.0)	2.8 (SD 0.9)	0.60*	All ns

t1, 1-month assessment; t6, 6-month assessment; t12, 12-month assessment; PPedsQL, parent-report PedsQL; SPedsQL, self-report PedsQL; BDI II, Beck Depression Inventory II; BAI, Beck Anxiety Inventory; IFS, Impact on Family Scale; CHIP, Coping Health Inventory for Parents; FAD, Family Assessment Device; FSS, Family Support Scale; ns, non significant. *Repeated measures ANOVA, followed by pairwise comparisons using post hoc *t*-tests; **Friedman tests on complete sets, followed by pairwise comparisons using Wilcoxon matched-pairs signed-ranks tests.

t6 (r = 0.59, $P < 0.001$) and t12 (r = 0.58, $P < 0.001$), and for self-report HRQL at t6 (r = 0.43, $P = 0.034$). Results for FSS subscales IK, FK and SO were similar and can be seen in Table IV.

Early predictors of HRQL at t12. HRQL at t1 correlated significantly with HRQL at t12 for both parent- (r = 0.57, $P < 0.001$) and self-report (r = 0.60, $P = 0.002$), but there were no significant correlations between family variables at t1 and either self- or parent-report HRQL at t12.

Multivariate analysis. Univariate analyses showed tumour site and PedsQL at t1 were significant determinants of both parent- and self-report PedsQL at t12. We used multiple regression analysis to determine whether IFS and FSS further contributed to parent and self-report HRQL at t12.

Parent-Report PedsQL

(i) Adding in IFS and FSS (total score) at t12: In this regression model, t12 PedsQL was negatively correlated with t12 IFS, and positively correlated with t12 FSS total level of support (both adjusted for PedsQL TSS at t1 and tumour site), but neither achieved statistical significance ($P = 0.077$ and 0.100, respectively).

(ii) Adding in IFS and component parts of FSS (IK, FK and SO): Using these three t12 FSS components gave a slightly better model than the t12 total FSS as reflected by the greater adjusted R^2 (0.61 vs. 0.56). From the model coefficients, t12 PedsQL was negatively correlated with t12 IFS ($P = 0.021$) and positively correlated with FSS (FK) ($P = 0.022$). Correlation for other FSS subscales did not reach significance.

Self-Report PedsQL

Although t12 PedsQL was negatively correlated with t12 IFS and positively correlated with t12 FSS, neither of these achieved statistical significance (both adjusting for tumour site and PQL at t1).

DISCUSSION

The study represents a prospective investigation of determinants of HRQL in children with brain tumours. While there are some data on the correlation between measures of family and parental function on adjustment in children with cancer [16,37,41–44], these studies have not specifically addressed HRQL in patients with brain tumours and their cross-sectional nature limits their ability to assist understanding of antecedent causality, as opposed to temporal association. Moreover, most previous articles have relied upon parental report [16,30,37,43,45], whereas we have investigated the relationship between HRQL using both parent-report and child-report PedsQL, and a range of demographic, tumour, treatment and family variables. Relationships of the variables to parent-report and child-report HRQL were qualitatively similar. More statistically significant relationships were seen with parent-report HRQL, probably reflecting the larger numbers of children for whom parent-report scores were available although shared method variance may also account for this.

We found no relationship between HRQL and age, gender or SES at any time. These findings contrast with data from others who reported that older age at diagnosis is a predictor of long-term HRQL in children diagnosed with medulloblastoma and cerebellar

TABLE IV. Correlates Between Family/Carer Variables and HRQL in Patients: r, Unless r_s Indicated

	BDI II (r_s)	BAI (r_s)	IFS	CHIP total	FAD general functioning	FSS total	FSS partner/ spouse	FSS informal kinship	FSS formal kinship	FSS social organisations	FSS professional services
Concurrent correlations between family and carer variables and HRQL at t1, t6 and t12											
t1 variables and t1 HRQL											
PPedsQL	−0.21 (n = 33)	−0.24 (n = 31)	−0.45* (n = 30)	0.25 (n = 33)	0.09 (n = 31)	0.17 (n = 33)	0.15 (n = 33)	0.08 (n = 33)	0.06 (n = 33)	0.30 (n = 33)	−0.05 (n = 33)
SPedsQL	−0.03 (n = 24)	−0.14 (n = 23)	−0.53** (n = 23)	0.21 (n = 24)	0.07 (n = 23)	0.02 (n = 23)	0.04 (n = 24)	−0.13 (n = 24)	−0.02 (n = 24)	0.30 (n = 24)	0.05 (n = 24)
t6 variables and t6 HRQL											
PPedsQL	−0.45** (n = 33)	−0.43* (n = 33)	−0.47** (n = 34)	−0.02 (n = 33)	−0.02 (n = 32)	0.59*** (n = 33)	0.25 (n = 33)	0.65*** (n = 33)	0.35* (n = 33)	0.60*** (n = 33)	0.18 (n = 33)
SPedsQL	−0.25 (n = 25)	−0.19 (n = 25)	−0.54** (n = 25)	−0.20 (n = 25)	0.15 (n = 25)	0.43* (n = 25)	0.23 (n = 25)	0.47* (n = 25)	0.02 (n = 25)	0.38 (n = 25)	0.29 (n = 25)
t12 variables and t12 HRQL											
PPedsQL	−0.25 (n = 34)	−0.00 (n = 34)	−0.55*** (n = 35)	0.21 (n = 34)	−0.13 (n = 33)	0.58*** (n = 34)	0.29 (n = 34)	0.55** (n = 34)	0.46** (n = 34)	0.39* (n = 34)	0.17 (n = 34)
SPedsQL	−0.35 (n = 27)	0.08 (n = 27)	−0.42* (n = 27)	0.09 (n = 27)	−0.20 (n = 27)	0.34 (n = 27)	0.27 (n = 27)	0.34 (n = 27)	0.16 (n = 27)	0.32 (n = 27)	−0.00 (n = 27)
Early family and carer correlates of HRQL at 1 year											
t1 variables and t12 HRQL											
PPedsQL	−0.07 (n = 35)	−0.20 (n = 33)	−0.16 (n = 32)	0.016 (n = 34)	0.04 (n = 33)	0.12 (n = 35)	0.13 (n = 35)	0.05 (n = 35)	0.01 (n = 35)	0.14 (n = 35)	0.03 (n = 35)
SPedsQL	0.06 (n = 27)	−0.17 (n = 26)	−0.17 (n = 26)	0.04 (n = 27)	−0.07 (n = 26)	0.08 (n = 27)	0.24 (n = 27)	−0.11 (n = 27)	−0.30 (n = 27)	0.15 (n = 27)	0.18 (n = 27)

HRQL, health-related quality of life; r, Pearson's correlation coefficient; r_s, Spearman's correlation coefficient; t1, 1-month assessment; t6, 6-month assessment; t12, 12-month assessment; PPedsQL, parent-report PedsQL; SPedsQL, self-report PedsQL; BDI II, Beck Depression Inventory II; BAI, Beck Anxiety Inventory; IFS, Impact on Family Scale; CHIP, Coping Health Inventory for Parents; FAD, Family Assessment Device; FSS, Family Support Scale. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

astrocytomas [46]. Younger age, female gender and low SES have also been associated with poorer behaviour and adjustment in other studies of children treated for brain tumour [45,47,48] . These correlations were not apparent in our data.

Although our results suggest that infratentorial tumour location and associated hydrocephalus are important factors in determining HRQL, the presence of hydrocephalus appears most important shortly after diagnosis but its effect decreases with time. The persistence of poorer HRQL in children with infratentorial tumours may be accountable by other factors such as the risk of posterior fossa syndrome [49]. There was a consistent relationship between reduced self-report HRQL and exposure to radiotherapy and/or chemotherapy. This might be explained by the immediate subjective impact of acute side effects (nausea, hair loss, additional hospitalisation) and to the stress of radiation delivery, while parents may focus greater concern on the long-term consequences of treatment. The deleterious effects of intracranial irradiation on neurocognitive and behavioural outcome are well documented. Bull et al. [30] have also demonstrated a significant reduction in health status following the addition of chemotherapy to craniospinal irradiation in children with medulloblastoma.

The significant relationship between HRQL measured early after diagnosis and approximately 1 year later offers an opportunity to identify those most at risk of poor HRQL later on. Our data show that family variables, particularly the impact that diagnosis has on the family, and the perceived helpfulness of support available, are important mediators of concurrent HRQL. The support provided by family relatives as measured by the FSS FK subscale appeared to be the most important source of support 12 months after diagnosis in our cohort. Our finding that concurrent family factors are important in determining outcome is consistent with observations by Carlson-Green et al. [37], who found that family and demographic variables best predicted behaviour problems and adaptive behaviour, emphasising the importance of considering such factors when considering outcome in children with brain tumours.

Increased parental stress has been shown to be associated with poorer social and emotional functioning in children with cancer [43] but we found only sporadic correlations between measures of parental anxiety and depression and parent-report HRQL. Unlike other studies [16,48], we found no evidence of a significant relationship between aspects of family functioning, as measured by the FAD, and HRQL. The power of this study is reduced by the patient sample size, but the findings are strengthened by the similar results using parent- and child report HRQL.

Multivariate analysis demonstrates that tumour site and HRQL early after diagnosis are the most important determinant of HRQL at 1 year. Our data also suggest that measures to increase support and reduce familial stress may improve HRQL in the short term; early interventions in this sphere may have long-term benefit. Larger, disease-specific multicentre trials will be necessary to further test this.

ACKNOWLEDGMENT

We acknowledge the financial support from the CLIC Sargent Charity, and the Bowles Bequest and the advice and support of Professor Peter Cooper, Consultant Paediatrician, Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa.

REFERENCES

1. Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): An epidemiological study. Lancet 2004;364: 2097–2105.
2. Peris-Bonet R, Martinez-Garcia C, Lacour B, et al. Childhood central nervous system tumours—Incidence and survival in Europe (1978–1997): Report from Automated Childhood Cancer Information System project. Eur J Cancer 2006;42:2064–2080.
3. Lannering B, Marky I, Lundberg A, et al. Long-term sequelae after pediatric brain tumors: Their effect on disability and quality of life. Med Pediatr Oncol 1990;18:304–310.
4. Mostow EN, Byrne J, Connelly RR, et al. Quality of life in long-term survivors of CNS tumors of childhood and adolescence. J Clin Oncol 1991;9:592–599.
5. Zebrack BJ, Gurney JG, Oeffinger K, et al. Psychological outcomes in long-term survivors of childhood brain cancer: A report from the childhood cancer survivor study. J Clin Oncol 2004;22:999–1006.
6. Eiser C, Vance YH, Horne B, et al. The value of the PedsQLTM in assessing quality of life in survivors of childhood cancer. Child Care Health Dev 2003;29:95–102.
7. Cardarelli C, Cereda C, Masiero L, et al. Evaluation of health status and health-related quality of life in a cohort of Italian children following treatment for a primary brain tumor. Pediatr Blood Cancer 2006;46:637–644.
8. Odame I, Duckworth J, Talsma D, et al. Osteopenia, physical activity and health-related quality of life in survivors of brain tumors treated in childhood. Pediatr Blood Cancer 2006;46:357–362.
9. Barr RD, Simpson T, Whitton A, et al. Health-related quality of life in survivors of tumours of the central nervous system in childhood—A preference-based approach to measurement in a cross-sectional study. Eur J Cancer 1999;35:248–255.
10. Meeske KA, Patel SK, Palmer SN, et al. Factors associated with health-related quality of life in pediatric cancer survivors. Pediatr Blood Cancer 2007;49:298–305.
11. Speechley KN, Barrera M, Shaw AK, et al. Health-related quality of life among child and adolescent survivors of childhood cancer. J Clin Oncol 2006;24:2536–2543.
12. Fluchel M, Horsman JR, Furlong W, et al. Self and proxy-reported health status and health-related quality of life in survivors of childhood cancer in Uruguay. Pediatr Blood Cancer 2008;50:838–843.
13. Penn A, Lowis SP, Hunt LP, et al. 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. Eur J Cancer 2008;44:1243–1252.
14. Eiser C. Children with cancer, the quality of life. Mahwah, New Jersey: Lawrence Erlbaum Associates, Inc.; 2004.
15. Wallander JL, Varni JW, Babani L, et al. Family resources as resistance factors for psychological maladjustment in chronically ill and handicapped children. J Pediatr Psychol 1989;14:157–173.
16. Varni JW, Katz ER, Colegrove R, Jr., et al. Family functioning predictors of adjustment in children with newly diagnosed cancer: A prospective analysis. J Child Psychol Psychiatry 1996;37:321–328.
17. De Clercq B, De Fruyt F, Koot HM, et al. Quality of life in children surviving cancer: A personality and multi-informant perspective. J Pediatr Psychol 2004;29:579–590.
18. Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. Qual Life Res 2001;10:347–357.

19. Wallander JL, Schmitt M, Koot HM. Quality of life measurement in children and adolescents: Issues, instruments, and applications. J Clin Psychol 2001;57:571–585.
20. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: Reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39:800–812.
21. Office of the Deputy Prime Minister. The English Indices of Deprivation 2004: Summary (revised). http://www.commdepartmenties.gov.uk/documents/commdepartmenties/pdf/131209.pdf (accessed October 2, 2008).
22. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97–109.
23. Desai KI, Nadkarni TD, Muzumdar DP, et al. Prognostic factors for cerebellar astrocytomas in children: A study of 102 cases. Pediatr Neurosurg 2001;35:311–317.
24. Grill J, Viguier D, Kieffer V, et al. Critical risk factors for intellectual impairment in children with posterior fossa tumors: The role of cerebellar damage. J Neurosurg 2004;101:152–158.
25. Mabbott DJ, Spiegler BJ, Greenberg ML, et al. Serial evaluation of academic and behavioral outcome after treatment with cranial radiation in childhood. J Clin Oncol 2005;23:2256–2263.
26. Merchant TE, Lee H, Zhu J, et al. The effects of hydrocephalus on intelligence quotient in children with localized infratentorial ependymoma before and after focal radiation therapy. J Neurosurg 2004;101:159–168.
27. Mulhern RK, Merchant TE, Gajjar A, et al. Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol 2004;5:399–408.
28. Poretti A, Grotzer MA, Ribi K, et al. Outcome of craniopharyngioma in children: Long-term complications and quality of life. Dev Med Child Neurol 2004;46:220.
29. Reimers TS, Ehrenfels S, Mortensen EL, et al. Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. Med Pediatr Oncol 2003;40:26–234.
30. Bull KS, Spoudeas HA, Yadegarfar G, et al. Reduction of health status 7 years after addition of chemotherapy to craniospinal irradiation for medulloblastoma: A follow-up study in PNET 3 trial survivors on behalf of the CCLG (formerly UKCCSG). J Clin Oncol 2007;25:4239–4245.
31. Beck AT, Steer RA, Ball R, et al. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess 1996;67:588–597.
32. Beck AT, Steer RA, Brown GK. BDI-II Manual. San Antonio, TX: The Psychological Corporation, Harcourt Brace and Company; 1996.
33. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: Psychometric properties. J Consult Clin Psychol 1988;56:893–897.
34. Stein RE, Jessop DJ. The impact on family scale revisited: Further psychometric data. J Dev Behav Pediatr 2003;24:9–16.
35. Epstein NB, Baldwin LM, Bishop DS. The McMaster Family Assessment Device. J Marital Fam Therapy 1983;9:171–180.
36. McCubbin H, McCubbin MA, Patterson JM, et al. CHIP-Coping Health Inventory for parents: An assessment of parental coping patterns in the care of the chronically ill child. J Marriage Family 1983;45:359–370.
37. Carlson-Green B, Morris RD, Krawiecki N. Family and illness predictors of outcome in pediatric brain tumors. J Pediatr Psychol 1995;20:769–784.
38. Eiser C, Havermans T, Eiser JR. Parents' attributions about childhood cancer: Implications for relationships with medical staff. Child Care Health Dev 1995;21:31–42.
39. Patistea E. Description and adequacy of parental coping behaviours in childhood leukaemia. Int J Nurs Stud 2005;42:283–296.
40. Dunst CJ, Trivette CM, Deal AG. Enabling and empowering families: Principles and guidelines for practice. Cambridge, MA: Brokklyn Books; 1988.
41. Robinson KE, Gerhardt CA, Vannatta K, et al. Parent and family factors associated with child adjustment to pediatric cancer. J Pediatr Psychol 2007;32:400–410.
42. Trask PC, Paterson AG, Trask CL, et al. Parent and adolescent adjustment to pediatric cancer: Associations with coping, social support, and family function. J Pediatr Oncol Nurs 2003;20:36–47.
43. Colletti CJ, Wolfe-Christensen C, Carpentier MY, et al. The relationship of parental overprotection, perceived vulnerability, and parenting stress to behavioral, emotional, and social adjustment in children with cancer. Pediatr Blood Cancer 2008;51:269–274.
44. Phipps S, Mulhern RK. Family cohesion and expressiveness promote resilience to the stress of pediatric bone marrow transplant: A preliminary report. J Dev Behav Pediatr 1995;16:257–263.
45. Mulhern RK, Carpentieri S, Shema S, et al. Factors associated with social and behavioral problems among children recently diagnosed with brain tumor. J Pediatr Psychol 1993;18:339–350.
46. Roncadin C, Dennis M, Greenberg ML, et al. Adverse medical events associated with childhood cerebellar astrocytomas and medulloblastomas: Natural history and relation to very long-term neurobehavioral outcome. Childs Nerv Syst 2008;24:995–1002.
47. Barrera M, Schulte F, Spiegler B. Factors influencing depressive symptoms of children treated for a brain tumor. J Psychosoc Oncol 2008;26:1–16.
48. Foley B, Barakat LP, Herman-Liu A, et al. The impact of childhood hypothalamic/chiasmatic brain tumors on child adjustment and family functioning. Child Health Care 2000;29:209–223.
49. Wolfe-Christensen C, Mullins LL, Scott JG, et al. Persistent psychosocial problems in children who develop posterior fossa syndrome after medulloblastoma resection. Pediatr Blood Cancer 2007;49:723–726.

Pediatr Blood Cancer 2010;55:1377–1385

Child-Related Determinants of Health-Related Quality of Life in Children With Brain Tumours 1 Year After Diagnosis

Anthony Penn, MBBCh, MRCPCH,[1,2,3]* Robert I. Shortman, BSc (Hons), Mphil,[4]
Stephen P. Lowis, BA (Hons), BM, BCh, MRCP, PhD,[2] Michael C.G. Stevens, MD, FRCP, FRCPCH, FRCR,[2,5]
Linda P. Hunt, BSc, MSc, PhD, Cert Ed (Tech), CStat,[5] Renee J. McCarter, BA (Hons), MA CPsychol, AFBPsS, PhD,[4]
Andrew L. Curran, MBBCh, BaO, MRCP, MRCPCH, DipCH, DRCOG,[1]
and Peta M. Sharples, MB BS, DCH, MRCP, PhD, MRCPCH, FRCP, FRCPCH[1]

Objectives. Infratentorial tumour site and health-related quality of life (HRQL) 1 month after diagnosis have been shown to predict HRQL 1 year after diagnosis in children with brain tumours. This study aimed to identify additional early child-related determinants of parent- and child-report HRQL. ***Methods.*** Longitudinal prospective study. Semi-structured interviews took place approximately 1 and 12 months after diagnosis. HRQL was measured using the self- and parent-report Pediatric Quality of Life Scales (PedsQL 4.0) Total Scale Score and Health Utilities Index Mark 3 (HUI3) multi-attribute utility function. Child variables included performance and verbal IQ, general memory, selective attention executive function, behaviour problems, adaptive behaviour, symptoms of depression and anxiety and event related anxiety. Univariate analyses were used to identify potential early predictors of HRQL. Regression analysis was then used to identify the most important determinants of HRQL at 1 year. ***Results.*** Thirty-five patients completed the 12-month interviews. Multivariate analysis showed infratentorial tumour site remained an important determinant of HRQL 1 year after diagnosis. Infratentorial tumour site and selective attention at 1 month generally best predicted poor self- and parent-report HRQL at 12 months. Adaptive behaviour and performance IQ may be important. ***Conclusion.*** Selective attention and infratentorial tumour site are most important in predicting both parent- and self-report HRQL at 1 year after diagnosis. Larger prospective studies are needed to confirm these findings. Cognitive remediation or/and pharmacological intervention, particularly aimed at children with infratentorial tumours may improve attention and subsequently HRQL and both merit further investigation. Pediatr Blood Cancer. 2010;55:1377–1385. © 2010 Wiley-Liss, Inc.

Key words: adaptive behaviour; behaviour; brain tumour; CNS tumour; cognition; health-related quality of life, HRQL; paediatric; psychosocial; quality of survival

INTRODUCTION

Brain tumours are the second most common form of paediatric cancer, accounting for over 20% of cases in European children [1]. Approximately 65% of children treated for brain tumour now achieve long-term survival [2]. Survivors of childhood brain tumours may have difficulties re-integrating into normal life, maintaining peer relationships and attaining normal academic milestones [3–5]. Measurement of quality of life (QOL) and more specifically Health-Related Quality of Life (HRQL) have therefore become increasingly important in quantifying morbidity in children with brain tumours and in identifying strategies to provide relevant support. Studies of long-term survivors of childhood brain tumours have shown that their QOL is lower than that observed in either normal peers or in other childhood cancer survivors [6–13].

Recent research by our group showed clinically significant reductions in parent and child-reported HRQL at 1, 6 and 12 months after diagnosis of a brain tumour [14]. A wide range of risk and resistance factors have been postulated to moderate outcome in children with brain tumours [15]. Interventions targeted at either decreasing risk, or strengthening resistance factors could possibly improve long-term outcome and HRQL. In addition, the identification of early predictors of poor HRQL may allow for identification of and targeted intervention for those at highest risk. While there are some data which link measures of family and parental function with adjustment in children with cancer [16–21], these studies have not specifically addressed HRQL in brain tumour patients. Their cross sectional nature limits their ability to assist understanding of causality, as opposed to association, and they do not include child variables that may modulate HRQL. Previous work by our group reported a concurrent correlation between HRQL and family support and an inverse correlation with family stress. However, we found no evidence that family factors modulate future HRQL in children with brain tumours 1 year after diagnosis [22]. Moreover, there are little data available concerning the relative importance of behavioural, emotional or cognitive function as determinants of HRQL in children with brain tumours.

Possible neurocognitive factors which have been shown to be compromised in children with CNS tumours and may be important in modulating HRQL include intelligence (PIQ and VIQ), memory, attention and executive functioning [23–25]. Through its effect on general intelligence, radiotherapy has been shown to be important in predicting HRQL in long-term survivors of childhood brain tumours [26]. A recent study by Papazoglou et al. (2009) [27] identified parent reported attention problems within 3 years of diagnosis predicted adaptive behaviour 3–5 years later. In addition, a child's emotional and behavioural status may contribute to feelings of worthlessness, isolation and subsequently impact on HRQL. There is some evidence that methylphenydate may improve the establishment of social relationships with peers in children with ADHD [28].

[1]Department of Paediatric Neurology, Frenchay Hospital, Bristol, UK; [2]Department of Paediatric Oncology, Bristol Royal Hospital for Children, Bristol, UK; [3]Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [4]Department of Neuropsychology, Frenchay Hospital, Bristol, UK; [5]Department of Clinical Sciences at South Bristol, University of Bristol, Bristol, UK

Grant sponsor: CLIC Sargent; Grant sponsor: Bowles Bequest.

Conflict of interest: Nothing to declare.

*Correspondence to: Anthony Penn, C/o Rosy Bousfield, Institute of Child Life and Health, 6th Floor, UBHT Education Centre, Upper Maudlin Street, Bristol BS2 8AE, United Kingdom.
E-mail: antpenn@doctors.org.uk

Received 3 September 2009; Accepted 14 June 2010

DOI 10.1002/pbc.22743
Published online 15 October 2010 in Wiley Online Library (wileyonlinelibrary.com).

It is now generally accepted that any comprehensive assessment of HRQL should include, when possible, information from both child and parent, since each view may provide valid, but differing, results [14,29,30].

Previous work by our group looking at tumour (grade, site, presence of hydrocephalus at diagnosis), treatment (treatment with chemotherapy or radiotherapy in the first year after diagnosis) and family variables has shown that infratentorial tumour site and HRQL early after diagnosis are the most important influences of HRQL at 1 year [22]. In this study, we report on the relationship between child variables and parent- and child-report HRQL at 12 months after diagnosis.

PATIENTS AND METHODS

This was part of a longitudinal prospective cohort study using matched controls. Only the tumour patients are discussed here. Ethical approval for the study was gained from Central and South Bristol Research Ethics Committee. All parents provided written consent, and children gave assent where appropriate [14].

Participants

All children and young people with primary intracranial tumours, aged between 0 and 18 years, referred to a regional paediatric neurosurgical unit (Frenchay Hospital, Bristol) from April 2003 to April 2005, were approached to take part in the study (Table I).

HRQL and other outcome data were collected at interviews conducted approximately 1 (t1) and 12 (t12) months after diagnosis. All patients who completed t12 interviews were included in this analysis. Patients too young for particular versions of the HRQL instruments used were excluded from analysis using that particular version alone, and not from all analyses (please see dependent variables below for age range of HRQL instruments).

Interviews were face-to-face to avoid placing a high demand on children's expressive and receptive language skills and to maximise building of rapport [31]. Parents and children were interviewed independently, to avoid possible influence on their separate responses by one another. With the exception of a small number of t1 interviews, assessments were undertaken by the same pair of researchers (A.P. and R.I.S.), each of which performed the same tests at each interview. Assessments took approximately 2 hr, and both direct testing and questionnaires were conducted in the same order for all interviews. Care was taken to ensure that patients and controls were not fatigued, with short breaks allowed to facilitate this.

Dependent Variables

The Pediatric 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 4-week period immediately prior to interview. Scores range from 0 to 100 with higher scores representing better HRQL. Age-specific versions of both parent-report (applicable for ages 2–18) and self-report (applicable for ages 5–18 years) are available. There are four domains; physical, emotional, social and school; and three summary scores: The psychosocial summary collates the emotional, social and school domains; the physical summary is identical to the physical domain score; and the total scale score (TSS), an overall summary of all four domains. Higher scores represent better HRQL [32]. The TSS was used in this analysis. The relationship between parent- and self-report HRQL has been reported in a previous paper [14].

Health Utilities Index Mark 3 (HUI 3). The HUI is a generic, preference-based system designed to measure health status and HRQL. We used the more recently developed HUI3, rather than the HUI2, as it is the more descriptive system, and has full structural independence [33].

The HUI3 consists of eight attributes (domains) selected according to the importance placed on them by parents in the general public [34,35]. The domains comprise vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. Measures of disability for each attribute are converted into single attribute utility function (SAUF) scores with interval scale properties. The multiplicative Multi-Attribute Utility Function (MAUF) incorporates all eight attributes, and represents overall HRQL. SAUF scores range from 0.00 to 1.00, with higher scores representing better HRQL. MAUF scores ranges from −0.36 to 1.00, defined 0.00 = death and 1.00 = perfect health. Negative scores therefore represent health states considered worse than death. The HUI3 proxy-report can be used in children aged 5 and above. The self-report HUI3 can be used in children aged 8 and above. We used the proxy-report at t1 and t12 and the self-report at t12.

The HUI3 has been used to estimate health status at the population level and in survivors of childhood cancer [36,37]. It has also been used to evaluate HS and HRQL in survivors of central nervous system tumours in Canada and the UK [10,38].

Independent Variables

Demographic and Illness-Related Variables. Neither gender, age of the child at diagnosis nor socio-economic status (SES) had been found to be related to HRQL in our earlier analysis [22]. Furthermore, of the illness-related variables we had studied, namely site (supra- vs. infratentorial) and grade of the tumour (high vs. low grade based on the revised WHO classification system) [39], the presence or absence of hydrocephalus at diagnosis (confirmed radiologically), and the use of cranial irradiation and chemotherapy. Infratentorial tumour site emerged as the main tumour/treatment-related determinant of HRQL at 1 year [22]. Given the small sample size, and subsequent limitations on the number of variables for multivariable analysis (see below), only tumour site is considered here.

Child-Related Variables

These included measures of cognitive and behavioural/emotional outcome. All measures are well-established, have good validity and reliability and have been previously used in studies of childhood cancer. Measures were either direct, face-to-face assessments of function or questionnaire based. In multivariate analysis, HRQL at t1 strongly predicted HRQL at t12 [22], and was therefore included in our analysis.

Directly Observed Measures

Age appropriate Wechsler Intelligence scales were used to measure performance and verbal IQ (PIQ and VIQ). Wechsler Intelligence Scale for Children-Third Edition (WISC-III^{UK}) [40] was used to measure Performance and Verbal IQ in participants aged 6–16. Participants over 16 were tested with the Wechsler Abbrevi-

TABLE I. Demographic, Disease and Treatment Characteristics of Brain Tumour Patients

Age at Diag.	Age at t1	Age at t12	Sex	Tumour type	Surgery	Hydrocephalus	Tumour site	Radiotherapy	Chemotherapy
6.2	6.4	7.4	F	Right occipital ependymoma	GTR	N	S	Y	Y
2.6	2.7	3.7	M	Cerebellar LG astrocytoma	GTR	Y	I	N	N
1.9	2.0	2.9	M	Cerebellar ependymoma	STR	N	I	N	Y
12.3	12.5	13.5	M	Pineal germ cell tumour	Biopsy	Y	S	Y	Y
7.6	7.7	8.8	F	Cerebellar LG astrocytoma	STR	Y	I	Y	N
3.6	3.9	5.1	F	Cerebellar LG astrocytoma	STR	Y	I	N	N
12.7	12.8	13.9	F	Pineal LG astrocytoma	Biopsy	Y	S	N	N
1.5	1.8	2.6	F	Cerebellar LG astrocytoma	GTR	Y	I	N	N
12.0	12.2	13.1	M	Pineal germ cell tumour	Biopsy	Y	S	Y	N
11.1	11.3	12.4	M	Medulloblastoma	STR	Y	I	Y	Y
7.5	7.7	8.7	F	Medulloblastoma	STR	Y	I	Y	Y
14.8	15.0	16.3	M	Right parietal HG astrocytoma	STR	Y	S	Y	Y
4.0	4.2	5.1	M	Hypothalamic LG astrocytoma	STR	Y	S	N	N
13.8	13.9	14.9	M	Right parietal LG astrocytoma	STR	N	S	N	N
5.8	6.0	6.9	M	Left peri-ventricular LG astrocytoma	Biopsy	N	S	Y	N
2.2	2.7	3.2	M	left lateral ventricular choroid plexus papilloma	GTR	Y	S	N	N
16.2	16.5	17.3	M	Pituitary germ cell tumour	Biopsy	N	S	Y	N
1.5	1.8	2.8	M	Left fronto-parietal ependymoma	GTR	N	S	N	Y
14.1	14.2	15.3	F	Left frontal parafalcine Meningioma	STR	N	S	N	N
13.5	13.7	14.6	M	Pineoblastoma	STR	Y	S	Y	Y
9.1	9.3	10.3	M	Right fronto-parietal ependymoma	GTR	N	S	N	N
13.1	13.2	14.2	F	Optic nerve LG astrocytoma	STR	N	I	Y	N
6.4	6.4	7.7	F	Fourth ventricle ependymoma	GTR	Y	I	Y	N
9.2	9.3	10.4	F	Hypothalamic LG astrocytoma	STR	Y	S	Y	N
4.2	4.3	5.3	F	Cerebellar LG astrocytoma	GTR	Y	I	N	N
9.6	9.7	10.7	F	Craniopharyngioma	STR	N	S	Y	N
11.8	12.0	12.9	M	Craniopharyngioma	STR	Y	S	Y	N
11.6	11.7	12.7	F	Hypothalamic LG astrocytoma	STR	Y	I	Y	Y
16.4	16.6	17.6	M	Cerebellar HG astrocytoma	STR	Y	I	Y	Y
8.7	8.9	9.9	F	Cerebellar LG astrocytoma	STR	Y	I	N	N
15.9	16.0	17.0	F	Cerebellar LG astrocytoma	STR	Y	I	Y	N
3.7	3.9	4.9	F	Cerebellar LG astrocytoma	GTR	N	I	N	N
7.6	7.8	8.8	M	Cerebellar LG astrocytoma	GTR	Y	I	N	N
9.2	9.4	10.4	F	Medulloblastoma	STR	Y	I	Y	Y
15.2	15.3	16.3	M	Cerebellar LG astrocytoma	STR	Y	I	Y	N

Diag, diagnosis; t1, 1-month assessment; t12, 12-month assessment; PPedsQL, parent-report PedsQL; SPedsQL, self-report PedsQL; PHUI, parent-report HUI; SHUI, self-report HUI; F, female; M, male; LG, low grade; HG, high grade; GTR, gross total resection; STR, sub-total resection; S, supratentorial; I, infratentorial; Y, yes; N, No.

ated Scale of Intelligence (WASI) [41], and children ages 3–5 years, the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) [42].

The Test of Everyday Attention for Children (TEA-Ch) [43] was used to measure selective attention. The TEA-Ch provides measures of selective, sustained and divided attention and attention control and switching. We used the 'sky search-visual selective attention' age-scaled score, which is relatively free from the influence of motor slowness.

The Children's Memory Scale (CMS) [44] provides a measure of the child's visual and verbal learning, recall and recognition; its summary score, the General Memory Index (GMI), was used in this analysis as a global measure of memory function in children aged 5–16 years. The Wechsler Memory Scale was used for children aged over 16 years.

The Behaviour Rating Inventory of Executive Functioning (BRIEF) [45] parent questionnaire was used to measure executive functioning in children aged 5 years and older. The summary 'Global Executive Composite' score was used for this analysis.

Questionnaire-Based Measures

The Child Behaviour Checklist (CBCL) [46,47] is a well-validated and widely used measure of child behaviour, can be used from 1.5 to 18 years, and was used to obtain parental rating of externalising and internalising behaviour problems in their child. It was completed by the main caregiver. The CBCL externalising scale provides a measure of under-controlled behaviours such as aggression; the internalising scale a measure of over-controlled behaviours such as unhappiness, and withdrawal.

The Vineland Adaptive Behaviour Scales (VABS), Survey Form [48] is a parent report questionnaire and was used to attain a general measure adaptive behaviour, that is the daily activities required for personal and social sufficiency for all children. There are three functional domains: communication, daily living skills and socialisation, and for children younger than 6 years an additional Motor Skills domain. We used the Adaptive Behaviour Composite Score, a summary of the four domains in this study.

The Birleson Depression Scale (BDS) [49,50] was used to assess symptoms of depression in the child. It is a self-report questionnaire, and can be used in children aged >8 years. The children indicate how often they have experienced various depressive feelings, thoughts and behaviours over the past week as 'most', 'sometimes' or 'never'.

The Revised Children's Manifest Anxiety Scale (RCMAS) [51] was used to assess symptoms of general anxiety. It is a 37-item self-report inventory evaluating apprehensive, oversensitivity/concentration and physiological factors of anxiety, and can be used in children aged >7 years.

The Children's Impact of Events Scale (IES) [52] is a self-report instrument that was developed to assess intrusive re-experiencing of the trauma and avoidance of trauma-related stimuli. It was initially developed for adults, but has proven useful for children aged >8 years [53–55].

Statistics

A series of univariate regression analyses were undertaken to determine which of the child variables measured at t1 were most strongly related to HRQL at t12. Variables significant at the 10% were considered for inclusion into a multiple regression model, together with tumour site and HRQL at t1. We then eliminated non-significant variables in a backwards fashion, but using all available cases at each step. Model checking included individually adding in all the other predictor variables (i.e. not just those identified from the univariate analysis), to check that none would significantly 'improve' the model.

RESULTS

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 HRQL assessment at any time-point. Two patients withdrew following t1 assessment, leaving 35 patients who completed t12 assessment and who formed the basis of this analysis. Table I provides demographic, diagnosis and treatment details.

For patients who completed t12 assessment, the median age at diagnosis was 9.1 years (range 1.5–16.4), and 10.4 (2.6–17.6) at t12. Median time from definitive diagnosis to t1 assessment in the tumour patients was 1.8 months (range 0.8–5.0 months), and to t12 assessment 13.8 months (range 11.2–18.7 months). The complexity of post-operative management was the main cause of delay in completing t1 assessments. The mean scores for overall HRQL (defined by PedsQL TSS and HUI3 MAUF) at t1 and t12 are shown in Table II.

With the exception of one patient, for whom assessment took place in hospital, all assessments were at home.

The Relationship Between HRQL (PedsQL TSS) and Child Variables

See Table III for results of univariate regression analysis of t1 variables and t12 HRQL. See Table IV for the multivariate regression model.

Regression Model for Parent-Report PedsQL at t12. Tumour site, parent-report PedsQL, parent-report HUI3, PIQ, VIQ, adaptive behaviour (VAB), general memory (CMS), selective attention (TEA-Ch SS) and child anxiety (RCMAS) at t1 were considered for regression analysis. The final model with best fit included tumour site, selective attention and adaptive behaviour.

Regression Model for Self-Report PedsQL at t12. Tumour site, self-report PedsQL, PIQ, VIQ, general memory (CMS), selective attention (TEA-Ch SS) and child anxiety (RCMAS) at t1 were considered. The final model with best fit included tumour site and selective attention.

Regression Model for Parent-Report HUI3 MAUF at t12. Tumour site, parent-report HUI3 MAUF, PIQ, VIQ, adaptive behaviour (VAB) and selective attention (TEA-Ch) at t1 were considered. The final model with best fit included tumour site, selective attention and adaptive behaviour.

Regression Model for Self-Report HUI3 MAUF at t12. Tumour site, PIQ and selective attention (TEA-Ch) at t1 were considered (self-report HUI3 was not assessed at t1). Only PIQ was statistically significant.

DISCUSSION

We have investigated the relationship between HRQL and a comprehensive battery of behavioural, emotional and cognitive variables using both parent-report and child-report PedsQL. We have previously identified poor early HRQL and infratentorial tumour site as important predictors of lower HRQL 1 year after diagnosis

TABLE II. Summary of PedsQL Total Scale Score and HUI3 Multi-Attribute Utility Function for Parent- and Self-Report for Brain Tumour Patients at t1 and t12 and Other Variables Measured at t1

	t1 Mean (SD) unless stated	t12 Mean (SD)
PedsQL Total Scale Score		
Parent-report	61.2 (20.1), n = 33	76.6 (16.6), n = 35
Self-report	73.4 (18.0), n = 24	81.3 (10.9), n = 27
HUI3 multiple attribute utility function		
Parent-report	0.53 (0.36), n = 26	0.74 (0.29), n = 29
Self-report	NA	0.84 (0.21), n = 27
Performance IQ	92.6 (17.7), n = 29	
Verbal IQ	96.3 (16.7), n = 29	
TEA-Ch (Sky search)	7.6 (3.6), n = 20	
Selective attention		
CMS/WMS	86.6 (23.5), n = 21	
General memory		
BRIEF GEC	54.2 (11.3), n = 20	
Executive function		
VABS composite	88.8 (16.0), n = 34	
Adaptive behaviour		
CBCL Internalising	54.5 (9.1), n = 33	
Behaviour problems		
CBCL externalising	50.9 (11.3), n = 33	
Behaviour problems		
BDS	Median 6 (range 1–18), n = 20	
Depressive symptoms		
RCMAS	41.2 (9.7), n = 21	
Anxiety symptoms		
IES	13.6 (9.3), n = 21	
Event-related stress		

t1, one month assessment; t12, 12 month assessment; PedsQL, Pediatric Quality of Life Inventory; HUI3, Health Utilities Index Mark 3; PPedsQL, parent-report PedsQL; SPedsQL, self-report PedsQL; PHUI3, parent-report HUI3; SHUI, self-report HUI3; PIQ, Performance Intelligence Quotient; VIQ, Verbal Intelligence Quotient; TEA-Ch, Test Of Everyday Attention for Children; CMS, Children's Memory Scales; WMS, Wechsler Memory Scale; BRIEF GEC; The Behaviour Rating Inventory of Executive Functioning Global Executive Composite; VABS, Vineland Adaptive Behaviour Scales; BDS, Birleson Depression Scale; RCMAS, Revised Children's Manifest Anxiety Scales; IES, (Children's) Impact of Events Scale.

[22]. Poorer HRQL in children with infratentorial tumours may be accounted for by factors such as posterior fossa syndrome [56] or the cranial nerve deficits often seen with these tumours, though as only four children in our cohort were diagnosed with posterior fossa syndrome, we were unable to assess its effect on HRQL. Our findings are in contrast to those of Aarsen et al. (2006) [57] who found no significant difference in HRQL between children with infratentorial and supratentorial tumours. This analysis shows that child variables, particularly attention and adaptive behaviour early after diagnosis may be more important in predicting HRQL 1 year after diagnosis than HRQL.

Selective attention appears to be more important than other studied cognitive measures, in predicting HRQL. As selective attention is required in both the academic and social context, where important information must be selected from extraneous distractions in the environment, this is perhaps expected. Importantly, our findings add impetus to those of Papazoglou et al. (2009) [27] in identifying, directly measured, as opposed to parent-reported attention as an important predictor of later QOS. Importantly, cognitive remediation [58,59] as well as pharmacological intervention [60], usually with methylphenidate, may improve attention and thus possibly HRQL. Encouragingly, methylphenidate has been shown to be generally well-tolerated by survivors of childhood brain tumour and leukaemia, though close monitoring for at risk groups is advised [61].

It is surprising, however, that none of the self-report emotional variables measured appeared to affect HRQL 1 year after diagnosis. This, and differences between parent and self-report HRQL, may be explained by the tendency of children with a cancer diagnosis to utilise 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 [62–64].

Similarities and differences have emerged between parent- and self-report HRQL (using the PedsQL and HUI3) and between the two HRQL measures. The PedsQL is a measure developed using the psychometric approach, and the HUI, a population, preference-based utility approach. Despite this, relationships of tumour site and the cognitive and emotional health variables to parent-and child-report HRQL using both measures were similar. For the parent- and self-report PedsQL and for the parent-report HUI3, selective attention and infratentorial tumour site appear important in determining HRQL 1 year after diagnosis.

Adaptive behaviour at t1 was significantly positively associated with both parent-report HRQL measures, but not with self-report. Shared method variance may account for this as the VAB is parent reported. PIQ was only found to be important in predicting HRQL using the self-report HUI3.

Measuring emotional health and cognitive outcomes in children is challenging: for many of their constructs (i.e. RCMAS, BDS, TEA-Ch and CMS), questionnaires are not suitable or available for

Pediatr Blood Cancer DOI 10.1002/pbc

TABLE III. Univariate Regression Analysis Using t1 Variables to Predict Overall Health-Related Quality of Life at t12

Independent variables (all measured at t1)	Dependent variables			
	PPedsQL t12	SPedsQL t12	PHUI3 t12	SHUI3 t12
PPedsQL t1	0.48 (0.12), n = 33, $P = 0.001$	NA	NA	NA
SPedsQL t1	NA	0.36 (0.10), n = 24, $P = 0.002$	NA	NA
PHUI3 t1	25.6 (8.0), n = 26, $P = 0.004$	NA	0.46 (0.15), n = 26, $P = 0.004$	NA
Performance IQ	0.41 (0.18), n = 29, $P = 0.027$	0.22 (0.11), n = 26, $P = 0.052$	0.0087 (0.0028), n = 28, $P = 0.004$	0.0063 (0.0020), n = 21, $P = 0.005$
Verbal IQ	0.40 (0.19), n = 29, $P = 0.048$	0.22 (0.12), n = 26, $P = 0.076$	0.0063 (0.0032), n = 28, $P = 0.062$	0.0032 (0.0028), n = 21, $P = 0.26$
TEA-Ch (Sky search) selective attention	2.23 (0.95), n = 20, $P = 0.030$	1.23 (0.60), n = 20, $P = 0.054$	0.0489 (0.0148), n = 20, $P = 0.004$	0.016 (0.008), n = 18, $P = 0.072$
CMS/WMS general memory	0.25 (0.14), n = 21, $P = 0.090$	0.17 (0.09), n = 21, $P = 0.064$	0.0017 (0.0026), n = 21, $P = 0.52$	0.0011 (0.0010), n = 19, $P = 0.28$
BRIEF GEC executive function	−0.08 (0.36), n = 20, $P = 0.83$	−0.24 (0.20), n = 20, $P = 0.26$	−0.0010 (0.0061), n = 20, $P = 0.88$	−0.0012 (0.0031), n = 18, $P = 0.70$
VABS composite adaptive behaviour	0.50 (0.15), n = 34, $P = 0.003$	0.20 (0.12), n = 26, $P = 0.11$	0.0059 (0.0028), n = 28, $P = 0.045$	0.0019 (0.0016), n = 20, $P = 0.26$
CBCL internalising behaviour problems	−0.41 (0.31), n = 33, $P = 0.20$	−0.24 (0.23), n = 25, $P = 0.30$	−0.0049 (0.0058), n = 27, $P = 0.41$	−0.0009 (0.0030), n = 20, $P = 0.77$
CBCL externalising behaviour problems	−0.10 (0.26), n = 33, $P = 0.69$	−0.26 (0.18), n = 25, $P = 0.17$	0.0002 (0.0049), n = 27, $P = 0.96$	−0.0001 (0.0026), n = 20, $P = 0.97$
BDS depressive symptoms	−0.68 (0.84), n = 20, $P = 0.43$	−0.40 (0.52), n = 20, $P = 0.45$	−0.0020 (0.0148), n = 20, $P = 0.89$	0.0007 (0.0061), n = 19, $P = 0.91$
RCMAS anxiety symptoms	−0.87 (0.33), n = 21, $P = 0.015$	−0.43 (0.21), n = 21, $P = 0.057$	−0.0102 (0.0062), n = 21, $P = 0.12$	−0.0025 (0.0029), n = 19, $P = 0.41$
IES event-related stress	0.26 (0.40), n = 21, $P = 0.53$	0.07 (0.25), n = 21, $P = 0.78$	0.0076 (0.0068), n = 21, $P = 0.28$	−0.0012 (0.0030), n = 19, $P = 0.69$

Values are expressed as B Coefficient (SE).

SE, standard error; t1, 1-month assessment; t12, 12-month assessment; PedsQL, Pediatric Quality of Life Inventory; HUI3, Health Utilities Index Mark 3; PPedsQL, parent-report PedsQL; SPedsQL, self-report PedsQL; PHUI3, parent-report HUI3; SHUI, self-report HUI3; PIQ, Performance Intelligence Quotient; VIQ, Verbal Intelligence Quotient; TEA-Ch, Test Of Everyday Attention for Children; CMS, Children's Memory Scales; WMS, Wechsler Memory Scale; BRIEF GEC; The Behaviour Rating Inventory of Executive Functioning Global Executive Composite; VABS, Vineland Adaptive Behaviour Scales; BDS, Birleson Depression Scale; RCMAS, Revised Children's Manifest Anxiety Scales; IES, (Children's) Impact of Events Scale.

TABLE IV. Multivariate Regression Model for Health-Related Quality of Life at t12

	Variable	Regression coefficient (SE)	*P*-value
PPedsQL t12, final model (n = 20)	Tumour site (0 = infra, 1 = supra)	18.7 (4.3)	0.001
	TEA-Ch SS (selective attention) t1	2.05 (0.57)	0.002
	VABS (adaptive composite) t1	0.32 (0.14)	0.034
	Constant	23.7 (12.4)	
SPedsQl t12, final model (n = 20)	Tumour site (0 = infra, 1 = supra)	13.9 (2.9)	<0.001
	TEA-Ch SS (selective attention) t1	1.19 (0.40)	0.009
	Constant	64.9 (3.8)	
PHUI3 t12, final model (n = 20)	Tumour site (0 = infra, 1 = supra)	0.16 (0.09)	0.089
	TEA-Ch SS (selective attention) t1	0.0459 (0.0116)	0.001
	VABS (adaptive composite) t1	0.0067 (0.0028)	0.031
	Constant	−0.28 (0.25)	
SHUI3 t12, final model (n = 21)	PIQ t1	0.0063 (0.0020)	0.005
	Constant	0.26 (0.18)	

t1, 1-month assessment; t12, 12-month assessment; PedsQL, Pediatric Qualitiy of Life Inventory; HUI3, Health Utilities Index Mark 3; PPedsQL, parent-report PedsQL; SPedsQL, self-report PedsQL; PHUI3, parent-report HUI3; SHUI, self-report HUI3; PIQ, Performance Intelligence Quotient; TEA-Ch, Test Of Everyday Attention for Children; VABS, Vineland Adaptive Behaviour Scales.

those most likely to be most affected, namely the younger children and infants. One is therefore forced to either ignore these children, or rely on proxy-report measures. In our study, we have tried to be inclusive, and therefore recruited children of all ages, despite their being, for some constructs, no age appropriate measures.

The power of this study is reduced by the patient sample size and the heterogeneous nature of our sample, but the findings are strengthened by the similar results using two different parent- and child-report HRQL measures. While our patients were unselected, their distribution is not representative of the child brain tumour population and we caution against generalising these results to those, which may emerge after longer periods of follow-up. Larger, multicentre trials, ideally of patients with specific subsets of paediatric brain tumours such as pilocytic astrocytomas or medulloblastoma will be necessary to confirm or refute our results and establish the relative importance of tumour, treatment, family and child predictors of HRQL in this population.

Interventions aimed at remediating limitations in emotional health or cognition should use HRQL as an outcome measure, particularly for survivors reporting poor outcome [65]. We have demonstrated that children with selective attention deficits early after diagnosis with a brain tumour are more likely to have decreased HRQL a year later. Cognitive remediation [58,59] as well as pharmacological intervention [60], may improve attention and subsequently HRQL and both merit further investigation.

ACKNOWLEDGMENTS

We acknowledge the financial support from CLIC Sargent, and the Bowles Bequest and the advice and support of Professor Peter Cooper, Consultant Paediatrician, Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa.

REFERENCES

1. Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS-project): An epidemiological study. Lancet 2004;364:2097–2105.
2. Peris-Bonet R, Martinez-Garcia C, Lacour B, et al. Childhood central nervous system tumours—Incidence and survival in Europe (1978–1997): Report from Automated Childhood Cancer Information System project. Eur J Cancer 2006;42:2064–2080.
3. Lannering B, Marky I, Lundberg A, et al. Long-term sequelae after pediatric brain tumors: Their effect on disability and quality of life. Med Pediatr Oncol 1990;18:304–310.
4. Mostow EN, Byrne J, Connelly RR, et al. Quality of life in long-term survivors of CNS tumors of childhood and adolescence. J Clin Oncol 1991;9:592–599.
5. Zebrack BJ, Gurney JG, Oeffinger K, et al. Psychological outcomes in long-term survivors of childhood brain cancer: A report from the childhood cancer survivor study. J Clin Oncol 2004;22:999–1006.
6. Eiser C, Vance YH, Horne B, et al. The value of the PedsQLTM in assessing quality of life in survivors of childhood cancer. Child Care Health Dev 2003;29:95–102.
7. Cardarelli C, Cereda C, Masiero L, et al. Evaluation of health status and health-related quality of life in a cohort of Italian children following treatment for a primary brain tumor. Pediatr Blood Cancer 2006;46:637–644.
8. Jenkin D, Danjoux C, Greenberg M. Subsequent quality of life for children irradiated for a brain tumor before age four years. Med Pediatr Oncol 1998;31:506–511.
9. Odame I, Duckworth J, Talsma D, et al. Osteopenia, physical activity and health-related quality of life in survivors of brain tumors treated in childhood. Pediatr Blood Cancer 2006;46:357–362.
10. Barr RD, Simpson T, Whitton A, et al. Health-related quality of life in survivors of tumours of the central nervous system in childhood—A preference-based approach to measurement in a cross-sectional study. Eur J Cancer 1999;35:248–255.
11. Meeske KA, Patel SK, Palmer SN, et al. Factors associated with health-related quality of life in pediatric cancer survivors. Pediatr Blood Cancer 2006;49:298–305.
12. Speechley KN, Barrera M, Shaw AK, et al. Health-related quality of life among child and adolescent survivors of childhood cancer. J Clin Oncol 2006;24:2536–2543.
13. Fluchel M, Horsman JR, Furlong W, et al. Self and proxy-reported health status and health-related quality of life in survivors of childhood cancer in Uruguay. Pediatr Blood Cancer 2008;50:838–843.
14. Penn A, Lowis SP, Hunt LP, et al. 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. Eur J Cancer 2008;44:1243–1252.
15. Eiser C. Children with cancer, the quality of life. Mahwah, NJ: Lawrence Erlbaum Associates, Inc.; 2004.
16. Carlson-Green B, Morris RD, Krawiecki N. Family and illness predictors of outcome in pediatric brain tumors. J Pediatr Psychol 1995;20:769–784.
17. Robinson KE, Gerhardt CA, Vannatta K, et al. Parent and family factors associated with child adjustment to pediatric cancer. J Pediatr Psychol 2007;32:400–410.
18. Trask PC, Paterson AG, Trask CL, et al. Parent and adolescent adjustment to pediatric cancer: Associations with coping, social support, and family function. J Pediatr Oncol Nurs 2003;20:36–47.
19. Colletti CJ, Wolfe-Christensen C, Carpentier MY, et al. The relationship of parental overprotection, perceived vulnerability, and parenting stress to behavioral, emotional, and social adjustment in children with cancer. Pediatr Blood Cancer 2008;51:269–274.
20. Phipps S, Mulhern RK. Family cohesion and expressiveness promote resilience to the stress of pediatric bone marrow transplant: A preliminary report. J Dev Behav Pediatr 1995;16:257–263.
21. Varni JW, Katz ER, Colegrove R, Jr., et al. Family functioning predictors of adjustment in children with newly diagnosed cancer: A prospective analysis. J Child Psychol Psychiatry 1996;37:321–328.
22. Penn A, Lowis SP, Stevens MC, et al. Family, demographic and illness-related determinants of HRQL in children with brain tumours in the first year after diagnosis. Pediatr Blood Cancer 2009;53:1092–1099.
23. Aarsen FK, Van Dongen HR, Paquier PF, et al. Long-term sequelae in children after cerebellar astrocytoma surgery. Neurology 2004;62:1311–1316.
24. Anderson V, Godber T, Smibert E, et al. Neurobehavioural sequelae following cranial irradiation and chemotherapy in children: An analysis of risk factors. Pediatr Rehabil 1997;1:63–76.
25. Mulhern RK, Palmer SL, Reddick WE, et al. Risks of young age for selected neurocognitive deficits in medulloblastoma are associated with white matter loss. J Clin Oncol 2001;19:472–479.
26. Reimers TS, Mortensen EL, Nysom K, et al. Health-related quality of life in long-term survivors of childhood brain tumors. Pediatr Blood Cancer 2009;53:1086–1091.
27. Papazoglou A, King TZ, Morris RD, et al. Parent report of attention problems predicts later adaptive functioning in children with brain tumors. Child Neuropsychol 2009;15:40–52.
28. Brown RT, Dingle A, Dreelin B. Neuropsychological effects of stimulant medication in children's learning and behaviour. In: Reynolds CR, Fletcher-Janzen E, editors. Handbook of clinical child pharmacology. New York: Wiley; 1997.
29. De Clercq B, De Fruyt F, Koot HM, et al. Quality of life in children surviving cancer: A personality and multi-informant perspective. J Pediatr Psychol 2004;29:579–590.
30. Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. Qual Life Res 2001;10:347–357.
31. Wallander JL, Schmitt M, Koot HM. Quality of life measurement in children and adolescents: Issues, instruments, and applications. J Clin Psychol 2001;57:571–585.
32. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: Reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39:800–812.
33. Horsman J, Furlong W, Feeny D, et al. The Health Utilities Index (HUI(R)): Concepts, measurement properties and applications. Health Qual Life Outcomes 2003;1:54.
34. Feeny D, Furlong W, Boyle M, et al. Multi-attribute health status classification systems. Health Utilities Index. Pharmacoeconomics 1995;7:490–502.
35. Feeny D, Furlong W, Torrance GW, et al. Multiattribute and single-attribute utility functions for the Health Utilities Index Mark 3 system. Med Care 2002;40:113–128.
36. Manuel DG, Schultz SE, Kopec JA. Measuring the health burden of chronic disease and injury using health adjusted life expectancy and the Health Utilities Index. J Epidemiol Community Health 2002;56:843–850.
37. Pogany L, Barr RD, Shaw A, et al. Health status in survivors of cancer in childhood and adolescence. Qual Life Res 2006;15:143–157.
38. Glaser AW, Furlong W, Walker DA, et al. Applicability of the Health Utilities Index to a population of childhood survivors of central nervous system tumours in the U.K. Eur J Cancer 1999;35:256–261.
39. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97–109.
40. Wechsler D. Wechsler intelligence scale for children III (WISC-III). New York: The Psychological Corporation; 1991.
41. Wechsler D. WASI Wechsler Abbreviated Scale Of Intelligence. San Antonio, TX: Harcourt Assessment; 1999.
42. Wechsler D. Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R)- Manual. New York: The Psychological Corporation; 1989.
43. Manley T, Robertson IH, Anderson V, et al. The Test Of Everyday Attention For Children (TEA-Ch). Bury St Edmunds, UK: Thames Valley Test Company; 1999.
44. Cohen M. Children's Memory Scale Manual. San Antonio: The Psychological Corporation; 1997.
45. Gioia GA, Isquith PK, Guy SC, et al. Brief-behavior rating inventory of executive function-Parent Form Professional Manual. Psychological Assessment Resources, Inc.; 2000.
46. Achenbach TM, Rescorla LA. Manual for the ASEBA Preschool Forms and Profiles. Burlington, VT: University of Vermont, Research Centre for Children; Youth and Families; 2000.
47. Achenbach TM, Rescorla LA. Manual for the ASEBA school-age forms and profiles. Burlington, VT: University of Vermont, Research Centre for Children; Youth and Families; 2001.
48. Sparrow SS, Balla DA, Cicchetti DV. Vineland Adaptive Behaviour Scalse, survey form manual. Circle Pines: American Guidance Service, Inc.; 1984.
49. Birleson P. The validity of depressive disorder in childhood and the development of a self-rating scale: A research report. J Child Psychol Psychiatry 1981;22:73–88.
50. Birleson P, Hudson I, Buchanan DG, et al. Clinical evaluation of a self-rating scale for depressive disorder in childhood (Depression Self-Rating Scale). J Child Psychol Psychiatry 1987;28:43–60.
51. Reynolds CR, Richmond BO. Manual for the Revised Children's Manifest Anxiety Scale. Los Angeles: Western Psychological Services; 1985.
52. Horowitz M, Wilner N, Alvarez W. Impact of event scale: A measure of subjective stress. Psychosom Med 1979;41:209–218.
53. Shemesh E, Keshavarz R, Leichtling NK, et al. Pediatric emergency department assessment of psychological trauma and posttraumatic stress. Psychiatr Serv 2003;54:1277–1281.
54. Dyregrov A, Gjestad R, Raundalen M. Children exposed to warfare: A longitudinal study. J Trauma Stress 2002;15:59–68.
55. Dyregrov A, Kuterovac G, Barath A. Factor analysis of the impact of event scale with children in war. Scand J Psychol 1996;37:339–350.
56. Wolfe-Christensen C, Mullins LL, Scott JG, et al. Persistent psychosocial problems in children who develop posterior fossa syndrome after medulloblastoma resection. Pediatr Blood Cancer 2007;49:723–726.
57. Aarsen FK, Paquier PF, Reddingius RE, et al. Functional outcome after low-grade astrocytoma treatment in childhood. Cancer 2006;106:396–402.

58. Butler RW, Copeland DR. Attentional processes and their remediation in children treated for cancer: A literature review and the development of a therapeutic approach. J Int Neuropsychol Soc 2002;8:115–124.
59. Butler RW, Copeland DR, Fairclough DL, et al. A multicenter, randomized clinical trial of a cognitive remediation program for childhood survivors of a pediatric malignancy. J Consult Clin Psychol 2008;76:367–378.
60. Thompson SJ, Leigh L, Christensen R, et al. Immediate neurocognitive effects of methylphenidate on learning-impaired survivors of childhood cancer. J Clin Oncol 2001;19:1802–1808.
61. Conklin HM, Lawford J, Jasper BW, et al. Side effects of methylphenidate in childhood cancer survivors: A randomized placebo-controlled trial. Pediatrics 2009;124:226–233.
62. Canning EH, Canning RD, Boyce WT. Depressive symptoms and adaptive style in children with cancer. J Am Acad Child Adolesc Psychiatry 1992;31:1120–1124.
63. Jurbergs N, Russell KM, Long A, et al. Adaptive style and differences in parent and child report of health-related quality of life in children with cancer. Psychooncology 2007;17:83–90.
64. Phipps S, Steele RG, Hall K, et al. Repressive adaptation in children with cancer: A replication and extension. Health Psychol 2001;20:445–451.
65. Ness KK, Gurney JG, Zeltzer LK, et al. The impact of limitations in physical, executive, and emotional function on health-related quality of life among adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. Arch Phys Med Rehabil 2008;89:128–136.

A Detailed Prospective Longitudinal Assessment of Health Status in Children With Brain Tumors in the First Year After Diagnosis

Anthony Penn, MBBCH, MRCPCH,† ‡ Stephen P. Lowis, BA (Hons), BM, BCh, MRCP, PhD,† Michael C.G. Stevens, MD, FRCP, FRCPCH, FRCR,† § Robert I. Shortman, BSc (Hons), Mphil,‖ Linda P. Hunt, BSc, MSc, PhD, Cert Ed (Tech), Cstat,§ Renee J. McCarter, BA (Hons), MA CPsychol, AFBPsS, PhD,‖ Andrew L. Curran, MBBCh, BaO, MRCP, MRCPCH, DipCH, DRCOG,* and Peta M. Sharples, MB BS, DCH, MRCP, PhD, MRCPCH, FRCP, FRCPCH**

Purpose: To compare health status (HS) in children with brain tumors at 1 (t1), 6 (t6), and 12 (t12) months after diagnosis with "normal" controls. To assess the relationship between parent-report and self-report HS for patients at t12.

Methods: HS was assessed using the Health Utilities Index Mark III parent-report at all time points and self-report at t12. Twenty-nine patients and 32 controls were included in analysis of parent-report, and 21 patients and 22 controls in self-report HS at t12. Nonparametric analyses were used.

Results: Patients scored significantly lower than controls for global overall HS at all time points for parent-report and at t12 for self-report ($P_{max} = 0.009$). For parent-report, patients scored significantly lower than controls in the attributes of emotion, cognition, and pain at t1 and t6, in ambulation at t1 and in dexterity at t6. At t12, the difference was statistically significant for parent-report cognition only (all $P < 0.01$). No attributes reached significance for self-report at t12. For patients, correlations between parent-report and self-report were good ($r_s > 0.73$) for all Health Utilities Index Mark 3 scores with the exception of emotion and pain.

Conclusion: HS is significantly compromised in children with brain tumors over the first year after diagnosis, but improves with time. Parent-report and self-report differ, and both should be considered in assessing outcomes or defining interventions.

Key Words: pediatric, health status, brain tumor, CNS tumor

(*J Pediatr Hematol Oncol* 2011;33:592–599)

BACKGROUND

Brain tumors are the second most common form of pediatric cancer, accounting for over 20% of all cases in European children.[1] Approximately 63% of all children treated for brain tumor now achieve long-term survival,[2] but many are at significant risk of neurological, cognitive, behavioral, endocrine and sensory problems, impaired growth and infertility as a result of tumor and treatment.[3–6] They may have difficulties re-integrating into normal life, maintaining peer relationships, and attaining normal academic milestones.[7–11] Quality of survival (QOS), measured using standardized survey methods, has therefore become important in quantifying morbidity in children treated for cancer.

Health status (HS), defined as "the state of health of a person or population assessed with reference to morbidity, impairments, anthropological measurements, mortality, and indicators of functional status and quality of life"[12] is 1 modality commonly used to quantify disability and QOS in chronic illness, including childhood brain tumor.[10,13–20] Data from the adult literature suggests that from patients' perspective, quality of life (QOL) and HS are 2 different and distinct constructs, with greater emphasis on physical functioning rather than mental health when rating HS, and the reverse for QOL.[21]

HS, using the Health Utilities Index Mark 3 (HUI3)[22] has been shown to be compromised in survivors of childhood brain tumors in comparison with survivors of other childhood cancer and noncancer controls,[10,13,20] but to date, most of the research has focused on long-term HS, and to our knowledge, no longitudinal data and very little data are available on children soon after diagnosis and treatment. Early serial measurement of morbidity, including measurement of HS, may assist our understanding of its trajectory over time, and identify those at risk of later morbidity, facilitating early targeted intervention and evaluation of its efficacy. Routine assessment of HS may also help identify aspects of HS that are compromised, which may not be disclosed in standard clinical practice.[23]

Research by our group has shown significant reductions in parent-reported and child-reported HRQL[24] in children with brain tumor compared with normal controls. Deficits in cognition were found in adaptive behavior and parent-reported internalizing behavior problems (ie, unhappiness, depression, anxiety, and withdrawal), but not in self-reported anxiety and depression, at 1, 6, and 12 months after diagnosis of a brain tumor (manuscript in preparation). However, assessment of outcome in general, and emotional or social function in particular, may vary significantly depending on whether outcomes are self-reported or parent-reported.[25]

Received for publication May 2, 2010; accepted February 1, 2011.
From the Departments of *Paediatric Neurology; ‖Neuropsychology, Frenchay Hospital; †Department of Paediatric Oncology, Bristol Royal Hospital for Children; §Department of Clinical Sciences at South Bristol, University of Bristol, Bristol, UK; and ‡University of the Witwatersrand, Johannesburg, South Africa.
Financial support: CLIC Sargent Charity and the Bowles Bequest.
The authors declare no conflict of interest.
Reprints: Anthony Penn, MBBCH, MRCPCH, C/o Rosy Bousfield, Institute of Child Life and Health, 6th Floor, UBHT Education Centre, Upper Maudlin Street, Bristol, BS2 8AE, UK (e-mail: antpenn@doctors.org.uk).

In view of the paucity of published data on this subject, we aimed to measure HS in children with brain tumors at 1, 6, and 12 months after diagnosis, and to compare HS with "normal" controls. In addition, we sought to assess the relationship between parent-report and self-report HS for patients and controls at 12 months after diagnosis.

PATIENTS AND METHODS

This was part of a prospective cohort study of outcomes in children diagnosed with primary brain tumors and their parents compared with controls. Ethical approval for the study was gained from Central and South Bristol Research Ethics Committee. All parents provided written consent, and children gave assent wherever appropriate.

Participants

All children and young people with primary intracranial tumors, referred to a regional neurosurgical unit (Frenchay Hospital, Bristol) from April 2003 to April 2005, were approached to take part in the study. Controls matched for age, sex, and socioeconomic status (SES) were selected using the best friend's model.[24]

Interviews were conducted approximately 1 (t1), 6 (t6), and 12 (t12) months after diagnosis. They usually took place in the family home to ensure that both patients and parents were as comfortable and relaxed as possible. If a patient or control withdrew from the study, analysis of their "paired subject" was continued to ensure maximum data collection. All patients and controls who completed t12 interviews were included in the analyses.

Interviews were face-to-face to avoid placing a high demand on children's expressive and receptive language skills and to maximize building of rapport.[26] Parents and children were interviewed independently, to avoid possible influence on their separate responses by one another. All interviews were undertaken by the same researcher (A.P.).

Dependent Variables

HUI 3

The HUI is a generic, preference-based system designed to measure ability or disability for HS attributes. We used the more recently developed HUI3, rather than the HUI2, as it is the more descriptive system, and has full structural independence. The HUI3 has been used to estimate HS at the population level and in survivors of childhood cancer.[20,27] It has also been used to evaluate HS in survivors of central nervous system tumors in Canada and the United Kingdom.[14,15,28]

The HUI3 consists of 8 attributes (domains) selected according to the importance placed on them by the general population.[22] The domains comprise vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Measures of disability for each attribute are converted into single attribute utility function (SAUF) scores with interval scale properties. The multiplicative multi attribute utility function (MAUF) incorporates all 8 attributes, and represents overall HS. SAUF scores range from 0.00 to 1.00, with higher scores representing better HS. HUI3 MAUF scores ranges from −0.36 to 1.00, defined as 0.00 = death and 1.00 = perfect health. Negative scores therefore represent health states considered worse than death by the general public. Differences of 0.03 or greater for HUI overall HS (MAUF) and 0.05 or greater for SAUF represent meaningful changes.[29] The HUI3 proxy report by parents in this study and referred to as such, can be used for children aged 5 and over. The self-report HUI3 can be used by children aged 8 years and over.

Both the overall MAUF and single attribute levels can be aggregated into levels of disability (none, mild, moderate, and severe). For the purpose of this study, HUI3 levels of disability were grouped as either none/mild or moderate/severe to identify those patients with more than minor disability (such as near-sightedness or far-sightedness, which would be classified as "mild" disability).[30]

Independent Variables

Demographic and Illness-related variables

These included sex and age of the child at diagnosis and the SES of the family measured by the Income Deprivation Affecting Children Indices of the Index of Multiple Deprivation (below vs. above median score).[31] Illness-related variables included the site (supratentorial vs. infratentorial) and grade of the tumor (high vs. low grade based on the revised WHO classification system),[32] the presence or absence of hydrocephalus at diagnosis (confirmed radiologically), and the use of cranial irradiation and/or chemotherapy.

Statistical Analyses

Nonparametric methods were used throughout as none of the utility scores were normally distributed. To include all data, irrespective of complete pairing, Mann-Whitney *U* tests were used to compare patients and controls with respect to parent-report and child-report SAUF. Changes in HUI3 MAUF with time were assessed using Friedman test (3 time points) followed by Wilcoxon matched pairs signed-rank tests (pair-wise comparisons). Spearman rank correlation and group means differences were used to assess the relationship between parent and child reported HS at t12. The degree of correlation was categorized as small, medium, and large when correlation coefficients were smaller than 0.3, between 0.3 and 0.5, or larger or equal to 0.5, respectively.[33] Because we analyzed patients or controls whose "matched pair" withdrew from the study, n and group means for individual analyses varied (Tables 3, 4). All analyses were carried out using the SPSS version 15 (SPSS Inc, Chicago, IL). To adjust for multiple testing, we chose to use a 1% significance level.[34]

Although the utility scores were not normally distributed, because of their interval scale properties and in keeping with other studies, means, standard deviations, and ranges were used for their data summary.[14,30]

RESULTS

Of the 48 patients eligible for the study, 3 declined to participate. Seven patients died before t12 assessment, 2 withdrew from the study, and 7 patients were too young for parent-report HUI3 assessment. Controls were successfully recruited for all but 2 patients recruited to the study. Four controls having consented to the study declined further follow-up and 7 patients were too young for parent-report HUI3 assessment. There were therefore 29 patients (15 female) and 32 controls (15 female) for comparison of parent-report at t12. Three patients and 3 controls were too young for parent-report HUI3 at t1 and t6, and one t6 control assessment did not take place.

TABLE 1. Demographic, Disease, and Treatment Characteristics of Patients With Brain Tumor

Age at Diagnosis	Age t1	Age t6	Age t12	Time to t12	Sex	Tumor type	Surgery	Hydrocephalus	Tumor		Radiotherapy	Chemotherapy
									Site	Grade		
6.2	6.4	6.7	7.4	14.2	F	Right occipital ependymoma	GTR	N	S	H	Y	Y
12.3	12.5	13.0	13.5	14.0	M	Pineal germ cell tumor	Biopsy	Y	S	H	Y	Y
7.6	7.7	8.2	8.8	13.8	F	Cerebellar LG astrocytoma	STR	Y	I	L	Y	N
3.6	3.9	4.3	5.1	18.7	F	Cerebellar LG astrocytoma	STR	Y	I	L	N	N
12.7	12.8	13.4	13.9	14.2	F	Pineal LG astrocytoma	Biopsy	Y	S	L	N	N
12.0	12.2	12.7	13.1	13.0	M	Pineal germ cell tumor	Biopsy	Y	S	H	Y	N
11.1	11.3	11.9	12.4	14.9	M	Medulloblastoma	STR	Y	I	H	Y	Y
7.5	7.7	8.3	8.7	14.0	F	Medulloblastoma	STR	Y	I	H	Y	Y
14.8	15.0	15.6	16.3	17.8	M	Right parietal HG astrocytoma	STR	Y	S	H	Y	Y
4.0	4.2	4.7	5.1	13.1	M	Hypothalamic LG astrocytoma	STR	Y	S	L	N	N
13.8	13.9	14.4	14.9	12.6	M	Right parietal LG astrocytoma	STR	N	S	L	N	N
5.8	6.0	6.4	6.9	13.8	M	left peri-ventricular LG astrocytoma	Biopsy	N	S	L	Y	N
16.2	16.5	16.7	17.3	N8	M	Pituitary germ cell tumor	Biopsy	N	S	H	Y	N
14.1	14.2	14.9	15.3	13.9	F	Left frontal parafalcine meningioma	STR	N	S	L	N	N
13.5	13.7	14.2	14.6	12.8	M	Pineoblastoma	STR	Y	S	H	Y	Y
9.1	9.3	9.9	10.3	14.2	M	Right fronto-parietal ependymoma	GTR	N	S	H	N	N
13.1	13.2	13.7	14.2	12.8	F	Optic nerve LG astrocytoma	STR	N	I	L	Y	N
6.4	6.4	7.2	7.7	15.5	F	Fourth ventricle ependymoma	GTR	Y	I	H	Y	N
9.2	9.3	9.9	10.4	14.0	F	Hypothalamic LG astrocytoma	STR	Y	S	L	Y	N
4.2	4.3	4.7	5.3	13.3	F	Cerebellar LG astrocytoma	GTR	Y	I	L	N	N
9.6	9.7	10.2	10.7	13.0	F	Craniopharyngioma	STR	N	S	L	Y	N
11.8	12.0	12.3	12.9	12.8	M	Craniopharyngioma	STR	Y	S	L	Y	N
11.6	11.7	12.2	12.7	13.8	F	Hypothalamic LG astrocytoma	STR	Y	I	L	Y	Y
16.4	16.6	17.1	17.6	14.5	M	Cerebellar HG astrocytoma	STR	Y	I	H	Y	Y
8.7	8.9	9.3	9.9	14.2	F	Cerebellar LG astrocytoma	STR	Y	I	L	N	N
15.9	16.0	16.4	17.0	13.1	F	Cerebellar LG astrocytoma	STR	Y	I	L	Y	N
7.6	7.8	8.4	8.8	13.8	M	Cerebellar LG astrocytoma	GTR	Y	I	L	N	N
9.2	9.4	10.0	10.4	13.7	F	Medulloblastoma	STR	Y	I	H	Y	Y
15.2	15.3	15.8	16.3	12.0	M	Cerebellar LG astrocytoma	STR	Y	I	L	Y	N

F indicates female; GTR, gross total resection; HG, high grade; I, infratentorial; LG, low grade; M, male; N, No; PHUI, parent-report HUI; PPedsQL, parent-report PedsQL; S, supratentorial; SHUI, self-report HUI; SPedsQL, self-report PedsQL; STR, subtotal resection; t1, 1-month assessment; t12, 12-month assessment; Y, yes.

TABLE 2. HUI3 MAUF Parent-report Scores 1, 6, and 12 Months and Self-Report at 12 Months After Diagnosis

HUI3 MAUF	N	Mean	SD	Range	Moderate/severe N (%)	*P* value (patients vs. Controls)
Parent-report						
Brain tumors t1	26	0.53	0.36	–0.22-1.00	21 (81)	< 0.001
Controls t1	29	0.95	0.08	0.70-1.00	6 (29)	
Brain tumors t6	26	0.72	0.28	0.13-1.00	16 (62)	< 0.001
Controls t6	28	0.98	0.06	0.68-1.00	1 (4)	
Brain tumors t12	29	0.74	0.29	–0.15-1.00	18 (62)	< 0.001
Controls t12	32	0.96	0.09	0.63-1.00	4 (13)	
Self-report						
Brain tumors t12	21	0.84	0.21	0.06-1.00	10 (48)	0.009
Controls t12	22	0.94	0.13	0.56-1.00	3 (14)	

HUI3 indicates Health Utilities Index Mark 3; MAUF, Multi Attribute Utility Function; t1, 1-month assessment; t12, 12-month assessment.

Self-report HUI3 was not used at t1 or t6. The importance of attaining both parent-report and self-report measures of outcome emerged over time and at t12 both were used where applicable. Six patients and 10 controls were too young for self-report HUI3 at t12. Two patients, both aged 8 years, were unwilling/unable to complete self-report HUI3. There were therefore 21 patients and 22 controls for comparison of self-report HS at t12.

Median age at diagnosis for patients was 11.1 (range, 3.6-16.4). Median age at t12 was 12.4 (range, 5.1-17.6) for patients and 10.7 (5.1-18.9) for controls. Sex distribution was similar for patients (14 males) and controls (16 males). Median time from definitive diagnosis to t1 assessment was 1.7 months (range, 0.8-3.7 mo), to t6 was 7.8 months (range, 6.2-9.8 mo), and to t12 assessment was 13.8 months (range, 12.0-18.7 mo). The complexity of postoperative management was the main cause of delay in completing t1, and this subsequently affected the timing of t6 and t12 assessments.

The 2 patients who withdrew from the study both had a diagnosis of medulloblastoma. Table 1 provides demographic, diagnosis, and treatment details.

Difference in HS Between Patients and Controls

Overall HS Using HUI3 MAUF

Table 2 shows parent-report for all time points and self-report for t12 HUI MAUF scores for patients and controls.

There was a statistically significant difference between patients and controls for all comparisons between patients and controls (maximum $P = 0.009$). There were significant changes in parent-report HUI3 MAUF for patients across the 3 time points ($P = 0.005$, Friedman test, n = 26 patients with complete data). Further pair-wise comparisons showed a significant increase between t1 and t6 ($P = 0.006$, n = 26 pairs), but no further statistically significant improvement between t6 and t12 ($P = 0.74$, n = 26). There was no significant change in overall HS with time in controls ($P = 0.12$, n = 26 complete sets).

Incidence of Moderate/Severe Levels of Disability for MAUFs in Patients

Twenty-one (81%), 16 (62%), and 18 (62%) children with brain tumor had parent-report HUI3 MAUF scores in the moderate/severe range at t1, t6, and t12, respectively, compared with 6 (29%), 1 (4%) and 4 (13%) for controls. For self-report at t12, 10 (48%) of brain tumor patients rated their overall HS as moderate/severe compared with 3 (14%) of controls.

Differences in Single Attributes of HS Between Patients and Controls

Table 3 shows parent-report for all time points and self-report for t12 HUI SAUF scores for patients and controls. There were statistically significant differences between patients and controls at t1 for ambulation, emotion, cognition, and pain parent-report SAUFs (maximum $P = 0.002$). There were statistically significant differences between patients and controls at t6 for dexterity, emotion, cognition, and pain parent-report SAUFs (maximum $P = 0.008$). There were statistically significant differences between patients and controls at t12 for cognition parent-report SAUF ($P < 0.001$), but differences did not reach statistical significance for any self-report SAUF, although numbers were smaller.

Incidence of Moderate/Severe Levels of Disability for Single Attributes in Patients

At t1 and t6, the attribute most affected to a moderate/severe extent according to parent-report was pain. At t1, following pain in decreasing frequency, cognition, ambulation, dexterity, emotion, speech, and vision were most commonly affected. At t6, following pain in decreasing frequency, ambulation, dexterity, cognition, emotion, and speech were most commonly affected.

At t12 in decreasing frequency, cognition, pain, ambulation, dexterity, emotion, vision, hearing, and speech were affected for parent-report, and cognition followed by vision, hearing, speech, ambulation, dexterity, and pain for self-report. In general, there were fewer score in the moderate or severe range at t12 than at t1 or t6 (Table 3).

Subgroup Analysis

We have previously reported a significant relationship between tumor site and parent-report and self-report HUI3 MAUF at t12.[35] There were no significant correlations between HUI3 SAUFs and any other independent variables analyzed ($P > 0.01$ for all, data not shown).

TABLE 3. Comparison of HUI3 Single Attribute Utility Functions Between Brain Tumor Patients and Controls and Prevalence of Moderate/Severe Disability

	Brain Tumor Children				Controls				
HUI/3 SAUF	N	Mean	SD	Moderate/ Severe, N (%)	N	Mean	SD	Moderate/ Severe, N (%)	*P* value (Patients vs. Controls)
Parent-report t1									
Vision	26	0.96	0.11	2 (8)	29	0.99	0.02	0	0.521
Hearing	26	1.00	0.00	0	29	1.00	0.00	0	1.00
Speech	26	0.93	0.21	3 (12)	29	0.99	0.05	0	0.275
Ambulation	26	0.74	0.37	8 (31)	29	1.00	0.00	0	< 0.001
Dexterity	26	0.88	0.28	4 (15)	29	1.00	0.00	0	0.014
Emotion	26	0.93	0.10	4 (15)	29	0.99	0.02	0	< 0.001
Cognition	26	0.85	0.20	8 (31)	29	0.98	0.07	1 (3)	0.002
Pain	26	0.75	0.34	11 (42)	29	0.98	0.07	3 (10)	< 0.001
Parent-report t6									
Vision	26	1.00	0.01	0	28	0.99	0.02	0	0.705
Hearing	26	1.00	0.00	0	28	1.00	0.00	0	1.00
Speech	26	0.97	0.08	1 (4)	28	1.00	0.00	0	0.033
Ambulation	26	0.85	0.32	5 (19)	28	1.00	0.00	0	0.016
Dexterity	26	0.90	0.23	4 (15)	28	1.00	0.00	0	0.008
Emotion	26	0.96	0.08	2 (8)	28	1.00	0.00	0	0.004
Cognition	26	0.92	0.09	2 (8)	28	1.00	0.00	0	< 0.001
Pain	26	0.89	0.15	8 (31)	28	0.98	0.10	1 (4)	0.002
Parent-report t12									
Vision	29	0.97	0.09	2 (7)	32	1.00	0.01	0	0.330
Hearing	29	0.96	0.13	2 (7)	32	1.00	0.00	0	0.134
Speech	29	0.98	0.07	1 (3)	32	1.00	0.00	0	0.064
Ambulation	29	0.91	0.26	3 (10)	32	1.00	0.00	0	0.031
Dexterity	29	0.95	0.14	2 (7)	32	0.98	0.10	1 (3)	0.141
Emotion	29	0.97	0.07	2 (7)	32	0.99	0.05	1 (3)	0.056
Cognition	29	0.86	0.19	8 (28)	32	0.98	0.06	1 (3)	< 0.001
Pain	29	0.90	0.21	6 (21)	32	0.98	0.06	2 (6)	0.018
Self-report t12									
Vision	21	0.98	0.09	1 (5)	22	0.99	0.02	0	0.904
Hearing	21	0.98	0.11	1 (5)	22	1.00	0.00	0	0.306
Speech	21	0.98	0.05	0	22	1.00	0.00	0	0.143
Ambulation	21	0.94	0.19	1 (5)	22	1.00	0.00	0	0.069
Dexterity	21	0.95	0.12	1 (5)	22	0.98	0.12	1 (5)	0.045
Emotion	21	0.97	0.04	0	22	0.98	0.06	1 (5)	0.487
Cognition	21	0.92	0.11	3 (14)	22	0.97	0.09	2 (9)	0.012
Pain	21	0.94	0.22	1 (5)	22	0.99	0.03	0	0.369

HUI3 indicates Health Utilities Index Mark 3; SAUF, Single Attribute Utility Function; t1, 1-month assessment; t12, 12-month assessment; t6, 6-month assessment.

TABLE 4. Relationship Between Self-report and Parent-report at t12 for Brain Tumor Patients Using the HUI3 MAUF and SAUFs

HUI3 t12	N	Mean Bias (95% Confidence Interval)*	r_s	*P*
MAUF (overall score)	21	0.07 (0.00-0.14)	0.76	< 0.001
Vision	21	0.02 (−0.01-0.04)	0.73	< 0.001
Hearing	21	0.00†	1.00	—
Speech	21	0.01 (−0.01-0.02)	1.00	—
Ambulation	21	0.02 (−0.05-0.09)	0.82	< 0.001
Dexterity	21	0.01 (−0.04-0.06)	0.79	< 0.001
Emotion	21	0.02 (−0.02-0.06)	0.30	0.192
Cognition	21	0.04 (−0.00-0.09)	0.75	< 0.001
Pain	21	−0.03 (−0.14-0.08)	0.20	0.393

*Child group mean-parent group mean.

†Child results were idential to respective parent.

HUI3 indicates Health Utilcities Index Mark 3; MAUF, Multi Attribute Utility Function; *P*, significance for r_s; r_s, Spearman correlation coefficient; SAUF, Single Attribute Utility Function; t12, 12-month assessment.

Comparison Between Parent-report and Child-report HS at t12

Patients

Correlation between parent-report and self-report for overall HS (HUI3 MAUF) and the attributes of vision, hearing, speech, ambulation, dexterity, and cognition was good (range, $r_s = 0.73$ to $r_s = 1.00$), but correlation between self-report and parent-report for emotion and pain were moderate and poor ($r_s = 0.30$ and $r_s = 0.20$, respectively). In general, when self-report and parent-report were available, with the exception of pain, patients rated their own HS higher than their parents did. However, group mean differences (mean bias) were not significant for the MAUF or any SAUF at the 1% significance level (Table 4).

Controls

For global HS represented by HUI3 MAUF, correlation between parent-report and child-report was moderate ($r_s = 0.31$). It was not possible to perform meaningful analysis of the relationship between parent-report and self-report HS for controls at t12 for SAUFs as in most of the controls a maximum score of 1.00 was attained.

DISCUSSION

To our knowledge, this is the first time that HS has been measured prospectively in children with brain tumors over the first year after diagnosis and controls.

HS is severely compromised in children with brain tumors in the first year after diagnosis. This would be expected given the impact of recent diagnosis and treatment but differences in HS between patients and controls decreased over time, particularly in the first 6 months, as the patients' HS improved. This may be due to recovery postsurgical removal of tumor and relief of hydrocephalus, though we found no relationship between the presence of hydrocephalus at diagnosis and any aspects of HS at t12. Nevertheless, the number of parent-report and self-report overall HS (HUI3 MAUF) in the moderate/severe range, indicating a moderate or severe level of disability, remained high at 62% and 48%, respectively at t12.

We found statistically significant differences between patients and controls for half of parent-report SAUFs at 1 and 6 months after diagnosis: emotion, cognition and pain were affected at both time points. Differences were significant at t1 and approaching significant at t6 for ambulation, and approaching significance at t1 and significant at t6 for dexterity. This may have been due to the impact of multimodality treatment many of the children were still receiving, time in hospital, separation from family and friends, painful procedures, and neurological deficit. Evidence from larger studies is necessary to substantiate this, as this study was not powered to investigate reasons for changes in HS over time. At 12 months, the only parent-report SAUF to reach statistical significance was cognition. This is consistent with studies assessing HS using the HUI in children with brain tumors an average of 3 and 8 years after diagnosis.[14,19] The HUI2/3 attribute of cognition has been proposed as a screening tool in identification of survivors of childhood brain tumors who may require more detailed cognitive assessment,[14,20] and may be of similar use early after diagnosis, but further research is necessary to confirm this.

Although clinically meaningful differences of 0.05[29] between mean scores for patients and controls were present for the parent-report SAUFs of pain and ambulation, an average of 12 months after diagnosis, differences did not reach statistical significance. This is most likely due to the relatively small sample size in this study. This was also true for the SAUFs of ambulation, cognition, and pain for self-report HS.

With regard to the severity of disability reported by parents for the single attributes, pain was most commonly reported as being moderately or severely affected at 1 and 6 months after diagnosis, and affected more frequently than all attributes other than cognition at 12 months when approximately one-fifth of all patients were reported to be affected. This is concerning, as most of the patients with brain tumors will be off treatment 1 year after diagnosis and further investigation of pain symptoms in this population is warranted. This finding is in contrast to the largest study of HS in adult survivors of childhood brain tumors where pain and emotion were the only SAUFs not significantly different to general population controls.[10] Parent-report cognition, followed by ambulation, was also frequently compromised to a moderate or severe degree. These findings supports the incorporation of patient-reported outcome measures, such as the HUI, in clinical practice to identify and facilitate discussion and increase clinicians' awareness of their patients' symptoms and HS.

For self-report HS at 12 months, only 14% of tumor patients reported moderate or severe deficits for cognition, and 5% for vision, hearing, ambulation, dexterity, and pain, which is encouraging.

Agreement between parent-report and self-report HUI3 for overall HS (HUI3 MAUF) for brain tumor patients and for all SAUFs with the exception of emotion and pain was good. This may be explained by the greater emphasis on physical functioning in HS measures. This is in keeping with the previously published data on childhood cancer and other chronic illnesses where agreement was better for more observable (physical), compared with less observable (psychosocial) domains.[24,25,36] There are a number of possible explanations for the differences observed between self-rated and parent-rated emotion and pain. These include differences in the way children and parents interpret events, and in their adaptive style. Other factors include concepts such as response shift and variables relating to child personality and parental emotional status/QOL.[37–40] Children with cancer often use a repressive adaptive coping style: they consider themselves well adjusted, score high on defensive measures, and tend to report low levels of psychological and somatic distress.[37,41]

Our data shows that mean self-reported HS were higher (indicating better HS) than parent-report for overall HS and all SAUFs other than pain 1 year after diagnosis. However, differences did not reach statistical significance in our cohort. The reason why on an average, children rated their pain worse than their parents is unclear, but highlights the importance of consulting children themselves in both the clinical and research setting. Self-report HS 1 and 6 months after diagnosis would have been useful in further elucidating differences between parent-report and self-report in this study.

The power of this study was reduced by the patient sample size and the cohort included a heterogeneous group of children with regard to age, diagnosis, and subsequent treatment. Although our patients were unselected, their distribution is not representative of the child brain tumor population and we caution against generalizing these results to those which may emerge after longer periods of

follow-up. This may explain why there were no significant correlations between HUI3 SAUFs and tumor or treatment variables. Studies using larger numbers of patients treated in a similar way will be necessary to fully understand the relationship between such variables and HS, and other outcome measures in survivors of childhood brain tumor.

In summary, our data shows that HS is measurable and severely compromised in children with brain tumors early after diagnosis. Although HS improves over time, it is still significantly compromised 1 year after diagnosis. Although in general, agreement between parent-report and self-report was good, this was not true for the attributes of pain and emotion, emphasizing the importance of attaining both perspectives in future studies of HS in children with brain tumors or other chronic health problems. Further longitudinal research on HS in children with brain tumors in larger multicenter studies is necessary in the development of timely, targeted interventions to ensure optimal developmental trajectories and QOS.

ACKNOWLEDGMENT

The authors thank Professor Peter Cooper, Consultant Pediatrician, Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa, for his advice and support.

REFERENCES

1. Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. *Lancet*. 2004; 364:2097–2105.
2. Gatta G, Zigon G, Capocaccia R, et al. Survival of European children and young adults with cancer diagnosed 1995-2002. *Eur J Cancer*. 2009;45:992–1005.
3. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355:1572–1582.
4. Slavc I, Salchegger C, Hauer C, et al. Follow-up and quality of survival of 67 consecutive children with CNS tumors. *Childs Nerv Syst*. 1994;10:433–443.
5. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2009;101:946–958.
6. Ellenberg L, Liu Q, Gioia G, et al. Neurocognitive status in long-term survivors of childhood CNS malignancies: a report from the Childhood Cancer Survivor Study. *Neuropsychology*. 2009;23:705–717.
7. Lannering B, Marky I, Lundberg A, et al. Long-term sequelae after pediatric brain tumors: their effect on disability and quality of life. *Med Pediatr Oncol*. 1990;18:304–310.
8. Mostow EN, Byrne J, Connelly RR, et al. Quality of life in long-term survivors of CNS tumors of childhood and adolescence. *J Clin Oncol*. 1991;9:592–599.
9. Zebrack BJ, Gurney JG, Oeffinger K, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. 2004;22:999–1006.
10. Boman KK, Hoven E, Anclair M, et al. Health and persistent functional late effects in adult survivors of childhood CNS tumours: a population-based cohort study. *Eur J Cancer*. 2009;45:2552–2561.
11. Gurney JG, Krull KR, Kadan-Lottick N, et al. Social Outcomes in the Childhood Cancer Survivor Study Cohort. *J Clin Oncol*. 2009.
12. *Health Impact Assessment: main concepts and suggested approach*. Brussels: European centre for Health Policy; 1999. Ref Type: Pamphlet.
13. Alessi D, Dama E, Barr R, et al. Health-related quality of life of long-term childhood cancer survivors: a population-based study from the Childhood Cancer Registry of Piedmont, Italy. *Eur J Cancer*. 2007;43:2545–2552.
14. Barr RD, Simpson T, Whitton A, et al. Health-related quality of life in survivors of tumours of the central nervous system in childhood–a preference-based approach to measurement in a cross-sectional study. *Eur J Cancer*. 1999;35:248–255.
15. Bull KS, Spoudeas HA, Yadegarfar G, et al. Reduction of health status 7 years after addition of chemotherapy to craniospinal irradiation for medulloblastoma: a follow-up study in PNET 3 trial survivors on behalf of the CCLG (formerly UKCCSG). *J Clin Oncol*. 2007;25:4239–4245.
16. Cardarelli C, Cereda C, Masiero L, et al. Evaluation of health status and health-related quality of life in a cohort of Italian children following treatment for a primary brain tumor. *Pediatr Blood Cancer*. 2006;46:637–644.
17. Foreman NK, Faestel PM, Pearson J, et al. Health status in 52 long-term survivors of pediatric brain tumors. *J Neurooncol*. 1999;41:47–53.
18. Glaser A, Kennedy C, Punt J, et al. Standardized quantitative assessment of brain tumor survivors treated within clinical trials in childhood. *Int J Cancer Suppl*. 1999;12:77–82.
19. Mulhern RK. Correlation of the Health Utilities Index Mark 2 cognition scale and neuropsychological functioning among survivors of childhood medulloblastoma. *Int J Cancer Suppl*. 1999;12:91–94.
20. Pogany L, Barr RD, Shaw A, et al. Health status in survivors of cancer in childhood and adolescence. *Qual Life Res*. 2006; 15:143–157.
21. Smith KW, Avis NE, Assmann SF. Distinguishing between quality of life and health status in quality of life research: a meta-analysis. *Qual Life Res*. 1999;8:447–459.
22. Feeny D, Furlong W, Boyle M, et al. Multi-attribute health status classification systems. Health Utilities Index. *Pharmacoeconomics*. 1995;7:490–502.
23. Detmar SB, Muller MJ, Schornagel JH, et al. Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. *JAMA*. 2002;288: 3027–3034.
24. Penn A, Lowis SP, Hunt LP, et al. 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. *Eur J Cancer*. 2008;44:1243–1252.
25. Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. *Qual Life Res*. 2001;10:347–357.
26. Wallander JL, Schmitt M, Koot HM. Quality of life measurement in children and adolescents: issues, instruments, and applications. *J Clin Psychol*. 2001;57:571–585.
27. Manuel DG, Schultz SE, Kopec JA. Measuring the health burden of chronic disease and injury using health adjusted life expectancy and the Health Utilities Index. *J Epidemiol Community Health*. 2002;56:843–850.
28. Glaser AW, Furlong W, Walker DA, et al. Applicability of the Health Utilities Index to a population of childhood survivors of central nervous system tumours in the U.K. *Eur J Cancer*. 1999;35:256–261.
29. Horsman J, Furlong W, Feeny D, et al. The Health Utilities Index (HUI(R)): concepts, measurement properties and applications. *Health Qual Life Outcomes*. 2003;1:54.
30. Furlong WJ, Feeny DH, Torrance GW. *Health Utilities Index (HUI) Procedures Manual*. Dundas, ON, Canada: Health Utilities Inc.; 2000. Ref Type: Pamphlet.
31. Office of the Deputy Prime Minister. The English Indices of Deprivation 2004: Summary (revised). Communities and Local Government 2008 [cited 2008 Oct 2]; Available from: URL: http://www.communities.gov.uk/documents/communities/pdf/131206.pdf.
32. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol*. 2007;114:97–109.

33. Cohen L, Holiday M. *Statistics for Social Scientists*. London: Harper and Row; 1982.
34. Altman DG, Machin D, Bryant TN. *Statistics With Confidence*. 2nd ed. London, England: BMJ Books; 2000.
35. Penn A, Shortman RI, Lowis SP, et al. Child-related determinants of health-related quality of life in children with brain tumours 1 year after diagnosis. *Pediatr Blood Cancer*. 2010;55:1377–1385.
36. Parsons SK, Barlow SE, Levy SL, et al. Health-related quality of life in pediatric bone marrow transplant survivors: according to whom? *Int J Cancer Suppl*. 1999;12:46–51.
37. Jurbergs N, Russell KM, Long A, et al. Adaptive style and differences in parent and child report of health-related quality of life in children with cancer. *Psychooncology*. 2007;17: 83–90.
38. Davis E, Nicolas C, Waters E, et al. Parent-proxy and child self-reported health-related quality of life: using qualitative methods to explain the discordance. *Qual Life Res*. 2007; 16:863–871.
39. Eiser C, Eiser JR, Stride CB. Quality of life in children newly diagnosed with cancer and their mothers. *Health Qual Life Outcomes*. 2005;3:29.
40. Goldbeck L, Melches J. Quality of life in families of children with congenital heart disease. *Qual Life Res*. 2005;14:1915–1924.
41. Phipps S, Steele RG, Hall K, et al. Repressive adaptation in children with cancer: a replication and extension. *Health Psychol*. 2001;20:445–451.

ID#
_____

Date:_____
_

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

CHILD REPORT (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

ID#
_____

Date:_____
_

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month,** how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

HUI®

HEALTH UTILITIES INDEX®

INTERVIEWER-ADMINISTERED QUESTIONNAIRE

HUI23S4E.40Q

HEALTH UTILITIES INDEX MARK 2 AND MARK 3 (HUI2/3) 40-ITEM QUESTIONNAIRE FOR INTERVIEWER-ADMINISTERED, SELF-ASSESSED "FOUR WEEK" HEALTH STATUS ASSESSMENT

by
WJ Furlong, DH Feeny and GW Torrance
Health Utilities Inc., Dundas ON Canada
December 2003

Health Utilities Inc. (HUInc.)
88 Sydenham Street
Dundas ON, Canada L9H 2V3
Telephone (905) 525-9140, extension 22389 / 22377
Fax (905) 627-7914
furlongb@mcmaster.ca
http://www.healthutilities.com

HEALTH UTILITIES INDEX
Notes to researchers regarding the 40-item questionnaire for interviewer-administered, self-assessed "four week" health status assessment

The attached 40-item interviewer-administered questionnaire has been designed to ask the minimum number of questions, either in-person or by telephone, required to classify a subject's health status according to the classification systems of both Health Utilities Index Mark 2 and Mark 3 (HUI2 and HUI3). Question 41 is not an HUI® question but is included in this questionnaire because it is often useful to collect this information in health status measurement surveys.

This version of the questionnaire is phrased to elicit responses from a wide variety of subjects, aged 8 years and older, about their health status during the past 4 weeks, from their own perspective. Other versions are available to facilitate administration to proxy respondents (eg., family members and health professionals) and to focus questions on other assessment periods. The "current" health focus is often used in clinical studies and economic evaluations of health care programs, in which the concern is to monitor health changes due to treatment. The "usual" health focus has been used in population health surveys, where short-term illnesses like colds are not the major concern. Please contact HUInc to obtain copies of other versions of the questionnaire.

This questionnaire includes a prototype cover sheet of variables that are typically important for identifying each interview (eg., subject ID number and date). All copies of the questionnaire should be clearly marked as a HUInc. questionnaire.

For further information about the HUI® and to obtain a copy of the algorithm[1] for coding responses from the 40-item interviewer-administered questionnaire, please contact the following (and refer to questionnaire HUI23S4E.40Q: 2003-12-31):

William (Bill) Furlong
Health Utilities Inc. (HUInc)
88 Sydenham Street, Dundas ON, Canada L9H 2V3
Telephone (905) 525-9140, extension 22389
Fax (905) 627-7914
furlongb@mcmaster.ca
http://www.healthutilities.com

---

1. Furlong WJ, Feeny DH, Torrance GW. Health Utilities Index: Algorithm for determining Mark 2 (HUI2) / Mark 3 (HUI3) health status classification levels, health states, health-related quality of life scores, and single attribute level utility scores for 40-item interviewer-administered health status questionnaires. Health Utilities Inc., unpublished document; February 1, 1999.

PROTOTYPE COVER SHEET

HUI23S4E.40Q
HEALTH UTILITIES INDEX MARK 2 AND MARK 3 (HUI2/3)
40-ITEM QUESTIONNAIRE FOR
INTERVIEWER-ADMINISTERED, SELF-ASSESSED
"FOUR WEEK" HEALTH STATUS ASSESSMENT

STUDY TITLE:_____

ID NUMBER OF SUBJECT:_____

NAME OF SUBJECT:_____

NAME OF INTERVIEWER:_____

DATE OF INTERVIEW: _____

START TIME: _____ a.m./p.m.

END TIME:_____ a.m./p.m.

CONFIDENTIAL (when completed)

For office use only:

Name of person who collected completed questionnaire:_____

Date completed questionnaire received by office:_____

Health Utilities Inc. (HUInc)
88 Sydenham Street
Dundas ON, Canada L9H 2V3
Telephone (905) 525-9140, extension 22389 / 22377
Fax (905) 627-7914
furlongb@mcmaster.ca
http://www.healthutilities.com

HUI23S4E.40Q

HEALTH UTILITIES INDEX MARK 2 AND MARK 3 (HUI2/3)
40-ITEM QUESTIONNAIRE FOR
INTERVIEWER-ADMINISTERED, SELF-ASSESSED
"FOUR WEEK" HEALTH STATUS ASSESSMENT

The next set of questions ask about various aspects of your health. When answering these questions we would like you to think about your health and your ability to do things on a day-to-day basis, during the past four weeks. To define the 4 week period, please think about what the date was 4 weeks ago and recall the major events that you have experienced during this period. Please focus your answers on your abilities, disabilities and how you have felt during the past 4 weeks.

You may feel that some of these questions do not apply to you, but it is important that we ask the same questions of everyone. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

All information you provide is confidential. There are no right or wrong answers; what we want is your opinion about your abilities and feelings.

Interviewer:
For each question, read the entire sentence as written on the left-hand side of the page following the question number, emphasizing the words in italics, if any. Do not read the response options listed down the right-hand margin of the page. The answer given by the respondent to each question should be clearly marked beside the one appropriate code listed to the right side of the question.

VISION

1 During the past 4 weeks, have you been able to see well enough to read ordinary newsprint *without* glasses or contact lenses?

- O Yes → **Go to 4**
- O No
- O Don't know
- O Refused

2 Have you been able to see well enough to read ordinary newsprint *with* glasses or contact lenses?

- O Yes → **Go to 4**
- O No
- O Don't know / Didn't wear glasses or contact lenses
- O Refused

3 During the past 4 weeks, have you been able to see at all?

- O Yes
- O No → **Go to 6**
- O Don't know
- O Refused

4 During the past 4 weeks, have you been able to see well enough to recognize a friend on the other side of the street *without* glasses or contact lenses?

- O Yes → **Go to 6**
- O No
- O Don't know
- O Refused

5 Have you been able to see well enough to recognize a friend on the other side of the street *with* glasses or contact lenses?

- ○ Yes
- ○ No
- ○ Don't know / Didn't wear glasses or contact lenses
- ○ Refused

HEARING

6 During the past 4 weeks, have you been able to hear what is said in a group conversation with at least three other people *without* a hearing aid?

- ○ Yes → **Go to 11**
- ○ No
- ○ Don't know
- ○ Refused

7 Have you been able to hear what is said in a group conversation with at least three other people *with* a hearing aid?

- ○ Yes → **Go to 9**
- ○ No
- ○ Don't know / Didn't wear a hearing aid
- ○ Refused

8 During the past 4 weeks, have you been able to hear at all?

- ○ Yes
- ○ No → **Go to 11**
- ○ Don't know
- ○ Refused

9 During the past 4 weeks, have you been able to hear what is said in a conversation with one other person in a quiet room *without* a hearing aid?

- ○ Yes → **Go to 11**
- ○ No
- ○ Don't know
- ○ Refused

10 Have you been able to hear what is said in a conversation with one other person in a quiet room *with* a hearing aid?

- ○ Yes
- ○ No
- ○ Don't know / Didn't wear a hearing aid
- ○ Refused

SPEECH

11 During the past 4 weeks, have you been able to be understood *completely* when speaking your own language with people who do not know you?

- ○ Yes → **Go to 16**
- ○ No
- ○ Don't know
- ○ Refused

12 Have you been able to be understood *partially* when speaking with people who do not know you?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

13 During the past 4 weeks, have you been able to be understood *completely* when speaking with people who know you well?

- ○ Yes → **Go to 16**
- ○ No
- ○ Don't know
- ○ Refused

14 Have you been able to be understood *partially* when speaking with people who know you well?

- ○ Yes → **Go to 16**
- ○ No
- ○ Don't know
- ○ Refused

15 During the past 4 weeks, have you been able to speak at all?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

GETTING AROUND

16 During the past 4 weeks, have you been able to bend, lift, jump and run *without difficulty* and *without help or equipment* of any kind?

- ○ Yes → **Go to 24**
- ○ No
- ○ Don't know
- ○ Refused

17 Have you been able to walk around the neighbourhood *without difficulty* and *without help or equipment* of any kind?

- ○ Yes → **Go to 24**
- ○ No
- ○ Don't know
- ○ Refused

18 Have you been able to walk around the neighbourhood *with difficulty* but *without help or equipment* of any kind?

- ○ Yes → **Go to 24**
- ○ No
- ○ Don't know
- ○ Refused

19 During the past 4 weeks, have you been able to walk at all?

- ○ Yes
- ○ No → **Go to 22**
- ○ Don't know
- ○ Refused

20 Have you needed mechanical support, such as braces or a cane or crutches, to be able to walk around the neighbourhood?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

21 Have you needed the help of another person to walk?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

22 Have you needed a wheelchair to get around the neighbourhood?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

23 Have you needed the help of another person to get around in the wheelchair?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

HANDS AND FINGERS

24 During the past 4 weeks, have you had the *full use* of both hands and ten fingers?

- ○ Yes → **Go to 28**
- ○ No
- ○ Don't know
- ○ Refused

25 Have you needed the help of another person because of limitations in the use of your hands or fingers?

- ○ Yes
- ○ No → **Go to 27**
- ○ Don't know
- ○ Refused

26 Have you needed the help of another person with some tasks, most tasks, or all tasks?

- ○ Some tasks
- ○ Most tasks
- ○ All tasks
- ○ Don't know
- ○ Refused

27 Have you needed special equipment, for example special tools to help with dressing or eating, because of limitations in the use of your hands or fingers?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

SELF-CARE

28 During the past 4 weeks, have you been able to eat, bathe, dress and use the toilet without difficulty?

- ○ Yes → **Go to 31**
- ○ No
- ○ Don't know
- ○ Refused

29 Have you needed the help of another person to eat, bathe, dress or use the toilet?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

30 Have you needed special equipment or tools to eat, bathe, dress or use the toilet?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

FEELINGS

31 During the past 4 weeks, have you been feeling happy or unhappy?

- ○ Happy
- ○ Unhappy → **Go to 33**
- ○ Don't know
- ○ Refused

32 Would you describe yourself as having felt:
a) happy and interested in life, or
b) somewhat happy?

- ○ a → **Go to 34**
- ○ b → **Go to 34**
- ○ Don't know
- ○ Refused

33 Would you describe yourself as having felt:
a) somewhat unhappy
b) very unhappy
c) so unhappy that life is not worthwhile

- ○ a
- ○ b
- ○ c
- ○ Don't know
- ○ Refused

34 During the past 4 weeks, did you ever feel fretful, angry, irritable, anxious or depressed?

- ○ Yes
- ○ No → **Go to 37**
- ○ Don't know
- ○ Refused

35 How often did you feel fretful, angry, irritable, anxious or depressed:
rarely, occasionally, often, or almost always?

- ○ Rarely
- ○ Occasionally
- ○ Often
- ○ Almost always
- ○ Don't know
- ○ Refused

36 During the past 4 weeks did you feel *extremely* fretful, angry, irritable, anxious or depressed; to the point of needing professional help?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

MEMORY

37 How would you describe your ability to remember things, during the past 4 weeks:
(a) able to remember most things
(b) somewhat forgetful
(c) very forgetful
(d) unable to remember anything at all?

- ○ a
- ○ b
- ○ c
- ○ d
- ○ Don't know
- ○ Refused

THINKING

38 How would you describe your ability to think and solve day to day problems, during the past 4 weeks:
(a) able to think clearly and solve problems
(b) had a little difficulty
(c) had some difficulty
(d) had a great deal of difficulty
(e) unable to think or solve problems?

- ○ a
- ○ b
- ○ c
- ○ d
- ○ e
- ○ Don't know
- ○ Refused

PAIN AND DISCOMFORT

39 Have you had any trouble with pain or discomfort, during the past 4 weeks?

- ○ Yes
- ○ No → **Go to 41**
- ○ Don't know
- ○ Refused

40 How many of your activities, during the past 4 weeks, were limited by pain or discomfort:
none, a few, some, most, all?

- ○ None
- ○ A few
- ○ Some
- ○ Most
- ○ All
- ○ Don't know
- ○ Refused

41 Overall, how would you rate your health during the past 4 weeks?
(a) excellent
(b) very good
(c) good
(d) fair
(e) poor

- ○ a
- ○ b
- ○ c
- ○ d
- ○ e
- ○ Don't know
- ○ Refused

Thank you. That ends this set of questions.

TIME FINISHED:_____ a.m./p.m.

HUI®

HEALTH UTILITIES INDEX®

INTERVIEWER-ADMINISTERED QUESTIONNAIRE

Health Utilities Inc.
88 Sydenham Street, Dundas, Ontario, Canada L9H 2V3
Telephone (905) 525-9140, extension 22389; Fax (905) 627-7914

USER LICENSING AGREEMENT

1. Secrecy, Protection of Work and Intellectual Property Rights

Health Utilities Inc. (HUInc.) owns and shall retain copyright and all other intellectual property rights to all questionnaires, procedure manuals, coding algorithms and other technical information that it develops and distributes (the Ainformation@). This information is not for public release and HUInc. retains the exclusive distribution rights to this information. The User will have no rights in and to the same. The User shall not in any way do anything to infringe upon, harm or contest the ownership or validity of the HUInc.=s copyright or intellectual property rights as described herein. The User shall promptly notify HUInc. in writing of any and all infringements or misuses of HUInc.=s copyright which come to a User=s attention. The User shall co-operate with HUInc. to stop any such infringement.

All HUInc. technical documents, such as questionnaires and procedures manuals, used by the User will contain the following copyright notice:

8 Health Utilities Inc., Dundas ON Canada

The User will not divulge or disseminate HUInc. questionnaires, procedure manuals, coding algorithms or other technical information in whole or in part to any person outside a written licensing agreement.

2. Permission and Licensing Terms for Use of HUInc. Proprietary Materials and Information

Permission to use HUInc. proprietary materials (e.g., questionnaires and procedure manuals) and proprietary information (e.g., algorithms for converting sets of questionnaire responses into HUI attribute levels) is granted under license. These materials and information may be used only with written permission from HUInc. and under the terms of the license.

Permission for use of HUInc. proprietary materials and information is granted one project at a time, and the User will obtain permission in writing from an authorized representative of HUInc. to use or modify or distribute these materials or information.

HUInc. grants non-exclusive, non-transferable license to use its materials and information in one project. This license does not permit selling, distributing, commercially exploiting or making the materials or information available on a network or through remote access technology.

All reports and publications by the User will reference appropriate HUI-related background published manuscripts, and HUInc. questionnaires and procedures manuals, according to the usual rules of citation.

3. Disclaimer

HUInc. provides materials and information Aas is@. HUInc. does not guarantee the materials and information nor provide warranties whatsoever, either expressed or implied, including, but not limited to, implied warranties of merchantability or fitness for a particular purpose. Users assume the entire risk as to quality and performance of the materials and information. HUInc. does not guarantee or warrant its copyright in the materials and information provided to the Client. In no event shall HUInc. be liable for any indirect, special, consequential or incidental damages or claims for loss of business or loss of profits, even if HUInc. shall have been advised of the possibility of such potential loss or damage.

Not for quotation or distribution without permission. All copies of this questionnaire should include a cover sheet that clearly acknowledges that it is a Health Utilities Index questionnaire developed by Health Utilities Inc. (see prototype attached).

Do not use this questionnaire without written approval from Health Utilities Inc. This questionnaire is one of many HUI® data collection instruments, and may not be the most appropriate for your study.

HUI23P4E.40Q

HEALTH UTILITIES INDEX MARK 2 AND MARK 3 (HUI2/3) 40-ITEM QUESTIONNAIRE FOR INTERVIEWER-ADMINISTERED, PROXY-ASSESSED "FOUR WEEK" HEALTH STATUS ASSESSMENT

by
WJ Furlong, DH Feeny and GW Torrance
Health Utilities Inc., Dundas ON Canada
September 2, 2002

Permission for use of this document is limited to one study and must be obtained in writing from:

Health Utilities Inc. (HUInc.)
88 Sydenham Street
Dundas ON, Canada L9H 2V3
Telephone (905) 525-9140, extension 22389 / 22377
Fax (905) 627-7914
furlongb@mcmaster.ca
http://www.healthutilities.com

Not for Quotation Without Permission

HEALTH UTILITIES INDEX

Notes to researchers regarding the 40-item questionnaire for interviewer-administered, proxy-assessed, "four week" health status assessment

The attached 40-item interviewer-administered questionnaire has been designed to ask the minimum number of questions, either in-person or by telephone, required to classify a subject's health status according to the classification systems of both Health Utilities Index Mark 2 and Mark 3 (HUI2 and HUI3). Question 41 is not an HUI® question but is included in this questionnaire because it is often useful to collect this information in health status measurement surveys.

This version of the questionnaire is phrased to elicit responses from a wide variety of proxy respondents (eg., parents, health professionals), about the health status of subjects aged 5 years and older, during the past 4 weeks. Other versions are available to facilitate administration to subjects answering on behalf of themselves and to focus questions on other explicitly defined assessment periods. The "current" health focus is often used in clinical studies and economic evaluations of health care programs, in which the concern is to monitor health changes due to treatment. The "usual" health focus has been used in population health surveys, where short-term illnesses like colds are not the major concern. Please contact HUInc to obtain copies of other versions of the questionnaire.

Note that for the purposes of describing the relationship between the subjects and respondents of these questionnaires we are using a broad definition of “proxy respondents”. Proxy respondents are defined as any respondents other than the subjects, and proxy respondents need not necessarily be answering on behalf of the subject (ie., proxy respondents may be explicitly answering on the basis of their own perspective).

This questionnaire includes a prototype cover sheet of variables that are typically important for identifying each interview (eg., subject ID number and date). All copies of the questionnaire should be clearly marked as a HUInc. questionnaire.

For further information about the HUI® and to obtain a copy of the algorithm[1] for coding responses from the 40-item interviewer-administered questionnaire, please contact the following (and refer to questionnaire HUI23P4E.40Q: 2002-09):

William (Bill) Furlong, Health Utilities Inc. (HUInc)
88 Sydenham Street, Dundas ON, Canada L9H 2V3
Telephone (905) 525-9140, extension 22389; Fax (905) 627-7914
furlongb@mcmaster.ca; http://www.healthutilities.com

1. Furlong WJ, Feeny DH, Torrance GW. Health Utilities Index: Algorithm for determining Mark 2 (HUI2) / Mark 3 (HUI3) health status classification levels, health states, health-related quality of life scores, and single attribute level utility scores for 40-item interviewer-administered health status questionnaires. Health Utilities Inc., unpublished document; February 1, 1999.

PROTOTYPE COVER SHEET

HUI23P4E.40Q
HEALTH UTILITIES INDEX MARK 2 AND MARK 3 (HUI2/3)
40-ITEM QUESTIONNAIRE FOR
INTERVIEWER-ADMINISTERED, PROXY-ASSESSED
"FOUR WEEK" HEALTH STATUS ASSESSMENT

STUDY TITLE:_____

ID NUMBER OF SUBJECT:_____

NAME OF SUBJECT:_____

NAME OF RESPONDENT:_____

RELATIONSHIP TO SUBJECT: _____

NAME OF INTERVIEWER: _____

DATE OF INTERVIEW: _____

START TIME: _____ a.m./p.m.

END TIME:_____ a.m./p.m.

CONFIDENTIAL (when completed)

For office use only:

Name of person who collected completed questionnaire:_____

Date completed questionnaire received by office:_____

Health Utilities Inc. (HUInc)
88 Sydenham Street, Dundas ON, Canada L9H 2V3
Telephone (905) 525-9140, extension 22389 / 22377
Fax (905) 627-7914
furlongb@mcmaster.ca; http://www.healthutilities.com

HUI23P4E.40Q

HEALTH UTILITIES INDEX MARK 2 AND MARK 3 (HUI2/3)
40-ITEM QUESTIONNAIRE FOR
INTERVIEWER-ADMINISTERED, PROXY-ASSESSED
"FOUR WEEK" HEALTH STATUS ASSESSMENT

The next set of questions ask about various aspects of (subject's name)'s overall health. When answering these questions we would like you to think about (his/her) health and ability to do things on a day-to-day basis, during the past 4 weeks. To define the 4 week period, please think about what the date was 4 weeks ago and recall the major events that (he/she) has experienced during this period. Please focus your answers on (subject's name)'s abilities, disabilities and how they have felt during the past 4 weeks.

You may feel that some of these questions do not apply to (subject's name), but it is important that we ask the same questions about each subject. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

All information you provide is confidential. There are no right or wrong answers; what we want is your opinion about (subject's name) abilities and feelings.

Interviewer:
For each question, read the entire sentence as written on the left-hand side of the page following the question number, emphasizing the words in italics, if any. Do not read the response options listed down the right-hand margin of the page. The answer given by the respondent to each question should be clearly marked beside the one appropriate code listed to the right side of the question.

VISION

1. During the past four weeks, has (subject's name) been able to see well enough to read ordinary newsprint *without* glasses or contact lenses?
   - O Yes → Go to 4
   - O No
   - O Don't know
   - O Refused

2. Has (subject's name) been able to see well enough to read ordinary newsprint *with* glasses or contact lenses?
   - O Yes → **Go to 4**
   - O No
   - O Don't know/Didn't wear glasses or contact lenses
   - O Refused

3. During the past four weeks, has (subject's name) been able to see at all?
   - ○ Yes
   - ○ No → **Go to 6**
   - ○ Don't know
   - ○ Refused

4. During the past four weeks, has (subject's name) been able to see well enough to recognize a friend on the other side of the street *without* glasses or contact lenses?
   - ○ Yes → **Go to 6**
   - ○ No
   - ○ Don't know
   - ○ Refused

5. Has (subject's name) been able to see well enough to recognize a friend on the other side of the street *with* glasses or contact lenses?
   - ○ Yes
   - ○ No
   - ○ Don't know/Didn't wear glasses or contact lenses
   - ○ Refused

HEARING

6. During the past four weeks, has (subject's name) been able to hear what is said in a group conversation with at least three other people *without* a hearing aid?
   - ○ Yes → **Go to 11**
   - ○ No
   - ○ Don't know
   - ○ Refused

7. Has (subject's name) been able to hear what is said in a group conversation with at least three other people *with* a hearing aid?
   - ○ Yes → **Go to 9**
   - ○ No
   - ○ Don't know/Didn't wear a hearing aid
   - ○ Refused

8. During the past four weeks, has (subject's name) been able to hear at all?
   - ○ Yes
   - ○ No → **Go to 11**
   - ○ Don't know
   - ○ Refused

9. During the past four weeks, has (subject's name) been able to hear what is said in a conversation with one other person in a quiet room *without* a hearing aid?

- ○ Yes → **Go to 11**
- ○ No
- ○ Don't know
- ○ Refused

10. Has (subject's name) been able to hear what is said in a conversation with one other person in a quiet room *with* a hearing aid?

- ○ Yes
- ○ No
- ○ Don't know/Didn't wear a hearing aid
- ○ Refused

SPEECH

11. During the past four weeks, has (subject's name) been able to be understood *completely* when speaking your own language with people who do not know you?

- ○ Yes → **Go to 16**
- ○ No
- ○ Don't know
- ○ Refused

12. Has (subject's name) been able to be understood *partially* when speaking with people who do not know (subject's name)?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

13. During the past four weeks, has (subject's name) been able to be understood *completely* when speaking with people who know (subject's name) well?

- ○ Yes → **Go to 16**
- ○ No
- ○ Don't know
- ○ Refused

14. Has (subject's name) been able to be understood *partially* when speaking with people who know (subject's name) well?

- ○ Yes → **Go to 16**
- ○ No
- ○ Don't know
- ○ Refused

15. During the past four weeks, has (subject's name) been able to speak at all?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

GETTING AROUND

16. During the past four weeks, has (subject's name) been able to bend, lift, jump and run *without difficulty* and *without help or equipment* of any kind?
- ○ Yes → **Go to 24**
- ○ No
- ○ Don't know
- ○ Refused

17. Has (subject's name) been able to walk around the neighbourhood *without difficulty* and *without help or equipment* of any kind?
- ○ Yes → **Go to 24**
- ○ No
- ○ Don't know
- ○ Refused

18. Has (subject's name) been able to walk around the neighbourhood *with difficulty* but *without help or equipment* of any kind?
- ○ Yes → **Go to 24**
- ○ No
- ○ Don't know
- ○ Refused

19. During the past four weeks, has (subject's name) been able to walk at all?
- ○ Yes
- ○ No → **Go to 22**
- ○ Don't know
- ○ Refused

20. Has (subject's name) needed mechanical support, such as braces or a cane or crutches, to be able to walk around the neighbourhood?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

21. Has (subject's name) needed the help of another person to walk?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

22. Has (subject's name) needed a wheelchair to get around the neighbourhood?
- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

23. Has (subject's name) needed the help of another person to get around in the wheelchair?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

HANDS AND FINGERS

24. During the past four weeks, has (subject's name) had the *full use* of both hands and ten fingers?

- ○ Yes → **Go to 28**
- ○ No
- ○ Don't know
- ○ Refused

25. Has (subject's name) needed the help of another person because of limitations in the use of his/her hands or fingers?

- ○ Yes
- ○ No → **Go to 27**
- ○ Don't know
- ○ Refused

26. Has (subject's name) needed the help of another person with some tasks, most tasks, or all tasks?

- ○ Some tasks
- ○ Most tasks
- ○ All tasks
- ○ Don't know
- ○ Refused

27. Has (subject's name) needed special equipment, for example special tools to help with dressing or eating, because of limitations in the use of his/her hands or fingers?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

SELF-CARE

28. During the past four weeks, has (subject's name) been able to eat, bathe, dress and use the toilet without difficulty?

- ○ Yes → **Go to 31**
- ○ No
- ○ Don't know
- ○ Refused

29. Has (subject's name) needed the help of another person to eat, bathe, dress or use the toilet?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

30. Has (subject's name) needed special equipment or tools to eat, bathe, dress or use the toilet?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

FEELINGS

31. During the past four weeks, has (subject's name) been feeling happy or unhappy?

- ○ Happy
- ○ Unhappy → **Go to 33**
- ○ Don't know
- ○ Refused

32. Would you describe (subject's name) as having felt:
a) happy and interested in life, or
b) somewhat happy?

- ○ a → **Go to 34**
- ○ b → **Go to 34**
- ○ Don't know
- ○ Refused

33. Would you describe (subject's name) as having felt:
a) somewhat unhappy
b) very unhappy
c) so unhappy that life was not worthwhile

- ○ a
- ○ b
- ○ c
- ○ Don't know
- ○ Refused

34. During the past four weeks, did (subject's name) ever feel fretful, angry, irritable, anxious or depressed?

- ○ Yes
- ○ No → **Go to 37**
- ○ Don't know
- ○ Refused

35. How often did (subject's name) feel fretful, angry, irritable, anxious or depressed:
rarely, occasionally, often, or almost always?

- ○ Rarely
- ○ Occasionally
- ○ Often
- ○ Almost always
- ○ Don't know
- ○ Refused

36. During the past four weeks did (subject's name) feel *extremely* fretful, angry, irritable, anxious or depressed; to the point of needing professional help?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Refused

MEMORY

37. How would you describe (subject's name)'s ability to remember things, during the past four weeks:
(a) able to remember most things
(b) somewhat forgetful
(c) very forgetful
(d) unable to remember anything at all?

- ○ a
- ○ b
- ○ c
- ○ d
- ○ Don't know
- ○ Refused

THINKING

38. How would you describe (subject's name)'s ability to think and solve day to day problems, during the past four weeks:
(a) able to think clearly and solve problems
(b) had a little difficulty
(c) had some difficulty
(d) had a great deal of difficulty
(e) unable to think or solve problems?

- ○ a
- ○ b
- ○ c
- ○ d
- ○ e
- ○ Don't know
- ○ Refused

PAIN AND DISCOMFORT

39. Has (subject's name) had any trouble with pain or discomfort, during the past four weeks?

- ○ Yes
- ○ No → **Go to 41**
- ○ Don't know
- ○ Refused

40. How many of (subject's name)'s activities, during the past four weeks, were limited by pain or discomfort: none, a few, some, most, all?

- ○ None
- ○ A few
- ○ Some
- ○ Most
- ○ All
- ○ Don't know
- ○ Refused

41. Overall, how would you rate (subject's name)'s health during the past four weeks?

(a) excellent	○ a
(b) very good	○ b
(c) good	○ c
(d) fair	○ d
(e) poor	○ e
	○ Don't know
	○ Refused

Thank you. That ends this set of questions.

TIME FINISHED:_____ a.m./p.m.