PAIN IN LONG-TERM SURVIVORS OF BRAIN TUMOURS IN CHILDHOOD
AN EXPLORATION OF THE BURDEN OF PAIN AND HEALTH-RELATED QUALITY OF LIFE OF LONG-TERM SURVIVORS OF BRAIN TUMOURS IN CHILDHOOD

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Master of Science

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TITLE: An Exploration of the Burden of Pain and Health-Related Quality of Life of Long-Term Survivors of Brain Tumours in Childhood

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ABSTRACT

**Background:** Health-related quality of life (HRQL) studies of survivors of brain tumours in childhood have reported numerous areas of morbidity. The burden of pain is identified inconsistently in this cohort, with limited exploration of this morbidity.

**Objective:** To explore the HRQL, with a focus on pain, in survivors greater than 10 years from diagnosis of a primary brain tumour in childhood or adolescence.

**Methods:** An exploratory cross-sectional study was undertaken using Health Utilities Index (HUI) questionnaires. Pain was characterized using a coloured analogue scale for self-perceived severity and a homunculus to identify the location of pain. Comparison of the single-attribute HRQL scores for participants with and without pain was undertaken. The stability of pain over a decade was established using available HUI2/3 survey data of the same cohort with imputation for missing variables.

**Results:** Twelve males and 13 females out of 37 eligible subjects participated in this study. Participants (mean time from diagnosis of 19.7 years) had mean multi-attribute HRQL scores of 0.79 (SD of 0.23) for HUI2 and 0.69 (SD of 0.29) for HUI3. Thirteen (52%) participants reported pain, with inter- and intra-individual differences in severity and location of discomfort. Comparison of single-attribute HRQL scores for participants with and without pain revealed considerably greater burdens of morbidity in sensation and emotion in the former group. Pain also increased from the initial interview (10 years prior) to the final interview.

**Conclusion:** As a group, long-term survivors of brain tumours in childhood have diminished overall HRQL. However there is variability between subjects. Pain appeared to be a persistent and significant burden in a subset of individuals, with those experiencing pain reporting greater severity of morbidities in other attributes. The findings of this study provide further insight into a poorly characterized phenomenon in this survivor cohort and warrant further study.
ACKNOWLEDGEMENTS

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# TABLE OF CONTENTS

**LIST OF TABLES** .......................................................................................................... vii

**LIST OF FIGURES** ....................................................................................................... ix

**DECLARATION OF ACADEMIC ACHIEVEMENT** ...................................................... xii

**INTRODUCTION** ........................................................................................................ 1
  Brain Tumours in Childhood ......................................................................................... 1
  Survivorship and Outcomes of Patients with Brain Tumours in Childhood ............... 2
  Quality of Life ................................................................................................................... 5
  Health-Related Quality of Life ....................................................................................... 5
  Measures of HRQL in Survivors of Brain Tumours in Childhood ............................... 11
  Previous Assessments of HRQL of Survivors of Brain Tumours in Childhood .......... 17
  *Summary of the Studies Reviewed* .............................................................................. 26

**METHODS** .................................................................................................................. 31
  Objective ......................................................................................................................... 31
  Study Design .................................................................................................................. 31
  Rationale .......................................................................................................................... 34
    Cross Sectional Study Design ...................................................................................... 34
      *Sample Selection* ...................................................................................................... 34
      *Measurement Instruments* ....................................................................................... 35
      *Proxy Reporting* ....................................................................................................... 41
    Longitudinal Study Design ......................................................................................... 41
  Protocol ............................................................................................................................ 42
    Procedures ..................................................................................................................... 42
    Subject Screening ......................................................................................................... 43
    Subject and Proxy Recruitment ................................................................................... 44
    Consent Process ........................................................................................................... 44
    Administration of Questionnaires ............................................................................... 44
    Non-Participants ........................................................................................................... 46
    Data Linkage ................................................................................................................ 46
    Demographic and Clinical Information ...................................................................... 46
    Data Management ....................................................................................................... 47
    *Scoring of HUI Questionnaire* ................................................................................ 47
# Analysis

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-Sectional Analysis</td>
<td>47</td>
</tr>
<tr>
<td>Description of Overall Cohort</td>
<td>48</td>
</tr>
<tr>
<td>General Quality of Life Rating</td>
<td>48</td>
</tr>
<tr>
<td>Health-Related Quality of Life</td>
<td>49</td>
</tr>
<tr>
<td>Proxy Reporting</td>
<td>49</td>
</tr>
<tr>
<td>Description of Participants Reporting Pain</td>
<td>50</td>
</tr>
<tr>
<td>Burden of Pain by HRQL</td>
<td>50</td>
</tr>
</tbody>
</table>

# Longitudinal Analysis

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
</tr>
</tbody>
</table>

# Ethical Considerations

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Ethics Board Approval</td>
<td>54</td>
</tr>
<tr>
<td>Study Risks, Identification and Management</td>
<td>54</td>
</tr>
<tr>
<td>Study Benefits</td>
<td>55</td>
</tr>
<tr>
<td>Confidentiality</td>
<td>56</td>
</tr>
<tr>
<td>Consent</td>
<td>57</td>
</tr>
</tbody>
</table>

# RESULTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-Sectional Study- Time Point 3 (2011 and 2012)</td>
<td>58</td>
</tr>
<tr>
<td>Overall Cohort</td>
<td>58</td>
</tr>
<tr>
<td>Description of Participants</td>
<td>58</td>
</tr>
<tr>
<td>Sociodemographic Factors and General Quality of Life</td>
<td>60</td>
</tr>
<tr>
<td>Health-Related Quality of Life</td>
<td>63</td>
</tr>
<tr>
<td>Participants Reporting Pain</td>
<td>68</td>
</tr>
<tr>
<td>Description of Participants with Pain</td>
<td>68</td>
</tr>
<tr>
<td>Proxy-Reporting for Participants with Pain</td>
<td>71</td>
</tr>
<tr>
<td>Health-Related Quality of Life of Participants with Pain</td>
<td>72</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
</table>

# DISCUSSION

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>84</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-Sectional Results</td>
<td>85</td>
</tr>
<tr>
<td>Overall HRQL</td>
<td>85</td>
</tr>
<tr>
<td>Single Attribute Analysis</td>
<td>86</td>
</tr>
<tr>
<td>Pain in Survivors of Brain Tumours in Childhood and Adolescence</td>
<td>89</td>
</tr>
<tr>
<td>Limitations</td>
<td>98</td>
</tr>
<tr>
<td>Implications of Findings</td>
<td>102</td>
</tr>
</tbody>
</table>

# CONCLUSION

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>105</td>
</tr>
</tbody>
</table>

# REFERENCES

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>106</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table 1. Summary of study design and patient characteristics in studies reviewed .......79
Table 2. Summary of study methods and outcome.................................................................29
Table 3. Summary of constructs used in the HUI2 Multi-Attribute System (aside from fertility) (Torrance, 1996)........................................................................................................38
Table 4. Summary of constructs used in the HUI3 Multi-Attribute System (Feeny, 1995) ........................................................................................................................................38
Table 5. Clinical features of subjects eligible to participate in study at time point 3 (n=37) ........................................................................................................................................59
Table 6 Self- and proxy- responses to direct questioning of overall health-related quality of life ......................................................................................................................................63
Table 7. Measurement of concordance between self- and proxy- ratings for HUI2 attributes ........................................................................................................................................67
Table 8. Measurement of concordance between self- and proxy- ratings for HUI3 attributes ........................................................................................................................................67
Table 9. Number of days participants reported experiencing pain within a one-week period........................................................................................................................................68
Table 10. Clinical characteristics of participants with and without pain............................69
Table 11. Reported location of pain as noted using homunculus and corresponding intensity based on coloured analogue scale rating .........................................................71
Table 12. Concordance between self- and proxy- reporting for pain as measured by interventions to alleviate symptoms (HUI2). .................................................................72
Table 13. Concordance between self- and proxy- reporting for pain as measured by number of activities limited by pain (HUI3).................................................................72
Table 14. Single-attribute utility scores for participants with (n=13) and without (n=12) pain ........................................................................................................................................73
Table 15. Frequency of severity of morbidity by attribute, stratified by participants with (n=13) and without (n=12) pain ..........................................................................................74
Table 16. Minimum, maximum and mean pain utility scores reported at each time point for HUI2 and HUI3. The prevalence of utility scores of equal to or greater than 0.80 are also presented ................................................................. 79

Table 17. Summary of the number of variables imputed for longitudinal analysis .......... 80

Table 18. Results of longitudinal analysis of the pain utility scores by linear mixed effects model; fixed factor is time. Results presented are of pooled data (initial dataset along with datasets with imputed missing values). T1= 2000/2001, T2= 2005/2006, and T3= 2011/2012 survey time points. ▲= increase in utility score, ▼= decrease in utility score .................................................................................. 81

Table 19. Results of longitudinal analysis of the multi-attribute utility scores by linear mixed effects model; fixed factor is time. Results presented are of pooled data (initial dataset along with datasets with imputed missing values). T1= 2000/2001, T2= 2005/2006, and T3= 2011/2012 survey time points. ▲= increase in utility score, ▼= decrease in utility score............................................. 82
LIST OF FIGURES

Figure 1. Schematic diagram of study methods used to explore the health-related quality of life in survivors of brain tumours in childhood over a ten-year period. Measures include the HUI2/3 questionnaire, as well as additional investigations to characterize the burden of pain experienced by the patient cohort. Sociodemographic and quality of life information was also captured at time point 3..............................................................33

Figure 2. A simplified human figure used to elucidate location of pain experienced by participant .................................................................40

Figure 3. Summary of cross-sectional study procedures. ..................................43

Figure 4. Highest education level achieved as reported by participants (n=25)........61

Figure 5. Mean overall quality of life as reported subjectively by participants as remembered at times 5 years in the past, the present and predicted 5 years in the future..................................................................................................62

Figure 6. Boxplot of median utility scores for cohort (n=24)..................................63

Figure 7. Single attribute level data for HUI2 (2a) and HUI3 (2b) for overall cohort (n=25). .................................................................65

Figure 8. Impact of pain (n=13) as measured by a) Number of activities limited by pain, and b) Interventions for relief of most severe pain in a 1 week period, for participants reporting pain within the week prior to the interview. ...............70

Figure 9. Overview of number of participants at each study time point\ as well as the prevalence of pain (self-reported). .................................................................76

Figure 10. Median overall HRQL and pain utility scores over a 10 year period, measured at five-year intervals. ........................................................................78
LIST OF ABBREVIATIONS

ANOVA ................................................................. Analysis of Variance
CAS ................................................................. Coloured Analogue Scale
CCSS ................................................................. Childhood Cancer Survivor Study
CGSS ................................................................. Canadian General Society Survey
CHQ ................................................................. Child Health Questionnaire
CNS ................................................................. Central Nervous System
HRQL ................................................................. Health-Related Quality of Life
HUI ................................................................. Health Utilities Index ®
ICC ................................................................. Intra-Class Correlation Coefficient
JD ................................................................. Neuro-Oncology Nurse (JoAnn Duckworth)
MCH ................................................................. McMaster Children’s Hospital
MMQL ................................................................. Minneapolis Manchester Quality of Life
PedsQL ................................................................. Pediatric Quality of Life Inventory
POGO ................................................................. Pediatric Oncology Group of Ontario
QALY ................................................................. Quality Adjusted Life Year
QOL ................................................................. Quality of Life
REB ................................................................. Research Ethics Board
SD ................................................................. Standard Deviation
SF-36 ................................................................. Medical Outcomes Short Form-36
TACQOL….. TNO-AZL Questionnaires for Children's Health-Related Quality of Life

T1……………………………………………………………………..Time point 1 (2000/2001)

T2……………………………………………………………………..Time point 2 (2005/2006)

T3……………………………………………………………………..Time point 3 (2011/2012)
DECLARATION OF ACADEMIC ACHIEVEMENT

The following is a declaration that the content of this thesis has been completed by Trishana Nayiager. The contributions of Drs R. Barr, A. Klassen, E. Pullenayegum and P. Rosenbaum in the research process, and Dr Solh and Ms. J. Duckworth in data collection are acknowledged.
INTRODUCTION

Brain Tumours in Childhood

Brain tumours, or neoplasms of the central nervous system (CNS), are among the most commonly diagnosed solid tumours in children and adolescents. According to the Canadian Cancer Statistics published in 2011, primary CNS tumours accounted for 16% (n=1, 039) of all newly diagnosed cancers in patients under 19 years of age between 2003 and 2007 in Canada (excluding Quebec) (Canadian Cancer Society, 2011). These proportions are similar to those observed in the US (Gurney et al., 2009).

Brain tumours are sub-categorized based on histology using the World Health Organization or the International Classification of Childhood Cancer definitions (Steliarova-Foucher, Stiller, Lacour & Kaatsch 2005; World Health Organization, 2000). In order of decreasing incidence, the classifications are gliomas/astrocytomas, medulloblastomas, ependymomas, and germ cell tumours. Most are diagnosed prior to the seventh year of life; the incidence of astrocytoma also peaks around the early teen years in addition to early childhood (Gurney, Smith & Bunin, 1999).

Histology, location of the primary tumour, age at diagnosis and extent of disease are used to determine what therapeutic intervention should be used as well as the specific treatment protocol to be employed (Pollack, 2008). An estimated 70% of pediatric CNS tumours are malignant and require aggressive therapy, which may include surgery, radiation and chemotherapy (Imbach, 2006). While treatment is required for survival, the
numerous assaults to the brain, including from the malignancy itself, as well as surgery, chemotherapy and radiation, often result in unintended adverse effects on the patient (Baron, Compton, Patel, Jacob & Harper, 2013). These complications are particularly deleterious given the young age and consequently developing nature of the brain of these patients. As such, it is not uncommon to observe immediate, long-term and chronic morbidities relating to the primary diagnosis of a CNS tumour (Baron et al., 2013; Pollack, 2008). Although there is no specified time for ‘late effects’, most investigators include as late effects any deleterious outcomes that are chronic or develop at least five years from diagnosis (Anderson et al., 2001A; Oeffinger, Eshelman, Tomlinson, Tolle & Schneider, 2000).

**Survivorship and Outcomes of Patients with Brain Tumours in Childhood**

By definition, an individual is considered a cancer survivor from the time of diagnosis through the remainder of his or her life (National Cancer Institute (NCI), 2012). Prior to the 1980s, children and adolescents diagnosed with a brain tumour had a poor prognosis. Technological advances leading to earlier diagnosis as well as improvement of treatment have increased survival. The five-year relative survival estimate for patients diagnosed with a CNS tumour (intracranial or intraspinal neoplasm) in childhood between 2002 and 2008 was 72.1% as noted by the National Cancer Institute in the USA (NCI, 2009).

However, survivors of CNS tumours in childhood are known to have significant long-term morbidities (late effects). The medical sequelae of the disease and treatment have been well-documented in the literature, with the most commonly cited issues being
cognitive deficits, short stature, osteopenia, endocrine deficiencies and second malignancy. Several large multi-centre studies have reported a high prevalence as well as severity of morbidity in this patient population. These late effects are noted to be greater in survivors of CNS tumours compared to survivors of other childhood cancers. In many cases, the survivor will develop combinations of these medical conditions (Oeffinger et al., 2006). In addition, these patients are noted to have visual and auditory limitations, and are often considered to be the group at highest risk for functional impairment (Hudson et al., 2003; Mulhern, Hancock, Fairclough & Kun, 1992; Mulhern et al., 1999). Location of the tumour and modalities of treatment have both been identified as contributory to these late effects (Anderson, 2003).

The complications of treatment have implications for integration into society and psychosocial development, with many survivors noted to have greater needs for educational support, lower rates of graduation from high school and college, higher likelihood of unemployment, less social supports, lower likelihood of getting married, and psychological distress in comparison to their siblings as well as to other childhood cancer survivors (Gurney et al., 2009). Numerous population-based studies undertaken in Canada and the USA, as well as in European countries, have reported similar sociodemographic outcomes (Armstrong et al., 2009; Barrera, Shaw, Speechley, Maunsell & Pogany, 2005; Hays et al., 1992; Koch et al., 2004; Langeveld et al., 2003; Lancashire et al., 2010; Mostow, Byrne, Connelly & Mulvihill, 1991).

It is apparent that survivors of brain tumours in childhood have numerous medical complications as well as difficulties with education, employment and social adaptation.
Specialized “survivorship clinics” are available to survivors of cancer in childhood. These clinics consist of a multidisciplinary team of healthcare professionals who provide systematic follow-up of survivors with the primary objective of health promotion, education and monitoring of long-term consequences of therapy (Aziz, Oeffinger, Brooks & Turoff, 2006; Pediatric Oncology Group of Ontario (POGO), 2006).

The Pediatric Oncology Group of Ontario (POGO) estimates that of the 80% of children and adolescents who will survive their cancer approximately 60% will experience a significant late effect of their disease or therapy (POGO, 2006). In addition to providing a clinical service to survivors, these clinics facilitate research into cancer survivorship. The Office of Cancer Survivorship at the National Cancer Institute defines cancer survivorship research as encompassing “the physical, psychosocial, and economic sequelae of cancer diagnosis and its treatment among both pediatric and adult survivors of cancer”. The emphasis of the research is to increase understanding with the objective of preventing and controlling adverse outcomes from the disease and treatment, as well as to provide guidelines for optimal follow-up and care (NCI, 2012).

While concerted efforts have been made to appreciate the medical complications and to characterize the sociodemographics of survivors of brain tumours in childhood and adolescence, patient reported outcomes, such as measures of health-related quality of life (HRQL), are gaining interest rapidly as an important outcome measure to appreciate the capabilities as well as burden of morbidity experienced by survivors and to gain insight into the lives of this patient population.
Quality of Life

The concept of “quality of life” (QOL) encompasses an individual’s overall perception of their well-being and incorporates multiple aspects of the person’s life, including physical and psychological health, as well as independence, social relationships, environment and beliefs including happiness and satisfaction (Center for Disease Control, 2011). The World Health Organization (WHO) summarized QOL as an “individual’s perception 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” (WHOQOL Group, 1995).

Health-Related Quality of Life

Health related quality of life (HRQL) is a component of QOL that relates specifically to the physical, social and mental health of an individual (Cella & Bonomi, 1995). Unlike the term “health”, which is often measured using objective or observable measures such as blood pressure or ability to walk, HRQL refers to the perceived physical, social and mental health of an individual within the context of a functional state and, according to one particular approach, the value of that health state (Center for Disease Control, 2011; Feeny, Furlong, Mulhern, Barr & Hudson, 1999). The focus on the perceived health state of the individual based on their reported functional capabilities is often described as a “narrow within the skin” approach to measuring HRQL (Ware, Brook, Davies & Lohr, 1981).
Traditional outcomes of cancer therapy focus on mortality and morbidity measures, such as event free survival, and overall survival (Heimans & Taphoorn, 2002). In the past few decades, patient-reported outcomes, particularly HRQL, has been embraced increasingly as an important measure of morbidity in clinical trials as well as in population health studies (McHorney, 1999; Osoba, 2011).

The inclusion of HRQL measures in clinical trials allows researchers to understand the burden of morbidity from disease and treatment within the context of an individual’s life. When measured using reliable instruments validated to the patient population, HRQL can provide valuable information on the design of new therapies by providing an alternate outcome measure, such as whether patients felt better, or it can be used to explore consequences of treatment that may not be otherwise measureable, and should be considered when testing novel or comparing medical interventions (Feeny et al., 1999). Clinicians can also use HRQL information to assist with treatment decisions and treatment alternatives for patients (Feeny et al., 1999). The degree to which a diagnosis or treatment will impact the daily functioning and overall well-being of an individual is of particular importance in populations of people with chronic diseases, which, by extension, can also include populations with long-term morbidities as a result of disease or treatment (Patrick & Erickson, 1993).

HRQL is also an important outcome for understanding the perceived well-being of a group of individuals, from specific disease groups to entire nations. The ability to quantify the overall health status of a population provides valuable information to policy makers and health administrators (Wennberg, 1990).
Measurement of HRQL is accomplished using self- or proxy-responses to capture the perceived health of an individual and uses these responses to generate a meaningful score that estimates the impact on overall QOL (Center for Disease Control, 2011). The questionnaires, often structured as multiple items or questions with specific multiple-choice responses, are designed to generate scores for key domains of health status. Feeny et al. (1999) proposed that one way to conceptualize health is to summarize key attributes (dimensions/domains) of health status including physical function, sensation, self-care and dexterity, cognition, pain and discomfort, and emotional and psychological well-being. These dimensions contribute collectively to the overall HRQL of the individual. Based on the design of the questionnaire, it is possible to generate scores for each of the individual domains as well as an overall HRQL score.

The resultant scores may be qualitative and describe the burden of morbidity using adjectives, or be quantifiable, with the burden of morbidity falling within a structured numerical scale allowing for analytical study. Scores from a reliable instrument that has been validated in the patient population can be interpreted directly to identify areas of particular morbidity, or can be referenced to another population, including those with other diagnoses, healthy controls or even the same cohort at another point in time. This indirect measurement of morbidity allows for comparison using statistical analyses or absolute differences. Some instruments have previously established levels of meaningful minimal clinically important differences.
Given the varying definitions of HRQL and the complexity of measuring perceived health in the context of daily living, multiple instruments have been created. Although these instruments often incorporate similar principles of measuring physical, psychological and social components to generate a measure of HRQL, the constructs used to define HRQL are variable and scale dependent (Fayed, Schiariti, Bostan, Cieza & Klassen, 2011). Most often HRQL measurement scales are divided into disease-specific health outcomes or generic functioning measures (Feeny et al., 1999).

Disease-specific questionnaires are designed to focus on areas established or hypothesized previously to be of relevance to the patient population under exploration. This type of questionnaire is often sensitive to small changes in HRQL over time and has considerable face validity. However, this type of instrument is limited in applicability as scores cannot be compared to other disease populations (Khanna, 2006; King, Tsevat, Moossy & Roberts, 2004; Tsevat et al., 1994).

Generic instruments, conversely, attempt to capture multiple areas of HRQL and can be used across populations, including healthy and diseased groups, thus facilitating comparisons between disease populations. In addition, this type of instrument does not pre-suppose areas of morbidity and consequently provides a more global representation of the capabilities of the population, which may be overlooked in disease-specific scales (Dowie, 2002).
Generic instruments can be classified as either health profiles or preference-based measures. Health profiles, which can be HRQL measures or measures of health status, describe an individual’s function based on one or more domains. These domains may be presented individually or consolidated as an overall summary score. Outcomes from health status instruments are beneficial for describing the functioning capabilities of a group.

Preference-based measures are also generic instruments. However, this type of instrument provides a single utility score for a specific state of health, on an established scale of 1 (perfect health) to 0 (equivalent to being dead). Similar to health profiles, scores may be generated for individual domains, such as physical functioning, or summarized as a single overall HRQL score. As these scores are referenced to a pre-defined scale, the results obtained can be used to describe the functional capabilities of a given population as well as allowing for direct comparison of HRQL scores to normal (healthy) or even other non-related diseased populations.

Preference-based measures may use direct estimation methods, such as willingness to pay, standard gamble or time trade-off, to generate a single score corresponding to a health state of the domain under study (Feeny et al., 1999; Streiner & Norman, 2008). This approach to preference-based measures simultaneously incorporates the capabilities and limitations (or positive treatment outcomes and side effects) within a single score.
A second technique used in preference-based measures is indirect estimation. In this scenario responses to items on the measurement scale are combined with pre-determined weights of specific health states referenced to the general population (Streiner & Norman, 2008). This results in a comprehensive health status utility score.

In addition to describing a population’s health, utility scores from preference-based measures can be incorporated into clinical trial outcomes to generate quality-adjusted life years (QALYs). This allows economists and policy-makers to compare outcomes from different disease populations and facilitates decision-making processes for funding of programs.

Selection of an appropriate measurement tool requires consideration of the study objective and outcome, the property of the measurement scale as well as the patient population. These factors include type of outcome, sensitivity of measurement scale, and previous use in the targeted patient population to assess reliability and validity. In addition, potential cognitive limitations of the subjects due to age or impairment must be considered, as the length of the instrument, language-level, required method of administration (interview or self-completion) and the use of proxy reporting will influence the selection of the most appropriate instrument (Tao & Parsons, 2005). The population under study must also find the scale acceptable with respect to the content and length so that the respondent remains engaged long enough to complete the questionnaire (Feeny et al., 1999; Streiner & Norman, 2008). Finally, as scales vary, the individual HRQL dimensions and corresponding definitions for the selected questionnaire should
also be considered carefully to ensure that the study objective will be addressed adequately and quantified with the given scale (Feeny et al., 1999).

**Measures of HRQL in Survivors of Brain Tumours in Childhood**

Survivors of brain tumours in childhood and adolescence have a high prevalence of long-term, chronic morbidities as a consequence of the disease itself as well as the treatment (Anderson et al., 2001A). These individuals have been identified to have a much greater burden of long-term medical, neurocognitive and psychosocial sequelae compared to survivors of other childhood cancers. This is particularly of relevance given the increasing incidence of pediatric brain tumour diagnoses as well as increase in the survival of affected children (Jemal et al., 2004; Smith et al., 2010).

Historically, the long-term sequelae of surviving a childhood brain tumour were characterized by neuropsychological outcomes, measured by intelligence tests and academic markers, and chronic medical complications, assessed by traditional health outcome measures including physical examination and laboratory results (Anderson, Northam, Hendy & Wrenhall, 2001B; Mulhern et al. 1992; Packer et al., 2003). Although these late effects of disease and treatment were well documented in the literature, the overall burden of morbidity as experienced by the survivors was not as well understood (Barr et al., 1994). In addition, attempts to capture the QOL of individuals were often undertaken as interviews to elicit sociodemographic characteristics, including marital status, educational level achieved and employment details (Mostow et al, 1991). Further, there was agreement that outcomes from surviving a brain tumour in childhood differed...
from the experience of survivors of CNS tumours occurring in adult life (Twombly, 2009).

Over the past two decades there has been an increasing interest in the QOL, and specifically health-related morbidity, as experienced by survivors of childhood brain tumours (Mulhern et al., 1998). The characterization of HRQL as perceived by the survivors is being recognized increasingly as important insights into the lives of these patients, and provides clinicians guidance into the late effects experienced by survivors as well as an alternate measure of the success of therapeutic protocols (Anderson et al., 2001A). As such, retrospective and prospective studies frequently include HRQL measures to assess the burden of morbidity experienced by such survivors, and to explore the potential factors that contribute to a perceived health state as outcomes from therapeutic interventions.

In addition, research has been dedicated to identifying commonly used questionnaires in research and evaluating the psychometric properties of generic as well as disease-specific instruments used to measure HRQL in survivors of brain tumours. A systematic review was undertaken by Klassen et al to identify the most commonly used HRQL measures in children with cancer and survivors of childhood cancers (Klassen, Anthony, Khan, Sung, & Klaassen, 2011). The terms “quality of life”, “health-related quality of life”, “quality adjusted life years”, “health status”, “functional status”, “well-being”, or “patient reported outcome” were used to search Embase, MEDLINE, CINAHL, EMBASE, PsycINFO, Cancerlit and Sociological Abstracts from inception to May 29, 2011. The primary objective of this team’s systematic review was to identify
pediatric measures used in research to evaluate HRQL of patients and survivors of childhood cancer. This review included studies of patients less than 30-years of age and utilized unmodified HRQL questionnaire. The patient populations within the studies could include multiple conditions provided that results were reported on childhood cancer patients. Intervention studies or studies of hematopoietic or stem cell transplant study subjects were excluded. The systematic review being undertaken by Klassen et al.’s team closely aligned with the objectives of the current thesis. As such collaboration was established and support was provided by T. Nayiager in the identification and review of eligible articles published between June 15, 2009 and May 25, 2011, as an up-date to the initial systematic review.

Of the 111 studies identified by the overall systematic review, 36 studies provided results on survivors, or mixed on-treatment patients and survivors, of brain tumours, either as a single population, or reported within a mixed cancer population. The measures used most often in these studies were the PedsQL (n=12), the Health Utilities Index (HUI) (n=9) and the Child Health Questionnaire (CHQ) (n= 6). Other measures included the Minneapolis Manchester Quality of Life (MMQL) (n=4), the TNO-AZL Questionnaires for Children's Health-Related Quality of Life (TACQOL) (n=3), the Quality of Life- Cancer Survivors (n=2), the Assessment of Quality of Life (n=1), and the KINDL (n=1). Two studies used more than 1 family of HRQL measures.
In a separate search of PubMed using the terms “quality of life”, “survivors”, “childhood”, “brain tumour,” with no restriction on age, it was determined that the Short-Form-36 (SF-36) is a commonly used instrument in HRQL studies of adult survivors of brain tumours in childhood. A synopsis of the PedsQL, HUI, CHQ and SF-36 is presented below.

The PedsQL is a family of instruments used in children and adolescents with acute and chronic health conditions, including patients undergoing treatment for, as well as survivors of, childhood cancers (Varni, 2013). The 23-question parent (proxy) and patient (self) reporting generic module measures four domains: physical functioning, emotional functioning, social functioning and school functioning. These can be summarized into two summary scores: a physical health summary score and a psychosocial health summary score. The cancer-specific module can be used in combination with the generic instrument. This disease-specific questionnaire explores health concepts pertaining to cancer-specific aspects of HRQL, which include treatment and procedural anxiety, cognitive ability, patient worry, physical self-appearance, and communication (Bhat et al., 2005). The generic and cancer-specific measures have been found to be reliable and valid in estimating the HRQL of children and adolescents with present and past histories of CNS tumours (Bhat et al., 2005). A specific brain tumour questionnaire is also available however this instrument is very similar to the cancer measure and appears to be applicable only to patients undergoing treatment.

Although the PedsQL is used extensively in research with children, there are conceptual and practical concerns about this family of instruments. A Canadian study of
the properties of the PedsQL, parent respondent, by Amin et al. (2012) involving children undergoing treatment for cancer identified validity issues using Rasch analysis (comparison of trait actually possessed versus level scored on scale), poor distribution across response categories for over half of the items, and potential bias in reporting of physical function by age, as well as differences in parent reporting based on the gender of the child.

In addition to the limitations outlined above, others have pointed out that the PedsQL uses negative phrasing exclusively, with respondents asked to identify problems in the identified areas (Fayed et al., 2011). This presents a logistical problem as positive factors are excluded and may not completely represent the HRQOL of the individual. In addition, the negative questioning connotes an interest into limitations and disability but not necessarily functioning (Fayed et al., 2011). The negative phrasing may also be psychologically burdensome for the respondent (Waters et al., 2009).

The HUI is a set of generic multi-attribute health status and HRQL instruments that capture the overall health status as well as individual single attribute of an individual’s health. This family of questionnaires includes different versions dependent on the type of administration (interview or self-completion), type of respondent (self, proxy-relative, proxy-clinician), number of questions (15 or 42), type of construct used to define the domains (HUI version 2 or HUI version 3) and language (available in > 20 versions). The HUI2 and HUI3 systems have been evaluated for their psychometric properties. The design of the HUI3 system is noted to be theoretically and empirically founded as the utility scores were ascribed and then validated in a random sample of
individuals within a community (Feeny et al., 2002). In addition, there is almost an even divide of negative and positive phrasing of questions (Fayed et al., 2011). The questionnaires have been used in a variety of populations, including epidemiological studies (Orpana et al., 2009) and in a wide range of ages (>5 years) and disease types, including children with cancer and survivors (Health Utilities Inc, 2011). A more detailed description and review of the HUI family of instruments is presented in the “Methods” section of this Thesis.

The CHQ is a generic multidimensional instrument that measures the physical and psychosocial health of children and adolescents. A proxy (parent)-reported questionnaire utilises 50 items to derive outcomes on individual scales, which can be aggregated further into overall physical and psychosocial scores (Landgraf, Abetz & Ware, 1996). The proxy (parental)-reported form (CHQ PF-50) has 10 individual scales: physical functioning, role limits secondary to emotional/behaviour, role limits secondary to physical health problems, bodily pain, mental health, self-esteem, general health, parental impact-time, parental emotional impact and behaviour. Responses are captured on four to six point Likert scales. A Dutch study of the reliability and validity of this tool in a general population of children established that the CHQ-parent form 50 was able to distinguish between healthy children and those with chronic conditions. The authors also demonstrated internal consistency reliability between related items, and test-retest reliability for all subscales aside from behaviour (Raat, Bonsel, Essink-Bot, Landgraf, Gemke, 2002). This instrument has been used also in assessing patients 1 to 18 years of age with cancer, including those with a history of brain tumours (Sung et al, 2003;
Sawyer, Antoniou, Toogood, & Rice M, 1999; Sands et al., 2001). The CHQ has also been shown to correlate with constructs of the HUI2 and HUI3 questionnaires in childhood cancer survivors (Nixon et al., 1999).

The SF-36 is a generic measurement scale that uses responses from 36-items to define eight domains constituting HRQL: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health (Ware, & Gandek, 1998). These subscales can be used to generate two summary scores for physical and mental health. Concordance with decreasing self-rated health and scores generated by the SF-36 questionnaire has been established (Jenkinson, Wright, & Coulter, 1994). In addition, large population-based studies of the SF-36 have generated country, age-group and gender specific normative data (Hopman et al., 2000). This scale has also been demonstrated to be valid and reliable in studies of adult survivors of childhood cancer (Barr et al., 1999, Glaser et al., 1999, Reulen et al., 2006). The SF-36 has been used previously in adolescents; however, there is limited information available about the validity of the instrument in this age group (SF-36.org, n.d.).

**Previous Assessments of HRQL of Survivors of Brain Tumours in Childhood**

A literature review using keywords of “quality of life”, “health related quality of life”, “health status”, “survivors”, “brain tumours”, and “child” was undertaken on Medline to explore the capabilities and limitations of survivors of brain tumours in childhood in high income countries. This review was restricted to studies that utilized HRQL instruments; the scores could be based on either self- or proxy- reporting. There was no restriction on age of survivors or minimum time from diagnosis. However,
subjects must have been diagnosed with a primary brain tumour during childhood or adolescence (<21 years of age). Studies that included a mixed population of cancer types or patients undergoing treatment as well as survivors were reviewed provided that information on brain tumour survivors was presented independently. The objective of this review was to provide a foundation of the previous work undertaken in the HRQL of survivors of brain tumours.

McMaster Children’s Hospital (MCH) was one of the first institutions to recognize the need for and subsequently develop a systematic measurement instrument to capture the multi-attribute health status of survivors of childhood cancers, which was piloted initially in brain tumour survivors to assess feasibility (Barr et al., 1994; Feeny, Furlong, Boyle & Torrance, 1995). The instrument developed at MCH was based on the HUI system and captured the global health status and severity of morbidity in subjects using self- or proxy-reporting (Feeny et al., 1995). Descriptive and quantitative outcomes from this small case series revealed a wide range of severity in morbidities experienced by survivors of childhood brain tumours, with the recommendation that HRQL should be a contributing measure of success in clinical trials (Barr, et al., 1999).

A second more comprehensive study was undertaken in the neuro-oncology follow-up clinic at MCH between 1993 and 1995 (Barr et al., 1999). Forty-one participants diagnosed with a brain tumour (irrespective of type, location and treatment), mean age of 9.5 years (range of 1.7 to 17.9 years), mean time from diagnosis of 3.3 years (range 0.2 to 8.6 years), underwent HRQL assessment using the 15-item HUI2/3 questionnaires. Questionnaires were completed by a nurse proxy as well as parent proxy;
subjects who were at least 9.5 years of age also completed a self-administered questionnaire. The severity and number of areas of morbidity in this cohort, as captured by the overall health utility score by the nurse reporting, ranged from 0.12 to 1.00 (median 0.92) for HUI2, and -0.27 to 1.0 (median 0.77) for HUI3, with negative scores reflecting states of health worse than being dead. Over three-quarters of participants were noted to have some level of morbidity (83% by HUI2 and 78% by HUI3). The authors reviewed the frequency and severity of morbidity of the single attributes for the HUI2 and HUI3 systems and noted that there was inter-subject variability in the degree of morbidity within a single attribute.

The authors also noted that the most common morbidities reported were in attributes predicted by clinical experience. The single-attribute utility scores for these attributes observed were much lower than the HUI3 data available from the 1991 Canadian General Society Survey (CGSS), using the results for the youngest age group of 15 to 19 years. These attributes included vision (30% reporting limitations in brain tumour survivors, versus 26% in CGSS), ambulation/mobility (19 % in brain tumour survivors versus 0% in the CGSS), emotion (26% in brain tumour survivors versus 21% in the CGSS) and cognition (68% in brain tumour survivors versus 24% in the CGSS).

In addition to these deficits, there was also an unexpected prevalence of pain reported for this cohort of patients, as 32% of brain tumour survivors were noted by nurse-reporting to have pain whereas the CGSS reported that 22% of individuals aged 15 to 19 years reported pain. The increased prevalence of pain was particularly surprising as previous literature did not suggest issues with discomfort in this patient population;
however a study undertaken in survivors of adult brain tumours did note that almost 50% of participants reported pain (Packer et al., 2003, Whitton, Rhydderch, Furlong, Feeny & Barr, 1997).

A complementary study was undertaken in Nottingham, UK, during the same time interval (Glaser et al., 1999). The patient population consisted of 30 survivors, mean age at assessment of 10.5 years (range 6 to 16 years) and at a mean of 4.1 years from diagnosis (range of 1 to 10 years). The 15-item HUI2/3 questionnaire, modified for the UK population, was completed by parents, children, physiotherapists and physicians. The results were similar to those reported in the McMaster study, with 79% of participants noted to experience some morbidity by both HUI systems. Comparison at a single attribute level identified similar areas of deficits, although the prevalence and degree of severity varied between the two populations. Once again, an unexpected high prevalence of pain was noted in this patient cohort, with approximately 30% reporting pain, which was similar to the results observed by Barr et al, (1999) in Hamilton, Ontario.

The identified morbidities, as experienced by the individual patients in the context of their daily lives, emphasized the need for further exploration of HRQL in survivors of brain tumours in childhood. Subsequent studies, including those using alternate measurement instruments, matched controls and large, population-based studies, also identified burdens of morbidity in this patient cohort.

In a single institution in California, a cohort of 25 brain tumour patients actively undergoing treatment and 109 post-therapy survivors (median time from diagnosis of 3.2
years for overall cohort), as well as their parents, completed the PedsQL 4.0 generic questionnaire (Bhat et al., 2005). In comparison to healthy children, patients (median age of 11.3 years) reported statistically significantly worse HRQL in all of the subscales, including physical health (which encompasses pain, measured as a single item within the eight item physical function scale), emotional and social functioning. In keeping with findings in the previous two studies, considerable variability between patients was noted.

A sub-analysis of the patient cohort revealed no evidence that patients further from diagnosis reported better HRQL than those treated more recently. Although this was determined by stratifying the patients based on time from diagnosis rather than following a single cohort through time, this result was of particular interest as it was anticipated that HRQL would improve with time for brain tumour survivors, as observed in children diagnosed with other types of cancers (Varni, Burwinkle, Katz, Meeske & Dickinson, 2002).

One study undertaken at the Memorial Sloan Kettering Cancer Center attempted to capture the influence of time on HRQL in a single cohort of patients as an outcome measure of an interventional study (Sands et al., 2010). Survivors of malignant brain tumours in childhood treated with the “Head Start 1” protocol consisting of myeloablative chemotherapy, autologous stem cell rescue and either no or delayed cranial radiation (Mason et al., 1998) were assessed in 1991 (N=25, mean time from diagnosis of 5.7 years) and again in 1997 (N=19, mean time from diagnosis of 11.6 years). Parents of these children (mean age of 8.1 years at T1 and 13.5 years at T2) completed the CHQ-PF50 questionnaire as a measure of HRQL at both time points, irrespective of the age of the
patient. Unlike previous studies, the findings noted that, as a group, physical and psychosocial scores were within normal ranges at both time points, including bodily pain (81% of patients in 1991 and 89.5% of patients in 1997) based on age-adjusted T-scores. Although as a group there appeared to be little difference between the survivors and their peers, a wide range of severity of disability was observed in these children. Interestingly, the authors also recognized a trend to improvement of role limitations due to physical functioning, but a significant decrease in general health between the two time points. This suggests that HRQL may change over time as perceived by the parents of survivors of brain tumours in childhood. Self-reporting may provide greater insight into the HRQL of these individuals and the influence of time from diagnosis, particularly when these survivors transition into adulthood.

The TACQOL measurement instrument is another tool that has been used in children who have survived brain tumours and has demonstrated a burden of morbidity experienced by this patient population. A study in the Netherlands of 38 children surviving low grade astrocytomas, one of the most frequently occurring tumours that require intervention, noted problems in physical, motor, cognitive, autonomy and social domains as reported by parents (Aarsen et al., 2006). Children reported a slightly better QOL, but still noted issues with motor, cognitive and social functioning. No specific details regarding pain were reported; however this was incorporated in the physical domain of the instrument. From the TACQOL questionnaire, the items directly soliciting information regarding pain are in reference to stomach ache or abdominal pain, and colic.
The challenges faced by survivors of brain tumours in childhood were also appreciable in large surveillance studies investigating the HRQL of survivors of childhood malignancies. The Childhood Cancer Survivor Study (CCSS), one of the largest studies undertaken, included 26 institutions across Canada and the US and explored the long-term outcomes of children and adolescents diagnosed with a malignancy between 1970 and 1986, with the availability of matched sibling controls (Packer et al., 2003). Armstrong et al. (2009) reviewed HRQL data for long term survivors of brain tumours in childhood (N=1877, range of 5 to 34 years of survival after diagnosis). The authors concluded that patients reported higher rates of impaired health status than their siblings, in overall health as well as mental health, functional impairment, activity limitation, pain and cancer-related anxiety, as measured by the SF-36 questionnaire and Cantril Ladder of Life (Armstrong et al., 2009). In keeping with the smaller brain tumour specific studies presented earlier, pain was observed to be a considerable morbidity in this study as measured by the SF-36, with brain tumour survivors being 7.9 times more likely to report experiencing pain than their siblings.

A similar study of adult survivors of childhood cancer was undertaken in the UK (Reulen et al., 2007). Retrospective analysis of the results demonstrated that CNS tumour survivors were found to have a SF-36 summary scores substantially lower than the population norms for mental health (difference of -0.1, 99% confidence interval of -2.2 to -0.9) and physical health (lower scores at all ages, ranging from -4.1 (-6.0 to -2.5) to -7.5 (-8.9 to -3.1), which includes pain. Patients with a history of CNS radiation also had significantly lower physical component summary scores than survivors of leukemia, who
were used as the reference group in the study. Stratification by age also demonstrated that individuals 25 years of age and older had increasing prevalence of physical health limitations.

Population-based studies of childhood cancer survivors also revealed a significant burden of morbidity, particularly in CNS tumour survivors. A cross-sectional Canada-wide study of a random sample of childhood cancer survivors diagnosed before 20 years of age between 1981 and 1990 and had survived at least five years from diagnosis were identified from 12 pediatric oncology centres and provincial cancer registries (Pogany et al., 2005). These individuals, as well as a cohort of the general population with no history of cancer, completed mailed HUI3 questionnaires. CNS tumour survivors accounted for 362 of the 2152 participants with a history of cancer. Increased impairment in all attributes contributing to HRQL was observed for cancer survivors as a group in comparison to population controls. However, a particularly large burden of morbidity was detected in survivors of CNS tumours in childhood. In comparison to other cancer survivors as well as controls, patients with prior CNS tumours had amongst the lowest overall HRQL, as determined by the percentage in the bottom quartile as well as mean summary scores. CNS tumour survivors were noted to have greater impairment in dexterity, ambulation, speech and cognition in comparison to other survivors. Single-attribute mean scores of CNS tumour survivors demonstrated particularly high burdens of morbidity in cognition, emotion and pain. Although the burden of pain would have influenced the overall health status summary score, unlike the CCSS study, there did not appear to be a large difference in the pain experienced by cancer survivors and controls.
The percent of CNS tumour survivors reporting pain was less than that in the controls (37% versus 44% respectively), but cancer survivors as a whole also reported less pain than controls.

Another cross-sectional Canada-wide study of survivors of cancer in childhood ($N=1334$, mean age 23 years, range of 15 to 37 years), who were greater than five years from diagnosis, was undertaken in those diagnosed between 1981 and 1990, using the SF-36 questionnaire (Maunsell et al., 2006). Again, CNS tumour survivors, in contrast to the majority of other childhood cancer survivors (aside from those with bone tumours), had lower overall HRQL scores than age- and gender-matched controls. Areas of greatest deficiencies were general health, physical function, physical role, vitality, social function and mental health. Unlike results from the CCSS study, but similar to the results seen by Pogany et al. (2005), bodily pain and emotional role were not identified as statistically different from controls.

The 15-item HUI3 instrument was used in a prospective population-based cohort study in Piedmont, Italy to assess the HRQL of long-term survivors (>five years from diagnosis) of childhood cancer (Alessi et al., 2007). Long-term CNS tumour survivors ($n=133$ out of 644 cancer survivors) as a group were identified to have the lowest overall HRQL in comparison to all other cancer types. Further, CNS tumour survivors were over represented (5 out of 11) in the group of individuals reporting an overall HRQL of lower than 0.00 (worse than death). In addition, these adolescents and adults (age range of 15 years to >35 years) with a history of primary CNS tumours had significant burdens of morbidity, by both prevalence and severity, in the areas of cognition, pain, and vision.
While most survivors did not indicate issues with emotion, those who did report difficulties noted a severe impairment. Problems with ambulation and dexterity were also identified by survivors, but these were not severe.

**Summary of the Studies Reviewed**

A preponderance of the studies reviewed reported a burden of morbidity amongst survivors of brain tumours in childhood, which were often greater than those observed in the normal population or in comparison to other childhood cancer survivors (Table 1 and Table 2). Some of these studies also identified an unexpected burden of pain, which is not well characterized. In addition, exploration of the influence of time on HRQL, undertaken either by stratifying patients by time from diagnosis or following a cohort of individuals over time, suggested that survivors of brain tumours in childhood may experience greater difficulty as they progress through life after completing treatment (Bhat et al., 2005; Sands et al., 2001).

There is still limited information available regarding the HRQL of long-term survivors of brain tumours in childhood and adolescence. In addition, the change of HRQL over time, particularly from childhood into adulthood, is relatively unknown. It has been suggested that burdens of morbidity may influence other issues pertaining to QOL, such as educational achievement and employability, and HRQL will change over time (Zebrack & Zeltzer 2003; Zeltzer et al., 2009). Furthermore, it is important to provide survivors the opportunity to self-report on their HRQL to best appreciate the burden experienced by this population (Recklitis, O’Leary & Diller, 2003).
MCH has a longstanding interest in the HRQL of survivors of brain tumours in childhood. Given the unanticipated prevalence of pain identified in several studies, an exploratory cross-sectional investigation was undertaken to capture the HRQL of survivors more than 10 years from diagnosis using the HUI2/3 system, as well as additional measures to better characterize the pain, including the potential relationship with other morbidities experienced by this patient population. In addition, the stability and severity of pain over time were explored using previously unpublished results of previous HUI2/3 survey data undertaken in the same cohort.
Table 1. Summary of study design and patient characteristics in studies reviewed, arranged by ascending order of publication date

<table>
<thead>
<tr>
<th>Study</th>
<th>Location, Methodology</th>
<th>Participants</th>
<th>Years of diagnosis</th>
<th>Age of survivors at time of survey</th>
<th>Time from diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barr <em>et al.</em>, 1999</td>
<td>Hamilton, ON, Canada</td>
<td>Prospective</td>
<td>41 survivors of brain tumours</td>
<td>Mean of 9.5 years (range of 1.7 to 17.9 years)</td>
<td>Mean of 3.3 years, range of 0.2 to 8.6 years</td>
</tr>
<tr>
<td>Glaser <em>et al.</em>, 1999</td>
<td>Nottingham, UK</td>
<td>Prospective</td>
<td>28 survivors of brain tumours</td>
<td>Mean of 10.5 years (range of 6 to 16 years)</td>
<td>Mean of 4.1 years, range of 1 to 10 years</td>
</tr>
<tr>
<td>Sands <em>et al.</em>, 2001</td>
<td>New York, NY, USA</td>
<td>Prospective, longitudinal</td>
<td>T1= 25 survivors of brain tumours, T2=19 survivors of brain tumours</td>
<td>Mean 11.82 years, SD 5.39</td>
<td>Mean of 4.26 years, SD of 4.41</td>
</tr>
<tr>
<td>Bhat <em>et al.</em>, 2005</td>
<td>Palo Alto, CA, USA</td>
<td>Prospective</td>
<td>109 survivors of brain tumours, 25 brain tumour patients on-therapy</td>
<td>Mean of 5.7 years, T2= mean of 11.6 years</td>
<td></td>
</tr>
<tr>
<td>Aarsen <em>et al.</em>, 2006</td>
<td>Netherlands</td>
<td>Prospective</td>
<td>38 survivors of low grade astrocytomas</td>
<td>Mean of 7.7 years, range 3.7 to 11.4 years</td>
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<tr>
<td>Pogany <em>et al.</em>, 2006</td>
<td>Canada</td>
<td>Retrospective</td>
<td>362 survivors of brain tumours (out of 2152 mixed cancers)</td>
<td>63.8% (1359) were reported to be greater than 16 years of age (all survivors)</td>
<td>Greater than 5 years</td>
</tr>
<tr>
<td>Maunsell <em>et al.</em>, 2006</td>
<td>Canada</td>
<td>Prospective</td>
<td>238 survivors of brain tumours (out of 1334 mixed cancers)</td>
<td>Mean of 23 years (SD 5.2) for brain tumour cohort</td>
<td>83.5% were 10 or more years from diagnosis</td>
</tr>
<tr>
<td>Reulen <em>et al.</em>, 2007</td>
<td>UK</td>
<td>Retrospective</td>
<td>2188 survivors of brain tumours (out of 10 189 mixed cancer survivors)</td>
<td>Mean of 30.4 years (all survivors)</td>
<td>23.5 years (Estimated based on mean age questionnaire completed - mean age at diagnosis)</td>
</tr>
<tr>
<td>Alessi <em>et al.</em>, 2007</td>
<td>Piedmont, Italy</td>
<td>Prospective</td>
<td>133 survivors of brain tumours (out of 691 mixed cancers)</td>
<td>15 to greater than 35 years (mean not specified)</td>
<td>Greater than 5 years (mean not specified)</td>
</tr>
<tr>
<td>Armstrong <em>et al.</em>, 2009</td>
<td>Canada and US</td>
<td>Retrospective</td>
<td>1877 survivors of brain tumours</td>
<td>Number of participant (%) with Study Specified Age Range: 0 – 14 years= 252 (13.4)</td>
<td>≥ 5 years</td>
</tr>
</tbody>
</table>
Table 2. Summary of study methods and outcome of studies reviewed, arranged by ascending order of publication date

<table>
<thead>
<tr>
<th>Study</th>
<th>Questionnaire</th>
<th>Self/Proxy *Primary (if applicable)</th>
<th>HRQL Outcomes for Survivors of Brain Tumours in Childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barr et al., 1999</td>
<td>HUI2/3</td>
<td>Proxy- nurse*</td>
<td>-Overall mean HUI2 score of 0.92 (range of 0.12 to 1.0)</td>
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<td></td>
<td></td>
<td>Proxy-parent</td>
<td>-Overall mean HUI3 score of 0.77 (-0.27 to 1.0)</td>
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<td></td>
<td></td>
<td>Self (&gt;9.5 years)</td>
<td>-Burdens of morbidity, as measured by prevalence, were noted in attributes of cognition, emotion, sensation, vision, mobility/ambulation, and pain. Pain was reported in 27% of participants by HUI2 and 32% by HUI3</td>
</tr>
<tr>
<td>Glaser et al., 1999</td>
<td>HUI2/3 UK</td>
<td>Proxy- parent</td>
<td>-Overall mean HUI2 score of 0.78 (range of 0.36 to 1.0)</td>
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<td></td>
<td></td>
<td>Proxy-physician</td>
<td>-Overall mean HUI3 score of 0.66 (range of 0.17 to 1.0)</td>
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<td></td>
<td></td>
<td>Proxy-physiotherapist*</td>
<td>-Burdens of morbidity, as measured by prevalence, were noted in attributes of emotion, cognition, self-care, pain. Pain was reported in 34% of participants by HUI2 and 28% by HUI3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Self (with help of play specialist for &lt;9 years)</td>
<td></td>
</tr>
<tr>
<td>Sands et al., 2001</td>
<td>CHQ-PF50</td>
<td>Proxy-parent</td>
<td>-Physical and psychosocial scores within normal range of peers based on adjusted T-scores at both time points</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>-Decreased general health at T2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Wide range of severity of disabilities at T1 and T2. Bodily pain was reported at greater than normal limits in 4 patients (16%) at T1 and 2 patients (10.5%) at T2.</td>
</tr>
<tr>
<td>Bhat et al., 2005</td>
<td>PedsQL (generic) 4.0</td>
<td>Proxy-Parent*</td>
<td>-Decreased physical health (incorporates pain score), emotional and social functioning in comparison to healthy controls</td>
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<tr>
<td></td>
<td></td>
<td>Self</td>
<td>-Increasing burdens in communication of illness and decreased social functioning as progress further from diagnosis.</td>
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<td></td>
<td></td>
<td></td>
<td>-Pain not explicitly stated to be a burden</td>
</tr>
<tr>
<td>Aarsen et al., 2006</td>
<td>TACQOL</td>
<td>Proxy-parent</td>
<td>-Difficulties with physical (incorporates pain), motor, cognitive, autonomy and social domains based on parent reporting</td>
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<td></td>
<td></td>
<td>Self (&gt;8 years)</td>
<td>-Difficulties with motor, cognitive and social functioning based on patient reporting.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Pain not explicitly stated to be a burden</td>
</tr>
</tbody>
</table>
Table 2 continued. Summary of study methods and outcome of studies reviewed, arranged by ascending order of publication date

<table>
<thead>
<tr>
<th>Study</th>
<th>Questionnaire</th>
<th>Self/Proxy *Primary (if applicable)</th>
<th>HRQL Outcomes for Survivors of Brain Tumours in Childhood</th>
</tr>
</thead>
</table>
| Pogany et al., 2006    | HUI3          | Self                               | -Lower overall HRQL scores in brain tumour survivors in comparison to controls as well as other cancer survivors  
-Overall mean score for brain tumour survivors of 0.75 (SD of 0.26)  
-Areas of greatest burdens of morbidity by mean HUI score were cognition (0.87), emotion (0.92) and pain (0.93)  
-Areas of greatest burdens in comparison to other cancer survivors were cognition, dexterity, speech and ambulation.  
-37.3% of CNS Tumour survivors reported experiencing pain |
| Maunsell et al., 2006  | SF-36         | Self                               | -Lower overall HRQL scores in brain tumour survivors in comparison to age and gender matched controls, as well as most other cancer survivors.  
-Decreased general health, physical function, physical role, vitality, social function and mental health compared to controls  
-Bodily pain reported by CNS survivors was not found to be significantly different from controls |
| Reulen et al., 2007    | SF-36         | Self                               | -Decreased physical summary component score on CNS survivors in comparison to general population, as well as leukemia survivors.  
-Increased physical health limitations of CNS survivors with age based on stratification  
-Pain not explicitly identified to be a burden in CNS survivors |
| Alessi et al., 2007    | HUI3          | Self                               | -Worst overall HRQL seen in brain tumour survivors in comparison to other cancer types.  
-Greatest morbidity observed in domains of cognition, pain and vision.  
-35.3% of CNS survivors reported pain  
-Severity of pain identified to be greater in CNS survivors in comparison to survivors with other malignancies |
| Armstrong et al., 2009 | SF-36, Cantril Ladder of Life | Self                               | -Higher rates of impairment in overall health, mental health, functional impairment, activity limitation, pain and cancer-related anxiety in comparison to siblings.  
-Relative risk of pain for CNS survivors was 7.9, 95% CI=5.5 in comparison to siblings |
METHODS

Objective

The primary objective of this study was to explore the prevalence and burden of pain in a cohort of survivors of brain tumours in childhood who were at least ten years from diagnosis. Secondary objectives included investigating the correlation of responses between participant and participant-identified proxy reporting, determining other areas of morbidity, and examining the trajectory of the prevalence and severity of pain over a decade. The following hypotheses were generated a priori based on the literature available and guided the design of this study:

1. In long-term survivors of brain tumours in childhood greater than 35% of respondents will report pain as measured by the HUI2/3 questionnaire.

2. The expected correlation between proxy- and self-reported pain will be less than 0.40 for both HUI2 and HUI3.

3. Other areas of increased morbidity will be identified in the overall cohort, including in attributes of emotion and cognition.

4. Pain will be persistent in the overall cohort over a period of 10 years.

Study Design

The work presented in this thesis is part of a longitudinal prospective cohort study that commenced in 2001 and attempted to characterize the change in HRQL, and in particular pain, over a ten-year period. The initial study (2001/2002) identified survivors who were diagnosed with a primary brain tumour in childhood at MCH at least two years prior. At the commencement of the initial study, individuals who were less than five years
of age at the time or who had relapsed or had progression of the disease were excluded. Eligible and consenting participants were followed at five-year intervals over a ten year period (Figure 7). Participants as well as a proxy completed the HUI2/3 instrument as a measure of HRQL at each of the three time points (2001/2002, 2005/2006 and 2011/2012). Self-reports of the presence of pain on at least one occasion in the week prior to the survey resulted in additional questions (independent of the HUI system) to characterize the pain. These additional questions included the exploration of the frequency, location and intensity of the pain. The outcome of the results collected at the 2001/2002 and 2005/2006 time points have been presented previously by other authors (Barr, 2006, Horsman et al., 2006, Horsman et al., 2007).

The work presented in this thesis is primarily from the last time point (2011/2012) of the longitudinal study. The methodology and outcomes were approached as a cross-sectional study with the intended purpose of exploring the HRQL, with a focus on pain, of long-term survivors of a primary brain tumour in childhood at a single institution. In addition to the HRQL instrument and pain measures, sociodemographic as well as overall QOL were collected in order to provide a more complete understanding of this cohort. The previous results from the longitudinal study provided an opportunity to explore the persistence of pain over a decade in the same group of individuals. Imputation was undertaken for data missing due to any reason for non-participation, aside from a subject who died and was excluded from the longitudinal analysis. A summary of the methods for this thesis is shown in Figure 1.
Figure 1. Schematic diagram of study methods used to explore the health-related quality of life in survivors of brain tumours in childhood over a ten-year period. Measures include the HUI2/3 questionnaire, as well as additional investigations to characterize the burden of pain experienced by the patient cohort. Sociodemographic and quality of life information was also captured at time point 3.
Rationale

Cross Sectional Study Design

A cross-sectional study design was selected to address the primary objective of exploring the burden of pain in long-term survivors of brain tumours in childhood. This type of study design is well-suited to provide estimations of the prevalence and burden of morbidity at a single point in time in a pre-specified population, and when the item of interest is not well-described in the literature. Cross-sectional studies are limited in the determination of attribution of outcomes to the primary disease. This is particularly the case when there is a considerable period of time from the exposure to the outcome. As the current study population was at least ten years from their primary brain tumour diagnosis, this limitation is important. However, the objective of this study was to estimate and describe the burden of pain in long-term survivors, rather than to determine causality. As such, this study design was deemed appropriate for this context. This point is further established by the collection of data being restricted to HRQL, sociodemographic information and overall QOL, and not attempting to investigate potential causes of pain.

Sample Selection

A consecutive sample was undertaken, with recruitment restricted to a single institution. This increased feasibility as well as decreased selection bias as all eligible subjects were given the opportunity to participate, rather than a random sampling of patients.
All participants diagnosed with a brain tumour at least ten years prior at MCH, irrespective of subsequent disease, and who had been receptive to previous similar HRQL studies, were invited to participate in this study. Limited exclusion criteria allowed for the inclusion of the maximum number of participants and provided an overview of this patient population. In addition, it was recognized that the interviewer-administered questionnaire could exclude potential participants and create a bias based on geographical proximity to the hospital. As such all subjects were given the opportunity to undertake the interview in-person or over the phone. Clinical information for the identified eligible cohort was available and as such comparison for systematic differences between participants and non-participants was undertaken.

**Measurement Instruments**

Measurement of HRQL of participants was undertaken using the interviewer-administered Health Utilities Index (HUI®) questionnaire (HUI23S1E.40Q), which has been validated previously in brain tumour survivors (Barr et al., 1999, Glaser et al., 1999). The HUI family of instruments is used widely in clinical research, often for cross-sectional studies, and these are referenced to the Canadian population in the Canadian General Social Survey (Furlong et al., 2001). In addition, clinically important differences of greater than 0.05 for single attribute utility scores, and 0.03 for multi-attribute scores have been established previously and accepted by the clinical and research communities (Horsman, Furlong, Feeny & Torrance, 2003).
The HUI2/3 interviewer-administered questionnaire is a single measurement instrument comprised of 40 items that utilizes responses to generate single attribute HRQL levels and utility scores as well as overall health status and HRQL. These questions are based on capabilities at the time period of the questionnaire, which for this project was defined as a one-week recollection period. This was beneficial as it provided an estimate of the burden of morbidity at a point in time while accounting for possible day-to-day variances, including weekdays and weekends. The HUI2 system provides estimates of morbidity burden for seven specific attributes: sensation, mobility, emotion, cognition, self-care, pain and fertility. The HUI3 system maps onto eight variables: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. These attributes, aside from fertility, were considered in this study.

The HUI2/3 utilizes a branching-logic format to classify a person’s comprehensive health status using algorithms corresponding to responses to questions (Furlong, Feeny, Torrance & Barr, 1998). The mapping of questions onto attributes has been established previously, based on prior studies and experience of the creators of the HUI questionnaires (Furlong et al., 1998). The number of questions is dependent on the attribute as well as the response. HUI3 vision, for example, requires responses to a set of five questions, while ambulation capability is determined on responses to seven questions. A response of “perfect” function would result in an automatic “not applicable” score to subsequent questions relating to the same attribute. A response of functional limitation requires responses to further questions in order to establish a level.
In some cases there are overlaps between questions in the HUI2 and HUI3 systems. For example, those used to define HUI3 levels of vision, hearing and speech are used in combination to generate the level for the HUI2 attribute of sensation. Similarly, responses for HUI2 mobility are derived from responses that are used to generate levels for HUI3 ambulation and dexterity. A detailed description of the responses and corresponding levels can be found on Tables 1 through 8 in the HUI procedures manual (Furlong et al., 1998). The levels generated can be converted to single- and multi-attribute utility scores using multiplicative functions. These utility scores describe the burden of morbidity within the context of relative desirability of a given functional state (Furlong et al., 1998). The syntax for the algorithm to derive the single attribute levels as well as single- and multi-attribute utility scores was made available through an in-kind student grant for this project.

Single attribute level scores were determined. The levels are assigned a numerical value, with 1 being no disability and the upper limit (severe morbidity) ranging from four to six, depending on the attribute in question. The single attribute levels were categorized into four previously established levels of disability: none, mild, moderate and severe (Furlong et al., 1998). These disability levels are based on preference scores rather than functional capacity, and as such have ordinal and not interval properties. The conversion to the four descriptor levels for each attribute was undertaken as it allowed for easier comprehension of the degree of disability, and for identification of areas with a high prevalence of morbidity. Interval-level single attribute utility scores as well as multi-
attribute utility scores were also generated for both HUI2 and HUI3 systems, which enabled parametric testing of hypotheses.

HUI2 and HUI3 are noted to have overlapping attributes. A previous study undertaken in a cohort of pediatric brain tumour survivors demonstrated very good agreement with respect to the frequency of morbidity for overlapping attributes (Barr et al., 1999). However, the constructs differ between HUI2 and HUI3 (Table 3 and Table 4) (Feeny et al., 1995). As such, these two systems are considered to be complementary, and both were used in this study. The 2 systems were combined into a single questionnaire using specific grouping and ordering of questions as recommended by HUIInc.

Table 3. Summary of constructs used in the HUI2 Multi-Attribute System (aside from fertility) (Torrance et al., 1996)

<table>
<thead>
<tr>
<th>Attribute name</th>
<th># of Levels</th>
<th>Construct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensation</td>
<td>4</td>
<td>See, hear and speak</td>
</tr>
<tr>
<td>Mobility</td>
<td>5</td>
<td>Walk, bend, lift, jump, and run</td>
</tr>
<tr>
<td>Emotion</td>
<td>5</td>
<td>Amount of worry</td>
</tr>
<tr>
<td>Cognition</td>
<td>4</td>
<td>Learning and remembering school work</td>
</tr>
<tr>
<td>Self-Care</td>
<td>4</td>
<td>Eat, bath, dress, and use the toilet.</td>
</tr>
<tr>
<td>Pain</td>
<td>5</td>
<td>Intervention for pain</td>
</tr>
</tbody>
</table>

Table 4. Summary of constructs used in the HUI3 Multi-Attribute System (Feeny et al., 1995)

<table>
<thead>
<tr>
<th>Attribute name</th>
<th># of Levels</th>
<th>Construct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision</td>
<td>6</td>
<td>Read newsprint and recognize friend across street</td>
</tr>
<tr>
<td>Hearing</td>
<td>6</td>
<td>Hear conversation in group setting</td>
</tr>
<tr>
<td>Speech</td>
<td>5</td>
<td>Being able to be verbally understood</td>
</tr>
<tr>
<td>Ambulation</td>
<td>6</td>
<td>Walking</td>
</tr>
<tr>
<td>Dexterity</td>
<td>6</td>
<td>Use of hands and fingers</td>
</tr>
<tr>
<td>Emotion</td>
<td>5</td>
<td>Happiness</td>
</tr>
<tr>
<td>Cognition</td>
<td>6</td>
<td>Memory, ability to solve problems</td>
</tr>
<tr>
<td>Pain</td>
<td>5</td>
<td>Limitation of activity</td>
</tr>
</tbody>
</table>
Both HUI2 and HUI3 require the respondent to affirmatively identify experiencing pain. However, each system measures pain in a different manner. The HUI2 construct for pain is based on the type of intervention, ranging from occasional pain requiring limited non-prescription drugs or self-control of activities with no impact on normal activities (level 2), to severe pain, not relieved with medications and disrupting normal activities (level 5) (Torrance et al., 1996). The HUI3 pain construct is based on activity limitation. Individuals with mild to moderate pain that does not limit activities are considered a level 2, while participants with severe pain that limits most activities are considered a level 5 (Feeny et al., 1995). The individual responses to each of the pain-related questions provided further insight into pain experienced by individuals in this cohort, in addition to the generation of attribute levels and utility scores.

In addition to the HUI questions, it was recognized that further exploration of pain should also be undertaken to include identification of the location and intensity, as assigned directly by the participant. As such, a simplified human figure (homunculus), as show in Figure 2, was used for participants to identify the location of the pain. Further exploration was undertaken using a coloured analogue scale (CAS) on which individuals indicated the intensity of pain by the brightness of the colour red, which was then mapped to a number on a scale of 0 (no pain) to 10 (worst pain ever experienced). This has been used previously in participants with pain, and provides a direct quantitative value on a subjective attribute (McGrath, 1996).
One consideration regarding the HUI instruments is that these are restricted to health-related capabilities only. Consequently, sociodemographic details were gathered to provide a more complete understanding of this patient cohort. Questions were developed by review of articles, as well as by consultation with an expert in the area (Hoven, Lannering, Gustafsson & Boman, 2010, Zeltzer et al., 2008, S. Saigal (personal communication, April 7, 2011)).

Cantril’s ladder is a measure of overall well-being, asking individuals to place their present, past and future QOL, defined as life satisfaction, on a ladder with ten steps, with the lowest rung representing the worst QOL (1) to the top rung (10) the best QOL (Cantril, 1965). This self-anchoring tool has been used previously to estimate the psychological well-being of survivors of childhood cancers, including those with brain tumours (Zeltzer et al, 2009). Cantril’s Ladder was used in this study, with participants
being asked to rate their QOL on a scale of 1 to 10 at present, then reflecting on five years ago, and then imagining it five years into the future. This provided a measure of satisfaction with life in general at present, as well as providing insight into whether participants felt life improved over time.

Proxy Reporting

Proxy reporting is used commonly in HUI2/3 measurements of HRQL, with the parent or health-care provider as the alternative to self-reporting (Fluchel et al., 2008. Fu et al., 2006). In this cross-sectional study (T3), subjects were asked to select an individual who they felt knew them best. Given the age range of participants, it was felt more appropriate to allow the subjects to select a proxy of their choosing as a parent responder may not be able to provide information if the participant no longer lived at home. The use of a subject-selected proxy in this study was exploratory in nature.

Longitudinal Study Design

Similar cross-sectional studies were undertaken in 2000/2001 and 2005/2006 for this same cohort, using the eligibility criteria outlined previously. The availability of HUI2/3 scores at these two previous time points provided the unique opportunity for the exploration of the stability of pain over a decade using a linear mixed effects model for longitudinal analysis. A repeated measures analysis is particularly attractive as it allows for assessment of change over time at an individual and at a group level, while controlling for within-subject correlations. This decreases the chance of committing a Type I error.
Missing data are a concern for studies, particularly when a group of individuals is followed over a length of time, as the exclusion of participants without data results in reduction of sample size, and consequently power (Altman & Bland, 2007). This would result in the increase chance of committing a Type II error. Imputation is an accepted technique often used for missing survey data, and allows analysis of an entire set of data (Stern et al., 2009). In order to decrease the potential for bias and to maximize the data collected, scores were imputed for missing data of participants who responded “don’t know” at any of the three time points, or had missing data due to non-participation for reasons other than death, beyond time point 1. The increased degree of uncertainty of the imputed values was accounted for by the generation of five sets of imputed data, which were pooled along with the initial data set at the time of analysis. Linear mixed effects models are able to handle imputed data sets.

Protocol

Procedures

Upon approval from the Research Ethics Board at Hamilton Health Sciences/Faculty of Health Sciences, study procedures commenced. A summary of the study procedures are depicted in Figure 3.
Subject Screening

Initial screening of potential subjects was undertaken by the neuro-oncology nurse (JD). Patient lists were reviewed to identify patients who were diagnosed with a primary brain tumour at MCH between January 1985 and December 1998. Individuals with disease that had relapsed or progressed were still eligible for participation, provided that they were free of disease at the time of the study. In addition, eligible subjects must have participated in previous HRQL studies that were undertaken at time points 1 (2000/2001) and 2 (2005/2006) in order to have complete data sets.
Subject and Proxy Recruitment

Subjects who met the inclusion criteria were then contacted by JD for a brief introduction to the study. Interested individuals were given the option of meeting in-person or having a follow-up phone call with a study team member for study consent and questionnaire administration. Participants were also asked by the nurse if they would be comfortable having someone respond about their health (proxy point of view), and if acceptable, to identify an individual who “knew them well” who would be willing to respond to the proxy questionnaire.

Consent Process

Follow-up phone calls, as well as in-hospital and community interviews, were undertaken by a trained member of the research team. Consent was obtained through review of the study question, as well as the procedures, potential risks, benefits and voluntariness of participation. A written consent form was presented to the participant and proxy if the meeting occurred in person, or mailed ahead of time to the participant for consents that were obtained over the phone. All questions posed by the subject or proxy were answered. Once all questions had been addressed and the individual affirmed willingness to participate, consent was obtained in writing.

Administration of Questionnaires

Interviews were undertaken separately for subjects and proxies, with the person not being interviewed being asked to relocate physically outside of hearing range. In order to ensure a standardized approach, the instructions as well as the questions listed on
the questionnaire were read verbatim to the participant. Minimal additional instructions or prompting were provided, with clarification being given only as requested by the participant. Attempts were made to have the participant complete the questionnaire in its entirety.

Participants reporting “yes” to pain were asked to complete two additional tasks: (i) a homunculus (Figure 2) was used to identify locations of pain throughout the body, with (ii) the intensity of pain experienced at each location indicated on a CAS.

Upon completion of the HUI2/3, participants were asked a set of sociodemographic questions regarding educational level, living situation, relationship status, children, employment and possession of a valid driver’s licence. All participants were then asked to evaluate their life on a scale of 1 to 10 (10 being the “best”), at present, as they remembered it five years ago, and how they felt it would be five years ahead.

HUI2/3 interviews were then undertaken with the proxy, with the participant asked to move out of the vicinity in which the interview was occurring.

Procedures were identical for subjects undertaking the questionnaire in person or over the phone. However, in the latter circumstance, the consent form, copies of the CAS with the participants instructed to draw a line indicating discomfort, and the homunculus were completed by the participant at home and then returned to the study centre by mail using a stamped, pre-addressed envelope. All participants were given or mailed copies of the signed consent forms.
Non-Participants

Patients who declined participation were not asked for proxy interviews, nor was any further communication attempted for study purposes. Reasons for non-participation were recorded if provided. Multiple attempts were made to contact all eligible subjects. However, some participants were not contactable. Survival status for non-contactable individuals was attempted through the Cancer Care Ontario registry, via POGO.

Data Linkage

The above procedures of screening and administration of the HUI2/3 questionnaire were undertaken at two previous time points: the first in 2000/2001, and then again in 2005/2006. Unique patient identifiers allowed for data linkage and facilitated a longitudinal analysis of this cohort of survivors of brain tumours in childhood over a ten-year period. Given the length of time between surveys, separate Research Ethics Board approvals as well as participant consents were obtained at each time point with an indication made that data linkage would occur.

Demographic and Clinical Information

Demographic and clinical data, which included the age at diagnosis of the primary tumour and the age at the time of interview; primary brain tumour subtype, location of tumour, extent of surgery, nature of treatment; and relapse and progression, were collected for all eligible subjects by JD. Data for consenting participants were provided for analysis with study identifiers, while data for non-participants were provided without any identifiers to enable comparison of the two groups.
Data Management

Data was transcribed directly from the questionnaires onto spreadsheets on Excel (v. 2010) by two investigators. Random checks were undertaken to confirm correct data transcription. To ensure confidentiality, only non-identifying data were entered onto spreadsheets. All analysis was undertaken using SPSS version 20.

Scoring of HUI Questionnaire.

The responses to each question were entered onto a database in Excel, then coded and converted into SPSS. Using syntax provided by HUIInc, single attribute utility scores and multi-attribute utility scores were generated for HUI 2 and HUI3 systems. A second database was created that included subject ID, as well as demographic, clinical, sociodemographic, QOL and HRQL data. This dataset was used for analysis.

Analysis

Cross-Sectional Analysis

All data collected within this study were assumed to have a normal distribution and were independent, unless stated otherwise. Descriptive statistics included measures of central tendency and dispersion (mean and standard deviation for continuous variables; frequency, median, mode and range for categorical variables). Comparisons between groups for continuous variables were undertaken using parametric tests. Two-tailed paired or independent t-tests were used to determine the mean difference. Levine’s Test for Equality of Variances was used to test for homogeneity of variance. If the value was significant (p < 0.05) an unequal variance t-test was used. If the value was not significant
Student’s t-test was used (Ruxton, 2006). Non-parametric tests, including Chi-square, Fisher’s exact test and odds ratios, were used to compare categorical data (Norman & Streiner, 2007). A p-value of less than 0.05 was taken to indicate a statistically significant difference for all tests, and resulted in the rejection of the null hypothesis (no difference between groups). No adjustments were made for multiple testing as this is an exploratory study.

**Description of Overall Cohort**

Demographic, sociodemographic and clinical characteristics of the participants at the third time point were reviewed using descriptive statistics. Comparisons of demographics of participants and non-participants were undertaken to explore potential systematic differences between the two groups. Clinical data of participants were also appraised critically for representativeness by reviewing published data on survivors of brain tumours in childhood. Sociodemographic data were presented using descriptive statistics and provided a comprehensive life status assessment of this cohort.

**General Quality of Life Rating**

Participants rated their general QOL subjectively for the present, 5 years prior (past), and 5 years imagined into the future using Cantril’s Ladder. A one-way repeated measures analysis of variance (ANOVA) was used to evaluate the perceived change in QOL over time. This statistical method is superior to multiple paired t-tests as it allows for the comparison of multiple groups, while accounting for within-subject correlation. This decreases the chance of committing a Type I error. Listwise deletion occurred, with
participants with incomplete data excluded from the statistical analysis exercise. Mauchly’s test of sphericity was reviewed, and the appropriate correction was applied, as required. Pairwise comparison allowed for interrogation of change in QOL between time points.

Health-Related Quality of Life

Results were generated using algorithms provided by HUInc and analyzed independently for HUI2 and HUI3 systems. Overall multi-attribute scores (continuous variable) were reviewed using descriptive statistics. Single attribute level scores were categorized by disability using the HUI2 and HUI3 classification systems, using scheme A (Furlong et al., 1998). The ordinal, single attribute level data were reviewed as frequency and mode, and illustrated using a histogram. Attributes in which greater than fifty percent of participants reported “mild” or worse difficulties were identified as areas with a ‘high’ prevalence of morbidity.

Proxy Reporting

Responses from proxy respondents were evaluated for agreement (inter-rater concordance). Single attribute level data were reviewed for percent exact agreement based on four levels of disability: none, mild, moderate, severe, which have been established previously (Feng, Bernier, McIntosh & Orpana, 2009). A two-way mixed effects model, patient-random, instrument-fixed, intra-class correlation coefficient (ICC) was used to analyse concordance for single- and multi-attribute utility scores. This method of analysis is appropriate for continuous variables, and is an accepted measure of
inter-rater reliability. The resultant score is interpreted based on anchoring of 0 (no agreement) and 1.0 (perfect agreement) and using the reference criteria outlined by Altman (1991). Concordance was measured by ICC given the small sample size and the potential for poor distribution across all cells of the contingency table.

**Description of Participants Reporting Pain**

Clinical and demographic details of the sub-group reporting pain were reviewed using descriptive statistics. Formal statistical comparison of the characteristics between the pain and no-pain groups was not undertaken due to the small sample size and, consequently, lack of power to evaluate statistical significance.

The individual responses to pain-related questions on the HUI2/3 questionnaire, as well as the location (homunculus) and intensity (CAS), were reviewed in order to appreciate the burden of pain experienced by this cohort. Exploration of the possible correlation between the maximum intensity of pain measured by the CAS and the single-attribute HUI2 and HUI3 pain scores was undertaken using non-parametric correlation tests. The CAS was multiplied by a factor of (-1) to allow for higher values to indicate better health, in keeping with the HUI scores.

**Burden of Pain by HRQL**

Single-attribute utility scores for participants reporting pain and those reporting no pain were compared for clinically significant differences using the pre-established criteria of greater than 0.05 (Horsman et al., 2003). The mean scores of the two groups were also analyzed for statistical significance using Student’s t-test. However, due to the small
sample size, results were interpreted with caution given that the result could be minimized erroneously or over inflated.

The multi-attribute utility scores were described in relation to the results of the single attribute scores. However, results were not compared directly between the pain and no-pain groups due to the contribution of pain to the overall HRQL score.

**Longitudinal Analysis**

Longitudinal analysis occurred through data linkage by participant study identifiers. The results from this cross-sectional study were combined with a database containing scores of HRQL for cross-sectional studies undertaken 5 and 10 years prior (Barr, 2006). The clinical and demographic data of the original cohort were reviewed and described. The mean utility scores for each time point were used to generate a line graph, and allowed for exploration of potential trends over time.

A linear mixed effects model was selected to analyse the change in the burden of pain over time. This method is used commonly for correlated data, such as repeated measures of survey respondents, as it allows for comparison of the means between groups while decreasing the possibility of committing a type 1 error. A linear mixed effects model describes a relationship between a response variable and covariates, using the equation: $Y=X\beta+ u +e$, where $Y$, $\beta$, $u$ and $e$ are vectors, and $X$ represents a design matrix. In this study, the response or dependent variable was pain ($Y$) and the single fixed effect was time ($\beta$), where $X$ was a matrix relating the observations of pain to time, with the addition of random effect capturing within-individual correlation ($u$) and residual error ($e$).
(SPSS, 2005). This analysis was executed with the assumption that variances were constant over the study period, and that there was normal distribution of the residuals and random effects. This statistical method compares the mean utility score between the baseline survey time point and subsequent survey time points (2000/2001 and 2005/2006 study), and provided information about the change of pain over time in this cohort.

A repeated measures ANOVA is also able to describe trends over a period of time. However, this type of statistical method requires balanced, complete datasets for each case. This requirement results in excluding cases with incomplete data, and has implications for a potentially biased result if the remaining cases were not representative of the entire population.

A linear mixed effects model is superior to a repeated measures ANOVA as it is able to handle unbalanced data. However, the problem of missing data due to non-participation and “don’t know” would also lead to a loss of power. As such, multiple imputation using the fully conditional specification method with predictive mean matching was undertaken for subjects in whom data were missing due to non-participation at time point 2 or 3, or who responded “don’t know” at any time point. (Rubin, 1987). Missing data was imputed five times using SPSS version 20, using automatic method, with no defined constraints. The 5 complete data sets were pooled along with the original data set for analysis to decrease the degree of uncertainty. All assumptions were met for using imputation, namely that the data were missing at random, it was appropriate to impute the data (excluding participants who died during the study.
period), and imputation had been used previously for HUI data (Statistics Canada, 2007). Imputation was undertaken at the utility score level, rather than at the question response level due to the large number of variables (i.e. 41 questions x 3 time points). Linear mixed effects models are able to handle imputed data.

The change in pain scores over time at a cohort level was evaluated for statistical and clinical significance based on the results of the linear mixed effects modelling. The F-values presented in the “Type III Tests of Fixed Effects” for the original and individual imputed datasets were reviewed for statistical significance with respect to time. This acted as an indicator of statistically significant changes of pain over the study period. If indicated, further investigation was undertaken for pairwise comparisons of statistical significance. The regression coefficients were examined also for estimates of clinically significant differences, which was possible as this model only regressed onto one factor (time).

For pairwise comparison, the linear mixed effects model was run twice, once with T3 as the reference time point, to provide estimated differences for T1 to T3 (10 years) and T2 to T3 (5 years). The second pairwise analysis used T1 as the reference, which provided the estimated difference from T1 to T2 (5 years).

The persistence of pain at an individual level over the 10-year span of the study was also of interest. The covariate matrix generated for the linear mixed effects model allowed for the generation of ICCs by dividing the variance of the random effects by the
sum of the variance of the random effect and the variance of the residual. This provided
the degree of within-individual correlation of pain measured over the span of the study.

The above analysis was also undertaken for the multi-attribute utility scores as a
study of the change in overall HRQL over time in survivors of brain tumours in
childhood.

**Ethical Considerations**

**Research Ethics Board Approval**

Prior to the commencement of any study procedures, application was made to the
Hamilton Health Sciences/Faculty of Health Sciences Student Research Ethics Board
(REB). Submitted documents included the REB application, a copy of the protocol, which
outlined the study rationale, objectives and procedures, as well as consent forms for
subject and proxy respondents. Risks and benefits to subjects as well as society were
outlined in the application as well as the consent forms. The approved protocol was used
to guide study procedures, and any changes were approved formally by the REB prior to
implementation.

**Study Risks, Identification and Management**

The study was considered to be of minimal risk. Although the HUI2/3
questionnaire was designed carefully and used in the general population as well as with
patients having various diseases and conditions, it is possible that the questions could
make the participants feel vulnerable or emotional. Interviewers were trained to present
all questions and response choices as written using a neutral tone. Participants were
informed prior to the interview that if they felt upset or uncomfortable answering any of
the questions, the item could be skipped, or the interview could be discontinued. In
addition, participants were encouraged to contact the clinical team if they felt upset by the
questionnaire, or were concerned about their health. Reassurance was also provided that
the information from the research would not be referenced back to the individual
participant, nor would the information become a part of the participant’s medical record
or made available to the treating team.

Participants were also requested to identify a proxy to respond to the questionnaire
about the subject’s health. This was presented as optional to the subject to prevent placing
either the subject or proxy into an uncomfortable setting. In addition, participants
undertook the questionnaire first and were authorized to indicate if any questions should
be skipped by the proxy. Finally, responses from subjects and proxies were not made
available to either party.

**Study Benefits**

This study was judged to present minimal benefit to the individual participant.
However, it was extremely valuable in understanding and appreciating the health status of
long-term survivors of brain tumours in childhood. To the best of our knowledge, this
study was the first to measure HRQL in a cohort of brain tumour survivors over a ten-
year period, and was expected to provide important information to the clinical community
caring for patients with this type of cancer. In addition, this information is believed to be
relevant to counselling families with children diagnosed with brain tumours in regard to their potential HRQL in the future, and understanding their child’s long-term needs.

Confidentiality

Efforts were made throughout the study to respect the confidentiality of study subjects. JD was responsible for screening potential subjects as well as for the initial contact to ascertain interest for participation. The names and contact information of subjects expressing interest in the study were forwarded to the study team to arrange for full consent and questionnaire administration. No additional attempts were made by team members to contact subjects who had declined participation or were lost to follow-up. Unique subject identifiers were used to identify the questionnaires, and were also used on the study database; no names were captured.

Clinical and demographic data for the entire cohort were also abstracted by JD from the medical charts and were entered into a database by study identifier only. Minimal disease and demographic information was obtained for non-participants in order to assess for systematic differences between the participants and those who did not participate. Data presented for non-participants did not containing any identifying information. The Pediatric Oncology Group of Ontario was queried for the status of survivorship using POGO identifiers.

Consent forms, which contain the subjects’ names, were kept in a separate location from the questionnaires. All hard-copies of patient-level data were kept securely
in a locked office at MCH, and databases with identifying information were kept on secure, password-protected servers, and accessed through password-protected computers.

Consent

Consent forms were written in keeping with Good Clinical Practice, Tri-Council Policy Statement, and REB requirements. The consent forms were amended as required to reflect changes to the protocol, and approved by the REB prior to use. Separate consent forms were created for subjects and for proxies.

Subjects were contacted initially by JD and provided a brief overview of the study. All individuals expressing interest in the study were given the option to meet in person or to have a consent form mailed to their home with a follow-up phone call by a study team member. Prior to initiation of the interview, a study team member reviewed the consent form with the subject and proxy and addressed any questions raised. The consent form was signed by the subject or proxy respondent as well as by the study team member. The original copy of the consent form was kept in a locked research office in a file kept separate from the patient data, and a copy was given to the family immediately or mailed back to the participant with a thank-you letter. Participants were encouraged to contact the Principal Investigator, JD or the REB if they had any additional questions at any point in time.
RESULTS

Cross-Sectional Study- Time Point 3 (2011 and 2012)

Overall Cohort

Description of Participants

Recruitment to this study occurred between February 1, 2011 and March 31, 2012. Of the 37 subjects identified as eligible for participation, 25 (67.6%) consented and completed study requirements successfully. Reasons for non-participation included: subject not interested in participating in the study and declined at time of contact by neuro-oncology nurse (n=3), subject indicated interest in participation but could not be contacted for subsequent interview (n=3), and subject lost to follow-up (n=6). Cancer Care Ontario was queried through POGO for survival status of the participants classified as lost to follow-up; no subjects were registered as having died in Ontario.

Twelve males and 13 females participated in the study. The mean age of the cohort was 28 years (standard deviation (SD) of 4.1) at the time of the interview. Subjects were between 13.2 years and 27.5 years from initial diagnosis (mean of 19.7, SD of 4.31).

Table 5 depicts the type of disease, initial clinical features, treatment and survival status for this group. None of the participants were being treated actively for their brain tumour at the time of the interview, although ten participants (40%) were noted to have experienced a recurrence of the original tumour or a second malignancy.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants (n=25)</th>
<th>Non-Participants (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain tumour subtype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astroglial tumour</td>
<td>16 (64%)</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>PNET/Medulloblastoma</td>
<td>6 (24%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (8%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td><strong>Site of primary tumour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infratentorial- posterior fossa/cerebellum</td>
<td>13 (52%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Infratentorial- brain stem</td>
<td>2 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Supratentorial-hemisphere/basal ganglia</td>
<td>5 (20%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Supratentorial- optic pathway</td>
<td>4 (16%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (4%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td><strong>Extent of resection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Biopsy only</td>
<td>2 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Single resection</td>
<td>21 (84%)</td>
<td>11 (92%)</td>
</tr>
<tr>
<td>Multiple resections</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation only</td>
<td>1 (4%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Surgery only</td>
<td>6 (24%)</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>Chemotherapy and/or radiation</td>
<td>18 (72%)</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Shunt (Yes)</td>
<td>5 (20%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td><strong>Disease outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-Free/ Stable-Disease Survival</td>
<td>15 (60%)</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>Recurrence of any CNS Tumour</td>
<td>3 (12%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>3 (12%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Non-CNS Second Malignancy</td>
<td>4 (16%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*At time of last contact, based on initial tumour

Comparison of participant and non-participant groups revealed as few differences, however these were not considered to be substantive; formal statistical comparison for type of cancer and treatment received was not undertaken due to the small sample size. Individuals diagnosed with PNET/medulloblastoma or ependymoma were represented only in the participant group. Participants were also noted to have primary brain tumours.
in numerous infratentorial and supratentorial sites, while non-participants did not have primary tumours in the infratentorial-brain stem or supratentorial-optic pathway. There was also a higher proportion of individuals who participated in the study who received chemotherapy and/or radiation.

Interviews for consenting subjects occurred at MCH \((n=15)\), in the community \((n=4)\) or by phone \((n=6)\). All participants voiced an understanding of the tasks and were able to undertake the interview-administered questionnaires. Two participants reported visual impairment. For these participants the location of pain was determined on the basis of description of the area on their body. One participant had difficulty with speaking but was able to provide responses to questions through a sibling. Answers were confirmed with the participant directly prior to being recorded. Another member of the family provided the proxy-reporting.

Twenty-three participants identified proxies to answer the HUI questionnaire designed for proxy-reporting of HRQL. The proxy’s relationship to the participant included parent \((n=13)\), partner \((n=9)\) and friend \((n=1)\). Two proxies were not reachable by phone despite multiple attempts.

**Sociodemographic Factors and General Quality of Life**

Review of the self-reported sociodemographic features of the sample revealed that ten participants \((40\%)\) lived with a partner, thirteen \((52\%)\) lived with their parents and two \((8\%)\) lived with others or alone. Three \((12\%)\) of the individuals not living with partners reported being in a relationship.
The majority of patients had completed at least a high school level of education, as depicted in Figure 4. Eighteen (72%) of the 25 participants reported being employed or currently in school, 5 (25%) were unemployed, and 2 (8%) were on sick leave or disability. Slightly less than half (11 out of 25) reported having a driver’s licence.

![Image of pie chart showing education levels of participants.]

Figure 4. *Highest education level achieved as reported by participants (n=25)*.

When asked about overall general QOL on a scale of 1 to 10, with 10 being the highest, participants reported scores ranging from 6 to 10 (mean of 8.46) at the time of the interview. Two participants felt they could not predict how their life would be in five years, and were excluded from further analysis. Figure 55 depicts the conjectured QOL at five years prior, at the present time, and five years into the future; it can be seen that participants had an overall favourable view of their future QOL.
Review of the ANOVA output to address the question of perceived QOL over time revealed that Mauchly’s Test of Sphericity was significant ($p<0.001$), and as such, Greenhouse-Geisser correction was applied. The resultant F-ratio of 59.78 was noted to be significant ($p=0.001$), indicating that participants reported a difference in their QOL over time. Pairwise comparisons of the time points revealed an anticipated improvement in QOL to occur between the present and future (mean increase of 2.46, $p=0.001$). The difference in the mean scores reported for the past to present (increase of 1.69) was not significant.
Overall utility scores were calculated for 24 of the 25 participants as one individual reported “don’t know” for the HUI2 question relating to sensation, and the HUI3 question relating to emotion. A burden of morbidity was prevalent in the cohort as the mean multi-attribute utility score for HUI2 was 0.79 (SD of 0.23), median of 0.88 (minimum of 0.16 to maximum of 1.00), and for HUI3 was 0.69 (SD 0.29), median of 0.77 (minimum of -0.19 to maximum 1.00). Overall utility scores can be seen in Figure 6. Nineteen of the 25 participants directly self-reported overall HRQL as “very good” or “excellent” (Table 6).

![Boxplot of median utility scores for cohort (n=24).](image)

**Figure 6. Boxplot of median utility scores for cohort (n=24).**

<table>
<thead>
<tr>
<th>Table 6. Self- and proxy- responses to direct reporting of overall HRQL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Excellent</td>
</tr>
<tr>
<td>Very good</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Fair</td>
</tr>
<tr>
<td>Poor</td>
</tr>
</tbody>
</table>
Review of the single attribute level data (Figure 77) revealed that greater than 50% of the cohort indicated at least a mild burden of morbidity in the attributes of cognition (60%) and pain (52%) in both HUI2 and HUI3. Sensation difficulties were noted in slightly less than half of the individuals (46%) as well as emotion (40%) as measured by HUI2. The greatest variation in disability was reported in the attributes of emotion and pain (HUI2) and cognition (HUI3) by single attribute utility scores. As a group the highest burdens of morbidity were in attributes of mobility, emotion and pain (HUI2), and dexterity, cognition and pain (HUI3). The results observed support Hypothesis #3, which stated that in addition to pain, other areas of morbidity would be identified, including attributes of emotion and cognition.
1 participant responded "Don't know" therefore not included

Figure 7. Single attribute level data for HUI2 (2a) and HUI3 (2b) for overall cohort (n=25).
M.Sc. Thesis - T. Nayiager; McMaster University – Health Research Methodologies

Twenty-three proxies responded to questions regarding the HRQL of long term survivors. Four individuals were unable to answer at least one question despite being encouraged to provide an answer. The mean multi-attribute utility score based on 19 proxies was 0.83 (range of 0.37 to 1.00) for HUI2, and 0.67 (range of 0.02 to 1.00) for HUI3. Proxies were also asked to reflect on the overall HRQL of the subject. Eighteen (81%) of the 22 proxies who responded perceived the subject’s HRQL to be “very good” or “excellent” (Table 6).

Comparison of the overall utility score between self and proxy reported HRQL was noted to be clinically significantly different for HUI2 (0.79 versus 0.83), but not for HUI2 (0.69 versus 0.67). Evaluation of agreement between subject and proxy multi-attribute utility scores was calculated for the 18 pairs who had complete data. The ICC for the multi-attribute score for HUI2 was 0.745 (95% CI of 0.438 and 0.896), and 0.929 (95% CI of 0.822 to 0.973) for HUI3.

Percent exact agreement for single attribute scores was determined based on four levels of disability: none, mild, moderate, severe, as defined by Health Utilities Index Procedures Manual. Calculation of ICCs for single-attribute utility scores was also undertaken to determine correlation of the self and proxy responses (Table 7 and Table 8) (Furlong et al. 1998). In both HUI2 and HUI3 there was poor agreement (ICC<0.5, and low % exact agreement) for the attributes of emotion and pain. Cognition was also identified to have poor concordance for HUI2 and HUI3 by exact agreement (65% and 48% respectively). This was also reflected in the ICC, where it was correlation for
cognition was calculated to be 0.28 for HUI2, however, was within an acceptable range (0.75) for HUI3. Very good to perfect agreement by ICC was seen in the attributes of self-care (HUI2), and hearing, speech, dexterity and ambulation (HUI3).

Table 7. Measurement of concordance between self- and proxy- ratings for HUI2 attributes

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Exact agreement 4 levels</th>
<th>% Exact Agreement 4 levels</th>
<th>ICC Utility scores (95% CI lower, upper)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensation</td>
<td>17/20</td>
<td>85</td>
<td>0.828 (0.828, 0.971)</td>
</tr>
<tr>
<td>Mobility</td>
<td>18/23</td>
<td>78</td>
<td>0.743 (0.484, 0.882)</td>
</tr>
<tr>
<td>Emotion</td>
<td>10/19</td>
<td>53</td>
<td>** (**, 0.423)</td>
</tr>
<tr>
<td>Cognition</td>
<td>15/23</td>
<td>65</td>
<td>0.280 (**, 0.615)</td>
</tr>
<tr>
<td>Self-Care</td>
<td>23/23</td>
<td>100</td>
<td>1.0 (1.0, 1.0)</td>
</tr>
<tr>
<td>Pain</td>
<td>11/22</td>
<td>50</td>
<td>0.444 (0.037, 0.724)</td>
</tr>
</tbody>
</table>

**Minimal correlation, undefined (King’s College London, 2013)**

Table 8. Measurement of concordance between self- and proxy- ratings for HUI3 attributes.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Exact agreement 4 levels</th>
<th>% Exact Agreement 4 levels</th>
<th>ICC Utility scores (95% CI lower, upper)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision (n=23)</td>
<td>17/23</td>
<td>74</td>
<td>0.946 (0.877, 0.977)</td>
</tr>
<tr>
<td>Hearing (n=20)</td>
<td>20/20</td>
<td>100</td>
<td>1.0 (1.0, 1.0)</td>
</tr>
<tr>
<td>Speech (n=23)</td>
<td>22/23</td>
<td>96</td>
<td>0.955 (0.897, 0.981)</td>
</tr>
<tr>
<td>Ambulation (n=23)</td>
<td>22/23</td>
<td>96</td>
<td>0.869 (0.716, 0.942)</td>
</tr>
<tr>
<td>Dexterity (n=23)</td>
<td>21/23</td>
<td>91</td>
<td>0.869 (0.717, 0.942)</td>
</tr>
<tr>
<td>Emotion (n=20)</td>
<td>15/20</td>
<td>75</td>
<td>0.418 (** 0.720)</td>
</tr>
<tr>
<td>Cognition (n=23)</td>
<td>11/23</td>
<td>48</td>
<td>0.751 (0.498, 0.886)</td>
</tr>
<tr>
<td>Pain (n=22)</td>
<td>10/22</td>
<td>45</td>
<td>0.286 (**, 0.625)</td>
</tr>
</tbody>
</table>

**Minimal correlation, undefined (King’s College London, 2013)**
Participants Reporting Pain

Description of Participants with Pain

Fifty-two percent (n=13) of participants reported experiencing pain or discomfort at least once in the week prior to the interview, with most experiencing pain on less than half of the days (Table 9). This finding supports Hypothesis #1 as the number of long-term survivors reporting pain was greater than 35%.

Table 9. Number of days participants reported experiencing pain in week prior to interview

<table>
<thead>
<tr>
<th># Days with Pain</th>
<th>Frequency</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Days</td>
<td>2</td>
<td>8%</td>
</tr>
<tr>
<td>6 Days</td>
<td>0</td>
<td>8%</td>
</tr>
<tr>
<td>5 Days</td>
<td>1</td>
<td>12%</td>
</tr>
<tr>
<td>4 Days</td>
<td>1</td>
<td>16%</td>
</tr>
<tr>
<td>3 Days</td>
<td>3</td>
<td>28%</td>
</tr>
<tr>
<td>2 Days</td>
<td>4</td>
<td>44%</td>
</tr>
<tr>
<td>1 Day</td>
<td>2</td>
<td>52%</td>
</tr>
<tr>
<td>0 Days</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Clinical features and treatment of the primary brain tumour of participants with and without pain are summarized in Table 10. Demographics of participants with pain were found to be similar to those participants without pain with respect to age at diagnosis (7.65 years versus 8.81 years) and age at time of interview (27.1 years versus 28.8 years). Nine males and 4 females reported pain. Survivors with pain were also similar to their counterparts without pain with respect to life achievements (results not shown), and a reported similar overall QOL (mean of 8.3 for the group with pain versus 8.6 for participants without pain). Formal statistical analysis was not undertaken due to the small sample size.
The impact of pain can be seen in Figure 8. Most participants reported that pain did not limit their activity (69%), and could be controlled with either no intervention, limitation of activities, or non-prescription medications, such as non-steroidal anti-inflammatory drugs (69%).
Figure 8. Impact of pain (n=13) as measured by a) Number of activities limited by pain, and b) Interventions for relief of most severe pain in a 1 week period, for participants reporting pain within the week prior to the interview.

This cohort of long-term survivors reported varied locations of pain, throughout the body and not solely restricted to the head, as can be seen in Table 11. Most common areas of pain were lower extremities (n=12), head (n=6) and back (n=5). Lower extremities and the back were also associated with the most extreme pain scores of 10.0 and 9.0 respectively, as measured by the CAS. Other areas of notable pain included upper extremity (max 8.0) and abdomen (max 8.0). The pain intensity experienced in the
head was noted at a minimum of 3.4, and maximum of 6.8. Exploration of possible correlation between maximum pain intensity for each participant as measured by the coloured analogue scale and the single-attribute HUI2 and HUI3 pain scores using Pearson’s correlation coefficient was 0.38 and 0.45, respectively.

Table 11. Reported location of pain as noted using homunculus and corresponding intensity measured using coloured analogue scale ratings

<table>
<thead>
<tr>
<th>Location</th>
<th>Frequency reported</th>
<th>Median Pain Intensity</th>
<th>Maximum Pain Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>6</td>
<td>3.4</td>
<td>6.8</td>
</tr>
<tr>
<td>Eyes</td>
<td>1</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Back</td>
<td>5</td>
<td>3.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Upper Extremity</td>
<td>4</td>
<td>2.8</td>
<td>8.0</td>
</tr>
<tr>
<td>Abdomen</td>
<td>2</td>
<td>6.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Lower Extremity</td>
<td>12</td>
<td>4.4</td>
<td>10</td>
</tr>
</tbody>
</table>

Proxy-Reporting for Participants with Pain

There was fair concordance of self- and proxy-ratings of pain when measured by activity limitation (HUI3, ICC of 0.286) and moderate concordance between self- and proxy- ratings as measured by interventions to alleviate symptoms (HUI2, ICC of 0.444). In keeping with hypothesis #2 the agreement between self- and proxy- reporting of the severity of pain as measured by HUI3 was less than 0.4. However, agreement of severity of pain by symptom relief (HUI2) was greater than 0.4, and therefore did not support Hypothesis #2.
Exact agreement by levels of severity of pain, as assigned by the 22 patient-proxy pairs, was minimal. Review of the responses revealed that 50% of pairs reported the same type of intervention to alleviate pain symptoms (Table 12) and 45% had exact concordance for the amount of activity limited by pain (Table 13). Proxies more under-reported the severity of pain experienced by the subject.

Table 12. Concordance between self- and proxy-reporting for pain as measured by interventions to alleviate symptoms (HUI2)

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Mild</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 13. Concordance between self- and proxy-reporting for pain as measured by number of activities limited by pain (HUI3)

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Mild</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>22</td>
</tr>
</tbody>
</table>

Health-Related Quality of Life of Participants with Pain

As anticipated the multi-attribute utility scores of participants with pain demonstrated lower overall HRQL than did scores in participants without pain for both HUI2 (0.66 versus 0.94, significance of 0.001) and HUI3 (0.53 versus 0.88, significance of 0.002). Although these values were noted to be statistically and clinically significant,
pain is included in the determination of the overall utility score, and therefore the value could not be interpreted directly. As such, further investigation into the single attribute utility scores was undertaken.

Participants with pain had equal or greater burden of morbidity than participants without pain in all attributes measured by HUI2 and HUI3 (Table 14). Clinically significant differences of greater than 0.05 between the two groups were noted in areas measured by HUI2: sensation, mobility, self-care, and emotion, and by HUI3: vision, speech, ambulation, dexterity and cognition. All participants noted to have severe burdens of morbidity endorsed experiencing pain (Table 15).

Table 14. Single-attribute utility scores for participants with (n=13) and without (n=12) pain. Attributes shaded in grey indicate clinical or statistical significant difference between groups.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Pain (mean)</th>
<th>No Pain (mean)</th>
<th>Clinically Significant Difference (&gt;0.05)</th>
<th>Statistically Significant Difference (p&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUI2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensation</td>
<td>0.83</td>
<td>0.99</td>
<td>-0.16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mobility</td>
<td>0.89</td>
<td>0.98</td>
<td>0.09</td>
<td>0.20</td>
</tr>
<tr>
<td>Emotion</td>
<td>0.75</td>
<td>0.97</td>
<td>-0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>Cognition</td>
<td>0.94</td>
<td>0.90</td>
<td>0.04</td>
<td>0.15</td>
</tr>
<tr>
<td>Self-Care</td>
<td>0.92</td>
<td>1.00</td>
<td>-0.08</td>
<td>0.34</td>
</tr>
<tr>
<td>Vision</td>
<td>0.89</td>
<td>1.00</td>
<td>-0.11</td>
<td>0.10</td>
</tr>
<tr>
<td>Hearing</td>
<td>0.99</td>
<td>1.00</td>
<td>-0.01</td>
<td>0.37</td>
</tr>
<tr>
<td>Speech</td>
<td>0.94</td>
<td>1.00</td>
<td>-0.06</td>
<td>0.23</td>
</tr>
<tr>
<td>Ambulation</td>
<td>0.86</td>
<td>1.00</td>
<td>-0.14</td>
<td>0.13</td>
</tr>
<tr>
<td>Dexterity</td>
<td>0.92</td>
<td>0.98</td>
<td>-0.06</td>
<td>0.49</td>
</tr>
<tr>
<td>Emotion</td>
<td>0.96</td>
<td>0.98</td>
<td>-0.02</td>
<td>0.61</td>
</tr>
<tr>
<td>Cognition</td>
<td>0.82</td>
<td>0.88</td>
<td>-0.06</td>
<td>0.45</td>
</tr>
</tbody>
</table>
Table 15. Frequency of severity of morbidity by attribute, stratified by participants with \((n=13)\) and without \((n=12)\) pain

<table>
<thead>
<tr>
<th></th>
<th>Participants With Pain</th>
<th>Participants Without Pain</th>
<th>Participants With Pain</th>
<th>Participants Without Pain</th>
<th>Participants With Pain</th>
<th>Participants Without Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>None</td>
<td>Mild</td>
<td>Mild</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Sensation</td>
<td>3</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Mobility</td>
<td>9</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Emotion</td>
<td>5</td>
<td>9</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Cognition</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Self-Care</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vision</td>
<td>6</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hearing</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Speech</td>
<td>11</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ambulation</td>
<td>10</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Dexterity</td>
<td>12</td>
<td>10</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Emotion</td>
<td>9</td>
<td>10</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cognition</td>
<td>7</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Although both systems measures cognition and emotion, the underlying constructs used to define the attributes are different., and accordingly, differences in the scores of these attributes were observed in this study. Emotion, as defined by “worry” on HUI2, was compromised in the group experiencing pain, while emotion, as defined by “happiness” on HUI3, was not. Similarly, cognition, as defined by “memory, thinking, and solving day-to-day problems” on HUI3 was noted to be decreased in individuals with pain, but not when defined as “learning and memory” on HUI2.


Longitudinal analysis was also undertaken to explore the burden of pain in the same cohort at five-year intervals, over a 10-year time period. HUI utility scores collected in 2011/2012 (time point of current study) (T3) were matched by participant ID to data collected in 2005/2006(T2) and 2000/2001 (T1). The cross-sectional results from the previous time points have been presented previously. Aside from one subject who died between T1 and T2, the data from all subjects at each time point were used in the longitudinal analysis. A summary of the number of participants accrued at each time point, as well as the prevalence of pain reported at each time point, can be seen in Figure 9.
132 children diagnosed with a Brain Tumour at McMaster Children’s Hospital between January 1, 1985 and December 31, 1998

Initial Screening
59 subjects eligible

2000/2001 Cross-sectional study
40 participants
35% reported experiencing pain

73 Subjects excluded (screening by clinic nurse):
Prior to initial study:
11 were alive but history of relapse or progressive disease
27 died after relapse or progression
16 died without relapse or progression
19 excluded based on age (<5 years), short interval from diagnosis (<2 years), not able to speak English or lost to follow-up

19 Non-participants:
6 Declined participation
7 Non-responders
2 Unable to complete questionnaire
4 Lost to follow-up

2005/2006 Cross-sectional study
37 participants
27% reported experiencing pain

3 Non-participants:
1 Died between survey time points
2 Declined participation

2011/2012 Cross-sectional study
25 participants
52% reported experiencing pain

12 Non-participants:
3 Declined participation
3 Non-responders
6 Loss to follow-up

Figure 9. Overview of number of participants at each study time point as well as the prevalence of pain (self-reported).
A total of 39 subjects who participated at the initials time point were included in the longitudinal analysis. During the course of the study, 26 individuals were noted to be disease free or have stable disease; 5 had recurrence of tumour, 3 had progressive disease, and 5 had a second malignancy, including meningioma.

The median pain and median overall utility scores for the participants at each time point are depicted in Figure 10. From the graph it appears that pain was fairly stable between T1 and T2 and most individuals reported being pain-free or having pain that did not limit their activity or that they required limited intervention for pain relief. Irrespective of this stability of pain, the overall HRQL scores changed, with a decrease as measured by the HUI2 and an increase by HUI3. An increase of pain by T3, as reflected by the decrease in the utility score, was observed in the group as a whole. The overall HRQL scores for both HUI2 and HUI3 were noted to decrease by T3, as would be anticipated by the increased burden of pain reported by the group.
Figure 10. Median overall HRQL and pain utility scores over a 10 year period, measured at five-year intervals.

Additional examination of the original data at each time point was undertaken.

Table 16 highlights the minimum and maximum pain utility scores reported for each system. Most participants were noted to have a pain utility score of equal to or over 0.80.
Table 16. Minimum, maximum and mean pain utility scores reported at each time point for HUI2 and HUI3. The prevalence of utility scores of equal to or greater than 0.80 is also presented.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td># of Participants</td>
<td>39*</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>% pain</td>
<td>35</td>
<td>27</td>
<td>52</td>
</tr>
<tr>
<td>HUI 2 Pain Utility Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min/Max</td>
<td>0.00/1.00</td>
<td>0.42/1.00</td>
<td>0.00/1.00</td>
</tr>
<tr>
<td>Mean</td>
<td>0.93</td>
<td>0.96</td>
<td>0.90</td>
</tr>
<tr>
<td># with utility ≥0.80 (%)</td>
<td>32 (82%)</td>
<td>32 (86%)</td>
<td>21 (84%)</td>
</tr>
<tr>
<td>HUI 3 Pain Utility Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min/Max</td>
<td>0.48/1.00</td>
<td>0.00/1.00</td>
<td>0.00/1.00</td>
</tr>
<tr>
<td>Mean</td>
<td>0.95</td>
<td>0.93</td>
<td>0.85</td>
</tr>
<tr>
<td># with utility ≥0.80 (%)</td>
<td>34 (89%)</td>
<td>33 (89%)</td>
<td>21 (84%)</td>
</tr>
</tbody>
</table>

*1 participant did not respond to pain question for HUI3 system (n=38)

Of the 25 individuals who provided responses at all 3 time points, 36% (9/25) reported no pain at all three survey administrations, while 40% reported pain on more than one occasion.

Exploration of pain over time was also undertaken using statistical analysis. A complete data set was generated using imputed data for missing values. A description of the imputation procedures can be found in the “Methods” section of this Thesis. The number of values imputed at each time point can be seen in Table 17. The imputed datasets along with the original data were pooled for analysis.
Table 17. Summary of the number of variables imputed for longitudinal analysis

<table>
<thead>
<tr>
<th>Time-point</th>
<th>Attribute</th>
<th># of Values Available</th>
<th># of Value Imputed-Missing-Participants</th>
<th># of Values Imputed-Non-Participants</th>
<th># of Values Used in Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000/2001</td>
<td>HUI2- Pain</td>
<td>39</td>
<td>0</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>HUI2- Overall</td>
<td>37</td>
<td>2</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>2001</td>
<td>HUI3- Pain</td>
<td>38</td>
<td>1</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>HUI3-Overall</td>
<td>37</td>
<td>2</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>2005/2006</td>
<td>HUI2- Pain</td>
<td>36</td>
<td>1</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>HUI2- Overall</td>
<td>33</td>
<td>4</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>2006</td>
<td>HUI3- Pain</td>
<td>36</td>
<td>1</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>HUI3-Overall</td>
<td>33</td>
<td>4</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>2011/2012</td>
<td>HUI2- Pain</td>
<td>25</td>
<td>0</td>
<td>14</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>HUI2- Overall</td>
<td>24</td>
<td>1</td>
<td>14</td>
<td>39</td>
</tr>
<tr>
<td>2012</td>
<td>HUI3- Pain</td>
<td>25</td>
<td>0</td>
<td>14</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>HUI3-Overall</td>
<td>24</td>
<td>1</td>
<td>14</td>
<td>39</td>
</tr>
</tbody>
</table>

Analysis of change in pain over time by HUI2 was facilitated using a linear mixed effects model. F-values of the original and the imputed data sets were not significant, as determined by a p-value of >0.05. As anticipated the pairwise comparison of the five-year interval changes (2000/2001 to 2005/2006, and 2005/2006 to 2011/2012) as well as the change over ten years (2000/2001 to 2011/2012), were not statistically significant (Table 18). In addition, these time points were also noted to be clinically similar with an increase of pain utility score (interpreted as a decrease of burden of pain) by 0.029 at T2, and a slight decrease (0.032) of the utility score between T2 and T3.
Table 18. Results of longitudinal analysis of the pain utility scores by linear mixed effects model; fixed factor is time. Results presented are of pooled data (initial dataset along with datasets with imputed missing values).
↑= increase in utility score, ↓= decrease in utility score

<table>
<thead>
<tr>
<th>HUI System</th>
<th>Time point</th>
<th>Estimate</th>
<th>St. Error</th>
<th>Stat. Sig.</th>
<th>Clinical Sig. (&gt;0.05)</th>
<th>95% Confidence Interval</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUI2</td>
<td>T1 to T2</td>
<td>↑ 0.029</td>
<td>0.0286</td>
<td>0.315</td>
<td>No</td>
<td>-0.085 – 0.027</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 to T3</td>
<td>↓ 0.032</td>
<td>0.030</td>
<td>0.286</td>
<td>No</td>
<td>-0.027 – 0.061</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1 to T3</td>
<td>↓ 0.003</td>
<td>0.030</td>
<td>0.910</td>
<td>No</td>
<td>-0.055 – 0.061</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HUI3</td>
<td>T1 to T2</td>
<td>↓ 0.021</td>
<td>0.529</td>
<td>0.692</td>
<td>No</td>
<td>0.088 – 0.357</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 to T3</td>
<td>↓ 0.202</td>
<td>0.062</td>
<td>0.002</td>
<td>Yes</td>
<td>0.078 – 0.326</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1 to T3</td>
<td>↓ 0.223</td>
<td>0.066</td>
<td>0.002</td>
<td>Yes</td>
<td>0.089 – 0.357</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In contrast, the F-values resulting from the HUI3 pain utility scores over time was statistically significant (p<0.05) for the five datasets containing imputed data; the original dataset comparing T1 and T2 to T3 was not significant, with a p-value of 0.071. Review of the pairwise comparison revealed both statistically and clinically significant increases in the burden of pain between the five-year period of 2005/2006 and 2011/2012 (decrease of utility score by 0.20, standard error 0.06, significance p<0.01). This marked decrease in pain utility score was also noted over the ten-year study period (estimated decrease of 0.223, standard error 0.07, significance of p<0.01).

Generation of ICCs was also undertaken to provide an estimate of the stability of pain at an individual level. The within-individual correlation for pain was fair, with the ICC calculated at 0.41 as measured by HUI2 and 0.40 by HUI3. It can be interpreted that, although pain is a consistent burden of morbidity in this cohort, only a few participants experience a persistent level of pain at each time point.
Finally, the overall HRQL over time was also investigated for this cohort. The median overall utility scores for the original data at each time point can be seen in 10. It was noted that, although the pain score contributes to the generation of the overall utility score, the line graph revealed that the mean HRQL utility scores and the pain utility scores did not follow the same trajectory.

Analysis of the linear mixed effects model results using pooled data from the original and imputed datasets for the HRQL mean utility scores by HUI2 revealed significance of the F-value in some but not all of the datasets generated. Pooled pairwise comparisons of the initial time point to the subsequent time points were not statistically significant (Table 19). However, there was a clinically significant increase in HRQL between T1 and T2, but marked decrease between T2 and T3.

Table 19. Results of longitudinal analysis of the multi-attribute utility scores by linear mixed effects model; fixed factor is time. Results presented are of pooled data (initial dataset along with datasets with imputed missing values). T1= 2000/2001, T2= 2005/2006, and T3= 2011/2012 survey time points. \(\uparrow\) = increase in utility score, \(\downarrow\) = decrease in utility score.

<table>
<thead>
<tr>
<th>HUI System</th>
<th>Time point</th>
<th>Estimate</th>
<th>St. Error</th>
<th>Stat. Sig.</th>
<th>Clinical Sig. (&gt;0.03)</th>
<th>95% Confidence Interval</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUI2</td>
<td>T1 to T2</td>
<td>(\uparrow0.031)</td>
<td>0.03</td>
<td>0.304</td>
<td>Yes</td>
<td>-0.089</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 to T3</td>
<td>(\downarrow0.068)</td>
<td>0.041</td>
<td>0.121</td>
<td>Yes</td>
<td>-0.020</td>
<td>0.155</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1 to T3</td>
<td>(\downarrow0.037)</td>
<td>0.040</td>
<td>0.358</td>
<td>Yes</td>
<td>-0.045</td>
<td>0.119</td>
<td></td>
</tr>
<tr>
<td>HUI3</td>
<td>T1 to T2</td>
<td>(\uparrow0.017)</td>
<td>0.065</td>
<td>0.793</td>
<td>No</td>
<td>-0.148</td>
<td>0.113</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 to T3</td>
<td>(\downarrow0.173)</td>
<td>0.068</td>
<td>0.015</td>
<td>Yes</td>
<td>0.036</td>
<td>0.310</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1 to T3</td>
<td>(\downarrow0.155)</td>
<td>0.066</td>
<td>0.021</td>
<td>Yes</td>
<td>0.024</td>
<td>0.287</td>
<td></td>
</tr>
</tbody>
</table>
This decrease between 2005/2006 and 2011/2012 was even more pronounced in the HUI3 multi-attribute scores, with significant differences seen statistically and clinically (regression estimate of -0.173, standard error of 0.068, statistical significance of p=0.015). The change over the ten years also reflected this decrease in HRQL over the long-term (regression estimate of -0.155 from time point 1 to time point 3, standard error of 0.066, significance of p=0.021). There was no perceivable change between T1 and T2. The within-individual correlations for the overall HRQL were calculated to be 0.48 for HUI2, and 0.37 for HUI3.
DISCUSSION

Surviving a brain tumour in childhood is not without consequence with multiple medical late effects cited in the literature. Given the precarious balance between interventions required for cure and the ensuing long-term sequelae, HRQL has gained increasing recognition as an important outcome in pediatric oncology research studies (Schwartz & Sprangers, 2003). This current exploratory study undertaken in 25 survivors of brain tumours diagnosed in childhood or adolescence provides insight into the HRQL of long-term survivors of CNS malignancies.

Of the 31 eligible participants contacted, 81% (N=25) completed the interviewer-administered HUI2/3 questionnaires, which is noteworthy given that survivors were all greater than ten years from their initial diagnosis. The high rate of participation is not uncommon in oncologic studies; survivors of cancer are not to be responsive to research and specifically, welcoming the opportunity for self-reporting of health (Turner et al., 2009). Of the individuals who did participate the majority provided responses to all items on the HUI2/3 questionnaires. This is felt to be partially attributable to the use of interviewer-administered questionnaires as previous studies of childhood cancer survivors have noted that this population has a propensity to respond “don’t know” or leave responses blank to mailed questionnaires relating to HRQL (Ness et al., 2005).

Formal comparison between disease and treatment characteristics of participants and non-participants was not undertaken due to the small sample size. On review, participants appeared to have received more intensive intervention by means of radiation
and chemotherapy. However, the proportions of brain tumour sub-types, site of primary
tumour, extent of resection and mode of therapeutic intervention were diverse and similar
to the patient characteristics reported in the CCSS, which was a large, North-American
multi-centre study of long-term survivors of cancer in childhood and adolescence,
including those with brain tumours (Packer et al., 2003).

Cross-Sectional Results

Overall HRQL

As a group long-term survivors of brain tumours in childhood and adolescence
were found to experience a compromised overall HRQL, with a resultant overall HUI2
mean score of 0.79 (SD 0.23), median of 0.88, and HUI3 mean score of 0.69 (SD 0.29),
median of 0.77. This cohort of survivors reported greater burdens of morbidity, including
a clinically significant difference of >0.03, than is observed in the general population. A
US population-based report of the HRQL of adults aged 18-44 revealed a HUI2 mean
score of 0.89 (median of 0.92) and HUI3 score of 0.86 (median of 0.93) (Luo, Johnson,
Shaw, Feeny & Coons, 2005). Of note, the US-based study oversampled Hispanic and
non-Hispanic Blacks to be representative of the ethnic composition of the US. Therefore
comparisons the study cohort and the population based data should be approached
cautiously. A smaller, population-based study was undertaken in Canada using the HUI3
questionnaire (Pogany et al., 2006). Individuals between the ages of 20 and 37 without a
history of cancer had a mean score of 0.85, which is once again higher (and clinically
significant different) than the mean score observed in our cohort of long-term survivors
of brain tumours. In both the US and Canadian studies the assessment was by self-completion, which may have had an influence on the responses.

With respect to other childhood cancer survivor studies, the mean HUI scores observed in the current study were within the range of scores reported in other studies of survivors of childhood brain tumours and using the HUI family of instruments (Alessi et al., 2007; Barr et al., 1999; Glaser et al., 1999).

The overall mean HRQL score from this study was noticeably lower than the median, which prompted further investigation. Examination of the distribution of the individual patient scores revealed that there was a wide range in the overall utility scores, including one report of a “very poor” HRQL of 0.16 as measured by the HUI2 system and “as significant as a state that is worse than being dead” (-0.19) by the HUI3 system. It would appear that a sub-group of individuals within this cohort experience considerable morbidity even many years after diagnosis.

**Single Attribute Analysis**

A high prevalence of morbidity in attributes of cognition, pain, sensation and emotion was observed in our cohort of survivors of brain tumours in childhood. This was consistent with Hypothesis #1, which anticipated a high prevalence of participants reporting pain, and Hypothesis #3, which noted additional areas of morbidity, in particular in cognition and emotion. Further, participants also reported a high burden (severity) of morbidity in areas of physical functioning, including the attributes of mobility, ambulation, dexterity and vision, as well as in areas of executive functioning,
demonstrated by the scores in emotion and cognition. Pain was also established to be a prevalent and considerable burden among those interviewed.

The breadth of physical and other morbidities observed, although well documented in the literature, is not fully understood. Many survivors experience functional deficits that do not match the area of the primary brain tumour. It has been postulated that, although a tumour may occur in a single area of the brain, there is overlap in function and therefore decreased ability in one area has ramifications for other capabilities. Baron Nelson et al. (2013) provide the example of cognition, which relies on the processes of thinking, memory, perception and language. As HRQL attempts to capture the functional capabilities of an individual within the context of daily living, it is possible that the deficits observed could be a result of any number of limitations within a complex process required to perform the desired function. That is, the measure of the specific morbidity could be confounded by deficits in other areas.

The HUI2/3 system explores functional capabilities of an individual. This may require multiple cognitive processes in addition to the attribute under investigation. Therefore this measure may be particularly sensitive to burdens in functional capabilities and as such evaluates a process of abilities as opposed to a single observable attribute. For example, “vision” is measured based on the response to the question “Have you been able to see well enough to recognize a friend on the other side of the street without glasses or contact lenses?” This question requires that the respondent utilise multiple faculties in
addition to sight, including memory, perception and thinking, as the item also specifies that the individual is able to distinguish between a friend and a stranger.

Unlike most survivors of non-CNS malignancies in childhood, as noted previously and once again established in this study, there continues to be a high prevalence of morbidity detected many years after diagnosis in survivors of brain tumours in childhood. This was observed in the study by Alessi et al (2007) in which the overall HRQL scores for childhood leukemia survivors greater than 15 years of age was 0.85 in comparison to CNS tumour survivors who had a score of 0.73, as measured by the HUI3 questionnaire. Pogany et al., (2006) also identified survivors of childhood brain tumours to have poorer health utility scores in comparison to most other primary cancer survivors, again measured using the HUI3. Reulen et al., (2007) also found that long-term survivors of brain tumours in childhood treated with radiotherapy scored significantly lower physical component score than survivors of leukemia and most other cancers (aside from survivors of bone tumours and neuroblastoma treated with radiotherapy. It is possible that in children with brain tumours, the assault to the young brain at a time of crucial development may result in cognitive limitations. Functional impairment that may also become increasingly apparent as the brain develops, and even more so as these individuals attain an age associated with expectations of increasing independence, potential demands on physical activity, and integration into society (Anderson et al., 2001B; Radcliffe et al., 1992, Mulhern & Palmer, 2003; Sands et al., 2001). The increased limitations may also contribute to previous observations that survivors of brain tumours are at greater risk than other childhood cancer survivors of having difficulty with
educational achievement, employment and social supports, and maintaining relationships (Armstrong et al., 2009; Barrera et al., 2005; Gurney et al., 2009; Hays et al., 1992; Koch et al., 2004; Langeveld et al., 2003; Lancashire et al., 2010; Mostow, et al., 1991).

**Pain in Survivors of Brain Tumours in Childhood and Adolescence**

In keeping with Hypothesis #1 pain was reported in greater than 35% of respondents. This establishes a burden of pain in long-term survivors with over half of the participants reporting experiencing pain the week prior to the interview. Interestingly, discomfort was not limited to the head, but was also identified to be present in various locations through the body. The presence of pain in survivors of CNS tumours in childhood has been reported inconsistently. Previous studies have noted the presence of pain, including an increased prevalence in comparison to normal controls and other cancer survivors, while others have found no pain, or pain at levels similar to childhood cancer survivor and non-cancer comparison groups (Alessi et al., 2007; Armstrong et al., 2009; Barr et al., 1999; Glaser et al., 1999; Pogany et al., 2006).

It is possible that the discrepancies between the burden of pain observed in various studies, including this current study, could be attributed partially to the use of self- or proxy-reporting (Sands et al., 2001). This is related to Hypothesis #2, which stated that expectation of correlation between self- and proxy- reported pain would be fair (less than 0.4). In this study it was observed that there was only fair correlation of pain when measured by activity limitation (HUI3), and slightly above fair when measured by interventions to alleviate pain (HUI2).
In keeping with other studies it was observed in the current study that overtly observable attributes, such as mobility, had good correlation between the proxies (parent, spouse or friend) and the participants, while less observable attributes, such as emotion and pain, had poorer correlation, particularly when it came to severity of the morbidity (Barr et al., 1999; Bhat et al., 2005; Glaser et al., 1999). Interestingly, in the current study there was poor agreement between participants and proxies in attributes that, as a group, were identified by participants to have increased burden of morbidity. It is possible that “very good” to “perfect” health is easier to rate than the degree of poor health. This was seen in the attribute of pain in which the presence or absence of morbidity was identified correctly by most proxies (17 out of 22); however, only 45 to 50% of proxies were able to identify the severity of pain correctly as measured by the amount of activity limitation and by the type of intervention to alleviate symptoms. Of the five discordant pairs, four proxies under-reported the presence of pain in the participants. The results are also in keeping with poor prediction of pain by spouses of chronic pain sufferers (Sorbi et al., 2006).

The questionnaire itself may also be instrumental in the reporting of pain by the subject. From literature reviewed for this thesis, studies that utilized the HUI family of instruments to explore HRQL were more likely to explicitly provide results for pain as well as identify pain as a concern for long-term survivors of brain tumours in childhood (Alessi et al., 2007; Barr et al., 1999; Glaser et al., 1999; Pogany et al. 2006). The current study, which also used the HUI system of instruments, also identified pain as a burden in this cohort. The increased reporting of pain may be a result of the wording of the
questions by the HUI family of questionnaires as participants were requested to report whether they experienced any pain or discomfort within the past week. In addition, the interpretation of pain or discomfort was made by the respondent and did not preclude any location within the body or type of pain experienced. Further pain was not defined by the interviewer nor was any attempts made at that time, by a health care professional or member of the research team to differentiate between the pain or symptoms reported by the subject. This is different from the CCSS in which participants responded to a question framed around being informed by a doctor or health care professional that they were experiencing pain in very specific areas of the body (Lu et al., 2011). The response to the CCSS questionnaire is contingent on the experience of pain being identified through routine medical care, as well as for the participant to recall a discussion with a member of the health care team. Also, the HUI family of questionnaires provides a single attribute score for pain, which may facilitate the reporting of pain.

Further, certain studies attempted to explore HRQL and pain using novel or disease-specific questionnaires. Consequently enquiry into pain was often limited to specific body areas preconceived to be a problem, such as the head or abdomen, which may have limited the exploration of pain and thus resulted in under-reporting (Lu et al., 2011; Streiner & Norman, 2008). The results of the current study, which utilised generic questionnaires, concurred with the possibility of this limitation as it was demonstrated that survivors of brain tumours in childhood experienced pain in multiple areas of the body, including but not limited to the head.
In addition, many survivors of brain tumours in childhood have received radiation therapy to the brain, which is associated with long-term cognitive dysfunction (Lawrence et al., 2010). As such, it is possible that measurement instruments with increased complexity may result in under-reporting of pain due to limited comprehension of the question itself. The HUI2/3 items related to pain had an average Flesch-Kincaid grade level of 6.7 (minimum of 4.1, maximum of 9.1), which, coupled with interviewer administration, would increase the possibility of the brain tumour survivors being able to understand and respond to the questions.

In the current study of survivors of brain tumours in childhood it was observed that 52% of participants reported experiencing pain on at least one occasion in the past week. However, of those reporting pain, the majority expressed that the pain did not occur daily, and that the most severe pain experienced within the past week restricted none or very few of their daily activities and either did not require any intervention or could be controlled with over-the-counter medications or self-control of activities. While participants report limited requirements for therapeutic intervention for their pain, it is unclear whether their pain was managed effectively. Further exploration into the type of pain and the potential role of counselling regarding methods to control pain, needs to be pursued.

Further exploration of pain and the association with other attributes of HRQL revealed a more complex picture and potentially a greater understanding of the actual burden experienced by this subgroup. Individuals reporting discomfort were found to
have equal or greater burdens of morbidity in all attributes compared to their pain-free counterparts. Areas of clinically significant difference included those of physical functioning, cognitive processing and fretfulness. The most conspicuous difference was the increased worry and fretfulness, as measured by the HUI2 attribute of emotion. As a group, however, participants with pain had mean single attributes of greater than 0.8 for all attributes aside from the HUI2 emotion score of 0.75. The most remarkable finding, however, was that all individuals reporting a severe burden of morbidity in any attribute also endorsed experiencing pain. In addition, participants with pain comprised 71% of individuals noting a moderate level of morbidity measured at a single attribute level.

The increased difficulties with movement, sensation and dexterity are not unexpected in individuals with pain and this was supported by the increased prevalence of extremity pain, particularly of the lower extremities, reported by participants. Further, 30% of survivors with pain directly endorsed discomfort limiting at least some of their daily activities. The greater morbidity in physical functioning in survivors with symptomatic pain may be a result of the neurological complications, such as peripheral neuropathy and motor dysfunction, as well as neurosensory system difficulties, including visual deficits, which have been described as common long-term consequences in survivors of CNS tumours (Deliganis, Geyer & Berger, 1996; Gayre, Scott, Feuer, Saunders & Siatkowski, 2001; Packer et al., 2003; Sonderkaer et al., 2003). These medically significant late effects are thought to be related to both tumour involvement and therapeutic intervention, including radiation, platinum-based chemotherapy and antibiotics (Turner et al., 2009).
It is also possible that neurosensory changes may influence pain independently, and, more specifically, the perceptions of pain. As such, individuals identified to have greater neurological morbidity may also experience a heightened sense of pain. This is postulated to be a potential mechanism of the chronic pain that is often observed in patients with a history of traumatic brain injury (Nampiaparampil, 2008; Sherman, Goldberg & Bell, 2005).

The presence of pain may also influence neurocognitive functioning; in the current study, long-term survivors reporting pain also self-reported difficulty with memory, thinking and solving of day-to-day problems. The negative impact of pain on neurocognitive processing has been demonstrated in studies of patients with and without known histories of assaults to the brain or neurologic disorders (Hart, Martelli & Zasler, 2000). Specifically, areas of attentional capacity, processing speed and psychomotor speed were identified as the most significantly affected areas in these individuals (Hart et al., 2000). Grigsby, Rosenberg & Busenbark (1995) also found that individuals with chronic pain performed more poorly with respect to information processing compared to individuals with traumatic brain injury.

Neuropsychological late effects, including mood irregularities such as anxiety and depression, are well-documented in the literature for patients with a history of CNS malignancy in childhood and have been attributed to tumour type, location and extent, as well as treatment (Turner et al., 2009; Gragert & Ris, 2010). Pain also may play a role in emotional morbidity, defined by worry, as this was found to be a clinically significantly
greater burden in individuals with pain than in those without pain in the current study. This finding is in keeping with observations of decreased emotional functioning, including heightened anxiety, reported in pain sufferers, and is well-described in the literature and considered one of six essential domains included in the evaluation of chronic pain in clinical studies (Turk et al., 2003).

Somewhat surprisingly emotion as measured by happiness did not differ significantly between the two groups. Diminished happiness was not identified as a significant burden for the overall cohort, which is unlike the CCSS that demonstrated increased depression and decreased expectation of future life satisfaction in brain tumour survivors (Zebrack & Zeltzer, 2003; Zeltzer et al., 2008). The self-reported happiness experienced by the participants in the current study may be a consequence of the self-affirmed overall HRQL, with 24 of the 25 participants reporting at least “good” HRQL, and the optimism seen by the anticipated increase in general QOL over time. Other studies, including those involving children diagnosed with cancer, have also reported favourable outlooks by participants despite living with health conditions or disabilities; this phenomenon is given the term “disability paradox” to explain the appearance of moderate correlation between health status and QOL (Albrecht & Devlieger, 1999; Phipps & Srivastava, 1997; Phipps et al., 2001).

Correlation between direct reporting of maximum pain intensity at each location as measured by the coloured analogue scale and pain measured by intervention for symptom relief (HUI2 system) and activity limitation (HUI3 system) was moderate, with
ICCs of 0.38 and 0.45, neither of which was statistically significant. The strength of the correlation observed suggests that the numerous measures of pain severity may be related but not redundant. As pain is a subjective, multi-faceted process, the measurement of perceived intensity, activity limitation and level of intervention can be seen as complementary in the measure of pain. This idea of multiple domains to capture pain is emphasised in the IMMPACT consensus statement which provides guidance on the measurement of chronic pain in clinical trials (Turk et al., 2003). Other suggested core domains include emotional and physical functioning, which were areas that were also identified to be significantly different between participants with and without pain.

Sociodemographics, including social adjustments, and life and career pursuits, have been shown in previous studies to be compromised in individuals with brain tumours in comparison to healthy controls as well as to survivors of non-CNS malignancies (Lannering, Marky, Lundberg & Olsson, 1990; Pang et al., 2008). Although patients with pain had greater burdens related to their HRQL, there were similar distributions of social integration and adaptation including reported living situation, relationship status, ability to drive, educational level achieved and employment/student status as in their pain-free counterparts. Exploration of the severity of pain and distribution of sociodemographics was not undertaken due to the sample size. However, at a cursory overview it appears that there may be alternate factors that influence the variability seen within this cohort. Posited theories for variability include maladaptation and transition into adulthood as a consequence of health care needs and neurocognitive morbidities (Turner et al., 2009).
Exploration of pain at five-year intervals over a 10-year period established that pain is a persistent burden in survivors of brain tumours in childhood. Review of the raw data revealed that pain was endorsed by 35% of participants at the first time point and, although decreased at the second interview (27%), increased to 52% at the third interview when all individuals were deemed to be long-term survivors of brain tumours in childhood. Irrespective of the trend, 40% (n=10) of the 25 individuals who participated at all survey time points reported the presence of pain on at least 2 of the 3 interview time points. This suggests that a subgroup of survivors experience on-going pain.

Analysis of the pain utility scores, using imputation and longitudinal analytic techniques, supported the hypothesis of the continued prevalence of pain in the study cohort over time. This burden of morbidity was found to be relatively stable between the first two time points (5-year period), as measured by HUI2 and HUI3 systems. However, between the interviews at 2005 (T2) and 2010 (T3), although there was no increase in interventions to alleviate discomfort, there was a significantly increased amount of activity limitation. Accordingly, the within-individual correlation of pain over time, interpreted with an ICC, was fair. This would suggest that an individual with a history of a CNS malignancy in childhood may experience variability in the presence and severity of pain in survivorship.

The overall HRQL utility score, which incorporates the attribute of pain, also decreased between the second and third time points. The HUI3 system appeared to be more sensitive than HUI2 to the increased morbidity experienced by the cohort with a
A statistically and clinically significant decrease of HRQL over a 10-year period (regression estimate of -0.155 from time point 1 to time point 3, standard error of 0.066, significance of p=0.021). The within-individual correlations for overall HRQL for the ten-year study period were calculated to be 0.48 for HUI2 and 0.37 for HUI3. Interpreted as an ICC, this would suggest that the overall HRQL of individual long-term survivors of brain tumours in childhood varies over time for many of the survivors. This could be a reflection of a change in health status according to the ability of the individual or by a change in life requirements. This is consistent with the theory that the impact of morbidities increases or becomes more apparent as cancer survivors age and assimilate to adult life (Anderson et al., 2001B; Radcliffe et al., 1992, Mulhern & Palmer, 2003; Sands et al., 2001).

While pain contributes directly to the overall HRQL, in this study it was also demonstrated to influence morbidity in other areas and as such have a greater impact on the HRQL than is readily observed. This could explain the different rates of change of pain and HRQL over time. It is also possible that the other attributes change independently over time. However, this was not explored and is beyond the realm of this project.

**Limitations**

There are several limitations of the current study. It is possible that the burden of morbidity experienced by long-term survivors of brain tumours may be over-estimated due to selection bias. Participation in this study was limited to individuals who were
contactable and therefore either traceable through the health care system, such as being actively seen in the brain tumour survivor clinic or family doctor’s office, or reachable through the last listed telephone contact. It is conceivable that patients with less morbidity are more likely to move away from home and consequently may be more difficult to reach. As such, the recruitment strategy may select indirectly subjects with greater morbidity. A sensitivity analysis (best-case, worst-case scenarios) could be undertaken to assess the influence of the missing data on the overall results. In addition, once an individual was deemed a “non-participant” they were not approached again at a later time point for participation. This could further bias the results. It may have been appropriate to re-approach the individuals at the later time points even if they had not participated previously in the study. A comparison of the characteristics of the participants versus non-participants at each time point may also be beneficial to see if there are systematic differences between the two groups.

Although review of the initial diagnostic characteristics of participants and non-participants were suggestive of more intensive treatment of individuals who participated in the study and, by extension, suggestive of increased levels of morbidity, the demographic and disease characteristics as well as therapeutic interventions of participants were similar to those seen in the large, multi-centre CCSS (Packer et al., 2003). Therefore the results obtained in this study are thought to be representative of survivors of CNS tumours in childhood. In addition, morbidities observed in this study were similar to those reported in previous studies. Other reasons for non-participation
include individuals who were not able to schedule a time for the interview, as well as those who felt the study would result in increased distress.

The possibility also exists that the true prevalence of pain is overestimated in this study. On the HUI2/3 system participants are required to assess retrospectively pain experienced the week prior without investigation into pain beyond this period or the type of pain being reported (Furlong et al., 1998). While episodes of acute pain have been found to be recalled accurately within a one-week period, this method of retrospectively assessing pain has been found to potentially bias chronic pain sufferers to the over-reporting of pain (Singer, Kowalska, & Thode, 2001; Sorbi et al., 2006). The use of momentary assessments, such as electronic pain diaries, which are completed in real time throughout the identified period, may provide a better representation of the discomfort experienced by the cohort under study, particularly if survivors of childhood brain tumours experience chronic pain (Morren, van Dulmen, Ouwerkerk & Bensing, 2009). As the burden of pain in long-term survivors of brain tumours becomes better understood, more comprehensive, but costlier and more intensive measures, such as those used in chronic pain studies, can be justified for use.

Another consideration is the potential response shift when applied to longitudinal analysis. QOL measurement is founded on the assumption that an individual’s values do not change and, as such, changes in health would be reflected by the HRQL outcomes (Schwartz & Sprangers, 1999). However, “response shift” is the change in an individual’s values and perceptions, often in response to a change in health status, and may result in
alteration of values (Sprangers & Schwartz, 1999). This is often reported within the context of medical conditions, with patients asserting good self-reported health status despite medically worsening health. In the current study, all but one participant endorsed “good” overall HRQL when questioned directly; however, analysis of the multi-attribute health status scores as well as the single attribute scores indicated otherwise. This discrepancy may be accounted for by response shift bias.

In addition, it can be postulated that, as healthy individuals age, there would be an increase in pain over time, and therefore the increase in pain over a decade observed in the current study may be a reflection of this ‘developmental’ phenomenon. However, the contribution of the natural aging process to the burden of pain, as well as any normal intra-individual variation, would not be expected to reach the degree of change observed in this study. Furthermore, at the last time point of the survey, all patients were less than 40 years old, and therefore would not be anticipated to experience age-related changes in morbidity as demonstrated by the overall health status reference values for Canada and the USA (Fryback et al., 2007; Luo et al., 2005; Pogany et al., 2006).

Finally, this study is limited by small sample size, which has implications on the power to detect differences. This was an exploratory study and therefore statistical results should be interpreted with caution. Although this study is limited by the small sample size, as noted previously, the overall participant characteristics and morbidities observed are similar to those seen in other studies (Aarsen et al., 2006; Alessi et al., 2007;
Implications of Findings

The current cross-sectional and longitudinal studies undertaken at MCH established that pain is a common and persistent phenomenon in survivors of brain tumours in childhood. While it is unclear whether the pain experienced by this cohort is a result of the disease, treatment or consequences of other late effects, there appears to be a distinct relationship between pain and morbidity in other attributes contributing to HRQL, as individuals experiencing pain also reported increased levels of other morbidities.

The burden of pain in long-term survivors of brain tumours in childhood has been reported inconsistently in the literature. It is possible that study design, including the questions selected to delineate pain, the questionnaire, the primary respondent and time from diagnosis may influence the discrepancies seen. In the present study, results suggest that pain is a chronic burden in this cohort of individuals, with implications for other areas of compromised HRQL.

This finding has important implications for the clinical surveillance of survivors. Given the high prevalence of pain, clinicians following patients with a history of CNS malignancy in childhood should be aware of pain when individuals present with other more easily visualized or reportable burdens of morbidity, such as increased anxiety and compromised dexterity. Conversely, clinicians could use the reporting of pain as a screening question to identify and further explore other areas of morbidity in survivors.
It should also be considered that the presence of pain in conjunction with other morbidities may have health-related implications. For example, decreased mobility secondary to pain may put patients at an increased risk of osteopenia (Barr 1998). In addition, given the diversity in the location of pain, it is possible that survivors of brain tumours in childhood may not relate the present discomfort to their initial malignancy. It would therefore be important for clinicians to enquire about both anticipated and generalized pain, rather than discomfort limited strictly to the head.

The identification of pain by long-term survivors of brain tumours in childhood may also provide insight into other potential late effects that may not be well described yet. This is of particular importance as this patient cohort continues to age and may have changes in the type and severity of morbidity with either a decline or improvement in their HRQL.

This current study, while small in size, is in keeping with previous studies that revealed a burden of pain in long-term survivors of brain tumours. Additionally serial follow-up of the study cohort over a 10-year period revealed a persistence of pain over time. Future work needs to be undertaken to explore the pathology of the pain, including the type of pain experienced, what it could be attributed to, why individuals continue to be burdened by discomfort many years after treatment, as well as the diversity of the location of pain throughout the body. This may provide insight into potential interventions to control the pain. It would also be of interest to explore whether survivors attribute the pain to their malignancy and subsequent treatment or to another source. This
would provide insight to the treatment and supportive care measures that are offered to children with newly diagnosed brain tumours as well as to survivors of CNS malignancies in childhood and adolescence. Furthermore, the additional morbidity experienced by individuals experiencing pain, particularly the identified increased worry and fretfulness observed, warrants further study, including by qualitative and exploratory methods to better understand the potential relationship between these morbidities.
CONCLUSION

In conclusion, long-term survivors of brain tumours in childhood experience morbidity in physical and cognitive function, as measured by the HUI2/3 HRQL systems. Pain was reported frequently by participants in this study and had deleterious impacts on their overall health status as well as on the single attributes that contribute to HRQL. In addition, self-reporting should be used for assessing patients particularly when the goal is to measure less readily observable attributes, including pain. The cross-sectional and longitudinal studies that were undertaken provide further validation that pain is indeed a genuine phenomenon in survivors of brain tumours, and survivorship clinics should be aware of and interrogate patients regarding this late effect. Further work needs to be undertaken to better describe the daily pain and possible pathology resulting in the persistent discomfort experienced by patients with a history of CNS tumours in childhood.
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