THALAMIC TUMOURS IN THE MRI ERA

FINAL REPORT

FOR PERIOD

MAY 18, 2012 - DECEMBER 20, 2012

December 20, 2012

This project was financially supported by

C[17] RESEARCH NETWORK
&
BRAIN TUMOUR FOUNDATION OF CANADA

ACKNOWLEDGEMENTS

We would like to thank the C^{17} Research Network and the Brain Tumour Foundation of Canada for funding our project entitled: Thalamic Brain Tumours in Canada in the MRI Era.

In addition, the Principal Investigator would like to acknowledge the contributions of the study co-investigators, members of the pathology team at the Hospital for Sick Children in Toronto, site PIs of the participating centres, the national study coordinator at BCCH, study coordinators at participating sites, research manager and statistical support group for their involvement in this important project.

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1. INTRODUCTION

Thalamic tumours account for approximately 1% of all intracranial neoplasms[4]. Forty percent of thalamic tumours occur in the pediatric population, wherein thalamic tumours account for 2-5% of all brain tumours [4,8]. The vast majority of tumours are gliomas, but the pathology varies from the most benign pilocytic astrocytoma to the malignant glioblastoma. Treatment decision making is difficult, because the location within the thalamus makes surgical resection, one of the mainstays of brain tumour treatment, relatively hazardous. In addition, the natural history of thalamic tumours and the outcome after surgical resection, chemotherapy and/ or radiotherapy have not been well characterized. All reported series are relatively small case series, as might be expected considering the low incidence of these tumours[1-3,5-12]. There are only 6 recent studies dealing with thalamic tumours in the pediatric population (Kelly 1989; Drake et al. 1991; Villarejo, Amaya et al. 1994; Ozek and Ture 2002; Albright 2004; Fernandez et al. 2006) The earlier studies [2,3,7] may not be relevant to current management, because there have been significant advances in neurodiagnostic and surgical technology. These advances include MRI, which is the diagnostic tool of choice for thalamic tumours, and surgical technologies such as the ultrasonic surgical aspirator, advanced operating microscopes and frameless stereotaxy.

The goal of this study is to conduct a comprehensive retrospective clinical analysis of patients with thalamic tumours treated at pediatric neurosurgical centres across Canada over the last 20 years - a time period during which Magnetic Resonance Imaging (MRI) scans would have been available. This includes the presenting signs and symptoms, tumour location within the thalamus, Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) characteristics, pattern of tumour extension, histology and treatment. From this, we hope to extract information that will help us understand better how these tumours behave and grow. We may be able to find out positive or negative factors related to patient's prognosis. This in turn will allow for better patient's and physician's education, which may improve patient's quality of care and quality of life.

2. APPROVALS STATUS

The approval status for BC Children's Hospital (BCCH) is shown below in Table 1. The latest ethics approvals are also included in the appendices of this report.

Table 1. Study Approvals for BC Children's Hospital

Name of the Hospital	Date of Approval	Approval Expiry Date	Due for the Next Renewal
BC Children's Hospital - Vancouver	January 25, 2006	January 25, 2007	January 2007
BC Children's Hospital - Vancouver	January 09, 2007	January 09, 2008	January 2008
BC Children's Hospital - Vancouver	December 22, 2008	December 22, 2009	December 2009
BC Children's Hospital - Vancouver	November 23, 2009	November 23, 2010	November 2010
BC Children's Hospital - Vancouver	October 28, 2010	October 28, 2011	October 2011
BC Children's Hospital - Vancouver	October 7, 2011	October 7, 2012	October 2012
BC Children's Hospital - Vancouver	August 27, 2012	August 27, 2013	August 2013

3. IDENTIFYING STUDY PARTICIPANTS

Site PIs, who are mainly pediatric neurosurgeons, and their coordinators at each participating centre, identify charts and scans of patients, who meet the inclusion criteria for participating in the study during the study time period (1985 to 2008). Patients will be added to the study if they have sufficient information available in their chart and have a pathology sample of the resected tumour.

4. DEVELOPMENT OF STUDY DOCUMENTATION

4.1. Data Collection Forms

The Thalamic Tumour Study began in January 2006. Since that time, a data collection form and a study database have been created to support and document the study subjects. The data collection form (DCF) contains the following information:

1. Clinical features
2. CT/ MRI findings
3. Hydrocephalus treatment
4. Tumour treatment
5. Surgery description
6. Surgery complications
7. Pathology diagnosis from surgery
8. Radiation/chemotherapy treatment
9. Neurological Status
    - Pediatric Cerebral Performance Category Scale
    - Pediatric Overall Performance Category Scale

The DCF have been already submitted to the last year report, and have not changed since.

The study database is an excel database found at BCCH that contains all of the de-identified information as an electronic file for the purpose of data analysis.

4.2. Standard Operating Procedures

Included in the Thalamic Tumour Study documents are the Standard Operating Procedures (SOPs), which contain instructions for the coordination, management and implementation of the Thalamic Tumour Study at BC Children's Hospital. In addition to outlining the purpose and overall work process of the study, the SOPs provide a detailed description of the procedures, and serve as a guide and manual for the research staff.

The SOPs have been already submitted to the last year report, and apart from the new study coordinator's name (Mr. Ross Hengel), they do not include any additional changes.

5. STUDY OVERVIEW

BC Children's Hospital is the coordinating site for the study and has been leading the study since its conception. In addition to BCCH, there are 10 other investigating sites involved with the study. The participating centres include Alberta Children's Hospital in Calgary, The Mackenzie Health Science Centre in Edmonton, IWK Health Centre in Halifax, McMaster Children's Centre in Hamilton, Children's Hospital of Western Ontario in London, Children's Hospital of Eastern Ontario in Ottawa, The Hospital for Sick Children in Toronto, Winnipeg Children's Hospital in Winnipeg, Royal University Hospital in Saskatoon, and Montreal Children's Hospital in Montreal. All sites have been in communication with the national study coordinator at BCCH with regards to the progress of the study.

Study progression was anticipated to be much quicker than how it actually proceeded. Unfortunately, with this being a multi-centre study, it required strong compliance from all participating sites. Initially, there was delay with sub-sites proceeding with applications for ethics approval. Subsequently, obtaining ethics for all sites took longer than anticipated. A few of the participating sites experienced difficulties in obtaining ethics approval, particularly for the pathology review, resulting in further delays. Many of the ethics reviewers required the site's PI to include an approved ethics submission from one of the other participating sites with their own ethics submission for reference. Furthermore, another site was required by the ethics committee to obtain consent from families in order to process their pathology samples, making data collection more difficult. We also encountered a number of in-house challenges with the pathology departments of the participating institutions; one pathology department resisted the release of their limited tissue samples to send to Dr. Hawkins' lab in Toronto Hospital for Sick Children for analysis, and the pathology department of another site quoted exorbitant costs for the extraction of the pathology which was well beyond the budgeted amount. We have since successfully negotiated solutions for these issues and all sites obtained their appropriate ethics approvals and completed their portion of the data collection. A detailed representation of actual study progression can be seen in Figure 1.

All study progression, involving sub-sites, is complete. Out of the 11 study sites, all 11 sites have obtained ethics approval. In addition to this, all 10 sub-sites have signed the collaboration agreement with BCCH. All sites have, also, successfully completed the chart review stage and have had their radiological imaging reviewed by the central radiologist, at BCCH. Moreover, all sites have shipped their pathology specimens to Toronto for central review. The pathology review has begun and should be finished soon. Dr. Hawkins has been provisioned with funding and support to carry out her analysis and to send all pathology samples back to each participating study centre. A more detailed summary of individual site progress is illustrated in Figure 2.

All study data has been submitted by the 11 participating sites. In total, there are 75 completed case report forms and radiology samples, which have been sent to BCCH and added to the study. BCCH contributed 23 of the total 75 case reports included in this study. BCCH is also responsible for 15 of the total 65 pathology samples included in the study. Specific contributions made by each site are highlighted in Figure 3.

The current central pathology review is presented below:

Dr Hawkin's Lab has received 65 cases as part of the study for central pathology review. Of these, 6 were non-diagnostic. For the remaining cases, diagnoses are as follows:

1. Pilocytic astrocytoma, WHO grade 1: 28%
2. Diffuse astrocytoma, WHO grade 2: 22%
3. Anaplastic astrocytoma, WHO grade 3: 12%
4. Glioblastoma, WHO grade 4: 18%
5. Ependymoma: 8%
6. Pilomyxoid astrocytoma, WHO grade 2: 5%
7. Other: 5%

A tissue microarray is under construction which will include the astrocytoma cases with sufficient material (45 cases). Further, astrocytomas will be characterised for BRAF fusion status and H3.3 mutation status. A subset of 20 cases will be submitted for expression array analysis.

Once the final pathology report becomes available, all study data will be ready for statistical analysis. After this has occurred, the findings can be reported and published in a scientific journal.

Figure 1. Actual Study Progress Timeline

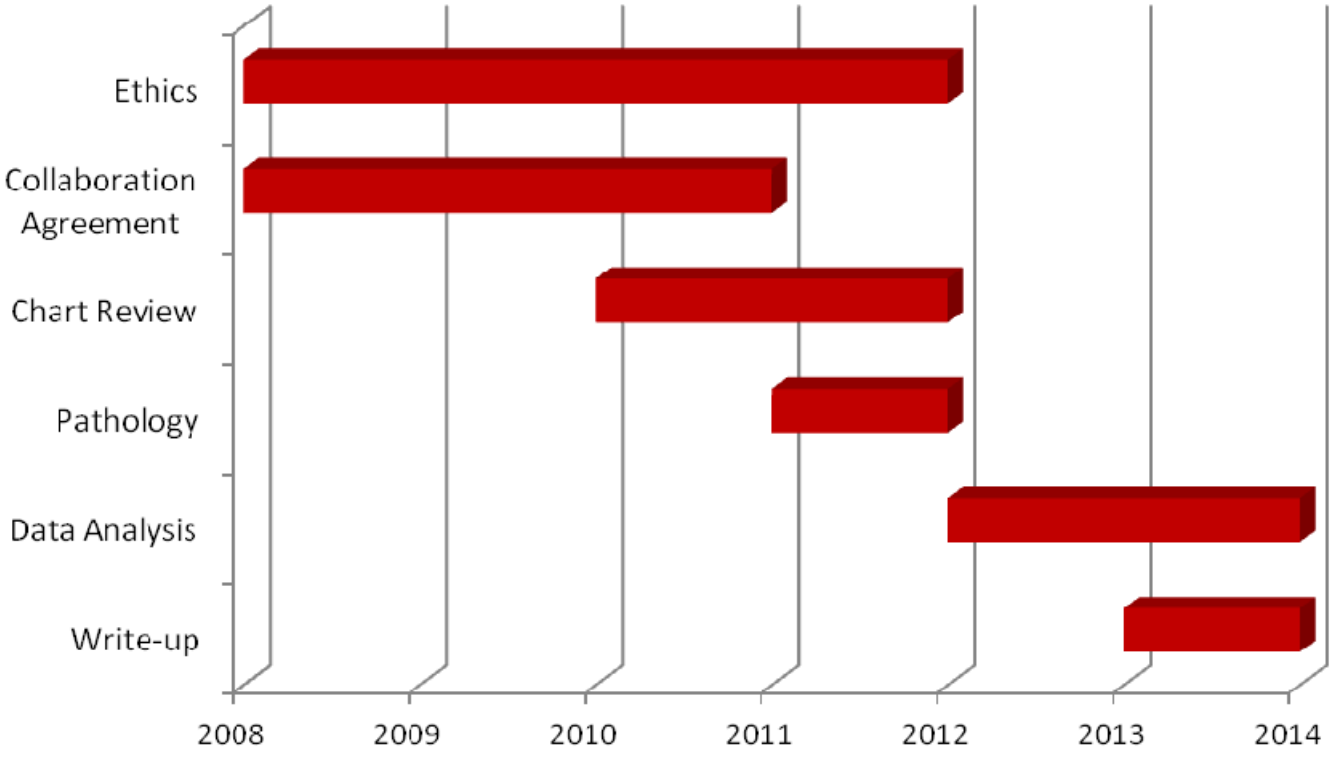


Figure 2. Individual Study Status of the Participating Centres

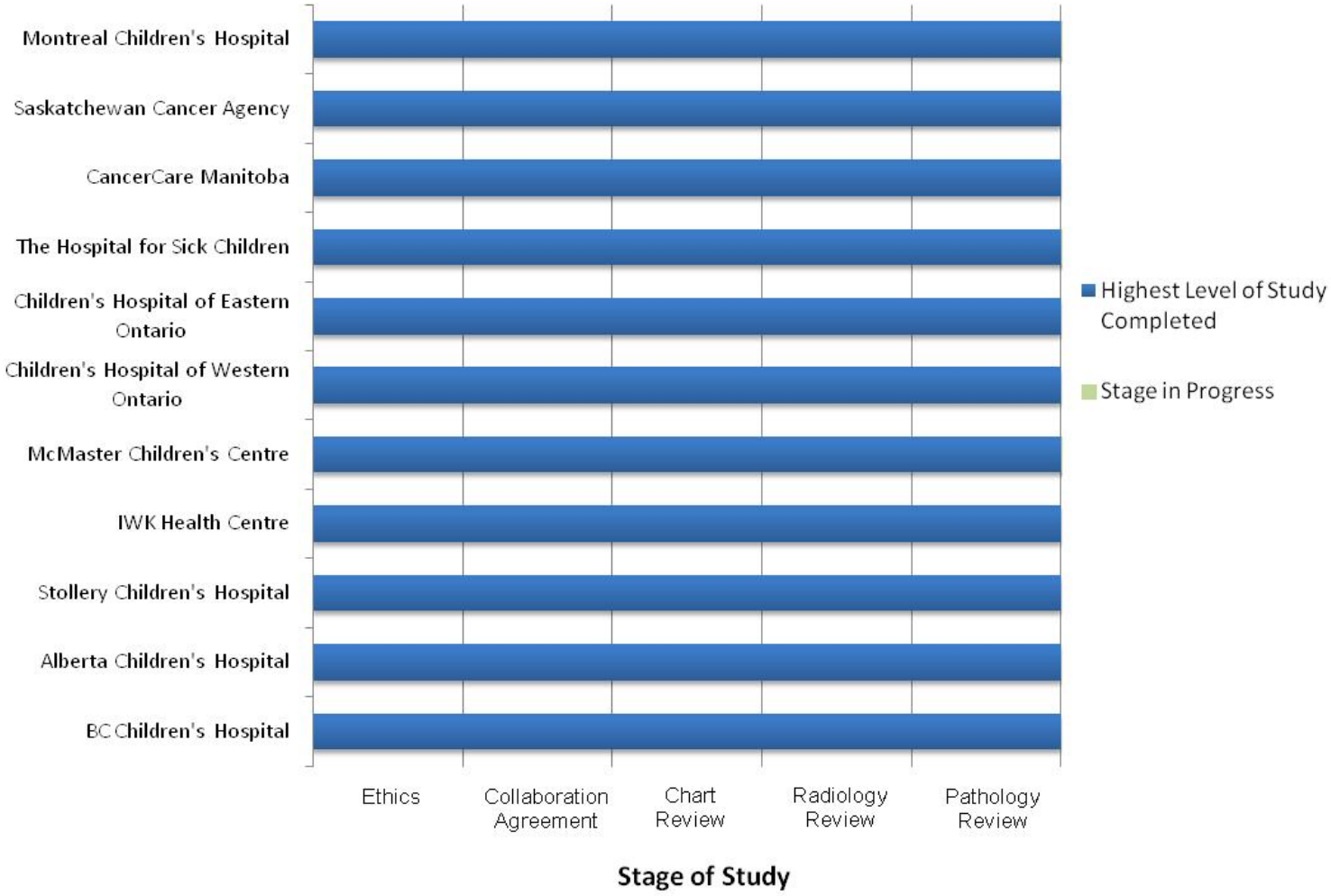
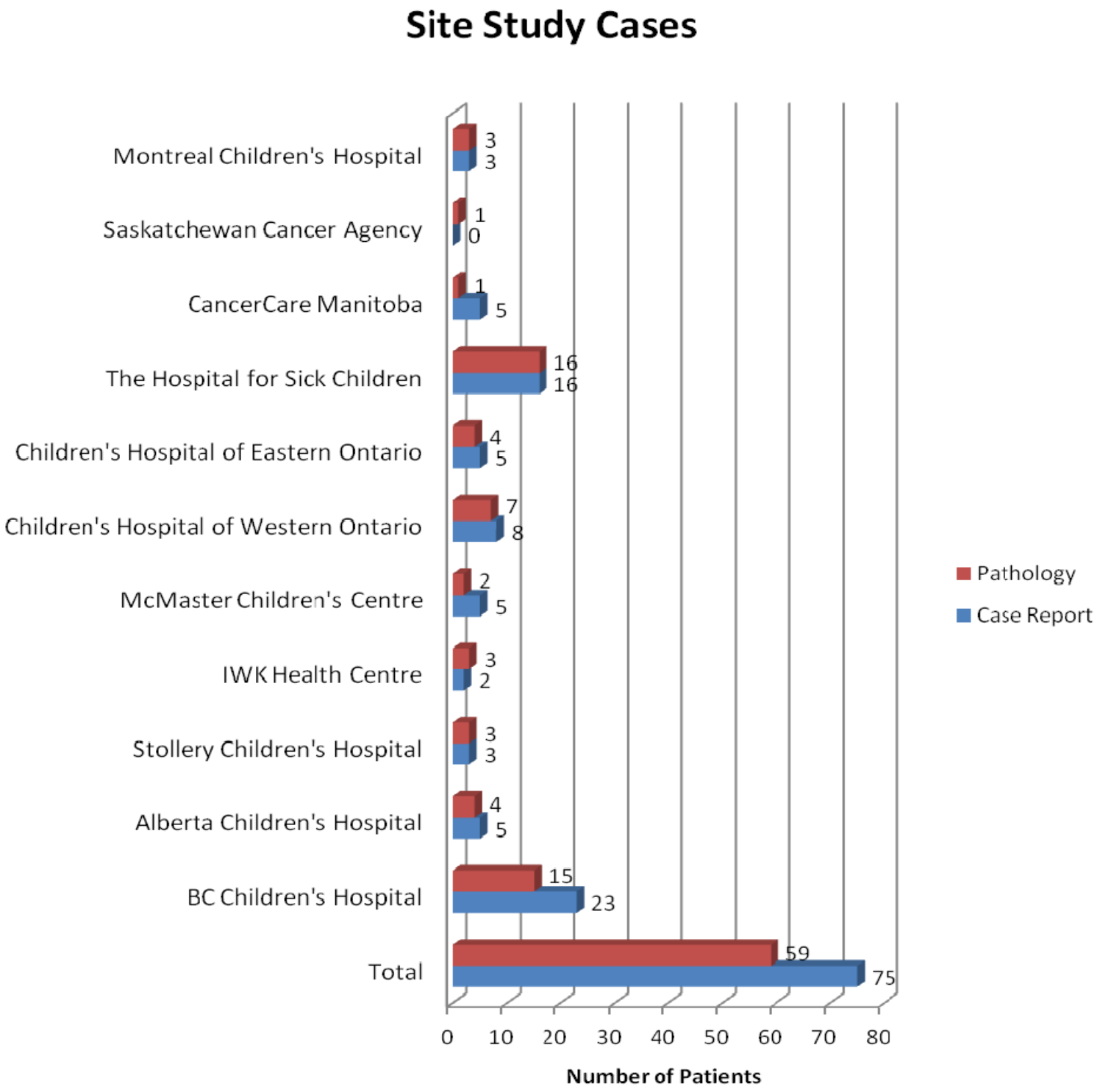


Figure 3. Patient Data Contribution from All Participating Centres to Date



5.2. Exclusion Summary

The coordinating centre has reviewed and excluded an additional 23 patients from the study due to missing diagnostic imaging or conflict. The exclusion summary, by site, is demonstrated in figure 4.

Figure 4. Subsite Exclusion Summary